TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™

INTERESTING CLINICAL VIGNETTES:
101 Ice Breakers for Medical Rounds

Texas Tech University Health Sciences Center (TTUHSC) Contributing Faculty

Jannette M. Dufour
Gurvinder Kaur
Cassandra Kruczek
Neha Mittal
Alan N. Peiris
Rebecca B. Sleeper

TTUHSC Contributing Trainees

Jessica Agrimor
Anna Calara
Sarah Jaroudi
Jeremy Moon
Sneha Raju
Shannon Rice
Kandis Wright

With Assistance from *Meredith Gavin*

Interesting Clinical Vignettes: 101 Ice Breakers for Medical Rounds

Texas Tech University Health Sciences Center (TTUHSC) Contributing Faculty
Jannette M. Dufour
Gurvinder Kaur
Cassandra Kruczek
Neha Mittal
Alan N. Peiris
Rebecca B. Sleeper

TTUHSC Contributing Trainees
Jessica Agrimor
Anna Calara
Sarah Jaroudi
Jeremy Moon
Sneha Raju
Shannon Rice
Kandis Wright

With Assistance from Meredith Gavin

Foreword

In West Texas, like many rural areas, a high demand for physicians persist. Providing general medical care to patients remains a time honored and gratifying vocation. Medicine has seen many technological advances. It has been challenging to maintain an interest in predominantly clinical specialties among trainees. If we are to maintain Internal Medicine at the gateway of providing care to adults we need a pipeline of young enthusiastic trainees. This book addresses this issue by providing a perspective on some interesting clinical vignettes.

We are very pleased that Dr. Alan Peiris and his colleagues initiated this book. Dr. Peiris is a well-recognized physician leader in education and scholarship. He was ably assisted by similarly talented TTUHSC faculty and trainees in diverse departments in our Lubbock campus. The inclusion of the Basic Science and Pharmacy perspective in this book of clinical vignettes is a major bonus. Internal Medicine remains a vast field, and there are multiple textbooks that provide specific and detailed information. The authors wisely chose not to duplicate such efforts. The main intent of this book is to stimulate interest in general Internal Medicine and assist in the generation of a broader clinical differential diagnosis. We found the cases stimulating and enthusiastically recommend this book to you

Steven L. Berk, MD
Dean, School of Medicine,
Executive Vice President and Provost,
Texas Tech University Health Sciences Center

Tedd L. Mitchell, MD
President,
Texas Tech University Health Sciences Center
August 2018

Preface

In Medicine we only recognize what we know and we only know what we critically read and evaluate.

The idea to describe interesting cases in General Medicine has been a goal of mine for a number of years. I enjoyed publishing a book on spot clinical diagnoses in Medicine with my fellow residents while in the United Kingdom[1]. Medicine, especially Internal Medicine, remains a fascinating and challenging field in which mastery is elusive. I also want to acknowledge the help of many mentors, they helped instill the perpetual learner model.

Writing a multi-author book is not for the faint of heart! Many expressed interest however only a few remained committed to this endeavor. The book has been a couple of years in the making. I am grateful to the entire group of trainees and faculty that made time in their busy schedules to help compile this book. It is especially gratifying that faculty encompassed many different fields participated in this endeavor. Drs. Jannette Dufour, Gurvinder Kaur and Cassie Kruczek and their teams provided a basic science background in the clinical cases. Dr. Rebecca Sleeper assisted in the Pharmacy therapeutics arena. Dr. Neha Mittal provided an Internist's perspective on the clinical cases. Our trainees Jessica Agrimor, Anna Calara, Sarah Jaroudi, Jeremy Moon, Sneha Raju, Shannon Rice and Kandis Wright came from very diverse backgrounds, however, their team spirit and participation was pivotal to the completion of this book. I am indebted to the entire group for their sense of good humor and esprit de corps.

The purpose of this book is to describe medical entities that hopefully will be of interest to you. We hope these cases will spur you towards additional reading on these and other similar topics. While the information contained may help you in managing patients, we do not recommend that this book be the sole source of reference for patient management. Appropriate consultation and the pursuit of second opinions in challenging and complex medical problems remains a time honored method of ensuring the patient gets the best care. The material contained in this book is provided at no cost as long as the source is fully acknowledged. As in any academic work there may be errors within this book or areas that you, the reader, disagree with the narrative for a variety of reasons. If so, we would be pleased to hear from you.

I want to thank my daughter Emma Peiris, MD (AOA, 2014) for sharing some of her interesting Internal Medicine cases. I want to also acknowledge the assistance and support I have received from Dean Steven Berk, MD and President Tedd Mitchell, MD and their commitment to excellence in medical education which makes Texas Tech University Health Sciences Center (TTUHSC) a great academic setting for faculty, students, and residents.

Alan N. Peiris, MD, PhD, FRCP (London), FACE, FACP
Professor, Vice-Chair and Chief of Geriatrics - Internal Medicine,
Myrick-Myers Endowed Chair in Geriatrics,
Executive Director – Clinical Research Institute,
Texas Tech University Health Sciences Center
alan.peiris@ttuhsc.edu

[1] A photographic quiz in medicine by Philip Ebden, Alan Peiris, Michael J. Dew. 216 p, Lloyd-Luke Medical Books, 1984. London, England. NLM ID: 8502049

Biography of Contributors

Faculty:

Jannette M. Dufour, PhD

Dr. Jannette M. Dufour received her PhD in Genetics and Cell Biology from Washington State University in 1999. She then trained as a postdoctoral fellow with the Islet Transplantation Group in the Surgical Medical Research Institute, Department of Surgery at the University of Alberta, Edmonton, Canada. In 2005, she joined the faculty at TTUHSC where she is currently a Professor in the Department of Cell Biology and Biochemistry and the Associate Dean for Research in the School of Medicine. She is the Director of the medical student research program and teaches anatomy, diabetes and transplantation immunology.

Gurvinder Kaur, PhD

Dr. Gurvinder Kaur received her PhD in Biomedical Sciences with a concentration in Cell Biology and Biochemistry from TTUHSC in 2012. She then trained as a postdoctoral fellow in the fields of transplantation immunology and diabetes from 2012-2016. She is currently an Assistant Professor in the Department of Medical Education, School of Medicine, TTUHSC and the Co-Associate Block Director for Clinically Oriented Anatomy.

Cassandra Kruczek, PhD

Dr. Cassandra Kruczek received her PhD in Biomedical Sciences with a concentration in Medical Microbiology and Immunology from TTUHSC in 2013. She joined the Department of Surgery at TTUHSC as a post-doctoral research associate from 2013-2014, then was an instructor in the Honors College at TTU. She is currently an Assistant Professor in the Department of Medical Education at TTUHSC.

Neha Mittal, MD

Neha Mittal completed her medical school from the SMS Medical College, India in 1999 and completed her IM residency from the University of Pittsburgh Medical Center (UPMC) McKeesport hospital in 2003. She joined Texas Tech in 2006. She is currently an associate professor in department of IM at the TTUHSC SOM and has been serving as clerkship director since 2012. She has been a recipient of the Robert Kimbrough professorship in medical education since 2017 and is a part of the core faculty of the TTUSHC IM residency program.

Alan N. Peiris, MBBS(London), MD(London), FRCP(London), MRCS(Eng)

Dr. Peiris is a British medical graduate (St. Bartholomews Hospital) and Tenured Professor of Medicine and Vice-Chair in the Department of Internal Medicine. He holds the Myrick-Myers Endowed Chair in Geriatrics. He was the holder of the TJ and Margaret Talkington Endowed Chair at TTUHSC in Endocrinology between 2015 and 2017. Dr. Peiris is the Executive Director of the Clinical Research Institute at TTUHSC. He is a board certified Internist in the US and UK (MRCP). His US specialty board certifications include Endocrinology and Geriatrics. His interests encompass clinical research, clinical medicine, bedside diagnosis and Vitamin D metabolism. He has published in many different research arenas and enjoys promoting research and scholarship efforts among trainees and faculty.

Rebecca B. Sleeper, PharmD, FCCP, FASCP, BCPS

Dr. Sleeper is a Professor of Pharmacy Practice in the Geriatrics Division and is Associate Dean of Curriculum at the Texas Tech University Health Sciences Center School of Pharmacy. She received her Doctor of Pharmacy from the University of Rhode Island and completed specialty residency training in Geriatric Pharmacotherapy from TTUHSC School of Pharmacy. She is a board certified Pharmacotherapy specialist and a fellow of the American College of Clinical Pharmacy and the American Society of Consultant Pharmacists. She is the co-editor of the textbook "Fundamentals of Geriatric Pharmacotherapy" and participates in the instruction of Pharmacy and Medical students in long term care, dementia care, and skilled nursing environments.

Trainees

Jessica Agrimor

Jessica Agrimor completed her pre-pharmacy coursework at Texas Tech University and is now a current fourth year pharmacy student at TTUHSC School of Pharmacy. During her years as a pharmacy student, she has been an active member and an officer for Student National Pharmaceutical Association, an organization that focuses on pharmacy and healthcare related issues geared towards serving the underserved community. She will be graduating this 2018 and plans to pursue a career in a retail or ambulatory care setting.

Anna Calara

Anna Calara graduated from The University of Texas at Austin in 2014 with a Bachelor of Science degree in Nutritional Sciences. She is pursuing an MD degree at TTUHSC in Lubbock, Texas and expects to graduate in 2019.

Sarah Jaroudi

Sarah Jaroudi graduated from the University of Houston in Houston, Texas with a Bachelor of Science degree in Nutritional Sciences in 2015. She is pursuing an MD degree at TTUHSC in Lubbock, Texas and is expected to graduate in 2019.

Jeremy Moon

Jeremy Moon graduated from the University of California, Los Angeles, California in 2015 with a Bachelor of Science degree in Physiological Sciences. He is currently pursuing an MD degree at TTUHSC, School of Medicine in Lubbock, Texas and is expected to graduate in 2019.

Sneha Raju

Sneha Raju graduated from The University of Texas at Austin in 2014 with a Bachelor of Science degree in Public Health and a Bachelor of Arts in Plan II Liberal Arts. She is pursuing an MD degree at TTUHSC in Lubbock, Texas and expects to graduate in 2019.

Shannon Rice

Shannon Rice is a fourth year doctor of pharmacy candidate and licensed intern with work experience in both community and hospital settings. She has been involved in projects such as the creation of a local antibiogram and medication use evaluations, and is published in the area of domestic animal reproduction. Her professional interests include infectious disease and antimicrobial stewardship.

Kandis Wright

In 2013, Kandis Wright graduated with a Bachelor of Science degree from the University of New Mexico in Albuquerque, New Mexico. She then pursued her MD/PhD degrees at the TTUHSC in Lubbock, Texas. She is currently finishing her PhD under mentor Dr. Jannette Dufour in the fields of transplant immunology and reproductive biology. She will complete her medical training upon the completion of her PhD.

Acknowledgements

A special thank you to Sarah Jaroudi and Kandis Wright for the extra "last minute" work which contributed significantly to the completion of this project. I also appreciate Meredith Gavin, one of our third year medical students at TTUHSC, Lubbock assisting with the editorial and formatting process. We also want to thank Josie Martinez and Staci Brown in the Clinical Research Institute (CRI) for assistance with this project. The CRI remains an unique and invaluable resource for TTUHSC faculty and trainees interested in scholarly activity and research.

Table of Contents:

1: Parkinson's Disease

Question:
A 63-year-old male with a 3-year history of Parkinson's disease comes into your office for his yearly physical exam. His wife accompanies him and complains about his recent gambling habits for the past year mentioning that he previously had no interest in gambling. The patient, however, does not seem to be concerned about driving more than an hour to play at casinos several times a week. His wife is concerned that he has lost more money than he states. She reports that her husband has no memory difficulties or challenges with activities of daily living. He has no past psychiatric history. His medications include pramipexole, metformin, and lisinopril.

What is the next best step in this patient's management?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Considering he has no prior psychiatric history, one should consider dopamine agonist induced impulse control disorders. Pramipexole is a second generation non-ergot dopamine agonist. Dopamine receptors, members of the G-protein coupled receptor family, are classified into two pharmacological groups based on their ligand recognition properties and their effects on cAMP production, the D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors. The major motor effects of dopamine are attributed to D2 receptor stimulation while D3 receptor stimulation has been implicated in both behavioral addictions and substance use disorders. Dopamine agonists have high binding affinity for D3 compared to D2 receptor and therefore, could be responsible for the dopamine agonist induced impulse control disorder.

Although frontotemporal dementia has also been implicated with pathological gambling, this patient's lack of cognitive or memory deficits makes this less likely. Reduction of the dopamine agonist should be considered if the pathological gambling is impairing this patient's functionality. Other options for treatment include dose tapering or replacing with another drug. It is important to note that tapering the dopamine agonist dose may lead to dopamine agonist withdrawal syndrome which has the potential to leave the patient with permanent psychological effects. When initiating this drug therapy, patients should be counseled that adjustments to this kind of medication should be done slowly under the supervision of a health professional.

Take Home Points

- Dopamine agonist therapy has been associated with impulse control disorders such as pathological gambling and hypersexuality.
- Patients with drug induced impulse control disorder can be tapered off the drug or can have the dopamine agonist replaced with another agent.
- Dopamine agonists may have a higher affinity for the D3 receptor which has been implicated in behavioral disorders and substance use disorders.

References:

1. Weiss HD, and Marsh L. Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. *Neurol Clin Pract*. 2012;2(4):267-274.
2. Kvernmo T, Hartter S, and Bürger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Therapeutics*. 2006;28(8):1065-1078.

2: Hip Pain

Question:
A 25-year-old medical student is complaining of right hip pain. He is an otherwise healthy individual with a history of mild ankle sprains. He points to the anterior portion of his right groin and describes the pain as a deep, dull ache. The pain worsens after he plays recreational basketball. He states that he has had the pain since high school but cannot recall a specific inciting event. He feels that his hip pain has started to interfere with daily life, especially when he has been sitting and studying for a prolonged period of time. He has seen his chiropractor and reports a normal X-ray of the affected area. His chiropractor diagnosed a groin pull and recommended exercises with over the counter (OTC) anti-inflammatory medications. The patient reports no improvement and is frustrated with his lack of progress. Upon gait examination, the patient swings his torso towards his affected side. His range of motion is reduced in flexion (less than 90°) and in internal rotation.

What is the most likely diagnosis and what is the best next step in the management of this patient?

Contributors: Jeremy Moon, Kandis Wright, Rebecca Sleeper

Answer:
Due to his lack of improvement with conservative management, gradual progression of his injury, and pain upon internal rotation and flexion of the hip, the patient is likely suffering from femoroacetabular impingement (FAI). In FAI three types of abnormalities can occur including: 1) Cam, characterized by an abnormal or aspherical femoral head, 2) Pincer, the over coverage of the femoral head by the acetabulum, or 3) Mixed, a combination of Cam and Pincer irregularities. Such abnormalities can cause acetabular labrum tears, premature degeneration of the joint, and possibly hip osteoarthritis later on. In this case, prolonged periods of sitting cause abnormal contact between the femoral head and acetabulum resulting in hip pain. FAI has been recognized as a fairly common cause of nonarthritic hip pain in adolescents and young active adults. Stress placed on the hips from participation in high-impact athletic activities during growth, new bone formations at the femoral head-neck junction, pediatric hip diseases, genetics, and developmental abnormalities are some factors believed to increase the risk of developing FAI.

The first step should be to perform the flexion, adduction, and internal rotation (FADIR) test also known as the impingement test which, if positive, induces a sharp pain in the anterior hip or groin. Following a positive test result, an anteroposterior and modified Dunn view (in which the hip is flexed 90° and abducted 20°) radiograph of the pelvis should be ordered. The imaging will reveal either a Cam, Pincer or Mixed irregularity. These radiologic findings are fairly subtle and may be overlooked. A magnetic resonance image (MRI) is best at visualizing FAI. Effective treatment for FAI is usually surgical given the anatomical origin of injury. Arthroscopy has been shown to be successful in regaining function and eliminating pain, as well as reducing the risk of developing future osteoarthritis. Other treatments may include reverse periacetabular osteotomy and hip replacement depending on the type of FAI and exacerbating factors.

Take Home Points

- Femoroacetabular impingement (FAI) should be suspected in younger patients who present with gradual hip pain that fails to improve with conservative treatment.
- FAI can be missed on X-ray, so a MRI should be used for diagnosis.
- Treatment of FAI normally involves arthroscopic surgery.

References:

1. Dooley PJ. Femoroacetabular impingement syndrome: Nonarthritic hip pain in young adults. *Can Fam Physician*. 2008;54(1):42–47.
2. Pun S, Kumar D, and Lane NE. Femoroacetabular Impingement. *Arthritis Rhuemato*l. 2015;67(1):17-27.

3: A Common Geriatric Issue

Question:
An 89-year old woman presents to the emergency room with nausea and vomiting, cognitive changes, arrhythmias, xanthopsia, and reports seeing halos in both fields of vision. She has a past history of chronic obstructive pulmonary disease, chronic renal insufficiency, and heart failure. Her recently added medications include clarithromycin and digoxin (0.125 mg daily), for lobar pneumonia and heart failure respectively. Her digoxin serum level is 1.5 ng/ml [0.5-2 ng/ml].

What is the likely etiology of her current presentation?

Contributors: Sarah Jaroudi, Cassie Kruczek, Neha Mittal, Alan Peiris

Answer:
In this case, digoxin toxicity may be attributed to the addition of clarithromycin and underlying renal failure. Clarithromycin is thought to prolong the clearance of digoxin by 1) inhibition of gut bacteria that metabolize digoxin to its inactive form (dihydrodigoxin) and 2) inhibition of P-glycoprotein transport systems which regulate the absorption of certain medications, including digoxin. Inhibition of these transporters may increase the overall bioavailability of digoxin. It is important to note that clarithromycin as well as digoxin clearance is impaired in patients with underlying renal failure. Clarithromycin alone can cause QT prolongation, torsades de pointes, and bradycardia in patients with coronary artery disease. Other macrolides, such as erythromycin and azithromycin have been shown to have less of an effect on the transport of digoxin, making them safer options if their use is indicated (although it is best to avoid administration of macrolides if possible).

Digoxin also has a narrow therapeutic index and so serum levels are utilized to assess drug toxicities. In elderly patients the desired upper limit for digoxin may be < 0.9 mg/dL and thus the digoxin level in this case can be described as supratherapeutic. The index range traditionally considered therapeutic for the general adult population is not an appropriate range for an elderly patient. Another indicator of digoxin toxicity is xanthopsia. When this occurs, patients report seeing yellow halos around lights or a general yellowish cast. While the exact mechanism of digoxin induced xanthopsia is unclear, it is believed that it is a selective, reversible effect on photoreceptors in the retina rather than damage to the optic nerve.

Physiological changes that normally occur with aging may affect the elimination half-life and volume of distribution of medications. A substantial amount of digoxin is eliminated via renal mechanisms. Given this patient's chronic renal insufficiency, the half-life of digoxin is further increased. When managing an elderly patient on digoxin, dosing needs to be individualized and, in general, start with smaller doses and increase doses cautiously. Depending on the severity of the patient's digoxin toxicity, the use of an antidote, digoxin immune Fab (Digibind), needs to be considered for effective management but has the downside of exacerbating existing hypokalemia, which can potentially lead to fatal arrhythmias.

Take Home Points

- A review of medications and stopping medications when appropriate assumes even greater importance in Geriatrics.
- Clarithromycin can prolong the clearance of digoxin. Renal failure has been associated with decreased clearance of digoxin and clarithromycin.
- Normal aging can affect the physiology of volume of distribution and half life of drugs.
- Individualize dosing for elderly patients and monitor for signs of digoxin toxicity such as xanthopsia.

References:

1. Currie GM, Wheat JM, and Kiat H. Pharmacokinetic Considerations for Digoxin in Older People. *Open Cardiovasc Med J*. 2011;5:130-135.
2. Ma TK, Chow KM, Choy AS, Kwan BC, Szeto CC, and Li PK. Clinical manifestation of macrolide antibiotic toxicity in CKD and dialysis patients. *Clin Kidney J*. 2014;7(6):507–512.

4: Sudden Unilateral Loss of Vision

Question:
A 65-year old male presents with sudden painless and complete loss of vision in his right eye. He has been experiencing myalgias and fatigue for about one to two weeks prior to his visual complaint. He has a past medical history of hypertension, atrial arrhythmia, and gout. Current medications include lisinopril, amlodipine, amiodarone, and pravastatin. Physical examination reveals a swollen pale optic disc in the right eye and a normal fundus examination of the left eye.

What is the most likely diagnosis and what concomitant diagnosis may you consider?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
Anterior ischemic optic neuropathy (AION) is the most common cause of acute optic neuropathy in the elderly. The swollen pale optic disc may lead one to consider papilledema, but papilledema usually presents bilaterally and is not associated with marked visual loss early on. Due to the sudden painless monocular loss of vision, central vein thrombosis can also be considered. This can be ruled out due to the absence of flame shaped retinal hemorrhages and venous engorgement that usually accompany central vein thrombosis.

AION may be arteritic or nonarteritic although both forms are associated with ischemic changes. Arteritic AION usually occurs due to giant cell arteritis. Majority of patients with giant cell arteritis report general fatigue, fever, jaw claudication, and pain prior to losing their vision. Evaluation should include an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are usually elevated in conjunction with giant cell arteritis. Nonarteritic AION is the most common form of AION. Its pathophysiology is unknown, but it has been associated with conditions such as diabetes mellitus, hypercoagulable state, and sleep apnea. Visual loss can occur due to occlusion of the short posterior ciliary arteries. Drugs such as phosphodiesterase type 5 (PDE-5) inhibitors, amiodarone, linezolid, isoniazid, and ethambutol have been linked to optic neuropathy. The mechanism behind amiodarone-linked optic neuropathy is unknown, however, analysis of ultrastructural changes in the human optic nerve showed primary lipidosis in patients with optic neuropathies taking amiodarone. This lipidosis could lead to an accumulation of intracytoplasmic lamellar inclusions in the optic nerve that would negatively impact axoplasmic flow resulting in optic nerve head edema.

Steroids are traditionally used to treat arteritic forms and have not been effective in non-arteritic forms. No accepted treatment for non-arteric AION exists and it is recommended to control vasculopathic risk factors. Management should include close follow up since visual compromise may occur in the other eye. It should be noted that AION is associated with a future risk of abdominal aneurysms. Studies have suggested that elevated serum homocysteine levels are a risk factor in the development of both optic neuropathies and abdominal aneurysms.

Take Home Points

- The differential for anterior ischemic optic neuropathy (AION) includes papilledema and central vein thrombosis.
- Amiodarone has been linked to optic neuropathy which may be due to lamellar inclusions that impair axoplasmic flow.
- Patients with AION may have an increased risk of abdominal aneurysms. Increased homocysteine levels maybe a risk factor for both abdominal aneurysms and AION

References:

1. Macaluso DC, Shults WT, and Fraunfelder FT. Features of Amiodarone-Induced Optic Neuropathy. *American Journal of Ophthamology*. 1999; 127(5):610-612.

5: Loop Diuretics in Heart Failure

Question:
A 79-year-old man enters hospice care for advanced heart failure with an ejection fraction of 21%. He is currently on statins, anticoagulants, angiotensin receptor blockers and carvedilol. A recent increase in dyspnea prompted his cardiologist to increase his furosemide from 20 mg to 40 mg daily. He reports that when he sucks on his furosemide instead of swallowing the appears to achieve a better diuresis.

How can this patient's observations be explained?

Contributors: Sarah Jaroudi, Kandis Wright, Alan Peiris

Answer:
In patients with severe heart failure (HF), absorption of orally administered furosemide may be delayed due to gastrointestinal edema. Furosemide is a loop diuretic that inhibits the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending loop of Henle. In healthy individuals, the diuretic effect of the drug is influenced by a variable absorption process that changes with gastric emptying and ingestion of food. To avoid administering higher oral doses to reach appropriate plasma levels in patients needing rapid diuretic action, intravenous furosemide administration is often used. Following intravenous injection, peak diuresis is achieved within 30 minutes while with oral administration, peak diuresis is achieved within 1.5 hours approximately.

There is evidence that sublingual administration of furosemide has a higher bioavailability, higher peak concentration and improved natriuretic response in healthy individuals compared to oral administration. Considering the variable oral bioavailability of furosemide, a sublingual route of administration may be a safer and faster acting alternative for patients, second to intravenous administration. As such, there may be some basis for the patient's observation because sublingual administration may allow for more rapid absorption and faster diuretic onset. However, more studies need to be done in patients with HF to assess the advantages of sublingual over oral administration of furosemide prior to adoption as a standard route of administration.

Take Home Points

- Furosemide is a loop diuretic that inhibits the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending loop of Henle.
- Absorption of oral furosemide can be negatively affected in certain individuals especially those with heart failure.
- Furosemide can be given intravenously to counteract the delay in absorption of oral formulations.
- Sublingual furosemide maybe an alternative therapeutic option that is easily absorbed subject to additional studies.

References:

1. Haegeli L, Brunner-La Rocca HP, Wenk M, Pfisterer M, Drewe J, and Krähenbühl S. Sublingual administration of furosemide: new application of an old drug. *Br J Clin Pharmacol*. 2007;64(6):804-809.
2. Buggey J, Mentz RJ, Pitt B, Eisenstein EL, Anstrom KJ, Velazquez EJ, and O'Connor CM. A reappraisal of loop diuretic choice in heart failure patients. *Am Heart J*. 2015;169(3):323-333.

6: Thyrotoxicosis

Question:
A 75-year-old man presents to the emergency department with dyspnea and acute onset of palpitations. He has a past medical history of hypertension, left ventricular failure and gastroesophageal reflux disease. The patient indicates he was told that he has thyroid enlargement but never followed up on the diagnosis. He had a coronary angioplasty with stent placement six weeks ago. His medications include furosemide, ramipril, carvedilol and simvastatin. He denies taking any other medications or over the counter supplements. Clinical examination indicates a goiter with atrial fibrillation. His thyroid function tests show that his free T4 is elevated and TSH is suppressed. Thyroid ultrasound indicates a multinodular goiter.

What was the likely etiology for his thyrotoxicosis?

What lab test may help confirm your suspicions?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Neha Mittal, Alan Peiris

Answer:
The patient underwent coronary angioplasty, which means he was exposed to radiologic contrast media, which can contain large amounts of iodine. The average dose may be as high as several thousand times the recommended daily intake of iodine. Normally, the thyroid gland autoregulates thyroid hormone synthesis and secretion in the presence of excessive amounts of iodine in the body. For instance, the inhibition of organic binding of iodine in the thyroid gland by excess iodide results in the cessation of thyroid hormone synthesis (Wolf-Chaikoff effect). In individuals with impaired autoregulation (multinodular goiter), exposure to high levels of iodine results in increased production of thyroid hormones resulting in iodine-induced hyperthyroidism (Jod-Basedow phenomenon).

The presentation here suggests the patient is suffering from the Jod-Basedow phenomenon because he has pre-existing thyroid disease. Thyrotoxicosis, especially in this patient with heart disease, can be concerning as it can lead to an increased demand on the myocardium and a heightened risk of arrhythmias. Patients who are elderly or live in iodine deficient areas are more susceptible to impaired autoregulation, which may occur between 2 and 12 weeks after the iodine exposure. Given that iodine based contrast media is used in coronary angioplasty, patients with risk factors should be closely monitored after the procedure. A 24-hour iodine excretion may be helpful in confirming your suspicions. To reduce the risk of complications in high risk groups, a reduction in dose of contrast media and administration of intravenous isotonic saline may be considered. It is also possible that his recent emergence of thyrotoxicosis is not related to iodine.

Take Home Points

- Contrast media is a rich source of iodine and puts patients with pre-existing thyroid disease or those living in iodine deficient areas at an increased risk of thyrotoxicosis.
- The Jod-Basedow phenomenon occurs when an individual is exposed to high levels of iodine leading to increased production of thyroid hormone. A multinodular goiter is often present.
- A 24-hour iodine excretion can confirm suspected thyrotoxicosis secondary to iodine exposure which may present 2-12 weeks after the exposure. This test may also be useful in determining if remote use of Amiodarone, which has a very long half-life, could be an etiologic factor in thyrotoxicosis.

<u>References:</u>

1. Ledingham D, Carey P, and Junejo S. The dangers of iodine-based contrasts in an elderly patient with thyroid disease. *BMJ Case Rep*. 2015;2015.
2. Heymann WR. Potassium iodide and the Wolff-Chaikoff effect: Relevance for the dermatologist. *J Am Acad Dermatol*. 2000;42(3):490-492.

7: Megestrol and Thrombosis

Question:
A 65-year-old male with metastatic pancreatic cancer is placed in hospice care. He is currently taking opiates and medications for opiate-induced constipation. The patient and his family are concerned about his ongoing weight loss over the past month and ask the physician for assistance with this new problem. He is prescribed megestrol acetate and takes it for about two weeks before discontinuing it without consulting his physician due to gastrointestinal side effects. He is subsequently admitted to the hospital with deep vein thrombosis and hypotension. No etiology emerges on preliminary clinical investigation. There is no evidence of pulmonary emboli.

What may have precipitated his recent decline?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:

Deep venous thrombosis may be seen as a manifestation of the patient's underlying malignancy (Trousseau's sign). However, megestrol acetate is also associated with an increased risk of thrombosis and pulmonary embolism. Megestrol acetate, a steroidal progestin, stimulates the appetite in cases of cancer associated cachexia as seen in this case and is commonly used to increase weight. In addition to its effects on the progesterone receptor, megestrol acetate has glucocorticoid properties with an affinity to the glucocorticoid receptor that is twice that of cortisol. Through these effects, it can suppress the hypothalamic pituitary axis via negative feedback leading to a low cortisol and adrenocorticotropic hormone. Abrupt cessation of megestrol acetate presents similarly to exogenous corticosteroid withdrawal and can precipitate hypotension due to cortisol deficiency. The presentation of adrenal insufficiency is complicated as it has been seen in patients who are actively taking megestrol acetate in addition to those who have abruptly stopped it. Patients should be given a glucocorticoid replacement if it is found that they stopped megestrol acetate abruptly. If a patient's medical history is unknown, a urine synthetic glucocorticoid screen can also be used to help discover if this is the cause of hypotension. In general, megestrol acetate should be used cautiously in the elderly with impaired mobility. Its hazardous properties are discussed in the Beers criteria and its effect on weight are minimal compared to the risks associated with the drug.

Take Home Points

- Megestrol acetate has been associated with an increased risk of deep vein thrombosis and pulmonary embolism.
- It is often used as an appetite stimulant for cancer associated cachexia.
- If abruptly stopped, megestrol acetate can cause adrenal insufficiency attributed to its actions on the glucocorticoid receptors.
- It is not recommended in the elderly due to their pre-existing increased risk for thrombosis.

References:

1. Mehta K, Weiss I, and Goldberg MD. Megace Mystery: A Case of Central Adrenal Insufficiency. *Case Rep Endocrinol*. 2015;2015:1-4.

8: Renal Cell Carcinoma and Elevated Liver Enzymes

Question:
A 73-year old man presents with hematuria and malaise. A comprehensive workup including urinalysis, complete blood count, comprehensive metabolic panel, and renal ultrasound is done. Liver function abnormalities are noted with an elevated alkaline phosphatase (ALP) at 358 U/I (normal <130 U/I) and γ-glutamyltransferase (GGT) at 684 U/l (normal < 60 U/l). Serum bilirubin and aminotransferases are unremarkable. An ultrasound of the liver reveals no abnormalities. He is not taking any medications and has no prior history of liver disease. Further investigation reveals a solid renal mass, which is subsequently removed. The pathology report indicates renal cell carcinoma.

What is a potential etiology of the abnormal liver function tests.?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:
This may be non-metastatic liver dysfunction associated with renal cell carcinoma also known as Stauffer's syndrome. Few patients with renal cell carcinoma present with the triad of abdominal pain, hematuria, and palpable flank mass. Renal cell carcinoma can be notoriously difficult to diagnose (Internist's tumor). It may present with a pattern suggestive of intrahepatic cholestasis as evidenced by the elevated ALP and GGT levels. Liver dysfunction may be the only manifestation of an occult renal tumor. Ultrasound results do not detect any abnormal liver histology and jaundice rarely accompanies symptoms. While the cause of the liver dysfunction is not clearly understood, it may be associated with secretions of cytokines, such as interleukin-6 (IL-6) released from the renal tumor. IL-6 can increase production of hepatic proteins such as ALP. The ALP and GGT are usually normalized after nephrectomy and a resurgence of ALP and GGT suggests recurrence of the tumor or metastases. Prompt investigations of this unique condition can lead to an early diagnosis of renal cell carcinoma. If the patient was taking medications, another diagnosis to consider would be phenytoin hepatotoxicity. Paraneoplastic syndromes are present in about 20% of patients with renal cell carcinoma. In addition to Stauffer's syndrome, other manifestations associated with renal cell carcinoma may include polycythemia, hypercalcemia, neuromyopathy, elevated erythrocyte sedimentation rate and hypertension.

Take Home Points

- Renal cell carcinoma can present with elevated ALP and GGT - Stauffer's syndrome.
- Cytokines released from renal cell carcinoma can increase production of hepatic proteins.
- ALP and GGT tend to normalize after nephrectomy

References:

1. Jangouk P, and Hashash JG. An Unusual Cause of Painless Jaundice. *Gastroenterology*. 2014;146(4):913-1138.
2. Kranidiotis GP, Voidonikola PT, Dimopoulos MK, and Anastasiou-Nana MI. Stauffer's syndrome as a prominent manifestation of renal cancer: a case report. *Case Journals*. 2009;2(1):49.

9: Yerba Mate Herbal Tea

Question:
A 45-year-old man presents with palpitations, fatigue, and poor sleep. His symptoms developed after he started a new, stressful job as a high frequency trader on Wall Street. His current medications include amlodipine 5 mg for hypertension and pravastatin 20 mg for elevated cholesterol. A strong history of ischemic cardiac disease runs in his family. Dietary history reveals he drinks yerba mate because a friend told him that it would help his cholesterol levels. He is exercising more to help improve his symptoms.

What would your next step be?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:

Considering that yerba mate contains caffeine, an initial approach would be to determine the amount and duration of yerba mate ingestion. The concentration of caffeine in yerba mate is similar to coffee, thus it can cause increased heart rate, anxiety and jitteriness, especially in individuals with increased caffeine sensitivity. Ingesting kola, cocoa, guarana as well as commercial drinks may produce symptoms related to caffeine excess. Yerba mate contains several chemicals reported to decrease cholesterol and triglycerides, promote vasodilation and exhibit antioxidant properties. Yerba mate has been used to promote weight loss and has been shown to play a role in suppressing adipocyte differentiation and decreasing inflammation. However, ingestion of large amounts of yerba mate over extended periods of time has been linked to increased risk of cancer (oral cavity, pharynx, larynx, lung, kidney, bladder). This may be due to the hot temperature of the beverage or contaminants such as polycyclic aromatic hydrocarbons introduced during processing.

Take Home Points

- Yerba mate is a caffeine concentrated beverage that can cause increased heart rate and anxiety.
- It has been proposed to decrease levels of cholesterol and promote weight loss.
- With increased consumption of energy drinks, excessive caffeine consumption should be assessed when interviewing patients.

References:

1. Dasanayake AP, Silverman AJ, and Warnakulasuriya S. Mate drinking and oral and oro-pharyngeal cancer: A systematic review and meta-analysis. *Oral Oncol*. 2010;46(2):82-86.
2. Heck CI, and de Mejia EG. Yerba Mate Tea (Ilex paraguariensis): A Comprehensive Review on Chemistry, Health Implications, and Technological Considerations. *Journal of Food Science* 2007;72:R138-R151.

10: Retinopathy

Question:
A 67 year-old female presents with visual complaints. She has a past medical history of hypertension, hyperlipidemia, and rheumatoid arthritis. The patient states she stopped taking lisinopril 10 mg once daily and atorvastatin 40 mg once daily for her hypertension and hyperlipidemia due to financial constraints. Her rheumatoid arthritis, however, seems to be under control for the past 10 years with hydroxychloroquine. Her follow up visits have been erratic due to health insurance issues. Her average blood pressure readings for the past two years at the office range around a systolic blood pressure of 150-160 and a diastolic blood pressure of 100-110. On physical examination, her visual acuity is greatly reduced along with visual field defects. No cotton-wool spots or flame-shaped hemorrhages are seen on funduscopic exam.

What is the likely cause of this patient's visual complaints?

Contributors: Sarah Jaroudi, Kandis Wright, Alan Peiris

Answer:
Retinal toxicity can be secondary to hydroxychloroquine. Hydroxychloroquine is a disease-modifying antirheumatic drug (DMARD) which has been used to treat malaria as well as autoimmune diseases, such as rheumatoid arthritis (RA) and lupus erythematosus. The drug is proposed to block toll-like receptors (TLRs), inhibit DNA synthesis and IL-6 secretion, and increase lysosomal pH. However the full mechanisms remain unknown.

Risk factors for toxicity can include: age over 60 years, duration of use for more than 5 years, use of tamoxifen, and concomitant liver and/or renal disease. The American Academy of Ophthalmology (AAO) recommends getting a baseline exam after starting the medication and following up with screening annually after 5 years. The most common screening test used is the Humphrey visual field test, which will show a partial or complete ring defect with central sparing. Other methods that can be used include optical coherence tomography (OCT) which will show thinning of the outer retinal layers or multifocal electroretinography (mfERG) which is sensitive to paracentral changes. Hydroxychloroquine is melanotropic and deposits in tissues like skin, ciliary bodies, and the retinal pigment epithelium. This drug can cause corneal verticillata (vortex keratopathy), a whorl like corneal pattern, which can be reversed if the drug is discontinued. This is usually asymptomatic and rarely presents with decreased visual acuity. Retinopathy is a more serious side effect that can lead to irreversible loss of central vision. Toxicity may be asymptomatic early on and may present when advanced as concentric ring atrophy also known as "bull's eye" retina. Patients may report loss of peripheral vision or a decrease in color vision.

Take Home Points

- Hydroxychloroquine has been associated with reversible corneal verticillata and irreversible retinal toxicity with loss of central vision.
- It is recommended to get a baseline eye exam after starting hydroxychloroquine and follow up with annual screening after 5 years.

References:

1. Pandya H, Robinson M, Mandal N, and Shah V. Hydroxychloroquine retinopathy: A review of imaging. *Indian J Ophthalmol*. 2015;63(7):570.
2. Browning DJ. Pharmacology of Chloroquine and Hydroxychloroquine (chapter 2). Hydroxychloroquine and Chloroquine Retinopathy. SPRINGER, 2014.

11: SSRI Sexual Dysfunction

Question:
A 60-year old female presents for a follow up visit regarding a new medication. She was started on escitalopram for depression along with cognitive behavioral therapy and states that she is feeling significantly better in terms of her mood and functionality. She recently got remarried and reports that reduced libido distresses her and her partner. She requests treatment for her libido and indicates her preference to stay on escitalopram or within the same class of agents given her mood improvement.

What options may you consider?

Contributors: Sarah Jaroudi, Kandis Wright, Alan Peiris

Answer:
Sexual dysfunction is common with antidepressants especially selective serotonin reuptake inhibitors (SSRIs) such as this patient's escitalopram and serotonin norepinephrine reuptake inhibitors (SNRIs). Depression can also act as another factor worsening her sexual dysfunction. It can impact quality of life and self-esteem and lead to medication non-compliance due to the adverse effects.

An alternate medication to consider for this patient given her request to remain in the same drug class is vortioxetine. Vortioxetine directly inhibits the serotonin transporter (SERT) and modulates serotonin receptor activity including antagonizing multiple serotonin (5-HT) receptors. It appears to have less adverse effects on all phases of sexual activity when compared to similar agents and could be considered in this patient. It is a tolerable drug and adverse effects seen may include gastrointestinal symptoms such as nausea. This group of agents may be associated with a higher risk of falls and fractures when used in patients 65 and older according to the Beers Criteria. If the patient was open to other modes of treatment, bupropion, a norepinephrine dopamine reuptake inhibitor could be considered. It is specifically used because it does not negatively affect sexual libido and is associated with weight loss in contrast to weight gain seen with other antidepressants. It is contraindicated in those with epilepsy as it lowers the seizure threshold. Alternate options include remaining on the escitalopram but reducing the dose, augmenting with another antidepressant, or using non-pharmaceutical agents including exercise or yoga.

Take Home Points

- Selective serotonin reuptake inhibitors can cause sexual dysfunction.
- Vortioxetine inhibits the serotonin transporter and has less adverse effects on sexual activity.
- Bupropion, a norepinephrine dopamine reuptake inhibitor can be used as an alternative although it lowers the seizure threshold.

References:

1. Jacobsen PL, Mahableswarkar AR, Chen Y, Chrones L, and Clayton AH. Effect of Vortioxetine vs. Escitalopram on Sexual Functioning in Adults with Well-Treated Major Depressive Disorder Experiencing SSRI-Induced Sexual Dysfunction. *J Sex Med*. 2015;12(10):2036-2048.

12: Intracranial Aneurysms

Question:
An otherwise healthy 50-year-old male with a past medical history of hypertension presents with evidence of an incidental intracranial aneurysm noted on neuroimaging. Computed tomography scans show that the aneurysm is located at the junction of the anterior communicating artery with the anterior cerebral artery. His hypertension is well-controlled with hydrochlorothiazide (HCTZ)/lisinopril. He also mentions a family history of intracranial aneurysms.

What hereditary diseases have an increased incidence of intracranial aneurysms?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Certain hereditary diseases are associated with an increased risk of intracranial aneurysms. For instance, Type IV (vascular type) Ehlers-Danlos syndrome (autosomal dominant connective tissue disorder) causes a reduced or abnormal secretion of collagen III (present in blood vessels) due to mutations in the COL3A1 gene thereby resulting in vascular fragility. Congenital heart disease such as coarctation of the aorta may cause intracranial aneurysms due to increased cerebral flow rates, hypertension and abnormalities in the development of neural ridge tissue. Hypertension is also a common feature in fibromuscular dysplasia and autosomal dominant polycystic kidney disease, two other systemic diseases that also have a higher incidence of intracranial aneurysms.

Enzymatic defects such as alpha-1 antitrypsin (protease inhibitor) deficiency are also related as they may cause increased proteolysis of structural proteins in the arterial wall. Other related syndromes with unknown causes of aneurysms include neurofibromatosis type 1, acromegaly, and Klinefelter's syndrome. Intracranial aneurysms can also be found in families with a history of aneurysmal subarachnoid hemorrhage (SAH). Families with SAH are at an approximately four fold increased risk of suffering ruptured intracranial aneurysms, compared to the general population. Although Marfan's syndrome (connective tissue disorder) was once thought to also be related as an etiologic factor, recent evidence has been less convincing. Intracranial aneurysms can also run in families without having any association with genetic disorders. A majority of these aneurysms are characterized as saccular aneurysms and occur in weak areas of arteries usually at bifurcations in the Circle of Willis. Screening for asymptomatic intracranial aneurysms can be considered in families with two or more first-degree affected members and should be done on a case-by-case basis. Typical screening modalities include computed tomography angiography (CTA) and magnetic resonance angiography (MRA). The benefits of treating an unruptured intracranial aneurysm must outweigh the post-operative risks.

Take Home Points

- Intracranial aneurysms can be seen in congenital diseases such as Type IV Ehler Danlos syndrome, coarctation of the aorta, fibromuscular dysplasia, and autosomal dominant polycystic kidney disease.
- Intracranial aneurysms are commonly located at bifurcations in the Circle of Willis.
- CTA and MRA are used for screening.

References:

1. Vega C, Kwoon J V, and Lavine SD. Intracranial aneurysms: current evidence and clinical practice. *Am Fam Physician*. 2002;66(4):601-608.

13: Memory Loss in a Young Individual

Question:
A 45 year-old male is seen in a primary care clinic and is accompanied by his parents who provide care for him. He is noted to have bilateral simian creases in his palms, epicanthic folds, and brachycephaly. His past medical history includes hypothyroidism and he is currently on levothyroxine with normal thyroid function tests. He is taking no other medications. His parents indicate that he has become more forgetful and less oriented than usual over the past several months. They mention that he has forgotten the date on a few occasions and at times is unable to recognize acquaintances.

What mental health issues are commonly associated with his condition and what may account for his symptoms?

Contributors: Sarah Jaroudi, Kandis Wright, Alan Peiris

Answer:
Alzheimer's disease (AD) is seen in a majority of individuals diagnosed with Down's syndrome (DS) and more than 70% will have AD by the age of 55-60 years. Amyloid β plaques which are characteristic of Alzheimer's disease are almost always seen in DS patients in addition to neurofibrillary tangles. Patients with DS, a trisomy 21 chromosomal disorder, have extra copies of the gene coding for amyloid precursor protein (APP) which may lead to early onset Alzheimer's disease. APP overexpression in both AD and DS is linked to endocytic changes, which can cause endosomal dysfunction. This disrupts many cellular processes including neuronal functioning, protein synthesis, and retrograde signaling. APP overexpression also leads to neurodegeneration of basal forebrain cholinergic neurons that are important for memory.

Other genes important in neuroinflammation, synaptic transmission, and alternative splicing of tau protein encoded on chromosome 21 may be involved in AD development in patients with DS. It is a challenge to diagnose AD in DS patients because their intellectual disabilities may make baseline memory assessment difficult.

Behavioral and psychiatric disorders including obsessive compulsive disorder and autism are associated with DS. Attention-deficit hyperactivity disorder (ADHD) is also seen with DS and may be due to altered norepinephrine levels.

Take Home Points

- Down's syndrome is associated with an increased risk for early onset Alzheimer's disease due to an extra copy of the amyloid precursor protein gene.
- Overexpression of the amyloid precursor protein may cause endosomal dysfunction and can interfere with the cholinergic neurons of the basal forebrain that play a role in memory.

References:

1. Hartley D, Blumenthal T, Carrillo M, DiPaolo G, Esralew L, Gardiner K, Granholm AC, Iqbal K, Krams M, Lemere C, Lott I, Mobley W, Ness S, Nixon R, Potter H, Reeves R, Sabbagh M, Silverman W, Tycko B, Whitten M, and Wisniewski T. Down syndrome and Alzheimer's disease: Common pathways, common goals. *Alzheimer's Dement*. 2015;11(6):700-709.

14: Erectile Dysfunction

Question:
A 74-year old male presents with erectile dysfunction. He has peripheral arterial disease and hypertension. The latter is well controlled on lisinopril/hydrochlorothiazide (HCTZ). He also reports 40 packs/year history of smoking. His LDL cholesterols are 60 mg/dL on a statin and his triglyceride levels are normal. The patient reports that coital movements and walking appear to reduce his erections.

What may be an etiology for his erectile dysfunction?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Pelvic steal syndrome also known as aortoiliac occlusive disease is a probable cause of this patient's symptoms. Atherosclerosis can lead to the narrowing of the common iliac, internal iliac, or external iliac arteries. The internal iliac artery supplies the pelvis while the external iliac artery supplies the lower extremities. Obstruction of the internal iliac artery is accentuated with increased movement and can cause secondary erectile dysfunction by diverting blood flow from the pelvis to the lower extremities. With severe stenosis, collateral arteries form to maintain blood flow and may lead to delayed presentation of symptoms. Patients may initially present with proximal claudication where they have pain in the buttock or thigh with movement that is relieved by rest. The triad of symptoms of buttocks or thigh claudication, impotence, and diminished femoral pulses is described as the Leriche syndrome.

Computed tomography angiography (CTA) has a high specificity and sensitivity for aortoiliac occlusive disease. For patients with renal disease, magnetic resonance angiography can be used to minimize the risks of using contrast agents. Medical management centers around reducing the patient's cardiovascular risks with antiplatelet agents along with controlling atherosclerotic risk factors such as smoking, hypertension, diabetes and dyslipidemia. Cilostazol can be used to improve walking distance. Lifestyle changes such as smoking cessation, diet modification (diet low in fat and saturated fatty acids and devoid of trans fatty acids) and regular exercise should be emphasized. Surgical treatment can be considered for those with symptoms causing significant lifestyle impairment. Endovascular methods such as percutaneous angioplasty with or without stents are preferred over revascularization procedures involving thromboendarterectomy or aortobifemoral bypass which are associated with more complications.

Take Home Points

- Aortoiliac occlusive disease can cause obstruction of the internal iliac artery leading to secondary erectile dysfunction.
- Leriche syndrome involves a triad of buttock or thigh claudication, impotence, and diminished femoral pulses.
- CTA has a high sensitivity and specificity for diagnosis of pelvic steal syndrome.
- Treatment involves reducing cardiovascular risk with lifestyle changes and antiplatelet agents.

References:

1. Wooten C, Hayat M, du Plessis M, Cesmebasi A, Koesterer M, Daly KP, Matusz P, Tubbs RS, and Loukas M. Anatomical significance in aortoiliac occlusive disease. *Clin Anat*. 2014;27(8):1264-1274.
2. Mahé G, Kaladji A, Le Faucher A, and Jaquinandi V. Internal Iliac Artery Stenosis: Diagnosis and How to manage it in 2015. *Front Cardiovasc Med*. 2015;2(33).

15: Diabetes and Dementia in the Elderly

Question:
An 82 year-old man with a past medical history of dementia and hypertension is referred for evaluation and management of his type 2 diabetes. He has had diabetes for approximately 20 years. His hypertension is well-controlled on lisinopril and hydrochlorothiazide. His current medications for diabetes consist of glyburide at 5 mg twice daily and metformin at 1000 milligrams twice daily. His chemistry profile is within normal limits and his hemoglobin A1c is 5.6%. He has had no reported episodes of hypoglycemia according to the nursing home where he now resides.

You are asked to provide input regarding diabetes management. What are your thoughts?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:
Patients with dementia may find it challenging to keep up with their diabetes self management which may lead to ongoing silent complications. They may also find it difficult to communicate their symptoms such as pain. On the other hand, individuals with poorly controlled diabetes may worsen their declining mental status through alternating severe hyperglycemic and hypoglycemic episodes. This will result in decreased quality of life, increased hospitalizations, risks for fractures and falls, fear of future attacks and decreased ability to perform daily tasks.

The absence of detectable hypoglycemia in this man with dementia does not exclude the existence of such events. Some of his episodes may have not been reported or may have been mistaken for dementia due to agitation. Hypoglycemia has been reported to present as fatigue or weakness in elderly patients which can pose a diagnostic challenge. Risks for hypoglycemia include malnutrition, numerous medications, older age, tight glycemic control and a care home residency. Given his age and cognitive status, his HbA1c is lower than optimal and it is likely that he is experiencing some hypoglycemic episodes, as a low normal HbA1c may be a marker for recurrent hypoglycemia in elderly patients. The American Diabetes Association Guidelines recommend HbA1c of 8-8.5% in older adults with cognitive impairment.

One of his medications, glyburide, has been associated with hypoglycemia and there have been deaths reported with its use. Glyburide is a sulfonylurea drug that acts on the pancreatic beta cells to stimulate insulin secretion by inhibiting the ATP-sensitive potassium channels (KATP), which leads to membrane depolarization, an increase in intracellular calcium and the release of insulin. It would seem reasonable to discontinue the glyburide and continue metformin since intensive diabetes control is not indicated given his likely lifespan.

A HbA1c of 8-8.5% is generally acceptable for the elderly in nursing homes since there is less emphasis on maintaining long term glucose control and more emphasis on quality of life and avoiding hypoglycemic symptoms on a daily basis. Macrovascular benefits take around 8 years to be evident which is another reason tight control is not indicated given his age. Through attention to these details, hypoglycemia can generally be avoided in elderly patients at higher risk.

Take Home Points

- Elderly patients with diabetes and dementia may be at an increased risk for hypoglycemia.
- Hypoglycemia in elderly patients with dementia can worsen symptoms of cognitive decline.
- These patients should be managed more conservatively with higher HbA1c goals of 8-8.5%.

References:

1. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, and Sinclair AJ. Hypoglycemia in older people - a less well recognized risk factor for frailty. *Aging Dis*. 2015;6(2):156-167.
2. American Diabetes Association. 11. Older adults: Standards of medical care in diabetes – 2018. *Diabetes Care* 2018;41(Suppl.1):S119-S125.

16: Somnolence

Question:
A 72-year-old man is seen for discomfort in his legs that has been negatively impacting his sleep schedule. He notes that it has been getting worse over the years and now occurs on a daily basis. The only alleviating factor is movement of his legs. Laboratory investigations including complete blood count, comprehensive chemistry profile, ferritin and thyroid function tests are unremarkable. He is started on pramipexole and reports considerable improvement in his symptoms. A month later, he is seen in the hospital after a road traffic accident. He is fortunate to have sustained minor injuries with no other individuals involved. His wife reports that he must have fallen asleep while driving.

What is a possible etiology for his presentation and what other manifestations may occur?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Pramipexole is a mixed partial/full dopamine agonist with high affinity for D3, D2, and D4 receptors, see case #1 for more information. It is typically used to treat Parkinson's disease and restless legs syndrome. Adverse effects of pramipexole include constipation, orthostatic hypotension, hallucinations and compulsive behaviors like pathological gambling and hypersexuality. Sleep attacks, which involve an abrupt onset of sleep, have also been reported in patients taking dopamine agonists. This can occur anytime without warning, for instance in the middle of a conversation or while driving as in our patient's scenario, and lasts from seconds to minutes. Sleep disturbances can also have a slow onset with drowsiness. Similar to narcolepsy, impaired hypothalamic orexin neurons may play a role in these sleep attacks.

Additionally, dopamine agonists increase the amount of central dopamine, thereby down-regulating dopaminergic input to the reticular activating system. The self-administered Epworth Sleepiness Scale (ESS) can be used to assess patients at a higher risk. Additional risk factors include obstructive sleep apnea, use of other sedatives, and poor sleep hygiene. Patients prescribed dopamine agonists should be educated about the risks and benefits of their use. They should be advised to report any sleep attack occurrences to their physician and not to drive if they fall asleep without warning due to safety concerns. Management can include terminating the drug, reducing the dose, and avoiding excessive alcohol consumption.

Take Home Points

- Sleep attacks that occur suddenly have been associated with pramipexole, a dopamine agonist.
- Impaired hypothalamic orexin neurons and downregulation of dopaminergic input to the reticular activating system may play a role in sleep attacks.
- If sleep attacks occur with pramipexole use, then the drug can be terminated or dosage can be reduced.
- It is important to warn patients about potential serious side effects before prescribing pramipexole.

References:

1. Plowman BK, Boggie DT, Morreale AP, Schaefer MG, Delattre ML, and Chan H. Sleep attacks in patients receiving dopamine-receptor agonists. *Am J Health Syst Pharm*. 2005;62(5):537-540.
2. Yeung EYH, Cavanna AE. Sleep attacks in patients with Parkinson's disease on dopaminergic medications: A systematic review. *Movement Disorders*. 2014;1(4): 307-316.

17: Post-Menopausal Osteoporosis

Question:
A 65-year old woman is referred for osteoporosis after having several falls. Her past medical history includes hypertension that is well controlled, hyperlipidemia and mild cognitive impairment. Her current medications include pravastatin and amlodipine. Her labs show a 25-hydroxyvitamin D level of 35 ng/mL and a serum creatinine of 2.8 mg/dL. Laboratory values of calcium, cortisol, and TSH are unremarkable and there is no evidence of monoclonal gammopathy. The patient denies any surgical history. Further workup shows that her bone mineral density estimated by a DEXA scan indicates a T score of -2 in the lumbar spine and -2.8 in the left femoral neck.

Aside from promoting dietary sources of calcium as an alternative to supplements, what additional measures would you consider?

Later she mentions that she previously took estrogen at the time of menopause to relieve hot flashes but only needed it for a few months. What are the guidelines on the use of estrogen for osteoporosis?

Contributors: Sarah Jaroudi, Kandis Wright, Neha Mittal, Alan Peiris

Answer:
Given her osteoporosis and history of falls, pharmacological therapy should be considered. The American College of Physicians (ACP) guidelines recommend the use of bisphosphonates or denosumab which have been shown to decrease risk of vertebral and nonvertebral fractures. However, bisphosphonate use may pose issues in patients with renal failure. In contrast to bisphosphonates, denosumab is not excreted renally and is well tolerated in patients with renal impairment. Some adverse effects include prolonged hypocalcemia, gastrointestinal distress and a denosumab-related increased risk of infection including bacterial cellulitis. Alendronate, risedronate, and zoledronic acid reside in the same class of bisphosphonates although no research has proven one to be more effective than the other. These drugs induce osteoclast apoptosis and suppress bone resorption. Denosumab is a human monoclonal antibody that prevents RANKL from activating RANK on the osteoclast surface ultimately blocking osteoclast maturation, function and survival. Denosumab may be favorable for those with poor compliance as it is an subcutaneous (SC) injectable given biannually. Denosumab may also have a role in glucocorticoid induced osteoporosis. Beneficial bone effects from Denosumab may rapidly wane on cessation of the agent but continued use up to 10 years appears to be linked ongoing improvement in bone mineral density without plateau.

Estrogen has been FDA approved for postmenopausal osteoporosis prevention, not treatment. Raloxifene (SERM) is FDA approved for treatment of osteoporosis, but similar to estrogen therapy, is contraindicated in those with active or past medical history of thromboembolic events. It also has a fatal risk of stroke in women with coronary artery disease. Measures to avoid osteoporosis in postmenopausal women should include counseling on lifestyle habits such as exercise, smoking cessation and limiting alcohol use. Calcium is best obtained through normal dietary components, however, in those unable to do this supplements are recommended. Adequate intake of calcium and Vitamin D remains the bedrock of osteoporosis management. Evidence indicates a large percent of patients treated for osteoporosis remain Vitamin D deficient indicating the need to monitor and address Vitamin D status on an ongoing basis.

Take Home Points

- Bisphosphonates and denosumab are recommended for osteoporosis to decrease the risk of vertebral and nonvertebral fractures.
- Postmenopausal estrogen therapy is FDA approved for osteoporosis prevention while raloxifene is FDA approved for osteoporosis prevention and treatment. Estrogen risks are well known. Raloxifene may reduce all cause mortality by about 10%, mainly due to a reduction non-cardiovascular non-cancer deaths.
- Lifestyle changes such as physical activity and reduction in smoking and alcohol use can further reduce the risk of developing osteoporosis. Monitoring and supplementing Vitamin D is also recommended.

<u>References:</u>

1. Qaseem A, Forciea MA, McLean RM, and Denberg TD. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017;166(11):818.

18: Abnormal Urinalysis in an Elderly Man

Question:
A 68-year-old man with a history of dementia is seen for an annual physical exam. The patient was recently admitted to a nursing home due to his progressive memory loss. Physical examination is unremarkable apart from his altered (unchanged from 2 months ago) mental status. He is afebrile and labs indicate normal electrolytes and complete blood count. The urine, which had a foul odor, is sent for culture following a urinalysis that revealed 26 white blood cells per high-power field and numerous bacteria.

Which antibiotic would you consider at this stage?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
According to the Infectious Diseases Society of America, antibiotics should not be considered in the treatment of asymptomatic bacteriuria until criteria such as fever, abdominal pain or dysuria present themselves.

Bacteruria is commonly seen in the elderly, especially those living in care facilities. It is worth noting that patients with early stages of dementia are more likely to have bacteria in their urine as well as develop urinary tract infections. Acute changes in mental status may be the only symptom of a urinary tract infection (UTI). Therefore, bacteriuria with acute change in mental status should be treated as a UTI. Creating a system to differentiate asymptomatic bacteriuria from UTIs can reduce the unnecessary use of antibiotics.

Asymptomatic bacteriuria can also be seen in diabetic women, pregnant women, men over the age of 60 and in patients with a spinal cord injury. *E. coli* is the most common organism isolated in patients with asymptomatic bacteriuria. Patients may carry the same strain for an extended period of time without any emerging symptoms. These strains share similar properties such as poor adherence to human uroepithelial cells and rarely express P-fimbriae or hemolysins. Expression of these virulence factors normally allow bacteria to adhere to the epithelial layer, facilitating invasion and preventing removal by urinary flow. Asymptomatic bacteriuria has also been explored as a therapeutic possibility in patients prone to recurrent UTIs, as it may protect the host from infection with virulent strains.

Empiric treatment of asymptomatic bacteriuria is one of the leading causes of antibiotic misuse and contributes to the emergence of antibiotic resistant strains of bacteria, including *Clostridium difficile*. Treatment may lead to symptomatic recurrences and in some cases, acute pyelonephritis. Exceptions maybe include asymptomatic bacterirua in pregnant women and patients undergoing invasive urological procedures.

Take Home Points

- Asymptomatic bacteriuria is common in diabetic women, pregnant women, men over the age of 60 and patients with a spinal cord injury.
- *E. coli* strains commonly cause asymptomatic bacteriuria and are less virulent as they rarely express P-fimbriae or hemolysins.
- Empiric treatment is not recommended as it can lead to antibiotic resistance and symptomatic recurrences. However, pregnant women and patients undergoing invasive urologic procedures are exceptions where treatment maybe indicated.

References:

1. Dasgupta M, Brymer C, and Elsayed S. Treatment of asymptomatic UTI in older delirious medical in-patients: A prospective cohort study. *Arch Gerontol Geriatr*. 2017;72:127-134.

19: A Glowing, Pink Skin Lesion

Question:
A 73-year-old man presents with pruritic plaques and patches in his axilla bilaterally. Cutaneous examination reveals irregular, scaly brown plaques. He has a past medical history of diabetes that is well controlled with a HbA1c of 6.3%. The only medication he takes is metformin 1,000 mg twice daily. He has no known microvascular or macrovascular diabetic complications. The affected lesions glow coral pink under Wood's light.

What is the diagnosis, likely organism and treatment?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
Erythrasma is the likely diagnosis. It is a chronic superficial infection that usually affects the intertriginous areas of the skin such as the axilla, groin, and interspaces of the toes. It presents as irregular brown patches or plaques with scaling. It is more commonly seen in diabetic patients, especially if the glucose values are uncontrolled. It is hypothesized that high levels of cutaneous free glucose may encourage the growth of the causative agent. Obesity may also be another predisposing risk factor.

Corynebacterium minutissimum is the most likely etiologic agent. *C. minutissimum* is a Gram positive, diphtheroid bacterium that is a normal part of the skin flora. Other infections caused by this organism include bacteremia and abscess formation, even in immune competent persons. Erythrasma is usually misdiagnosed as a dermatophytic infection. Differential diagnoses should include candidiasis, psoriasis, and dermatophytosis and tests should be done for these as coexisting infections can occur. The bacteria produce porphyrins that fluoresce with a coral pink color under Wood's light. Diagnosis may be missed if the patient recently bathed the area, as this may wash off the porphyrins temporarily. In this case, a biopsy or Gram staining can be done to confirm the diagnosis. The organism is not seen easily on routine hematoxylin and eosin staining and a potassium hydroxide preparation of a tissue scraping will be negative for fungal organisms, unless there is a concomitant fungal infection. Typically, the drug of choice is topical erythromycin which has shown cure rates as high as 100%. Other treatments include clarithromycin or tetracycline. Clarithromycin has been found to result in better patient compliance and is a more cost-effective treatment compared to erythromycin. Resolution of erythrasma can be confirmed with a negative Wood's light exam.

Take Home Points

- Erythrasma is a rash caused by *Corynebacterium minutissimum* that affects intertriginous areas such as the axilla, groin, and interspaces of the toes, commonly seen in patients with diabetes.
- Diagnosis can be made by fluorescence with a coral pink color under Wood's light or biopsy or Gram stain if the patient has bathed recently.
- Erythromycin, clarithromycin or tetracycline are used for treatment.

References:

1. Morales-Trujillo ML, Arenas R, and Arroyo S. Interdigital erythrasma: clinical, epidemiologic, and microbiologic findings. *Actas Dermosifiliogr*. 2008;99(6):469-473.

20: Androgen Deprivation Therapy

Question:
After falling at home a couple times, an 80-year old male was brought into the clinic by his daughter. He has a past medical history of prostate cancer with bone metastases and has been treated with androgen deprivation therapy for almost three years. His prostate cancer stage has not progressed and he currently has no symptoms.

In addition to a work-up for possible causes of falls and a discussion of prostate cancer management, what other important measure should be discussed with the patient and implemented at this time?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:
The patient should have his bone mineral density assessed. Intervention for the marked bone loss that occurs with anti-androgen therapy also needs to be considered. Taking either bisphosphonates or denosumab concurrently with the androgen deprivation therapy is important to implement within his treatment plan.

The American Society of Clinical Oncology suggests that patients with bone metastases start taking bisphosphonates after diagnosis. Bisphosphonates decrease bone loss by inhibiting osteoclast activity and inducing osteoclast apoptosis. Denosumab also inhibits osteoclast activity and prevents bone resorption although it works by a different mechanism. It is a monoclonal antibody that binds RANKL, which is necessary for activation of the RANK receptor on osteoclasts.

The patient also needs to be counseled on taking calcium and vitamin D supplements to promote healthy bones. Many patients on androgen deprivation therapy are not aware of the risks that come with the treatment and have never been previously screened for bone loss. Anti-androgen therapy is known to result in a five to ten fold increase in bone loss at all locations with an associated increased risk of fractures. The therapy causes a decrease in circulating levels of androgens and estrogens that normally promote bone generation. For patients just starting this type of therapy, it helps to have an initial dual-energy X-ray absorptiometry (DEXA) scan so that the patient's baseline bone mineral density is recorded and followed during the course of their treatment. The patient's lifestyle should also be evaluated in order to incorporate beneficial lifestyle changes such as smoking cessation, decreasing alcohol consumption and/or starting an exercise routine to maintain bone health. Other conditions to consider monitoring for cardiovascular risk and development of insulin resistance.

Take Home Points

- Bisphosphonates or denosumab to decrease bone loss should be considered in every patient on anti-androgen therapy
- Before anti-androgen treatment is initiated, a baseline DEXA scan is recommended.
- Adequate intake of calcium and an satisfactory 25(OH)D level is recommended since prostate cancer with bone metastases is a rare cause of secondary hyperparathyroidism.

<u>References:</u>

1. Kirk PS, Borza T, Shahinian VB, Caram MEV, Makarov DV, Shelton JB, Leppert JT, Blake RM, Davis JA, Hollenbeck BK, Sales A, and Skolarus TA. The implications of baseline bone health assessment at initiation of androgen deprivation therapy for prostate cancer. *BJU Int*. 2018;121(4):558-564.

21: Lower Extremity Rash

Question:
A 62-year-old man presents with an erythematous lesion involving his right lower leg. Inspection of the lesion reveals a tender rash with poorly defined margins. The lesion is warm to touch. The patient complains of chills, shaking, headaches and vomiting within the past 48 hours. He states that the lesion has enlarged rapidly. He reports that he has had a few similar episodes of cellulitis in the past. He denies any contact with animals. He denies any history of prior abrasions or trauma or contact with contaminated water.

What prophylactic measures can you recommend to this patient?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
Cellulitis has a 30% chance of recurring within 3 years after the first episode of cellulitis and infection is usually attributable to either *Streptococci* or *Staphylococci* species. Due to the recurrent nature of his cellulitis, Group A *Streptococci* are the most likely causative agent. Therefore, low-dose penicillin or amoxicillin should be recommended as prophylaxis. For patients allergic to penicillin, clindamycin or vancomycin may be used. Some studies have suggested that long periods of prophylactic antibiotic administration up to twelve months may prove effective at preventing recurrent episodes. Other options for administration include intramuscular injections every 14 days. Treatment is generally well tolerated, but side effects may include nausea and rash.

However, if the infection is unresponsive to antibiotics, cultures may need to be obtained since infections with antibiotic resistant organisms are becoming increasingly prevalent. In the United States, organisms such as *Vibrio vulnificus* may be the causative agent and people usually become infected from an open wound exposed to warm seawater containing *V. vulnificus* or by eating raw shellfish, especially oysters. Immunocompromised patients or those with liver disease are more susceptible to *V. vulnificus* infection.

Care should be taken to promptly treat and prevent recurrent cellulitis since numerous episodes are associated with increases in health care costs, morbidity, and mortality. Chronic diseases and immunosuppression may also be etiologic factors. Poorly controlled diabetes can lead to recurrent cellulitis and needs additional intervention. Other chronic conditions to consider include fungal infections, impetigo and lymphedema. Chronic lymphedema has been linked to a poorer response to prophylactic measures. A good foot examination is essential for evaluating possible foci of infection.

Erisipelas tends to affect more superficial layers of the skin and can be difficult to distinguish from cellulitis. Erisipelas maybe associated with blisters and the lesions generally have a better defined margin.

Take Home Points

- Low dose penicillin or amoxicillin may be administered to those with recurrent cellulitis to prevent future flare-ups.
- Patients with recurrent cellulitis should be monitored for other chronic conditions such as diabetes.

References:

1. Maxwell-Scott H, and Kandil H. Diagnosis and management of cellulitis and erysipelas. *Br J Hosp Med*. 2015;76(8):C114-C117.
2. Thomas K, Crook AM, Nunn AJ, Foster KA, Mason JM, Chalmers JR, Nasr IS, Brindle RG, English J, Meredith SK, Reynolds NJ, de Berker D, Mortimer PS, and Williams HC. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med.* 2013;368(18):1695-1703.

22: Nasal Blisters

Question:
A 71-year-old male presents with discomfort on the left side of his cheek and nose that has been present for the last two days. He mentions that he noticed some blisters that appeared this morning. He has not traveled abroad nor does he take any daily medications. He has not been in contact with anyone sick. On physical exam, he appears somewhat distressed and skin findings reveal clear to crusted hemorrhagic erythematous vesicles/papules on his left cheek and nasal tip.

What is the likely etiology of this Hutchinson sign and appropriate treatment?

Can you name the other Hutchinson signs?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Neha Mittal, Alan Peiris

Answer:
The mostly likely diagnosis is herpes zoster (shingles). The varicella zoster virus causes chickenpox in childhood and remains dormant in the sensory ganglia after the primary infection. A reactivation of varicella zoster virus results in shingles and is commonly attributed to waning immunity in the elderly.

Involvement of the nasociliary nerve (tip of the nose involvement), a branch of the ophthalmic division of the trigeminal nerve, is known as Hutchinson sign. This presentation typically precedes intraocular or corneal damage also referred to as herpes zoster ophthalmicus (HZO). HZO can involve structures such as the recti muscles and optic nerve sheath. Rare manifestations in immunocompromised patients include acute retinal necrosis which can result in blindness. Those exposed to HZO have a two to four times increased odds of experiencing a cerebrovascular event possibly because the ophthalmic division of the trigeminal ganglion also supplies afferent fibers traveling around the internal carotid artery. The virus exits these terminal fibers, replicates in the adventitia, subsequently enters the blood vessel and may induce a cerebrovascular event. The other Hutchinson sign is related to brown-black pigmentation extending to the proximal or lateral nail folds and may indicate subungual melanoma which requires confirmation with a biopsy. There is also a Hutchinson triad found in syphilis which involves sensorineural deafness, Hutchinson's teeth (notched upper incisors with wider spacing) and interstitial keratitis.

Urgent treatment with systemic antivirals for 7-10 days and an ophthalmology consultation can decrease ocular morbidities. Acyclovir can be used although both famciclovir and valacyclovir have easier dosing regimens for patient compliance. Patients with immunodeficiencies may need intravenous acyclovir to reduce the risk of dissemination. Contact and respiratory precautions are advised until lesions have fully crusted to avoid transmission. Prophylactic measures can be taken by giving the Shingrix vaccine to those over 50 years old in a two shot series which can decrease the incidence of postherpetic neuralgia and development of shingles. For post exposure prophylaxis, varicella zoster immunoglobulin can be used for those who have contraindications to the varicella zoster vaccine such as pregnant or immunocompromised patients.

Take Home Points

- The Hutchinson sign may be seen with reactivation of varicella zoster virus affecting the nasociliary nerve and may precede the development of herpes zoster ophthalmicus.
- Complications include acute retinal necrosis and cerebrovascular events.
- The other Hutchinson sign is indicative of subungual melanoma and Hutchinson triad is seen in syphilis.
- Urgent treatment with antivirals and an ophthalmology consult can reduce adverse outcomes.

References:

1. Erskine N, Tran H, Levin L, Ulbright C, Fingeroth J, Kiefe C, Goldberg RJ, and Singh S. A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. *PLoS One*. 2017;12(7):e0181565.

23: Birth Control and Nitrofurantoin

Question:
A 28-year-old female is referred for transient visual changes. She complains that when she stoops or bends down, her vision is obscured. Her current medications include oral contraceptives and nitrofurantoin for recurrent urinary tract infections. She has had a constant throbbing headache that began 6 months ago. Clinical examination reveals bilateral papilledema without any focal neurological deficits. She is 5'3" and has a body mass index (BMI) of 34. Imaging studies do not show any intracranial mass lesions. After a spinal tap reveals increased cerebrospinal fluid (CSF) pressures, a diagnosis of idiopathic intracranial hypertension is made.

Apart from suggesting that she lose weight, what other treatment options exist?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Her ongoing use of contraceptives and nitrofurantoin should be reevaluated since these agents have been linked to intracranial hypertension. The exact mechanism by which oral contraceptives and some antibiotics result in intracranial hypertension is not completely understood. However, with oral contraceptives the involvement of renin-angiotensin system is speculated since estrogen stimulates the hepatic production of renin substrate (angiotensinogen). In the case of nitrofurantoin, the development of a mismatch between cerebrospinal fluid (CSF) production by the choroid plexus and its absorption by the arachnoid villi is presumed. Product labeling differs between the USA and Canada. Nitrofurantoin is considered a category B (no risks found in humans) in the USA while it is not recommended during pregnancy in Canada.

Weight loss is commonly the first lifestyle intervention recommended along with a salt restricted diet. The initial drug of choice is acetazolamide, although it is associated with renal tubular acidosis and calcium phosphate stones. Relief of symptoms can be achieved with a lumbar puncture, though this is not a long term solution. In refractory cases, reduction of CSF pressures can be achieved surgically by optic nerve sheath fenestration (incision in the meningeal membranes surrounding the optic nerve) and ventriculoperitoneal or lumboperitoneal shunting. A non-surgical option may include intravenous indomethacin, which causes cerebral vasoconstriction reducing cerebral blood flow and lowering intracranial pressure. Treatment goals involve preserving vision as well as easing symptoms. Patients will need ongoing visual field monitoring along with visual acuity testing.

Take Home Points

- Oral contraceptives and nitrofurantoin have been linked to idiopathic intracranial hypertension.
- Lifestyle interventions include weight loss and a low sodium diet, while pharmacological management includes acetazolamide. Refractory cases can be treated surgically.
- Monitoring with ophthalmological exams is recommended.

References:

1. Bell S. Idiopathic Intracranial Hypertension (Pseudotumor Cerebri). *J Neurosci Nurs*. 2016;48(6):303-310.
2. Oelkers WK. Effects of estrogens and progestrogens on the renin-aldosterone system and blood pressure. *Steroids*. 1996;61(4):166-171.

24: Chest Pain in a Young Female

Question:
A 19-year-old woman presented with 3 days of chest pain. She had taken antacids without relief. She gave a history of swollen feet as a neonate and has short fourth metacarpals bilaterally. Physical examination revealed short stature and an elevated blood pressure. While in the emergency room, she had a full cardiac arrest and remained unresponsive to all resuscitative interventions.

What would you expect the post-mortem to reveal?

Contributors: Kandis Wright, Alan Peiris

Answer:
Post-mortem revealed aortic dissection and rupture in a patient with Turner's syndrome (Karyotype XO). Patients with Turner's syndrome are at increased risk for aortic dissection leading to rupture at a young age. The immediate mortality rate may be around 60%. The propensity for aortic dissection in Turner's syndrome is relatively unrecognized by both patients and physicians. Patients that ignore cardiac symptoms significantly increase their risk of death.

In aortic dissection, there is weakness or injury to the aortic wall causing blood flow between the tunica intima and tunica media connective tissue layers. This produces a false lumen, adjacent to the aorta, that compromises the true aortic lumen. The cause for increased rates of aortic dissection in patients with Turner's syndrome is not fully understood, but is thought to be similar to Marfan's syndrome, characterized by cystic medial degeneration/necrosis and abnormal connective tissue. Risk factors for aortic dissection include aortic dilatation, bicuspid aortic valves, coarctation of the aorta, hypertension, and pregnancy. In patients with Turner's syndrome, it is strongly linked to a history of fetal lymphedema associated with the presence of neck webbing and shield chest. Magnetic Resonance Imaging (MRI) can help visualize cardiac abnormalities in these patients.

Those without a structural malformation of the heart have a decreased risk of aortic dissection. Despite this, aortic dissection can still occur in healthy Turner's syndrome patients. Aortic dissection has been observed to typically occur at smaller aortic diameters compared to those without Turner's syndrome. Turner's syndrome patients should be established with a cardiologist for an echocardiography along with baseline blood pressure readings for the upper and lower extremities. To prevent aortic dissection, individuals with Turner's syndrome who are >18 years of age and have an ascending aortic size index >2.5 cm/m^2 need to be considered for an aortic operation.

Take Home Points

- Patients with Turner's Syndrome are at increased risk for aortic dissection and rupture.
- The risk for developing an aortic dissection is strongly linked to a history of fetal lymphedema, neck webbing, and shield chest in patients with Turner's syndrome.
- These patients need to be established with a cardiologist for constant monitoring even if they lack a cardiac abnormality and are healthy.

References:

1. Bondy CA. Aortic Dissection in Turner Syndrome. *Curr Opin Cardiol*. 2008;23(6):519-526.
2. Carlson M, Airhart N, Lopez L, and Silberback M . Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. *Circulation*. 2012 Oct 30;126(18):2220-6.
3. Turtle EJ, Sule AA, Webb DJ, and Bath LE. Aortic dissection in children and adolescents with Turner syndrome: risk factors and management recommendations. *Arch Dis Child*. 2015;100:662-666.

25: Heel Pain

Question:
A 44-year-old man comes in complaining of constant right heel pain (4 out of 10). He is an active runner who likes to participate in half-marathons multiple times a year. He runs 30-35 miles a week. He says the pain started more than half a year ago, but the pain has not gone away and recently it is starting to limit his runs. The pain seems to worsen after runs. He has been taking ibuprofen daily, which he states seems to not be helping much. He has no significant past medical history aside from an appendectomy 22 years ago. Family history is unremarkable for any major illnesses. Physical exam of the right heel demonstrates no signs of inflammation. There is slight tenderness to palpation along the Achilles tendon, but no limitation in passive or active range of motion. The patient states that he changes his running shoes regularly, but admits to not adequately resting his heel.

What considerations exist for this patient?

Contributors: Jeremy Moon, Gurvinder Kaur, Alan Peiris

Answer:
Tendinopathy is an umbrella term used to describe damage to tendons. Acute tendinopathy from excessive overload usually presents with classic inflammation and pain. However, recent studies have shown that chronic tendinopathies from repeated microtrauma are often non-inflammatory. Thus, the treatment for acute and chronic tendinopathy are vastly different. Excessive long-distance running and hill training are associated with Achilles tendinopathy. This patient most likely presents with chronic tendinopathy of his Achilles tendon due to his lack of inflammation on physical exam as well as the duration of his symptoms. Furthermore, the patient has not taken the proper time for his tendon to heal. Type III collagen (produced during the initial phase of tendon damage) maybe laid down in a haphazard manner, contributing to the irregular alignment and inferior biomechanical strength in the damaged tendon. Type III collagen is gradually replaced by type I collagen, resulting in a linear structured arrangement that eventually contributes to normal tendon ultrastructure.

Tendon rupture may be associated with fluoroquinolones and steroid injections. Achilles tendonitis may also be seen in ulcerative colitis, and systemic lupus, as such, systemic disorders also need to be considered. Rarely, cerebrotendinous xanthomatosis may produce tendon involvement similar to familial hypercholesterolemia. Alkaptonuria(ochronosis), congenital hypergalactosemia and congenital hypophosphatemia may involve tendons including the Achilles tendon with an increased propensity to tendon rupture.

In chronic tendinopathy, the repetitive microtraumas cause an increase in the weaker, less organized collagen type III (as opposed to the stronger collagen type I). Due to the lack of marked inflammation present in chronic tendinopathy, NSAIDs have been less effective in treating chronic Achilles and patellar tendinopathies. Some propose that eccentric exercises and soft-tissue mobilization techniques can reintroduce inflammation in poorly vascularized tendons, thus re-starting the healing process. There have been studies that demonstrate patients performing these kinds of physical rehabilitation exercises show marked improvement in function and pain in chronic tendinopathies. The basic science and treatment of tendinopathies is a changing field and there are new experimental treatments that may provide improved efficacy in the future. Regardless, there has been sufficient evidence to reconsider the use of anti-inflammatory agents in chronic tendinopathies.

Take Home Points

- Chronic tendinopathy—unlike acute tendinopathy—tends to be non-inflammatory, therefore NSAIDs are not effective as treatment.
- Physical rehabilitation techniques such as eccentric exercises and soft-tissue mobilization re-introduce inflammation to restart the healing process.

References:

1. Andres BM, and Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clin Orthop Relat Res*. 2008 Jul;466(7):1539-54.
2. Perretti M, Cooper D, Dalli J, and Norling LV. Immune resolution mechanisms in inflammatory arthritis. *Nat Rev Rheumatol*. 2017 Feb;13(2):87-99.

26: Hip Fracture

Question:
A 45-year-old female presents to your clinic with pain in her left hip after falling earlier in the day. She describes the pain as deep and sharp. She cannot abduct, flex or externally rotate her left leg. X-ray results confirm your suspicion of a non-displaced fracture along the femoral neck. The patient has a past surgical history of a Roux-en-Y gastric bypass 13 years ago. Her body mass index (BMI) remained steady at 39.5 during the years leading up to her surgery. Her current BMI is 24. She has no history of hip fractures in her family. When asked about other symptoms, the patient mentions general feelings of fatigue and infrequent dull achy pain in her limbs. She also has has some difficulty in getting out of low chairs. She takes non-steroidal anti-inflammatory drugs (NSAIDs) during these bouts of pain. She is also on lisinopril for her hypertension, which is well-controlled. Her last menstrual period was two weeks ago. Labs demonstrate normal renal function, but show moderate hypocalcemia and hyperparathyroidism.

What may have been contributed significantly to this patient's hip fracture?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
This patient has secondary hyperparathyroidism. Secondary hyperparathyroidism is most commonly caused by chronic renal failure. In the presence of normal renal function the most likely cause of this patient's symptoms is Vitamin D deficiency, at least partly related to her gastric bypass. There are several proposed mechanisms to explain the correlation of obesity with hyperparathyroidism. These include decreased sun exposure in morbidly obese patients, which reduces the production of vitamin D, and the sequestration of vitamin D in adipose tissue thus lowering serum vitamin D levels. Prolonged vitamin D deficiency can lead to reduced uptake of calcium in the gut and subsequent hypocalcemia and hyperparathyroidism.

Although gastric bypass is the gold-standard treatment for morbid obesity, secondary hyperparathyroidism has been shown to persist at 5-year post-operative check-ups. Bariatric surgery can worsen vitamin D deficiency for several reasons. It bypasses the active transcellular transport pathway in the small bowel that is responsible for 80% of vitamin D absorption, leaving only 20% oral absorption through the paracellular transport pathway. Patient non-adherence to recommended diets or supplements can also worsen vitamin D deficiency. Supplementation with high-dose vitamin D and calcium, close monitoring of vitamin D and calcium levels, continued follow-up, and patient compliance are necessary components when treating post-bariatric surgery patients. Current evidence may favor daily Vitamin D3, however, the best dosing frequency for vitamin D after gastric bypass remains to be clarified. Larger episodic vitamin D dosing has been associated with increased falls and fractures.

Take Home Points

- Obesity and gastric bypass correlate with vitamin D deficiency.
- Vitamin D deficiency can lead to secondary hyperparathyroidism with increased risk of fractures from prolonged hypocalcemia.
- Treatment includes high dose vitamin D and calcium supplemention, close monitoring of calcium and vitamin D levels, and continued follow-up.
- Consider other nutrient and vitamin deficiencies following gastric bypass

References:

1. Switzer NJ, Marcil G, Prasad S, Debru E, Church N, Mitchell P, Billington EO, and Gill RS. Long-term hypovitaminosis D and secondary hyperparathyroidism outcomes of the Roux-en-Y gastric bypass: a systematic review. *Obes Rev*. 2017 May;18(5):560-566.
2. Peiris AN, Youssef D, and Grant WB. Secondary hyperparathyroidism: benign bystander or culpable contributor to adverse health outcomes? *South Med J*. 2012 Jan;105(1):36-42.

27: False Positive Pregnancy Test

Question:
A 31-year-old P1G1001 (parity/gravidity) woman comes into your clinic complaining of abdominal pain and foul-smelling diarrhea for the past 2 weeks. She claims that she has had these bouts of diarrhea for the past several years, but stated that they resolve within a few weeks. Her menstrual cycles have been regular, occurring every 28 to 30 days. Her last menstrual cycle was 3 weeks ago. She is currently sexually active with her long-term boyfriend and uses condoms regularly. Her past medical history includes asthma and seasonal allergies. She is only on inhaled albuterol as needed. A serum beta human chorionic gonadotropin (beta-hCG) test is positive. There is no abdominal tenderness or guarding. Pelvic examination shows an empty uterus. Abdominal onogram does not indicate a pregnancy.

What is the most likely diagnosis in this patient?

Contributors: Jeremy Moon, Gurvinder Kaur, Alan Peiris

Answer:
A false-positive serum beta-hCG test along with the patient's presenting symptoms of atopy and gastrointestinal (GI) infections most likely indicates a diagnosis of selective IgA deficiency. The dimeric IgA2 subclass is the most prevalent immunoglobulin in mucosal secretions and protects mucosal surfaces such as the GI tract against bacterial and viral infections. In individuals with selective IgA deficiency, the protective barrier of the GI tract is impaired, resulting in infections.

Additionally, IgA deficiency results in the escape of molecules into the subepidermal and submucosal tissues due to impaired mucosal clearance of macromolecules and proteins. Increased mucosal antigen exposure to the systemic circulation may result in the formation of heterophile antibodies in the sera of IgA deficient individuals. These heterophilic antibodies can bind nonspecifically to the antibodies used in the beta-hCG assays, thereby, resulting in false-positive or "phantom" beta-hCG test in up to 30% of patients. Selective IgA deficiency is the most common immunodeficiency with prevalence ranging from 1/233 to 1/1000.

Most patients are asymptomatic, but many can present with nonspecific symptoms such as allergies, asthma, airway and/or GI infections, and autoimmune disease. Thus, a majority of patients remain undiagnosed. This is a potential problem in female patients because falsely elevated beta-hCG tests can lead to unnecessary procedures and medications. Selective IgA deficiency should be considered in patients with positive pregnancy tests, but no signs of pregnancy.

False-positive serum human chorionic gonadotrophin results are mostly due to interference by non-human chorionic gonadotrophin substances like luteinizing hormone and anti-animal immunoglobulin antibodies and the detection of pituitary human chorionic gonadotrophin. The false-positive human chorionic gonadotropin measurements are characterized by serum levels that are generally <1000 mIU/Ml. False positive pregnancy tests have been reported with several entities including lung cancer and bladder cancer with choriocarcinomatous differentiation. Even transfusion of solvent/detergent-treated plasma may result in a false positive pregnancy test. However, it should also be noted that molar pregnancies could result in a negative beta-hCG due to the "hook effect". This effect is a result of excessively high levels of beta-hCG saturating the antigens used in the assay. Obtaining a transvaginal ultrasound and considering quantitative (if needed with serial dilution) beta hCG testing is worth considering.

Take Home Points

- IgA heterophile antibodies are present in some IgA deficient patients and can cause false-positive beta-hCG tests, which should prompt follow-up with quantitative beta-hCG testing.

References:

1. Knight AK, Bingemann T, Cole L, and Cunningham-Rundles C. Frequent false positive beta human chorionic gonadotropin tests in immunoglobulin A deficiency. *Clin Exp Immunol*. 2005;141(2):333-337.
2. Yel L. Selective IgA deficiency. *J Clin Immunol*. 2010;30(1):10-16.

28: A Low-Tech Tool for the Diagnosis of Myasthenia Gravis

Question:
A 58-year-old man walks into your clinic complaining of double vision and muscle weakness that has progressed over the past few months. He states that the double vision and weakness is worse at the end of the day. He is concerned because he has not been able to work to provide for his family. This is his first time seeing a doctor and he does not know of any significant medical or family history. On physical examination, the patient's speech is slurred. He also has bilateral ptosis that is worse in the left eye as well as decreased muscle strength in neck extension and flexion. You are on a medical mission trip and unfortunately, the clinic does not have access to a serology lab and has a limited supply of medications.

What diagnostic test can be used to confirm your suspicion of myasthenia gravis?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
This patient most likely has myasthenia gravis (MG) due to his symptoms of double vision, muscle weakness that worsens throughout the day, and ptosis, MG is an auto-immune disease that impairs function of post-synaptic acetylcholine receptors. MG usually has worsening muscle weakness with repeated nerve stimulation due to depletion of acetylcholine. This is in contrast with Lambert Eaton syndrome (LEMS), which is a potential paraneoplastic syndrome (commonly small cell lung cancer) that impairs function of pre-synaptic voltage-gated calcium channels. LEMS has increased muscle strength after repeated contractions due to increased intracellular calcium.

In the absence of a proper lab or the medication such as an edrophonium (tensilon) test, another diagnostic test could be an ice-pack compress on the ocular region of the patient. Cold has been proposed to increase muscarinic activity by decreasing acetylcholinesterase activity. Acetylcholinesterase catalyzes the breakdown of acetylcholine, which is released by motor neurons at the neuromuscular junction to increase muscle activity. Increased levels of acetylcholine would improve ptosis in patients with MG, and as such provide supporting evidence for myasthenia gravis. Patient should be referred for more formal testing as well.

Surprisingly, the ice-pack test has a sensitivity of roughly 80%, which is comparable to the edrophonium tensilon test. Furthermore, the ice-pack test is much easier to implement with less risk than the edrophonium (tensilon) test, which should be performed in an intensive care unit (ICU). It may exacerbate neuromuscular weakness and cause acute exacerbation of bronchoconstriction in asthmati patients and worsen symptoms in patients with cardiac disease. However, the specificity of the ice-pack test has yet to be elucidated and it seems that the ice-pack test is only useful in patients presenting with ocular symptoms related to MG. Regardless, the ice-pack test is a useful diagnostic tool that can be utilized in rural or even hospital settings.

Take Home Points

- Cold can decrease acetylcholinesterase activity.
- A cold compress can restore ocular function in patients with MG.
- The ice-pack test has a 80% sensitivity for MG patients with ocular symptoms.

References:

1. Browning J, Wallace M, Chana J, and Booth J. Bedside testing for myasthenia gravis: the ice-test. *Emerg Med J.* 2011;28:709-711.
2. Baslo MB, Deymeer F, Serdaroglu P, Parman Y, Ozdemir C and Cuttini M. Decrement pattern in Lambert-Eaton myasthenic syndrome is different from myasthenia gravis. *Neuromuscul Disord*. 2006 Jul;16(7):454-8.

29: Abnormal Bleeding in an Elderly Man

Question:
An 83-year-old male comes into your clinic complaining of progressive dyspnea on exertion and some lightheadedness. He also noticed that he has been getting bloody noses more frequently, but thinks it is due to old age and dry air. However, he is most concerned about the recent appearance of gross blood in his stool. He feels fatigued and has pallor on examination. His past medical history is significant for type II diabetes and mild hypertension. He is currently on lisinopril and metformin. On physical examination, a harsh, crescendo-decrescendo systolic murmur is best heard at the right upper sternal border. Echocardiography confirms severe aortic stenosis and left ventricular hypertrophy. The international normalized ratio (INR) is normal at 1.1, but the partial thromboplastin time (PTT) is elevated at 40 sec (normal 25-35). His platelet count is within normal limits. His hemoglobin count is 9.6 g/dL.

What is the most likely cause of this patient's bleeding?

Contributors: Jeremy Moon, Cassie Kruczek, Alan Peiris

Answer:
This patient's history of aortic stenosis and recent mucosal and gastrointestinal bleeding is most likely indicative of Heyde's syndrome. Heyde's syndrome classically presents in the setting of severe aortic stenosis leading to mucosal bleeding from an acquired type 2A von Willebrand's disease and additional gastrointestinal bleeding from angiodysplasia both leading to anemia.

VWF is deficient because the increased shearing forces from severe aortic stenosis cause the coiled, multimer form of vWF to become uncoiled leaving it susceptible to cleavage by ADAMTS13. There are no known natural inhibitors of ADAMTS13 function, rather it is the conformation of vWF that determines if it will be cleaved. This subsequent decrease in vWF causes increased bleeding due to impaired platelet aggregation and destabilization of factor VIII. This explains the patient's increased PTT due to factor VIII destabilization. However, a normal PTT does not rule out vWF deficiency. Routine laboratory tests performed for von Willebrand disease such as vWF antigen levels and ristocetin cofactor activity maybe normal in Heyde's syndrome. In patients with normal vWF antigens *in vitro* platelet aggregration closure time using platelet function analyzers with collagen/adenosine diphosphate and epinephrine can be used to confirm the diagnosis of Heyde's syndrome.

Heyde's syndrome should be considered given the high incidence (5%) of aortic stenosis in adults over the age 65, with some studies showing a 100-fold increased risk of angiodysplasia in patients with aortic stenosis. Angiodysplasias are the most common vascular abnormalities of the gastrointestinal tract and the second leading cause of lower gastrointestinal bleeding in the elderly. The decreased gastrointestinal perfusion secondary to severe aortic stenosis may lead to hypoxia-induced blood vessel expansion and the development of fixed vasodilation leading to angiodysplasia.

Diagnosis of Heyde's syndrome is best established with measurement and function of vWF. The current gold-standard treatment of Heyde's syndrome is aortic valve replacement. The degree of coagulation abnormalities are negatively correlated with the mean transvalvular aortic gradient Treating patients with severe aortic stenosis with aortic valve replacement may lead to a major reduction in recurrent gastrointestinal bleeding.

Take Home Points

- Heyde's syndrome is a triad of aortic stenosis, coagulopathy and anemia.
- Coagulopathy occurs because of shearing of vWF during severe aortic stenosis.
- Angiodysplasia is associated with aortic stenosis and can cause GI bleeding.

References:

1. Hudzik B, Wilczek K, and Gasior M. Heyde syndrome: gastrointestinal bleeding and aortic stenosis. *CMAJ*. 2016;188(2):135-8.
2. Ledingham D. Heyde's syndrome: exploring the link between aortic stenosis and an acquired bleeding disorder. *BMJ Case Rep*. 2013;2013:bcr2013009306.
3. Loscalzo, J. From clinical observation to mechanism--Heyde's syndrome. *N Engl J Med.* 2012;367(20);1954-1956.

30: Treatment Resistant Parkinson's

Question:
A 55-year-old man comes into your clinic complaining of muscle weakness and difficulty walking. He says the symptoms started half a year ago, but have become progressively worse. His past medical history is significant for asthma and hypertension treated with albuterol and thiazides, respectively. Neurologic and physical exam strongly suggest Parkinson's disease. Treatment is started with L-Dopa and carbidopa, but after a few weeks, the patient comes in again complaining that treatment has not helped. Further questioning reveals that the patient was a welder for 36 years before he had to quit this past year.

What is the most likely cause of this patient's symptoms and why is this patient's disease resistant to treatment?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
Exposure to Manganese (Mn)-containing welding fumes can cause a dose-dependent progression of Parkinsonism syndrome, especially upper limb bradykinesia, limb rigidity, and impairment of speech and facial expression. Other possible causes of chronic Mn exposure include: liver disease, illicit drugs (such as ephedrone), and excessive consumption of Mn containing supplements. Mn is normally excreted in bile and thus chronic liver disease can cause chronically elevated serum levels of Mn. Ephedrone is an injectable psychostimulant popular in Russia that often has high levels of Mn contamination. Certain herbal supplements also contain Mn. The upper limit of oral Mn supplementation is about 9- 11mg/day in adults.

Parkinson's disease normally causes resting tremor, bradykinesia, rigidity, and postural instability. Dopamine levels are decreased due to dopamine neuron degeneration in the nigrostriatal pathway and patients are mostly responsive to L-Dopa treatment. However, in Mn-induced Parkinsonism syndrome, patients rarely present with resting tremors. They have gait impairment with dystonia and are resistant to L-Dopa treatment. This is because Mn accumulation in the brain affects the globus pallidus, which can be seen as a white hypersensitive region on T1-weighted magnetic resonance imaging (MRI) in these patients. Additional research has proposed that Mn disrupts the presynaptic release of dopamine and is a potent inducer of inflammatory microglia causing neuroinflammation. However, more research on the effects of Mn on other pathways and cells in the brain is needed to determine the mechanisms by which Mn-induced Parkinsonism is resistant to L-Dopa therapy. A dose dependent abnormality of the substantia nigra can be expected with Manganese toxicity. Currently, there is no treatment for this disease. Cessation of exposure to Mn is recommended when applicable.

Take Home Points

- Chronic Mn exposure can occur from liver disease, illicit drug use, and consumption of certain Mn containing supplements.
- Mn-induced Parkinsonism syndrome is resistant to L-Dopa treatment.

References:

1. Guilarte TR. Manganese and Parkinson's disease: a critical review and new findings. *Environ Health Perspect*. 2010;118(8):1071-80.
2. Kirkley KS, Popichak KA, Afzali MF, Legare ME, and Tjalkens RB. Microglia amplify inflammatory activation of astrocytes in manganese neurotoxicity. *J Neuroinflammation*. 2017;14(1):1999.

31: Tingling and Numbness in the Upper Extremities

Question:
A 66-year-old woman presents to your clinic with tingling and numbness along the ventral portion of her hand and weakness when writing or typing on her keyboard. She states that the pain is worse at night. She is retired and states that she does not use her wrists or hands very much. Light percussion of the median nerve on the distal palmar portion of her wrist reproduces the pain. Her past medical history is significant for a 18-year history of type 2 diabetes mellitus with end-stage renal disease needing long-term hemodialysis for the past 12 years. She also has a history of poorly controlled hypertension. Her mother as well as her maternal uncle also have type 2 diabetes mellitus and her paternal grandfather died of a heart attack at the age of 58. Her thyroid function tests were normal

What is the most likely diagnosis and what is the likely underlying predisposing condition?

Contributors: Jeremy Moon, Gurvinder Kaur, Alan Peiris

Answer:
This patient most likely has carpal tunnel syndrome, as evidenced by the positive Tinel's sign and classic description of symptoms. The underlying cause of her carpal tunnel syndrome is most likely mediated by amyloidosis from β2 microglobulin (β2M) deposition due to long-term hemodialysis rather than overuse injury. End-stage renal failure patients are unable to excrete these microglobulins, causing elevated serum levels that can lead to amyloidosis. Patients requiring long-term hemodialysis or peritoneal dialysis have also been shown to have an increased incidence of β2M amyloidosis as conventional hemodialysis fails to effectively remove β2M from the blood. This commonly manifests as carpal tunnel syndrome, bone cysts, arthropathies and rarely destructive spondyloarthropathy.

Amyloidosis is caused by deposition of insoluble amyloid fibrils that disrupt normal tissue function. Analysis of amyloid deposits reveal the presence of large quantities of a truncated variant of β2M that has a tenfold higher affinity for collagen than native β2M. Additionally, the presence of β2M modified by advanced glycation end products (β2M-AGE) in dialysis-related amyloidosis has also been reported. The β2M-AGE activates the mononuclear phagocytes and synovial fibroblasts by binding through AGE receptor thereby stimulating the production of proinflammatory cytokines. Inflammation further contributes to the development of destructive bone and joint lesions in patients. Treatment for this condition is renal transplantation, as the newly transplanted kidneys will be able to filter and excrete β2M. However, renal transplants can be difficult to acquire in older patients with comorbidities, and thus dialysis with special membranes to filter out the microglobulins is another treatment option. However, dialysis may only be effective in preventing progression of amyloid deposition, and will most likely be unable to cause regression of symptoms. Therefore, prevention of β2M accumulation in the serum through conservation of residual kidney function and early transplantation or usage of special dialysis membranes is necessary in this patient population. An extended carpal tunnel decompression surgery may be considered to provide immediate relief and improve quality of life.

Take Home Points

- Endstage renal failure and long-term hemodialysis can cause amyloidosis from β2M deposition.
- β2M deposition can cause inflammation of the median nerve causing carpal tunnel syndrome.
- β2M depiction can also cause bone cysts and arthropathies

References:

1. Scarpioni R, Ricardi M, Albertazzi V, De Amicis S, Rastelli F, and Zerbini L. Dialysis-related amyloidosis: challenges and solutions. *Int J Nephrol Renovasc Dis*. 2016;9:319-328.
2. Wilson SW, Pollard RE, Lees VC. Management of carpal tunnel syndrome in renal dialysis patientse using and extended carpal tunnel release procedure. *J Plast Reconstr Aesthet Surg*. 2008 Sep;61(9):1090-4.

32: Osteomalacia

Question:
A 38-year-old male presents to the clinic with bone pain in his right wrist after falling over in his home last night. His wrist is red, swollen and tender to palpation. X-ray results show a nondisplaced, extra-articular distal fracture of his radius. The patient states that he slipped while rising from his couch and landed on his right wrist. The patient expresses surprise on learning about his wrist fracture since he believes he sustained only a low-impact injury. The patient has a body mass index (BMI) of 18. His past medical history includes epilepsy (diagnosed when he was 15 years old) controlled with phenytoin. He also has seasonal allergies and occasional exertional asthma. He takes no other medications and does not have a significant family history. Dual energy X-ray absorptiometry (DEXA) scans reveal generalized decreased bone mineral density (BMD) with a T-score of -2.4.

What is the most likely cause of this patient's decreased BMD?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
The patient's radial fracture and decreased BMD results are most likely caused by his chronic use of antiepileptic drugs (AEDs) such as phenytoin. AEDs that induce cytochrome P450 enzymes, such as phenytoin, phenobarbital, carbamazepine and primidone, have been shown to increase the catabolism of vitamin D. This can lead to a deficiency of vitamin D and a subsequent increased risk of rickets in children and osteomalacia in adults. However, other AEDs, such as valproate, that do not induce cytochrome P450 have also been linked to decreased bone density through various proposed mechanisms: for example, inhibition of osteoblast cells, increased parathyroid hormone (PTH), and inhibition of intestinal calcium absorption. The effects of AEDs on BMD seem to be dependent on dosage and duration of treatment with AEDs. Newer generation AEDs such as lamotrigine, gabapentin, levetiracetam and topiramate need further study to determine their effects on BMD. Even gabapentin, which was initially brought to market as an AED and currently used for neuritis type pain may have bone changes. The risk of falling and thus sustaining a fracture is also increased in patients on AEDs, especially in the elderly.

Other risk factors involved with decreased BMD in epileptic patients on chronic AEDs include age, smoking, nutrition and exercise status. Many Americans may not be obtaining the required doses of calcium in their diet. Although there is no definitive preventive measure for patients with chronic AED use, patient education, vitamin D supplementation, adequate calcium intake in diet, lifestyle modifications and routine monitoring of serum vitamin D levels are the most likely effective means of preventing fractures. Bisphosphonates may have a role in fracture reduction and need additional studies in these patients.

Take Home Points

- AEDs can increase catabolism of vitamin D and decrease bone density.
- Vitamin D deficiency can increase risk of rickets and osteomalacia.

References:

1. Arora E, Singh H, and Gupta YK. Impact of antiepileptic drugs on bone health: Need for monitoring, treatment, and prevention strategies. *J Family Med Prim Care*. 2016;5(2):248-253.
2. Ma J, Johns RA, Stafford RS. Americans are not meeting current calcium recommendations. *Am J Clin Nutr*. 2007 May. 85(5):1361-6.

33: Ferumoxytol Use for Imaging in Renal Disease

Question:
A 78-year-old female presents with acute kidney injury a few weeks after she received a left kidney transplant. Imaging is required to assess the patency of the renal artery and vein. Ultrasonography was not diagnostic and magnetic resonance angiography (MRA) is being considered as an alternative. With her history of chronic renal insufficiency, the use of gadolinium based contrast agents are of concern.

What alternative agent can be used?

What dangerous adverse effect may occur with the use of a gadolinium based contrast agent?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:
Ferumoxytol is an ultrasmall superparamagnetic iron oxide that is used as an iron replacement in individuals with chronic kidney disease induced anemia. It can also be used off-label as a contrast agent for MRA or magnetic resonance imaging (MRI) safely in individuals with renal failure (further studies are pending). Ferumoxytol is a large molecule that does not easily leak out of the vasculature, nor is it efficiently cleared by the kidneys. It has a prolonged half-life in the circulation of 14-15 hours allowing for high quality imaging of both arterial and venous vasculature. Other uses include imaging of the aorta, deep vein thrombosis, and hepatic lesions. It is an intravascular agent in contrast to the extracellular based gadolinium. Ferumoxytol is cleared initially by macrophages in 1 to 3 days and then by the liver, spleen, and bone marrow where it can remain for up to 11 months. It is more expensive than gadolinium although costs vary based on region.

Gadolinium based contrast agents are associated with the risk of iatrogenic nephrogenic systemic fibrosis, which is not the case for ferumoxytol. Side effects include dizziness, nausea, and diarrhea, although hypotension and anaphylaxis have also been reported. The Food and Drug Administration (FDA) added a boxed warning regarding serious hypersensitivity reactions to reduce morbidity. Slow infusion along with monitoring the patient after the injection are recommended for patient safety. Ferumoxytol is contraindicated in pregnant individuals due to its Pregnancy Class C category.

The unique properties of ferumoxytol, including a high T1 relaxivity and longer intravascular half-life, may favor it as an optimal vascular imaging contrast agent. However, additional studies using this agent for imaging are needed prior to widespread adoption.

Take Home Points

- Ferumoxytl can be used safely in imaging as a contrast agent for non-pregnant patients with renal failure.
- It does not increase the risk of nephrogenic systemic fibrosis like gadolinium based contrast.

References:

1. Bashir MR, Bhatti L, Marin D, and Nelson RC. Emerging applications for ferumoxytol as a contrast agent in MRI. *J Magn Reson Imaging*. 2015;41(4):884-898.

34: Autoimmune Disorders in Pregnancy

Question:
A 29-year-old G2P1 woman at 15 weeks gestation comes into the clinic for a wellness check for her fetus. When asked about current symptoms, the patient mentions diffuse joint pain that began several years before her pregnancy. She manages the joint pain with acetaminophen as needed. She also uses eye drops frequently for dry eyes, which she attributes to her contacts. She has a past medical history of atopic asthma and eczema. Her maternal aunt was diagnosed with lupus at age 34. She currently takes no other medications than those already mentioned. Physical examination shows warmth and slight swelling of the patient's proximal interphalangeal joints. She also has mild conjunctival injection. A lab test is ordered and comes back positive for anti-nuclear and anti-ribonucleoprotein (RnP) antibodies.

What condition(s) is the neonate at risk for?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
This patient's presentation of conjunctivitis, dry eyes and diffuse joint pain along with family history of lupus and laboratory results positive for anti-RnPs (i.e. anti-SSA/SSB) are suggestive of Sjogren's syndrome. In particular, the marker anti-SSA (anti-Ro) has been shown to be associated with an increased risk (1-2%) of congenital heart block (CHB) in the neonate. CHB is diagnosed in utero, at birth, or within the neonatal period by the presence of an atrioventricular (AV) block. Anti-SSA antibodies are able to cross the placental barrier at roughly 12-weeks and can target developing fetal cardiac tissues for apoptosis. The subsequent damage and inflammation can lead to fibrosis of the AV node, myocardium, and overall conducting system leading to CHB.

CHB is usually diagnosed between 18 - 24th weeks of gestation. Fetal echocardiographic surveillance beginning from the early second trimester is recommended for antibody-positive mothers or mothers having babies with neonatal lupus erythematosus.

There are multiple components hypothesized to contribute to CHB, including anti-Ro antibodies that recognize cardiac proteins, a change of heart surface antigens during fetal development, genetics, and changes in the fetal environment. A lupus-like rash from maternal autoantibodies can also appear in these neonates (10-20%), but is usually self-limiting. Although rare, patients with high-titers of anti-SSA and concurrent positive results of anti-SSB antibodies should be counseled about the potential development of fetal CHB. Pregnant women with these high titers are recommended to receive obstetric sonograms and serial echocardiograms starting at 16 weeks gestational age to detect any fetal abnormalities. Although controversial, various regimens such as steroids, sympathomimetics, plasmapheresis, intravenous immunoglobulin, digoxin, diuretic and in utero pacing have been used for treatment of CHB.

Take Home Points

- Pregnant women who have lupus with anti-SSA titers have been shown to confer an increased risk of congenital heart block to their child.
- Corticosteroids and pacemakers could have therapeutic potential for CHB.

References:

1. Brucato A, Cimaz R, Caporali R, Ramoni V, and Buyon J. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. *Clin Rev Allergy Immunol*. 2011;40(1):27-41.
2. Yildirim A, Tunaoolu FS, Karaaoac AT. Neonatal congenital heart block. *Indian Pediatr.* 2013 May 8;50(5):483-8.

35: Failure to Thrive and Hepatitis C

Question:
A 54-year old man presents to your clinic complaining of generalized fatigue, depression and loss of appetite. He immigrated from South Korea to the United States over 10 years ago. Physical examination shows a depressed affect with delayed relaxation of tendon reflexes. Medical history is significant for hepatitis C that was successfully treated with pegylated interferon-alpha and ribavirin. He is not taking any other medications. The patient states that he drinks 1-2 beers and a glass of whiskey every night. His grandfather passed away from gastric cancer at age 68. The patient is concerned that he may have developed liver cancer and is asking for tests for malignant disease. Previous tests of hepatitis C viral loads showed complete remission. Patient does report his recent cholesterol check is higher than prior values.

What is most likely causing the patient's symptoms?

Contributors: Jeremy Moon, Cassie Kruczek, Alan Peiris

Answer:
The patient's symptoms of hyporeflexia, depression, appetite loss and possibly recent increase in cholesterol most likely indicate hypothyroidism caused by the patient's hepatitis C treatment. In patients with pegylated interferon-alfa and ribavirin treated hepatitis C, overall prevalence of hypothyroidism was shown to be roughly 20%, with 10% requiring treatment.

Interferon-alfa has been shown to cause autoimmune hypothyroidism by a variety of proposed mechanisms. These include direct inhibition of thyrocytes and stimulation of cytokines that increase the production of thyroid autoantibodies. Symptoms of hypothyroidism can often be masked by or confused with side-effects of interferon-alfa, which often include depression and fatigue. Therefore, routine monitoring of thyroid hormone levels should be considered along with appropriate treatment to maintain appropriate thyroid function in these patients. It is believed that thyroid function may eventually be restored after cessation of interferon-alfa therapy. Patients should also be screened for the presence of thyroid autoantibodies before, during and after antiviral therapies and warned of the potential effects of medications on thyroid function.

Recently, new guidelines regarding hepatitis C treatment have been adopted, due, in part, to side effects associated with pegylated interferon-alfa therapy. For those with chronic hepatitis C, a regimen of sofosbuvir and simeprevir may be recommended. These drugs are direct inhibitors of viral replication and have fewer reported side effects. They may be used in combination with ribavirin for the treatment of chronic hepatitis C infections. Treatment strategies should be based on viral genotype and patient's tolerance of medications. While the patient's drinking habits are not considered heavy at this stage, discussion of cutting back on the daily alcohol intake should be included as studies have shown the toxic effect of alcohol on thyroid cells.

Take Home Points

- Pegylated interferon-alfa and ribavirin can cause hypothyroidism. Lithium, amiodarone and tyrosine kinase inhibitors are also drugs that may cause hypothyroidism. Tyrosine kinase inhibitor related hypothyroidism may predict disease free survival in some cancers and as such may have prognostic significance.
- Hypothyroidism can be mistaken for side effects due to interferon-alfa administration.

References:

1. Hwang Y, Kim W, Kwon SY, Yu HM, Kim JH, and Choe WH. Incidence of and risk factors for thyroid dysfunction during peginterferon α and ribavirin treatment in patients with chronic hepatitis C. *Korean J Intern Med*. 2015;30(6):792-800.
2. Goyal G, Panag K, and Garg R. Prevalence of thyroid disorders in hepatitis C virus positive patients on interferon and antiviral therapy. *Int J Appl Basic Med Res*. 2016;6(4):245-248.

36: Patchy Hair Loss

Question:
A 27-year-old male presents complaining of patchy hair loss in several areas of his scalp. He reports no associated itching, pain or irritation with the hair loss. Examination shows several, well-defined, oval-shaped areas of hair loss in diameters ranging from 3 cm to 7 cm. At the periphery of these patches of hair loss, distal ends of the hair follicles appear considerably thicker than proximal segments. The patient states that this is the first time that anything like this has happened. The patient also states that his paternal grandmother had a similar episode of hair loss when she was younger. The patient recently moved and started a new job, but states that his stress does not seem overwhelming or unmanageable. His new roommate has two cats. The patient has a 5 year history of smoking, but stopped 6 months ago. Other past medical history and physical examination is unremarkable.

What is the most likely cause of this patient's alopecia?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
Lack of itching, scaling or crusting most likely excludes alopecia due to fungal origins. Furthermore, the "exclamation point" follicles and patterns of hair loss described during the physical exam are clinically diagnostic of alopecia areata. Lifetime prevalence of alopecia areata is estimated at 2%. The complete pathogenesis of this disease is unknown, but it is posited to be an autoimmune disorder with a genetic component. Individuals of any ethnic background can be affected with no difference between males and females. Although usually not necessary, a biopsy should reveal lymphocyte infiltration and inflammation around the hair follicle. Due to its autoimmune (T-cell-mediated) origins, topical or systemic steroids are often used to treat alopecia areata. However, topical application is less effective as it will not reach the hair bulb. Hair loss can also be seen in regions other than the scalp, such as eyebrows, eyelashes and pubic regions.

Recovery from alopecia areata can be variable, with some patients fully recovering and others having no hair regrowth at all. Alopecia areata may be associated with nail changes and other autoimmune disorders such as Hashimoto's hypothyroidism, type 1 diabetes, celiac disease or atopy. Coexistence of other autoimmune disorders and atopy is associated with a poor outcome. The greatest risk associated with alopecia areata is psychological in nature as the hair loss may be distressing to patients suffering from this disease.

Take Home Points

- Alopecia areata is an autoimmune (T-cell mediated) disorder with a history of sudden onset of well demarcated patchy hair loss.
- Exclamation point follicles, nail changes with fragility or shaggy pits, autoimmune disorders, and psychosomatic disease are associated with alopecia areata.
- Intralesional steroids (Kenalog) are the treatment of choice.

References:

1. Spano F, and Donovan JC.Alopecia areata: Part 1: pathogenesis, diagnosis, and prognosis. *Can Fam Physician*. 2015;61(9):751-756.
2. Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, Shapiro J. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. *J Am Acad Dermatol*. 2018 Jan;78(1):1-12.

37: Hyponatremia and AIDS

Question:
A 34-year-old female with a history of HIV infection that has progressed to AIDS comes into your clinic with a productive cough, fever and fatigue. She is poorly compliant with her antiretroviral therapy. Her chest X-rays show diffuse opacities in both lung fields. Sputum culture confirms a diagnosis of pneumocystis pneumonia and her most recent CD4+ count is below 50. Her condition begins to decline and she is hospitalized. Treatment with high-dose trimethoprim-sulfamethoxazole (TMP/SMX) is started. Several days after initiation of treatment, the patient becomes confused and agitated. Her serum sodium concentration is 119 mEq/L compared to her baseline of 138 mEq/L prior to treatment. She seems to be slightly confused and is only oriented to self and time, not place. Her mucus membranes are dry. She has slight orthostatic hypotension.

What is the cause of this patient's hyponatremia and what is the next best treatment option?

Contributors: Jeremy Moon, Cassie Kruczek, Alan Peiris

Answer:
Trimethoprim-sulfamethoxazole (TMP/SMX) is a combination antibiotic that blocks successive steps in nucleic acid synthesis. TMP/SMX is usually prescribed to patients with pneumocystis pneumonia caused by *Pneumocystis jirovecii*. However, TMP can also block epithelial sodium channels in the collecting duct, acting similarly to the potassium-sparing diuretic, amiloride. This can result in subsequent hyperkalemia and hyponatremia in patients receiving high-dose treatment of TMP/SMX.

Hyponatremia is more prevalent in individuals with HIV infection and patients with underlying renal insufficiency. The hyponatremia caused by TMP/SMX can be confused with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which can occur in patients with pneumonia. However, SIADH will often present with euvolemia, whereas TMP/SMX-induced hyponatremia will present with hypovolemia, increased serum renin, aldosterone and elevated urine sodium levels. A recent study demonstrated a 72.3% rate of hyponatremia (<135 mEq/L) in hospitalized patients treated with TMP/SMX.

Treatment for hyponatremia is fluid restoration with normal saline if TMP/SMX cannot be discontinued. Care should be taken not to correct hyponatremia too rapidly due to the risk of osmotic demyelination syndrome (ODS), characterized by flaccid paralysis, dysphagia and dysarthria. During states of hyponatremia, the brain utilizes mechanisms to prevent cerebral edema, which, in turn, leave it vulnerable to injury if the hyponatremic state is altered too quickly. Patients whose hyponatremia has been present for at least 2-3 days are most susceptible to ODS. In most cases, this hyponatremia is self-resolving with discontinuation of TMP/SMX.

Take Home Points

- TMP/SMX can block sodium channels in the collecting duct causing hyponatremia and hyperkalemia.
- Hyponatremia from TMP/SMX is more prevalent in patients with renal impairment or HIV.
- Hyponatremia from TMP/SMX presents with hypovolemia, increased serum renin and aldosterone, elevated urine sodium levels.

References:

1. Mori H, Kuroda Y, Imamura S, Toyoda A, Yoshida I, Kawakami M, and Tabei K. Hyponatremia and/or Hyperkalemia in Patients Treated with the Standard Dose of Trimethoprim-sulfamethoxazole. *Intern Med*. 2003;42(8):665-669.
2. Tsapepas D, Chiles M, Babayev R, Rao MK, Jaitly M, Salerno D, and Mohan S. Incidence of Hyponatremia with High-Dose Trimethoprim-Sulfamethoxazole Expsoure. *Am J Med*. 2016;129(12):1322-1328.

38: Infertility Treatment

Question:
A couple presents to your clinic with problems conceiving their first child. They have been attempting to conceive for the past two years. The wife is 28-years-old and has been screened for infertility, and tests demonstrate normal reproductive function and anatomy. Tests for the 29-year-old husband demonstrate low sperm count. Findings upon further physical examination appear normal. A repeat sperm count a month later confirms oligospermia. The husband has no significant past medical history, sense of smell is intact and has a normal 46 XY karyotype. An initial hormone evaluation demonstrates normal levels of prolactin and follicle stimulating hormone (FSH), but decreased levels of total and free testosterone. The patient has normal thyroid tests. The testosterone to estrogen (T/E) ratio is normal. The husband inquires about exogenous testosterone as a potential treatment for his infertility.

What is the best response by the physician?

Contributors: Jeremy Moon, Cassie Kruczek, Alan Peiris

Answer:
This patient most likely has idiopathic infertility (normal FSH and prolactin rules out other causes) with oligospermia. Low free testosterone is most indicative of intratesticular testosterone, which is most relevant to sperm production. In theory, exogenous testosterone can result in feedback inhibition on the hypothalamus and pituitary gland. This inhibition could decrease the production of endogenous testosterone and thus will lower the intratesticular testosterone concentration. Exogenous testosterone has also been associated with decreased testicular volume.

An alternative treatment for idiopathic infertility is clomiphene, a selective estrogen receptor modulator, which prevents estrogen's negative feedback on the hypothalamus and anterior pituitary gland. Therefore, clomiphene raises FSH and luteinizing hormone (LH) levels, which stimulates spermatogenesis and intratesticular testosterone production, respectively. This treatment has been proven to be fairly effective in males with normal T/E and FSH levels. However, clomiphene may cause emotional lability and have psychological changes such as aggressive behavior. It is also less likely to cause polycythemia than exogenous testosterone administration. Furthermore, patients with primary hypogonadism will not find as much success with clomiphene, because clomiphene acts by elevating FSH levels.

Other treatments, such as human chorionic gonadotropin (acts similarly to LH) and aromatase inhibitors (prevent testosterone conversion to estrogen), also have the potential to elevate sperm counts. Studies have suggested that supplementation of clomiphene therapy with antioxidants such as vitamins E and C, astaxanthin, glutathione and CoQ10 may augment elevation in sperm counts.

Take Home Points

- Treatment of idiopathic infertility in men with exogenous testosterone may actually cause negative feedback on intratesticular testosterone production, thus lowering sperm production.
- Clomiphene, an estrogen receptor modulator, can raise intratesticular testosterone production.

References:

1. Ring JD, Lwin AA, and Köhler TS. Current medical management of endocrine-related male infertility. *Asian J Androl*. 2016;18(3):357-363.
2. Ghanem H, Shaeer O, and El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. *Fertility and Sterility.* 2010;93(7):2232-2235.

39: Chronic Diarrhea

Question:
A 65-year-old woman comes into your clinic complaining of chronic diarrhea for the past year. The patient describes her stool as watery, but has not seen any visible blood in her stool. She is having 7 to 8 bowel movements every day. She cannot associate her diarrhea with any specific component of her diet (i.e. lactose or gluten). Occult blood testing is negative. Her last menstrual period was roughly 10 years ago. She is gravida 2 para 2. She has not travelled outside the United States in the past 2 years. Her past medical history is significant for type I diabetes, depression, and 40 years of smoking half a pack every day. Her current medications include glargine, aspart, fluoxetine, and lansoprazole. She states that she takes NSAIDs frequently for joint pain. Colonoscopy shows no abnormalities and her previous colonoscopies have also been normal. There is no significant family history. Physical examination is also not significant. BMI is 29 and temperature is 99.3 F. Stool examination is negative for ova and parasites and tests for *Clostridium difficile* are also negative.

What is the most likely cause of this patient's chronic diarrhea and what test would confirm this diagnosis?

Contributors: Jeremy Moon, Cassie Kruczek, Neha Mittal

Answer:
The patient's lack of recent travel history and duration of diarrhea makes infectious diarrhea an unlikely diagnosis. Furthermore, normal colonoscopies and lack of blood in the stool and other systemic symptoms also makes malignancy or irritable bowel disease an unlikely diagnosis. Irritable bowel syndrome is a possible diagnosis, but is usually a diagnosis of exclusion and other likely causes should be explored first. Therefore, microscopic colitis (MC) should be considered as a possible diagnosis.

The mean age of diagnosis of MC is 65 years old with a female predominance. Unfortunately, the exact pathogenesis of MC is unknown, even though it is thought that 10-20% of chronic diarrhea cases may be attributed to MC. Proposed mechanisms leading to MC associated pathology include: 1) autoimmune responses to luminal antigens 2) underlying genetics 3) hormonal causes and 4) an altered microbiome. A recent study indicated that patients with MC have decreased numbers of *Akkermansia spp.* in their gut, which in turn affects the thickness of the mucus in the colon.

There are two subtypes of microscopic colitis: lymphocytic colitis (LC) and collagenous colitis (CC). Both show normal colonoscopies, but can be diagnosed with an endoscopic biopsy: LC has increased intraepithelial lymphocytes and CC has a thickened subepithelial collagen band. Smoking, autoimmune disorders (i.e. type I diabetes, celiac disease, thyroid disorders) and certain medications (i.e. non-steroidal anti-inflammatories (NSAIDs), proton pump inhibitors, selective serotonin reuptake inhibitors) have been associated with MC.

Treatment for MC is not standardized, but options include lifestyle changes, avoidance of triggers, antidiarrheals such as loperamide, corticosteroids (low dose budesonide) and in severe cases colectomy.

Take Home Points

- In the elderly, microscopic colitis is the underlying cause of chronic diarrhea in 10-30% of cases.
- Diagnosis is made by an endoscopic biopsy which can differentiate the two subtypes: lymphocytic colitis and collagenous colitis.

References:

1. Park T, Cave D, and Marshall C. Microscopic colitis: A review of etiology, treatment and refractory disease. *World J Gastroenterol*. 2015;21(29):8804-8810.
2. Fischer H, Holst E, Karlsson F, Benoni C, Olesen M, Linden M, and Sjoberg K. Altered microbiota in microscopic colitis. *Gut*. 2015;64(7):1185-1186.

40: Bone Pain and Heart Failure

Question:
A 66-year-old male presents to your clinic with a history of progressive hearing loss and deep bone pain in his fingers and wrists for the past two years. His previous clinician diagnosed him with presbycusis and arthritis, however the patient feels that ibuprofen has not alleviated his symptoms and his hearing has worsened to the point where conversation has grown cumbersome. He has also noticed difficulty breathing and weakness upon exertion within the last few months. The patient finds himself sleeping most comfortably on his recliner chair. He also reports his hat size has changed recently. Physical examination demonstrates crackles bilaterally in the lower lobes of the lungs.

What is the the underlying cause of this patient's symptoms?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
This patient's hearing loss, deep bone pain, change in hat size and evidence of heart failure most likely indicate a diagnosis of Paget's disease of the bone. Laboratory testing for an isolated elevated alkaline phosphatase level and X-rays may aid in confirming this diagnosis. Elevated serum alkaline phosphatase levels in an individual with normal liver function may reflect increased bone metabolic activity indicative of increased bone remodeling. In individuals with liver disease, bone-specific alkaline phosphatase levels can be measured. The patient's hearing loss is most likely caused by compression of the vestibulocochlear nerve by increased osteoblastic activity characteristic of later stages of Paget's disease. The bone pain is most likely due to increased bone resorption from osteoclast activity and a rapid increase in bone pain may indicate progression into osteosarcoma (along with a rapid increase in alkaline phosphatase levels). Even though there is increased bone formation it is abnormal with decreased mechanical strength and can result in fractures or deformity.

The development of symptoms consistent with pulmonary edema may indicate a rare complication of Paget's disease, high-output heart failure. With rapid bone formation, blood flow is increased to the bone, often causing arteriovenous shunts that increase the venous return while simultaneously decreasing delivery of blood to other organs. Severe shunts can progress to high-output heart failure when the left ventricle is unable to compensate for the increased venous return, causing pulmonary edema.

Take Home Points

- Paget's disease can present with hearing loss and bone pain.
- High-output heart failure can occur in Paget's disease because of arteriovenous shunt malformations in the bone that cause increased venous return. Beri-beri (wet type) due to Thiamine deficiency has also historically been reported to cause high output cardiac failure.

References:

1. Tan A, and Ralston SH. Paget's disease of bone. *QJM*. 2014;107(11):865-869.
2. Mehta PA, and Dubrey SW. High output heart failure. *QJM*. 2009;102(4):235-241.

41: Substernal Mass

Question:
A 43-year-old female presents to your clinic complaining of bouts of syncope whenever she laughs. She says that these fainting spells have been worsening over the past year. She also notices that her face is more puffy than normal and says she gets more flushed than usual. She has a history of type I diabetes that is well-controlled with daily detemir and lispro. She denies any weight loss or night sweats. She also denies any excessive fatigue or changes in appetite. Physical examination shows mild, non-pitting edema of her face, but no significant abnormalities along the neck. Plantar and bicep reflexes are 2+ and symmetrical. Muscle strength is 5/5 and symmetric. Serum thyroid tests are normal. She does, however, mention a persistent cough and new dyspnea during her walks up to her 4th floor apartment during the past year. Chest X-ray reveals a deviated trachea with an opacity in the upper mediastinum.

What is the most likely diagnosis?

Contributors: Jeremy Moon, Gurvinder Kaur, Neha Mittal, Alan Peiris

Answer:
Syncope can be caused by a multitude of pathologies, however, the presence of a deviated trachea on chest radiograph most likely indicates the presence of a substernal mass. Although a deviated trachea can often indicate a tension pneumothorax or pleural effusion, the upper mediastinal opacity more likely indicates a mass. Based on the anatomical position, this substernal mass could be a teratoma, lymphoma, thymoma or goiter. The lack of neuromuscular weakness and ptosis makes the presence of a thymoma linked to myasthenia gravis unlikely. Furthermore, the lack of fever, night sweats or weight loss makes a lymphoma unlikely as well.

The most likely diagnosis is a substernal goiter that is compressing the vasculature such as the superior vena cava which decreases venous return to the right atrium. This can commonly lead to facial swelling and flushing. The obstructed venous drainage causes an increase in intracranial pressure compromising cerebral perfusion pressure (difference between the mean arterial pressure and the intracranial pressure). Pemberton's sign may be a useful technique during physical examination. Raising both arms vertically accentuates the compressive symptoms from a retrosternal goiter and should be done under close observation since syncope is possible. The induction of appropriate symptoms including pronounced facial plethora would indicate a positive test. Syncope can also be exacerbated when intrathoracic pressure increases as with laughter. The recurrent laryngeal nerve can also be compressed causing symptoms of hoarseness and dysphagia. Patients with substernal goiters can be euthyroid and may be asymptomatic for many years. Treatment is often referral to surgery for removal.

Take Home Points

- Teratomas, thymomas, lymphomas, thoracic aorta or goiter should be considered differential diagnoses for substernal masses.
- Substernal masses can compress the vasculature (superior vena cava) causing syncope.
- Substernal goiters can be euthyroid and asymptomatic.
- Surgery for removal is a treatment option.

Resources:

1. Crispo MM, Fidalgo G, Fix ML, Higgins GL 3rd. A case of superior vena cava syndrome demonstrating pemberton sign. *J Emerg Med*. 2012 Dec;43(6):1079-80.
2. Piteaud I, Abdennour L, Icke C, Stany I, Lescot T, and Puybasset L. Superior vena cava syndrome: cause of secondary raise of intracranial pressure after traumatic brain injury. *Ann Fr Anesth Reanim*. 2008;27(10):850-853.

42: Amenorrhea in the Female Athlete

Question:
A 17-year-old female comes into the clinic complaining of amenorrhea for the past 4 months. She is worried that she may be pregnant as she has had unprotected intercourse with her partner intermittently over the past year. She says that she has had no associated weight gain, nausea or changes in appetite recently. Her body mass index (BMI) is 19, and she says that her eating habits are fine. She is in good health otherwise and has no significant past medical or surgical history. Serum hCG levels are negative. Upon hearing the results, the patient is relieved and says that she is now able to focus more on her upcoming cross country event. She has been training vigorously because many college scouts will be present at her meet.

What is the most likely cause of this patient's amenorrhea and what is the best treatment?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
This patient most likely suffers from the female athlete triad. It is caused by a negative energy balance (caloric intake less than caloric use) which leads to multiple problems within the body. Specifically, it can cause a decrease in gonadotropin releasing hormone (GnRH), decreased levels of follicular stimulating hormone (FSH), and luteinizing hormone (LH) which leads to decreased estrogen levels. Decreased estrogen may result in dependent arterial vasodilation, which can reduce muscle perfusion, and cause an impaired endothelium.

The triad consists of low energy availability, menstrual dysfunction, and decreased bone mineral density. All components of the triad may be present (often at low prevalence 0-1.2%), but may also present with only one (16-60%) or two (2.7-27%) components. The triad can occur without an eating disorder in female athletes with inadequate caloric intake relative to levels of physical activity. The patient, if left untreated, is at increased risk for stress fractures, infertility, as well as decreased energy, depression, poor sleep and even suicide. Therefore, assessment of mood as well as bone density are necessary components of the exam.

A recent study demonstrated that there may be a male athlete triad similar to the female athlete triad, but consisting of low energy availability, hypogonadism, and decreased bone density.

Initial treatment should be non-pharmacological with restoration of a positive energy balance by increased calorie intake with or without decreased physical activity. Long-term treatment of the female athlete triad is multidisciplinary and trust must be maintained with the patient. Consistent information and successful collaboration from coaches, parents, psychologists, dietitians, and doctors is vital to adequate recovery.

Take Home Points

- The female athlete triad consists of: low energy, menstrual dysfunction, and decreased bone density.
- There may be a similar male athlete triad that includes hypogonadism.
- Adequate nutrition and management of physical activity are necessary components of the treatment plan, which is often multidisciplinary.

References:

1. Thein-Nissenbaum J, and Hammer E. Treatment strategies for the female athlete triad in the adolescent athlete: current perspectives. *Open Access J Sports Med*. 2017;8:85–95.
2. Tenforde AS, Barrack MT, Nattiv A, Fredericson M. Parallels with the Female Athlete Triad in Male Athletes. Sports Med. 2016 Feb;46(2):171-82.

43: Injuries in Sports-Specialized Young Athletes

Question:
A 12-year-old male presents to your clinic with his father and mother for his annual physical examination. The patient is within the 70th percentile for height and 50th percentile for weight. He is healthy and has no past medical history. His family history is not significant. The father mentions to you that he needs this physical examination for his son to be cleared to play in a competitive baseball league. When asked about physical activity, the patient tells the physician he pitches nearly every day for a few hours with his dad. The father proudly states that his son has not taken a single day off from baseball in over a year. No other sports are played as the father states that he wants his son to play Major League Baseball (MLB) and does not want other sports to distract his son.

What recommendations should the physician give to this family regarding the patient's physical activity?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
Sports specialization is defined by the following criteria: more than 8 months of a sports-specific training in one year and quitting other sports to focus on one main sport. Youth athletes (ages 7-18) that specialize are at a greater risk of injury compared to non-specialized peers. Furthermore, young athletes may burnout and become less likely to continue to play sports after suffering a sports-related injury. In this specific case, the patient is most likely to suffer from an overuse injury of the elbow (most common, but shoulder injury can also occur) due to the high-volume and specialized training associated with his pitching.

In a recent study of Little League baseball player injuries, at the conclusion of the season, 48% of players had an abnormal elbow MRI. The main type of abnormality involved injury to the medial epicondyle, including medial epicondyle fragmentation, edema within the medial epicondyle apophysis and distal humeral metaphysis, and disruption of the ulnar collateral ligament (UCL).

Regardless of sports specialization, more than 16 hours of sports activity per week has also been associated with increased risk of sports-related injuries. Playing multiple sports and encouraging unstructured free play can help reduce injury risk as well as burnout. If the patient and/or patient's family insist on sports specialization and high levels of physical activity, the patient should be monitored closely for burnout and injuries. It would also be appropriate to carefully explore the need for counseling since stress induced by parents requiring progeny to achieve excellence in sports can be associated with adverse social and academic accomplishments over the long term.

Take Home Points

- Youth athletes that specialize in one sport are at greater risk of injury and burnout.
- More than 16 hours of sports activity/week increases the risk of sports-related injuries.
- Encourage youth athletes to play multiple sports with unstructured free play.

References:

1. Myer GD, Jayanthi N, Difiori JP, Faigenbaum AD, Kiefer AW, Logerstedt D, and Micheli LJ. Sport Specialization, Part I: Does Early Sports Specialization Increase Negative Outcomes and Reduce the Opportunity for Success in Young Athletes? *Sports Health*. 2015;7(5):437-42.
2. Pytiak AV, Stearns P, Bastrom TP, Dwek J, Kruk P, Roocroft JH, and Pennock AT. Are the Current Little League Pitching Guidelines Adequate? A Single-Season Prospective MRI Study. *Orthop J Sports Med*. 2017;5(5):1-7.43:

44: Shortness of Breath After Long Bone Fracture

Question:
A 45-year-old woman comes into the emergency department after fracturing her femur during a ski trip. She is rushed into surgery to repair the fracture. Twenty one hours later, she shows an acute deterioration in mental status. She has a new petechial rash on her chest. She also has a fever and tachycardia. A computed tomography (CT) scan of the head shows no abnormal findings. Her complete blood cell count and electrolyte levels are normal. Her albumin levels are shown to be decreasing. She has no co-existing medical conditions and her husband states that she does not drink alcohol on a regular basis.

What should a clinician consider given her presentation?

Contributors: Jeremy Moon, Gurvinder Kaur, Alan Peiris

Answer:
Fat embolism syndrome should be considered. There are three major characteristics that aid in the diagnosis of this condition which include: neurological abnormalities, petechial rash, and respiratory insufficiency. Fat embolism may occur in younger patients after a long bone fracture, especially femur fracture. Although not clearly understood, two theories are postulated for the pathophysiology of fat embolism syndrome. The mechanical theory states that following large bone fractures or trauma, the fat droplets (from disrupted fat cells) are released into the venous system and then transported to the pulmonary capillary beds. Large fat droplets are trapped as emboli in the lung capillaries while small fat droplets travel through arteriovenous shunts to the brain. The biochemical theory proposes that hydrolysis of embolized fat into free fatty acids causes a complex microvascular inflammatory response which may have detrimental effects on the brain and other tissues.
An MRI with diffusion-weighted imaging may depict a characteristic pattern of disseminated hyperintense lesions in the white matter associated with cerebral fat embolism.

The clinician should try to exclude other causes of these symptoms such as pulmonary contusion and/or trauma to intra-thoracic vasculature, pulmonary embolism, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and medication side effects. With fat embolism syndrome, there is usually a 12-72 hour delay in when the symptoms arise as seen in this patient. Fat embolism syndrome first affects the nervous system and lungs. No specific test can be done to diagnose this, so it is largely a clinically based diagnosis. Serum albumin levels can also be checked. If albumin levels are seen to be decreasing, then it shows that the free albumin maybe attaching to lipid micelles. However, albumin levels can also decrease with any acute illness and specifically with sepsis or an inflammatory response to a surgery. Infusing albumin intravenously may help to increase the level of free albumin, though there is no treatment of choice for this condition. The use of steroids is controversial. Fixing the fracture early may reduce the risk of fat embolism syndrome.

Take Home Points

- Fat embolism can occur 12-72 hours after a long bone fracture.
- Presentation usually include neurological abnormalities, petechial rash and respiratory insufficiency.
- Low albumin may be a sensitive, but not specific indicator of fat embolism.

References:

1. Zhou Y, Yuan Y, Huang C, Hu L, and Cheng X. Pathogenesis, diagnosis and treatment of cerebral fat embolism. *Chinese J Traumatol*. 2015;18(2):120-123.
2. Mijalsi C, Lovett A, Mahajan R, Sundararajan S, Silverman S, and Feske S. Cerebral Fat Embolism: A case of rapid-onset coma. *Stroke*. 2015;46(12):e251-253.

45: Rhinitis and Fatigue

Question:
A 29-year-old male presents to your clinic with complaints of runny and stuffy nose, worsened especially with fatigue for the past few months. The nasal discharge is described as clear. When asked about potential triggers, the patient states that he does not seem to notice any occurrence patterns for his rhinitis. The patient also reports a mild cough, but denies any fever, chills, nausea or myalgia. However, he says he has gained 20 pounds since he quit smoking 7 months ago after he moved to the United States from Japan. The patient is most concerned about his fatigue as it seems to have increased with the increasing frequency of his episodes of rhinorrhea and nasal congestion. His wife also states that his snoring has been worsening over the past year. The patient has no other history of atopy or food allergies.

What is the possible cause of this patient's worsening fatigue?

Contributors: Jeremy Moon, Kandis Wright, Alan Peiris

Answer:
This patient has rhinitis with multiple possible etiologies (allergic, non-allergic, and mixed). Rhinitis affects anywhere from 30 to 60 million people in the United States and presents with variable severity including one or more symptoms of rhinorrhea with clear discharge, nasal congestion, sneezing or itching. Systemic symptoms can also include headaches, fatigue and sleep disturbances. Allergic rhinitis can be tested for using a thorough history and physical, allergen skin tests, and/or IgE serum assays. Nasal eosinophila maybe a sensitive marker for allergic rhinitis. Peripheral blood eosinophilia in chronic rhinosinusitis may indicate a deeper level of inflammation and a greater need for sinus surgery. If these tests are negative, non-allergic rhinitis should be considered, which often presents with symptoms of rhinorrhea and congestion rather than itching or sneezing. Common triggers of non-allergic rhinitis can be changes in weather/temperature, food, medications, smoke/fumes or odors.

This patient's fatigue could be related to obstructive sleep apnea (OSA), a condition characterized by upper airway disruption during sleep, as indicated by his recent history of weight gain and worsening snoring. A sleep study would aid in diagnosing this patient with OSA. Sleep apnea remains an often underdiagnosed entity in the clinic setting. Furthermore, allergic rhinitis and OSA can exacerbate the symptoms of each other. For instance, one proposed mechanism is that nasal congestion and nasal resistance cause increased mouth breathing, which can move the mandible and tongue inferiorly, further decreasing the pharyngeal diameter. Allergic rhinitis can also produce histamine, cytokines IL-1β and IL-4, and cysteinyl-leukotrienes (CysLTs) that attract inflammatory cells to the nasal passages. Additionally, OSA can exacerbate allergic rhinitis by producing inflammatory cytokines that cause inflammation leading to nasal congestion. Thus, the treatment of rhinitis with intranasal steroids, antihistamines or anticholinergics may also relieve symptoms of OSA.

Take Home Points

- Rhinitis can have allergic, non-allergic or mixed etiologies.
- Symptoms of fatigue, weight gain, and snoring in patients with allergic rhinitis may be caused by OSA.
- Allergic rhinitis may worsen OSA and vice versa.

References:

1. Schroer B, and Pien LC. Nonallergic rhinitis: common problem, chronic symptoms. *Cleve Clin J Med*. 2012;79(4):285-93.
2. Chirakalwasan N, and Ruxrungtham K.The linkage of allergic rhinitis and obstructive sleep apnea. *Asian Pac J Allergy Immunol*. 2014;32(4):276-86.

46: Shoulder Pain

Question:
A 54-year-old woman presents to your clinic with worsening right shoulder pain over the past 4 months. The pain is described as stiff, aching and deep. The pain is currently rated a 4/10, but can be increased to a 7/10 during certain movements. Active and passive range of motion is limited to 70° of arm abduction and 40° of external rotation. The right shoulder is also slightly tender to palpation over the glenohumeral joint and deltoid. No inflammation or redness is present. She recalls no trauma or inciting incident for the shoulder pain. The patient is most concerned about her inability to sleep at night due to the constant shoulder pain, regardless of her body positioning. Shoulder X-rays are negative for fractures. She has a past medical history of depression and states that she is undergoing menopause.

What is the most likely diagnosis for this patient?

Contributors: Jeremy Moon, Jannette M. Dufour, Neha Mittal

Answer:
This patient most likely suffers from idiopathic adhesive capsulitis, which is also known as frozen shoulder. Frozen shoulder has been estimated to affect 5.3% of the population, with the highest prevalence in 40 to 60 year old females . Mostly, restriction of active and passive range of motion during abduction and external rotation is noted**.** However, diagnosis of this condition may be unreliable as the symptoms could be vague and not clearly defined. Without a clear clinical or diagnostic test, frozen shoulder can often be confused with rotator cuff tendinopathy or calcification of the long head of the biceps tendon.

Radiographs are usually normal in frozen shoulder, but patients can present with reduced range of motion for flexion and external rotation, pain with movement, or pain at night. Frozen shoulder can be categorized as primary (idiopathic) or secondary, which is associated with a known cause such as rotator cuff disease, prolonged immobilization, or trauma. Furthermore, it has also been associated with diabetes and thyroid disease. Pathogenesis is theorized to be a combination of inflammation and fibrosis, but there is no clear consensus on specific mechanisms. Unfortunately, there is no definitive treatment option, but conservative treatment with non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy, or intra-articular steroid injections may aid with recovery. Joint mobilization exercises along with stretching appears better than stretching exercises alone in improving outcomes in this disorder. Frozen shoulder has an average duration of 30.1 months with great variation in certain patients, but up to 59% of patients may not regain full function after 4 years. Disrupted sleep, disability and anxiety associated with frozen shoulder can greatly affect a patient's quality of life and these concerns should be addressed as much as possible.

Take Home Points

- Frozen shoulder can be idiopathic or secondary to trauma or rotator cuff disease.
- There is no clear set of symptoms or diagnostic test, but this syndrome may still affect quality of life significantly and should be treated with NSAIDs, physical therapy or steroid injections.

References:

1. Ryan V, Brown H, Minns Lowe CJ, and Lewis JS. The pathophysiology associated with primary (idiopathic) frozen shoulder: A systemic review. *BMC Musculoskelet Disord*. 2016;17(1):340.
2. Maund E, Craig D, Suekarran S, Neilson A, Wright K, Brealey S, Dennis L, Goodchild L, Hanchard N, Rangan A, Richardson G, Robertson J, and McDaid C. Management of frozen shoulder: a systemic review and cost-effectiveness analysis. *Health Technol Assess*. 2012;16(11):1-264.

47: Hyperemesis

Question:
A 27-year-old male presents to the emergency room complaining of vomiting 40 times in the past two days and constant nausea. He states that the emesis is non-bloody. He states that he does not drink often, and his last drink was several weeks ago. He does, however, admit to cigarette and marijuana use. Physical exam is unremarkable and his complete metabolic panel is also unremarkable except for low potassium at 2.9 mEq/L and a mild elevation of his serum creatinine level of 1.51 mg/dL. The patient is started on intravenous (IV) fluids and ondansetron as an antiemetic. However, the patient continues to vomit uncontrollably and he complains that the medications have not helped his nausea nor his vomiting. He is admitted to the hospital due to his unremitting vomiting. Stool cultures, GI pathogen panel, and ova and parasite exams are all negative. Abdominal CT scan shows no abnormalities. During his admission, the patient takes more than 10 hot showers daily as he states that is the only thing that relieves his nausea.

How can this patient's symptoms be explained?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
This patient most likely suffers from cannabinoid hyperemesis. The combination of constant vomiting and hot baths may lead to severe dehydration and even pre-renal failure. Although cannabinoid products have antiemetic effects, there is a paradoxical hyperemesis that can occur with consistent or extreme use. Delta-9-tetrahydrocannabinol (THC), the main active ingredient in marijuana, has antiemetic effects in the hypothalamus, but it slows peristalsis and gastric emptying in the gut. In increased doses, peripheral effects of THC may overwhelm central effects, causing paradoxical nausea and emesis. Moreover, THC is lipophilic and may accumulate in fat.

Most antiemetic drugs such as ondansetron, promethazine or metoclopramide have not been shown to decrease vomiting or nausea. Lorazepam, haloperidol, proton pump inhibitors and intravenous sodium chloride can aid in treatment. In many cases, cessation of marijuana use resolves symptoms within a few days. However, many patients will try and use marijuana to treat their hyperemesis, which causes recurring or worsening episodes of hyperemesis. Recurring episodes of cannabinoid hyperemesis may be labeled as cyclic vomiting syndrome; these two syndromes are very similar and have no definitive diagnostic guidelines.

Counseling and educating patients about the mechanism of their nausea and vomiting is vital in preventing and treating this condition. Compulsive bathing is a commonly reported behavior with cannabinoid hyperemesis. It is theorized that the hot bathing causes vasodilation of cutaneous vessels, thus reducing blood flow to the gut and potentially relieving symptoms of nausea and vomiting. In patients presenting with unremitting vomiting and compulsive bathing behavior, cannabinoid hyperemesis should be considered as a potential cause. A urine drug screen should be considered and risk of acute renal failure as a result of volume depletion recognized early in the management approach.

Take Home Points

- Marijuana, although known as an antiemetic, can cause paradoxical nausea and vomiting with chronic and excessive use.
- Further use of marijuana during cannabinoid hyperemesis leads to worsening symptoms.
- Compulsive bathing with hot water to alleviate symptoms of nausea is commonly reported. Lorazepam, proton pump inhibitors, and IV fluids may aid in treatment, but other antiemetic drugs have not been shown to be effective.

References:

1. Habboushe J, and Sedor J. Cannabinoid hyperemesis acute renal failure: a common sequela of cannabinoid hyperemesis syndrome. *Am J Emerg Med*. 2014;32(6):690.e1-2.
2. Blumentrath CG, Dohrmann B, and Ewald N. Cannabinoid hyperemesis and the cyclic vomiting syndrome in adults: recognition, diagnosis, acute and long-term treatment. *Ger Med Sci*. 2017;15Doc06. doi: 10.3205/000247. eCollection 2017.

48: Pediatric Diarrhea

Question:
A mother brings her 4-year-old daughter into the clinic with a chief complaint of watery diarrhea for over two weeks. She has no past significant medical history and is taking no medications. She mentions that her daughter has about 5-7 bowel movements per day and seems fatigued. She has not traveled anywhere recently. A history of foods eaten in the past week includes home cooked chicken and rice along with raspberries and strawberries for snacks. Tests for celiac disease, bacterial stool cultures, and Giardiasis are negative.

What should be considered when ordering an ova and parasites test?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
Cyclospora cayetanensis, this parasite is not routinely included in the ova and parasites test and needs to be ordered specifically if suspected. More than one sample may be needed since there may be low shedding of the oocysts. In developed countries, *Cyclospora* is associated with imported foods such as raspberries, basil leaves, snow peas, and cilantro. Improved sample preparation and use of the TaqMan real-time PCR may offer a streamlined, rapid and robust assay for regulatory food testing for detection of *C. cayetanensis*. It is endemic in Haiti, Guatemala, Peru, and Nepal, thus *Cyclospora* should be suspected in travelers returning from these regions with prolonged watery diarrhea. This parasite takes about a week to become infectious and diarrheal symptoms may last for an average of 2-4 weeks or longer in immunocompromised patients.

Cyclospora infections have also been associated with Guillain-Barre syndrome (GBS) and reactive arthritis (Reiters syndrome), especially in adult patients. Interestingly, the onset of GBS and reactive arthritis has been observed following infections from several other enteric pathogens. In the case of reactive arthritis, it is hypothesized that the infectious agent enters the circulation, and antigens are delivered to the joints via monocytes. Through mechanisms of molecular mimicry, an autoimmune response to host antigens present in the synovial fluid is induced resulting in an inflammatory response. It is believed that a similar, infection induced autoimmune response directed against myelinated neurons is responsible for the onset of GBS following *Cyclospora* infection.

Prompt treatment of *Cyclospora* infections may reduce the risk of developing both GBS and reactive arthritis. Coinfection with other parasites such as *Cryptosporidium* may occur. *Cyclospora* infections can be treated with trimethoprim-sulfamethoxazole (TMP/SMX). Ciprofloxacin or nitazoxanide can be used for those with sulfa allergies, although studies have shown these therapies to be less efficacious than TMP-SMX.

Take Home Points

- *Cyclospora cayetanensis* presents as a watery diarrhea and has been associated with Guillain-Barre syndrome and reactive arthritis.
- If suspected, the test needs to be ordered separately as it is not routinely included in the ova and parasites test.
- Coinfection may occur with *Cryptosporidium*.

References:

1. Ortega YR, and Sanchez R. Update on Cyclospora cayetanensis, a Food-Borne and Waterborne Parasite. *Clin Microbiol Rev*. 2010;23(1):218-234.
2. Connor, B and andRiddle M. Post-Infectious Sequelae of Travelers' Diarrhea. *Journal of Travel Medicine*. 2013;20(5):303–312.

49: Retrograde Ejaculation

Question:
A 20-year-old male comes to your clinic with his healthy 22-year-old wife complaining of infertility. They have been trying to conceive a child for the past 15 months with no success. The patient's wife has two children from a previous relationship and was healthy in her most recent workups for fertility. The patient admits that he has had no emission during ejaculation and that this has occurred for the past two weeks. Family history is insignificant except for a paternal uncle and grandfather with diabetes mellitus. Post-ejaculatory urine microscopy is performed and confirms a diagnosis of retrograde ejaculation. When asked about other symptoms, the patient reports some numbness in his toes, but does not seem to notice much else.

What is a potential cause of this patient's retrograde ejaculation?

Contributors: Jeremy Moon, Jannette M. Dufour, Alan Peiris

Answer:
Retrograde ejaculation is often caused by a defect in the internal urethral sphincter that causes ejaculate to flow back into the bladder. Retrograde ejaculation is responsible for about 1% of all cases of male infertility in the United States. Hyperglycemia damages the internal urethral sphincter nerves, which can cause retrograde ejaculation. Normally, alpha-1 adrenergic stimulation of the sphincter prevents backflow of ejaculate into the bladder. This is different from anejaculation where there is a complete absence of ejaculate. Although this is an atypical presentation, with the only symptoms being peripheral neuropathy and retrograde ejaculation, diabetes mellitus (DM) should be considered especially given the patient's family history. Rarely retrograde ejaculation can precede the onset of type 1 diabetes. However, diabetic patients usually have the the disease for years prior to developing chronic urologic complications. Retrograde ejaculation is a well recognized complication of autonomic neuropathy in diabetes. Diabetic patients with retrograde ejaculation may have a higher frequency of erectile dysfunction. Post-ejaculatory urine should be evaluated routinely in diabetic patients with low ejaculate volumes and in aspermic infertility.

Treatment involves proper blood glucose control and sympathomimetics to increase alpha-1 adrenergic tone in the internal urethral sphincter. Sperm may also be harvested from the testis or the bladder to aid in fertilization. As stated earlier, this is a rare presentation as most individuals with diabetes who present with retrograde ejaculation have had diabetes mellitus (type 1 or type 2) for over 20 years. However, young patients presenting with retrograde ejaculation should still be screened for diabetes mellitus to rule it out as a potential cause. Other causes of retrograde ejaculation should also be considered such as surgery, multiple sclerosis, spinal cord injury, Parkinson's disease, or medications for high blood pressure (tamsulosin, terazosin), anti-psychotics or depression (selective serotonin reuptake inhibitors).

Take Home Points

- Patients with DM may have retrograde ejaculation due to hyperglycemic damage to the nerve to the internal urethral sphincter.
- Proper blood glucose control and an alpha-1 agonist may help restore tone to the internal urethral sphincter.

References:

1. Kam J, Tsang VH, Chalasani V. Retrograde Ejaculation: A Rare Presenting Symptom of Type 1 Diabetes Mellitus. *Urol Case Rep*. 2016;10:9-10.

50: Balance and Gait Abnormalities

Question:
A 64-year-old Caucasian woman presents to your clinic complaining of balance loss, nausea and persistent headaches that have been bothering her for the past few days. She states that she has never had an episode like this before. She denies any memory loss and her husband does not seem to notice any significant cognitive deficits. Deep tendon reflexes and muscle strength are all intact. However, her gait is broad-based and she has significant diplopia when looking to her right. She has a past medical history of mild hypertension and well-controlled diabetes mellitus. Her mother was diagnosed with breast cancer at 61 years of age, and her older sister was diagnosed with ovarian cancer last year. Cerebral hemorrhage or infarction is suspected, therefore a computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and brain stem are ordered. However, both these tests fail to find any significant pathology.

What is a possible diagnosis and what test should be ordered next to confirm this diagnosis?

Contributors: Jeremy Moon, Gurvinder Kaur, Alan Peiris

Answer:
In the presence of cerebellar dysfunction (diplopia and abnormal gait) and normal brain and brain stem CT or MRI, paraneoplastic cerebellar degeneration (PCD) should be considered as a diagnosis. In older women, an ovarian, breast or uterine malignancy can be a potential cause of PCD.

Anti-Yo or anti-Purkinje cell antibodies have been associated with these malignancies and can be detected in serum to aid in diagnosis of PCD. Furthermore, a chest and abdominal CT scan may aid in the detection of a tumor mass. Binding of these antibodies to tumor cells of affected patients suggest that these autoantibodies are primarily generated against the underlying neoplasm but can cross-react with Purkinje cell antigens. Recently, it has been demonstrated that these anti-Yo antibodies cause cerebellar Purkinje cell death by binding to the intracellular 62kDa Yo antigen. Less commonly, anti-Hu antibodies may be linked to PCD. Anti-Tr antibodies maybe associated with cerebellar degeneration in Hodgkin lymphoma.

PCD can also be caused by small cell lung carcinomas, gastrointestinal malignancies and Hodgkin's lymphoma. Symptoms of PCD can also precede any signs of malignancy, thus any unexplained cerebellar symptoms should be followed by screenings for these cancers. Treatment of PCD involves early resection and treatment of the causative cancer, but in most cases, symptoms of PCD rarely resolve completely. In some instances, PCD may indicate a recurrence of cancer.

Take Home Points

- Breast, ovarian or uterine malignancy can generate antibodies that target and kill Purkinje cells.
- Cerebellar degeneration may present with headaches, gait abnormalities and nystagmus.

<u>References</u>:

1. Negishi Y, Sakai K, Noguchi Y, Iwasaki N, and Kawai N. Paraneoplastic cerebellar degeneration caused by ovarian clear-cell carcinoma. *J Obstet Gynaecol Res*. 2014;40(2):614-617
2. Greenlee JE, Clawon SA, Hill KE, Wood B, Clardy SL, Tsunoda I, and Carlson NG. Anti-Yo antibody uptake and interaction with its intracellular target antigen causes Purkinje cell death in rat cerebellar slice cultures: A possible mechanism for paraneoplastic cerebellar degeneration in humans with gynecological or breast cancers. *PLOS one*. 2015;10(4):e0123446.

51: Non-Surgical Management of Nephrolithiasis

Question:
A 45-year-old woman presents with right flank pain radiating to the groin and says she has been nauseous and vomiting the past few days. A urinalysis shows an absence of casts and presence of microscopic hematuria. A computed tomography (CT) scan is ordered confirming the diagnosis of nephrolithiasis and shows a 9 mm stone in the right ureter. The patient is adamant in her refusal of surgical treatment. She tried calcium channel blockers for medical management but was intolerant of this medication and felt that it did not help her pain.

What is another medication that can be recommended to her?

Contributors: Sarah Jaroudi, Gurvinder Kaur, Alan Peiris

Answer:
Alpha adrenergic antagonists should be considered in medical management of nephrolithiasis. Since this patient's stone is >5 mm, it can be treated with medical expulsion therapy. If it was <5 mm, treatment would be conservative as the stone would pass spontaneously on its own. The human ureter contains both alpha- and beta-adrenergic receptors although alpha receptors predominate. Stimulation of the alpha receptors increases the force and frequency of ureteral contraction and peristalsis, respectively. Antagonism of alpha receptors has the opposite effects. Alpha adrenergic antagonists work by relaxing the smooth muscle of the ureters, decreasing the high pressure above the stone and increasing fluid transport. It also helps to reduce the pain while the stone passes and increases the rate at which it passes. Alpha blockers can induce a significant increase in expulsion rate and a shorter expulsion time in selected cases of nephrolithiasis.

Tamsulosin is most commonly used although any alpha adrenergic antagonist will work. Since the treatment depends on size of the stone, a CT scan will help determine the size. Although ultrasound may be easier, it does not offer the ability to calculate the size of stones. Whether or not medical expulsion therapy is indicated for patients depends on a) if pain is uncontrolled and b) lack of systemic sepsis. Patients should be made aware of the side effects associated with alpha adrenergic antagonists. Common side effects include cough, dizziness, and rhinitis. Some of the more serious but rare reactions include hypotension and hypersensitivity reactions but overall the drug has a low risk profile. They are contraindicated in patients who have had glaucoma surgery and those who are hypersensitive to sulfa drugs. Lifestyle preventive measures include keeping hydrated and reducing salt and protein intake.

Take Home Points

- Medical management of nephrolithiasis can include alpha-1 blockers, such as tamsulosin, which ease passing of larger stones greater than 5mm.
- Prevention measures include hydration and reduction in salt and protein intake.
- Side effects of alpha-1 blockers include cough, hypotension and rhinitis.

References:

1. Hollingsworth JM, Canales BK, Rogers MA, Sukumar S, Yan P, Kuntz GM, and Dahm P. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. *BMJ*. 2016;355:i6112.
2. Lipkin M, and Shah O. The use of alpha-blockers for the treatment of Nephrolithiasis. *Rev Urol*. 2006;8(Suppl 4):S35-S42.

52: Cryptosporidiosis

Question:
A family medicine clinic sees over 15 children during the summer with similar symptoms of moderate diarrhea lasting over 2 weeks. Other symptoms endorsed include abdominal pain, nausea and vomiting. Immunofluorescence microscopy reveals that 12 of the children are positive for *Cryptosporidium*.

What is the most likely route of transmission of this parasite and how can these infections be prevented?

Contributors: Sarah Jaroudi, Cassie Kruczek, Alan Peiris

Answer:
The children may have come into contact with the same body of contaminated water, most likely a swimming pool. The disease is spread via a fecal-oral route in humans and animals or via contaminated water or food and has a low infectious dose. The oocyst stage of *Cryptosporidium* is resistant to routine chlorine disinfection of pools allowing it to remain for 10 days or longer. Accidental ingestion of the oocysts (infectious stage) leads to infection. Outbreaks can be prevented by super chlorinating swimming pools known to be infected. Diarrhea remains the second leading cause of mortality among children in developing countries.

If a child has diarrhea and is diagnosed with *Cryptosporidium*, they should stay out of swimming pools for at least 2 weeks after the diarrhea stops due to prolonged shedding of oocysts in the stool. *Cryptosporidium* has a seasonal pattern and is more common in warm and rainy months. Immunocompetent hosts in developed countries can be asymptomatic or may show self limiting signs of watery diarrhea. Children under the age of 2 and people with HIV/AIDS or those immunocompromised are at a higher risk of infection. *Cryptosporidium* may also occur more frequently in patients with colon cancer. Both asymptomatic and symptomatic disease has been associated with growth delays and malnutrition in children. Those with an ApoE E4 (apolipoprotein E4) allele may have some protection against these growth deficits. This is especially true in children who frequently experience diarrheal diseases. Expression of this gene is thought to increase cholesterol availability to the brain, while simultaneously limiting cholesterol availability to pathogens such as *Crytosporidium*, limiting the pathogen's ability to proliferate.

Cryptosporidium is second to rotavirus as the leading cause of moderate diarrhea in children under the age of 2 according to the Global Enteric MultiCenter Study. This parasite can also cause extraintestinal symptoms such as pancreatitis, cholangitis, or biliary tract disease and can cause respiratory distress in immunocompromised individuals. The gold standard for diagnosis in the US is immunofluorescent microscopy. This parasite can also be diagnosed with microscopy by a modified acid fast stain, antigen detection, or nucleic acid amplification. The only FDA approved treatment is nitazoxanide. Safety of this drug has not been proven for children under the age of 1. Other drugs that are used off label include azithromycin, paromomycin, and rifaximin. Those with HIV/AIDS should receive anti-retroviral therapy. Further research is being done to identify a vaccine that can provide a strong mucosal immune response.

Take Home Points

- Outbreaks of *Cryptosporidium* have been associated with contaminated swimming pools.
- Infection may cause growth delays in children, however the ApoE E4 allele has been found to be protective against these growth delays.
- The only FDA approved treatment is nitazoxanide.

References:

1. Checkley W, White AC, Jaganath D, Arrowood MJ, Chalmers RM, Chen XM, Fayer R, Griffiths JK, Guerrant RL, Hedstrom L, Huston CD, Kotloff KL, Kang G, Mead JR, Miller M, Petri Jr WA, Priest JW, Roos DS, Striepen B, Thompson RC, Ward HD, Van Voorhis WA, Xiao L, Zhu G, and Houpt ER. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. *Lancet Infect Dis*. 2015;15(1):85-94.

53: Calciphylaxis

Question:
A 65-year-old woman is referred for the presence of painful violaceous ulcers on her lower extremities. She has a history of chronic renal disease due to uncontrolled diabetes and has been on hemodialysis therapy for 6 years. She has been taking warfarin for a year for cardiovascular disease. Labs were as follows: serum calcium 7.6 mg/dL (normal 8.4-10.2 mg/dL), serum phosphorus 5.5 mg/dL (normal 3-4.5 mg/dL), serum albumin 3 g/dL (normal 3.5-5.5 g/dL), serum parathyroid hormone 220 pg/mL (normal 10-65 pg/mL). Her history and physical exam along with lab results point toward uremic calciphylaxis.

What important differential diagnosis should be considered here?

What role does sodium thiosulfate play in her treatment and what are other treatment modalities?

What else is sodium thiosulfate commonly used for?

Contributors: Sarah Jaroudi, Jannette M. Dufour, Alan Peiris

Answer:
Calciphylaxis is characterized by calcification in the arterioles and typically presents with painful ulcers as plaques or nodules that can progress to necrotic lesions. It commonly occurs in patients with hyperparathyroidism due to renal impairment. It may also be associated with long-term warfarin use, hypoalbuminemia, steroids and diabetes. Her ulcers look similar to warfarin induced skin necrosis which occurs due to a hypercoagulable state from protein C deficiency. She has been on warfarin for a year so warfarin-induced skin necrosis does not seem likely but given the presentation should be considered. A skin biopsy would confirm calciphylaxis with calcification of the arterioles and intimal hyperplasia. Microthrombi with fibrin deposits would be seen with warfarin-induced skin necrosis. They have varying treatments so correct identification is important.

Calciphylaxis has high rates of mortality due to sepsis prompting quick treatment. Goals are to prevent infection and to promote wound healing. Intravenous (IV) sodium thiosulfate can be given during her dialysis treatments and is the main therapeutic agent. Sodium thiosulfate is commonly known for its use as a treatment for cyanide poisoning. Its mechanism of action is not clearly understood. It may act as a chelator to form excretable calcium thiosulfate or assist with inhibition of calcification. Adverse effects include nausea, hypotension, and volume overload. Based on the severity of the wound, wound care or antibiotics may be warranted. Surgical debridement is controversial and is done on a case by case basis. Pain control should also be included in a treatment plan. Morphine, codeine and hydrocodone produce toxic metabolites that are renally excreted and are not recommended in this patient given her dialysis status. Methadone or fentanyl can be used since they have no active metabolites. Her electrolytes should be stabilized and her underlying secondary hyperparathyroidism needs to be addressed. If therapy fails, then a parathyroidectomy can be discussed with the patient. Lastly, she should be referred to a dietician to ensure she is receiving the appropriate nutrients and to address protein energy malnutrition. The risk vs benefit of continuing warfarin should be individualized for this patient and avoidance of calcium supplements or calcium based phosphate binders can be recommended.

Take Home Points

- Calciphylaxis can be seen in patients with secondary hyperparathyroidism due to renal impairment.
- It has a poor prognosis with high rates of morbidity and mortality.
- Treatment entails IV sodium thiosulfate, wound care, analgesics, and cinacalcet.

References:

1. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, Kamdar MM, Steele DJ, and Thadhani RI. Calciphylaxis: Risk Factors, Diagnosis, and Treatment. *Am J Kidney Dis*. 2015;66(1):133-146.

54: Dyspnea and Travel

Question:
A 35-year-old female with a past medical history of coronary artery disease (CAD), hypertension, and hypothyroidism presented to the emergency room with nausea, shortness of breath and a nonproductive cough. She stated that her cough began 2 months ago and has been intermittent since. Cough suppressants and over the counter medications do not provide relief. Associated symptoms include fever and chest pain. Her current medications are amlodipine, levothyroxine, and a statin. The patient presented with a temperature of 102ºF and 88% oxygen saturation. Her vitals were otherwise unremarkable. She has an 11 pack year smoking history and currently lives in her RV which she has been driving cross country. She recently visited her family friend in Northern California and came back from the trip three days ago. On examination, the patient had a headache and felt fatigued. She denied nausea, vomiting, changes in weight and bowel movements. The patient was wheezing and had an impaired mental capacity. Labs and imaging were unremarkable. A toxicology screen was negative. Chest X-ray, blood and urine cultures were unremarkable.

What is the next step?

Contributors: Anna Calara, Kandis Wright, Neha Mittal

Answer:
This case involves fatigue, headache, dry cough symptoms with negative labs, blood and urine cultures, and a chest X-ray. Important details to consider when examining this patient is her social history. When asked more about her drive, she mentioned that she drove from Delaware to California and made several stops along the way. High altitude pulmonary edema (HAPE) is hydrostatic edema that develops into a very serious pulmonary hypertension (PH) unresponsive to oxygen administration. Normally during high altitude ascent, oxygen administration can reverse the physiological increase in pulmonary artery pressure. With HAPE, it is hypothesized that susceptible individuals have constitutional abnormalities in their pulmonary vasculature, ventricular dysfunction or reduced vascular capacity. HAPE is diagnosed when a patient has 2 or more pulmonary symptoms and 2 or more signs classified using the Lake Louise acute mountain sickness scoring system. This system scores headache, gastrointestinal symptoms, fatigue, dizziness, sleep difficulty, changes in mental status, ataxia, and peripheral edema based on symptom severity. Symptoms of HAPE usually appear 1-4 days after arrival at more than 2,500 meters (8,200 feet) above sea level.

Risk factors include cold temperature, recent upper respiratory infection (URI), young age, normal residence at low altitude, and oral contraceptive use. Though this patient may not have been mountain hiking, a drive across country involves changes in elevation and high altitude sickness should be considered.

Take Home Points

- HAPE is diagnosed when a patient has 2 or more pulmonary symptoms and 2 or more signs classified using the Lake Louise acute mountain sickness scoring system.
- Symptoms of HAPE usually appear 1-4 days after arrival at more than 2,500 meters (8,200 feet) above sea level.

References:

1. Gupta RK, Himashree G, Singh K, Soree P, Desiraju K, Agrawal A, Ghosh D, Dass D, Reddy PK, Panjwani U, and Singh SB. Elevated pulmonary artery pressure and brain natriuretic peptide in high altitude pulmonary edema susceptible non-mountaineers. *Scientific Reports*. 2012;19(6): 21357.

55: Diabetes Medical Management and Lower Limb Amputation

Question:
A 67-year-old male with a past medical history of uncontrolled type 2 diabetes mellitus presents to the hospital with swelling and a 4 cm ulceration on the plantar surface of his right foot including his first two toes. He says that he did not notice the ulceration until his daughter pointed it out earlier this morning. The patient was prescribed metformin when he was first diagnosed with diabetes 15 years ago but lately his hemoglobin A1c (HbA1c) levels continue to rise and are not within target range, current HbA1c is 9.6%. The patient says he is very active and walks everywhere because he does not own a car. He has peripheral neuropathy and has had ulcers in the past but was able to prevent their progressions with proper treatment and supportive care. However, this time he did not notice the ulceration because of its location. Imaging studies confirm the presence of necrotic tissue and the need to amputate his first and second toe.

The patient is distraught after hearing the news and asks what is the best next step to properly manage his diabetes?

Contributors: Anna Calara, Neha Mittal, Jannette M. Dufour

Answer:
In patients with inadequate glycemic control with metformin monotherapy and lifestyle changes, the American Diabetes Association recommends that a second agent be added to their medication regimen. Favorable second lines of treatment include sulfonylurea, basal insulin, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist or sodium-glucose co-transporter 2 (SGLT2) inhibitors. The agent that is added depends on a number of factors, including patient's choice, costs, health insurance, disease progression and drug characteristics. The goal is to achieve optimal HbA1c with minimal side effects, especially hypoglycemia. If the HbA1c target is not reached in 3 months a third agent can be added.

Patients with peripheral neuropathy, vascular complications and infections have an increased risk of lower limb amputations. Preventive measures and management of diabetes complications such as foot ulcers include the examination of the patient's feet on a daily basis. The presence of peripheral neuropathy can make it difficult for the patient to notice ulcerations without proper examination. It is recommended to use a mirror to properly exam the plantar surface of the feet. Inter-digital spaces should be examined closely because this location is prone to fungal infections. Optimal glycemic control is advantageous to decrease the risk of lower limb amputations.

SGLT-2 inhibitors have a black box warning against patients with underlying foot ulcers, peripheral neuropathy, or previous amputations. Although causation has yet to be determined, these medications have been associated with a greater risk of lower limb (toe) amputations. SGLT-2 inhibitors block the reabsorption of glucose in the proximal tubules of the kidney and are suitable for patients with diabetes with high glucose levels despite being on medications such as metformin and insulin. Considering this patient's history of ulceration and peripheral neuropathy, it is advised that this patient not be prescribed SGLT-2 inhibitors as a part of his diabetes management.

Take Home Points

- SGLT-2 inhibitors have a black box warning against patients with underlying foot ulcers and peripheral neuropathy.
- Patient with the assistance of family members should use a mirror to properly exam the plantar surface of the feet daily.

References:

1. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes – 2018. *Diabetes Care* 2018;41 (Suppl.1):S73-S85.
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, and Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
3. US Food and Drug Administration. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). 2017. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf.

56: Hypertension and Gout

Question:
A 52-year-old male presents to the emergency room with pain, redness and swelling of his left toe. Past medical history is significant for hyperlipidemia and hypertension (HTN). His current medications include a statin and hydrochlorothiazide (HCTZ). He denies history of trauma and pain in his other joints. He says that he went to bed early last night after watching a football game with his friends and felt completely fine before falling asleep, but woke up this morning feeling like his toe was broken. He can barely stand and cannot walk. He says that he has had similar symptoms on his right elbow and wrist. On examination, he was found to have a temperature of 100.3ºF and blood pressure of 160/93. His left big toe is red, swollen, warm and tender to the touch. Lab studies show serum uric acid of 12.5 mg/dl and a 24 hour uric acid excretion of 320 mg. X ray shows bone erosions on the medial side of the first metatarsal. Synovial fluid contained needle shaped crystals that were negatively birefringent under polarized light confirming a positive diagnosis for gout.

What is an alternative medication to HCTZ to control the patient's HTN?

Which species of dog are well known to have Urate Uroliths?

Contributors: Anna Calara, Kandis Wright, Alan Peiris

Answer:
The next step is to treat his HTN with a medication that does not exacerbate his acute gout. HCTZ is known to cause hyperuricemia and can exacerbate gout. Losartan is an angiotensin II receptor blocker/antagonist (ARB) that works by blocking the binding of angiotensin II to type 1 angiotensin II (AT) receptors. Therefore, angiotensin II cannot act as a potent vasoconstrictor, increase salt and water retention, or signal for the release of antidiuretic hormone (ADH), which ultimately decreases blood pressure and water retention. Losartan is commonly used to treat hypertension and is often chosen over angiotensin converting enzyme (ACE) inhibitors in patients with ACE inhibitor intolerance with symptoms such as cough.

High dose salicylate, indomethacin, and losartan are also known to have secondary uricosuric effects by increasing urinary excretion of uric acid by inhibiting the urate transporter 1 (URAT1) anion exchanger in the proximal tubule of the kidney. This capability of losartan makes it an excellent candidate for treating hypertension over ACE inhibitors in patients with gout or renal dysfunction. No other ARBs, including candesartan and irbesartan, or ACE inhibitors with the same uricosuric effects as losartan have been reported. Increasing the losartan dose above 50 mg/daily has not been shown to have additional benefits on lowering uric acid levels.

For this patient, losartan should be used to treat his HTN and, in combination with his gout medications (such as allopurinol, febuxostat, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids), to help lower his uric acid levels.

Dalmation dogs have over a 100 fold increase in urate uroliths than other breeds. Male Dalmatians are much more likely (16x) to be affected with urate uroliths than females.

Take Home Points

- The uricosuric effect is an increase in urinary excretion of uric acid by inhibiting the urate transporter 1 (URAT1) anion exchanger in the proximal tubule of the kidney.
- High dose salicylate, indomethacin, and losartan have uricosuric effects.
- Drugs with uricosuric effects should be considered in patients with hypertension and acute gout or a high risk of developing gout.

References:

1. Wolff ML, Cruz JL, Vanderman AJ, and Brown JN. The effect of angiotensin II receptor blockers on hyperuricemia. *Therapeutic Advances in Chronic Disease*. 2015; 6(6): 339-346.
2. Bartges JW, Osborne CA, Lulich JP, Unger LK, Koehler LA, Bird KA, Clinton CW, Davenport MP. Prevalence of cystine and urate uroliths in bulldogs and urate uroliths in dalmatians. *J Am Vet Med Assoc*. 1994 Jun 15;204(12):1914-8.

57: Cellulitis Treatment and Patient Decline

Question:

A 72-year-old female presents to the emergency room with a two day history of fever, (100.9ºF today) diarrhea, and worsening agitation. Recently she was discharged from the hospital with treatment for severe cellulitis: linezolid 600 mg orally twice a day for 14 days and tramadol 50 mg orally every 6 hours as needed for the pain. She is on day 8 of her antibiotic regimen. Her past medical history includes type II diabetes with neuropathic pain for which she is on a long-acting insulin regimen and nortriptyline 75 mg orally nightly. She reports that she has been in pain and often takes her pain medication three to four times a day. Her family denies dietary changes and recent sick contacts, however, they do note that she had been nauseated from the antibiotic resulting in a visit to her primary care provider five days ago. They state she was given a nausea pill that helped her greatly and are seriously concerned by her recent decline.

What could be contributing to the patient's symptoms?

Contributors: Anna Calara, Kandis Wright, Shannon Rice, Neha Mittal

Answer:
This patient most likely has serotonin syndrome, a constellation of symptoms that result secondary to the use of serotonergic medications. These include hyperthermia, hyperreflexia, and altered mental status with agitated features as well as diarrhea, tremor, and sweating. If left untreated it can quickly become life-threatening leading to rhabdomyolysis and seizures, thus an early diagnosis is critical. Serotonin syndrome often does not occur secondary to the use of a single serotonergic agent alone, rather, the combination of multiple medications.

The elderly population is at increased risk for this adverse drug event. The combination of nortriptyline, her tricyclic antidepressant (TCA); tramadol, an opioid analgesic that inhibits serotonin reuptake; linezolid, a antibiotic with monoamine oxidase inhibiting (MAOI) properties; and what we assume to be promethazine, an antiemetic with serotonin modulation, have lead to her adverse symptoms. When considering serotonergic agents, linezolid and tramadol are often shadowed by more obvious medications such as TCAs, MAOIs, and other antidepressants. Hydrocodone has changed from Schedule III to Schedule II agent. Therefore one could expect an increase in tramadol (Schedule IV) usage and the likelihood of serotonin syndrome, due to less apparent serotonergic combinations that may arise. Recognizing these less known serotonergic drugs is critical in preventing the prescription of contraindicated drug combinations. To treat serotonin syndrome remove the causative agents, in this case the linezolid, tramadol, and promethazine. Additionally, you could consider altering the patient's neuropathic pain regimen to a non-serotonergic medication such as gabapentin. Supportive care also needs to be provided which includes intravenous fluid, external cooling, and, in some cases, benzodiazepines for hyperreflexia and hyperthermia. There is no evidence supporting traditional antipyretics such as acetaminophen or ibuprofen in serotonin syndrome as the mechanism of elevation is not related to central thermoregulation.

Take Home Points

- Serotonin syndrome is a constellation syndrome secondary to serotonergic overload and is treated by removing the causative agents and providing supportive care.
- Serotonin syndrome typically occurs due to use of multiple medications, rather than the overuse of one single agent.
- Some serotonergic medications and classes include: tramadol, linezolid, promethazine, selective serotonin reuptake inhibitors (SSRIs), TCAs, and MAO Inhibitors.

References:

1. Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician*. 2008;54(7):988-992.
2. Quinn DK, and Stern TA. Linezolid and serotonin syndrome. *Prim Care Companion J Clin Psychiatry*. 2009;11(6):353-356.
3. Beakley BD, Kaye AM, and Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: A review. *Pain Physician*. 2015;18(4):395-400.

58: Encephalopathy after Gastrectomy

Question:
A 55-year-old male presents to the hospital with persistent vomiting and confusion 6 months after a subtotal gastrectomy for gastric adenocarcinoma. He vomits 3-4 times a day and woke up this morning feeling dizzy and unable to walk to his bathroom. Symptoms began one week ago and are progressive. The patient denies abdominal pain, weight loss, changes in appetite and bowel movements. He has no history of past ulcers, diabetes mellitus, cholecystitis, and chronic alcohol consumption. Family history is unremarkable. Review of systems is negative for abdominal pain, fever or jaundice. The abdomen is soft and not tender to palpation. Incision from his prior surgery shows good healing. Neurological exam reveals vision impairment, nystagmus, and gait ataxia. He was prescribed folate, iron, and vitamin B12 supplements following his surgery and does not take other medications. He states that he has been eating pureed food that is low in carbohydrates for several months. The patient states that before adhering to this diet he would experience cramping and diarrhea. He no longer experiences these symptoms but remains concerned about his new symptoms and whether they are diet related.

What is an important diagnosis and next step to consider in this patient?

Contributors: Anna Calara, Kandis Wright, Shannon Rice, Neha Mittal

Answer:
Given his recent gastrointestinal surgery, it is important to monitor his nutrition and vitamin levels. The cessation of cramping and diarrhea signifies that his dumping syndrome (rapid gastric emptying) has been resolved. Despite not having a history of alcohol use, one should suspect Wernicke encephalopathy resulting from thiamine (vitamin B1) deficiency. Thiamine is an essential water soluble vitamin found in meats, including pork and fish, whole grains, seeds, and breads that have been supplemented. It is a crucial vitamin needed for cell metabolism as it is a cofactor in dehydrogenase enzyme reactions in the Krebs cycle and the pentose phosphate pathway.

The classic triad of symptoms associated with Wernicke encephalopathy include abnormal eye movements, sudden onset of ataxia, and loss of consciousness. The complete triad is only found in a minority of patients, commonly alcoholic patients, but it can also present in non-alcoholic patients. It can appear in non-alcoholic patients in many clinical settings, for instance in elderly patients, patients undergoing chemotherapy and prolonged therapeutic fasting, patients post- bariatric surgery, and patients with gastrointestinal tumors and acquired immunodeficiency syndrome. Diagnostic tests for Wernicke encephalopathy include a complete blood count (CBC), liver function tests (LFTs), blood thiamine levels, and magnetic resonance image (MRI) for involvement of mammillary bodies, the dorsal medial nucleus of the thalamus, and periaqueductal gray matter. It is important to identify whether the presenting symptoms are a result of thiamine deficiency because if so, the symptoms are reversible and can be alleviated with thiamine supplementation.

Take Home Points

- The classic triad of symptoms associated with Wernicke encephalopathy include abnormal eye movements, sudden onset of ataxia, and loss of consciousness.
- Wernicke encephalopathy can appear in patients with gastrointestinal tumors or acquired immunodeficiency syndrome, patients who have undergone prolonged therapeutic fasting, chemotherapy or bariatric surgery, and elderly patients.

References:

1. Santos Andrade CS, Tavares Lucato LT, Garca Morais Martin M, Marques-Dias MJ, Antonio Pezzi Portela L, Scarabotolo Gattas G, and Costa Leite C. Non-alcoholic Wernicke's encephalopathy: broadening the clinicoradiological spectrum. *Br J Radiol*. 2010;83(989):437-446.
2. Kennedy, DO. B Vitamins and the Brain: Mechanisms, Dose, and Efficacy- A Review. *Nutrients*. 2016; 8(68):1-29.

59: Altered fat distribution in HIV

Question:
A 24-year-old female with a past medical history of diabetes, hypertension and HIV presents to the hospital with hematuria, edema and generalized pain. She was diagnosed as HIV positive 1 year ago and has been receiving the highly active antiretroviral therapy (HAART) regimen of raltegravir, lamivudine, darunavir, and ritonavir. Her viral load and CD4 count are within the recommended controlled range. She complains of recent weight loss and of excess skin around her neck and abdomen. Her current medications include metformin, hydrochlorothiazides, and antiretroviral therapy. Her blood pressure is 180/110 mmHg. On physical exam she appears to have excess fat in her lower abdomen and extremities. Fundoscopic exam is positive for white yellow deposits. Fat deposition is symmetrical and localized to her lower body. Patient denies use of alcohol and says that she was born with normal body fat distribution at birth.

What tests should be ordered?

Contributors: Anna Calara, Gurvinder Kaur, Neha Mittal

Answer:
Lipodystrophy is the loss of adipose tissue, which may occur in combination with pathological accumulation of adipose tissue at other distinct regions of the body. It can be inherited or acquired and based on the pattern of fat loss, lipodystrophy is classified as generalized or partial. Lipodystrophy can also develop secondary to HIV medication such as antiretroviral protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs). Studies have demonstrated that PIs disrupt adipocyte differentiation by down-regulating several adipogenic transcription factors. NRTI induced lipodystrophy has been attributed to mitochondrial toxicity, characterized by loss of mitochondrial DNA content or mitochondrial DNA mutations. The diagnosis is usually made clinically.

Differentiating acquired causes of lipodystrophy can be challenging. It is important to order a urinalysis in patients presenting with lipodystrophy as approximately 20% of the patients diagnosed with lipodystrophy are also found to have membranoproliferative glomerulonephritis type II (MPGN II). Urinalysis can identify proteinuria hematuria, cellular casts, and can differentiate glomerulonephritis from other causes of lipodystrophy. An uncontrolled systemic activation of the alternative pathway of the complement cascade is associated with MPGN II pathophysiology. Specifically, the loss of complement regulation is caused by serum C3 nephritic factor (C3NeF), an autoantibody directed against C3 convertase of the alternative pathway of complement cascade. Majority of the patients with acquired partial lipodystrophy can be identified by low levels of C3 and presence of C3NeF. Additionally, HAART-associated lipodystrophy is linked to changes in adiponectin levels. Insulin sensitizers may have a helpful role with data suggesting that metformin is preferred to pioglitazone.

Take Home Points

- Lipodystrophy is the loss of adipose tissue that can be inherited or acquired secondary to causes such as HIV medication and membranoproliferative glomerulonephritis.
- Urinalysis of patient with glomerulonephritis will contain proteinuria hematuria, and cellular casts.
- HAART-associated lipodystrophy is associated with altered levels of adiponectin.

References:

1. Fiorenza CG, Chou SH, and Mantzoros CS. Lipodystrophy: Pathophysiology and Advances in Treatment. Nature Reviews. *Endocrinology*. 2011;7(3),137-150.
2. Appel GB, Cook HT, Hageman G, Jennette JC, Kashgarian M, Kirschfink M, Lambris JD, Lanning L, Lutz HU, Rose NR, Salant DJ, Sethi S, Smith RJ, Smoyer W, Tully HF, Tully SP, Walker P, Welsh M Wurzner R, and Zipfel PF. Membranoproliferative Glomerulonephritis Type II (Dense Deposit Disease): An Update. *JASN*. 2005;16(5),1392-1403.

60: Nocturnal Polyuria

Question:
A 63-year-old female with a past medical history of osteoporosis and hypothyroidism presents to the hospital with a chief complaint of urinary frequency, nocturnal polyuria and urinary incontinence. Patient states that the symptoms began 2 weeks ago and that she frequently does not make it to the bathroom in time. She says that she has not been able to sleep well for the past two weeks and averages around 4-5 hours of sleep per night because her sleep is frequently interrupted. She voids around 3-5 times per night. She denies any pain and changes in sexual behavior or bowel movements. Her current medications include levothyroxine and alendronate. Physical examination was unremarkable.

What is the likely diagnosis and treatment?

Contributors: Anna Calara, Jannette M. Dufour, Neha Mittal

Answer:
Nocturnal polyuria is defined as nocturnal urine output greater than 20% to 33% of 24-hour urine output. Nocturnal polyuria is often associated with overactive bladder syndrome or benign prostatic enlargement in males. However, many patients do not find relief when treated with the designated medication. Instead, nocturnal polyuria is thought to be caused by an abnormal circadian rhythmic secretion of the antidiuretic hormone, arginine vasopressin (AVP). It is thought to affect a large portion of the population but is often under reported due to the misconception of its relation to aging. Even though it occurs more frequently in older individuals, it can also occur in the young and is equally prevalent in men and women. Although it may be benign, nocturnal polyuria is a burden due to disrupted sleep and social anxiety.

Studies have shown that nocturia can be treated with desmopressin, a synthetic analog for AVP. Desmopressin is a V2 receptor agonist. It is the therapy of choice and has a fast onset of action. It should be noted that there is a gender difference in the optimal prescribed dose. Adverse side effects include headache, hyponatremia, nausea and abdominal pain. These adverse effects are rare and tend to affect the older population. Awareness of nocturnal polyuria as its own syndrome rather than one caused by aging is important in helping patients realize that there is a treatment for this condition and that their sleep/social burden can be easily lifted. Other causes of nocturnal polyuria such as hyperglycemia, shifts in extracellular fluid on recumbency and an association with sleep apnea need consideration.

Take Home Points

- Nocturnal polyuria is thought to be caused by an abnormal circadian rhythmic secretion of the antidiuretic hormone, AVP.
- Treatment of choice for nocturia is desmopressin, a synthetic analog for AVP.

References:

1. Sand PK, Dmochowski RR, Reddy J, and van der Meulen EA. Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Women with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study. *The Journal of Urology*. 2013; 190:958-964.
2. Van Kerrebroeck P, Hashim H, Holm-Larsen T, Robinson D, and Stanley N. Thinking beyond the bladder: antidiuretic treatment of nocturia. *Int J Clin Pract*. 2010;64:807-816.

61: Postprandial Hypotension

Question:
A 74-year-old woman with a past medical history of hypertension, gastroesophageal reflux disease (GERD), hypothyroidism and obstructive sleep apnea presents to the hospital following a syncopal episode. Patient states that she was watching TV on her couch and just "passed out." She is accompanied by her son. He insisted his mother come because she has had 3 syncopal episodes in the past 2 weeks. He says that her second syncopal episode happened while she was standing and she may have fallen if she had been alone. He is worried that she is at risk of falling and is concerned about her. Her current medications include lisinopril, famotidine, and levothyroxine. Physical examination revealed a blood pressure of 140/80. Evaluation and tests eliminated cardiac causes and the patient was discharged with an ambulatory blood pressure monitor. During her follow up appointment, her monitor indicated that her syncopal episodes occur within 2 hours following a meal.

What is the diagnosis and best course of treatment?

Contributors: Anna Calara, Jannette M. Dufour, Neha Mittal

Answer:
Postprandial hypotension is a decrease in systolic blood pressure by 20 mmHg within 1 to 2 hours of eating a meal. Symptoms include syncope, dizziness, falls, weakness, coronary events and stroke. Risk factors include certain medications (diuretics or use of multiple drugs), premeal lower blood pressure, meal composition (high in carbohydrates), meal timing (breakfast and lunch), temperature of food (warm over cold), and comorbid conditions (Parkinson's disease, diabetes mellitus, hypertension). The mechanism for postprandial hypotension is not clear although it has been associated with a decreased sympathetic response to hypotension. There is no current treatment of choice for postprandial hypotension. Instead there are non-pharmacological recommendations such as drinking water before meals, administering hypotensive medications between rather than during meals, lying down in a semi-recumbent position for 90 minutes following a meal, and encouraging more frequent small meals with limited carbohydrates.

It is advised to first attempt the non-pharmacological means of treatment under the supervision of a primary care physician. It may also be worth discontinuing lisinopril with observation of subsequent blood pressure.

Take Home Points

- Postprandial hypotension is a decrease in systolic blood pressure by 20 mmHg within 1 to 2 hours of eating a meal.
- The mechanism of postprandial hypotension is not clear and nonpharmacological recommendations are currently the first line of treatment.

References:

1. Jansen RWMM, and Lipsitz LA. Postprandial Hypotension: Epidemiology, Pathophysiology, and Clinical Management. *Ann Intern Med*. 1995;122:286-295.
2. Luciano GL, Brennan MJ, and Rothberg MB. Postprandial Hypotension. *The American Journal of Medicine*. 2010;123(281):e1-281.e6

62: Novel Approach to Assessing Renal Function

Question:
A 35-year-old female with a past medical history of type 2 diabetes mellitus and hypertension presents to the hospital with complaints of pruritus, lethargy, fatigue, and bilateral lower extremity edema. Associated symptoms include nausea and vomiting. The swelling began 4 weeks ago, and the patient denies arthralgia, joint swelling and skin rash. Current medications include metformin, furosemide and ibuprofen as needed. Her blood pressure is 170/90 mmHg, heart rate is 95 beats per minute, and respiratory rate is 24 breaths per minute. Physical exam is remarkable for 3+ lower extremity edema up to her midcalf. No petechiae or purpura is present.

What tests should be ordered?

Contributors: Anna Calara, Sneha Raju, Gurvinder Kaur, Neha Mittal

Answer:
Diabetes mellitus accounts for 30% of glomerular disease. Hyperglycemia induced vascular dysfunction is primarily associated with the onset of diabetic nephropathy. Hypertension and genetic predisposition are other risk factors for the development of diabetic nephropathy. Lethargy, nausea, vomiting, fatigue, and pruritus are common symptoms of uremia which increases suspicion of renal disease. Glomerular filtration rate (GFR) is the clinician's primary window to assess kidney function, used to manage chronic kidney disease as well as recognize acute kidney injury. Serum creatinine has long been the most practical way to measure GFR. However, clinicians must be wary of using creatinine this way, as creatinine levels can vary based on age, sex, race, muscle mass, and diet.

Cystatin C is a marker that is being studied to replace creatinine as a measure of GFR. Additionally, Cystatin C is considered as a useful marker to detect early renal impairment in type 2 diabetic patients as it reflects both a decrease in GFR and an increase in albumin to creatinine ratio. Unlike creatinine, cystatin C is a protein that is produced at a stable rate in the body independent of age or muscle mass. Cystatin C is thought to estimate GFR more closely than serum creatinine. Serum creatinine can remain unchanged until GFR falls moderately, creating a delay in detection of acute kidney injury, while cystatin C levels are more sensitive to GFR changes. Using serum cystatin C instead of serum creatinine may therefore lead to earlier detection and therapeutic intervention of acute kidney injury or changes in chronic kidney disease. Serum cystatin C is not yet being used routinely as a marker of renal function due to increased cost of the test and the lack of availability of cystatin C assay. Equations using both creatinine and Cystatin C may facilitate better monitoring of renal function.

Take Home Points

- Cystatin C is a protein that is produced at a stable rate in the body independent of age or muscle mass.
- Cystatin C is a marker that is being studied to replace creatinine as a measure of GFR, and therefore, of kidney function because it is more sensitive to GFR changes.

References:

1. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce 3rd RD, Zhang YL, Greene T, and Levey AS. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008;51(3):395–406.
2. Jeon YL, Kim MH, Lee WI and Kang SY. Cystatin C as an early marker of diabetic nephropathy in patients with type 2 diabetes. *Clin Lab*. 2013;59(11-12):1221-1229.

63: Syncope and Bradycardia

Question:
A 65-year-old male with a past medical history of diabetes and hypertension presented to the hospital with sudden onset of weakness, palpitations and dizziness. The patient stated that he was at home when he suddenly "passed out" and does not remember what happened. He did not experience any symptoms prior to passing out suddenly. The patient's past medical history and family history are unremarkable. He doesn't take any prescription medications and takes over the counter aspirin for occasional headaches. On admission, he complained of substernal chest pain that did not radiate and was not associated with deep breaths or eating. His heart rate was 80 beats per minute. He had unremarkable orthostatic BP findings. A stress EKG was unremarkable. The patient was discharged and given a Holter monitor for 24 hours that later revealed bradycardia.

What diagnosis should be considered in this patient?

Contributors: Anna Calara, Cassie Kruczek, Neha Mital

Answer:
Sick sinus syndrome (SSS) should be considered in patients with syncope and unexplained palpitations. It is thought to arise due to degeneration of nodal tissue resulting in nodal depression or failure. Diagnosing this syndrome can be challenging since it involves a broad spectrum of diagnoses that revolve around sinus node dysfunction but can present with a normal EKG. These are classified under three main categories: sinus bradycardia, tachycardia and bradycardia-tachycardia.

A hallmark feature of SSS is when the heart does not respond to exertional stimuli. It is commonly found in the elderly and, if symptomatic, treatment often involves pacemaker implantation. Additionally, patients with amyloidosis, connective tissue disorders, Chagas disease, and hemochromatosis have an inherent risk of developing SSS due to cardiac damage. Development of this condition is also associated with the use of certain pharmaceutical agents, including several cardiac drugs such as beta-blockers, calcium channel blockers, and antiarrhythmics. It is also important to note that patients with SSS are at a great risk for developing atrial fibrillation. Persistence of syncope after placement of an appropriately functioning pacemaker indicates poor prognosis and need for close surveillance.

Take Home Points

- SSS is classified under three main categories: sinus bradycardia, tachycardia and bradycardia-tachycardia.
- Development of this condition is also associated with the use of certain pharmaceutical agents, including several cardiac drugs such as beta-blockers, calcium channel blockers, and antiarrhythmics.

<u>References:</u>

1. Keller KB, and Lemberg L. The sick sinus syndrome. *Am J of Crit Care*. 2006;15(2):226-229.
2. Walsh-Irwin C, and Hannibal GB. Sick Sinus Syndrome. *AACN Adv Crit Care*. 2015;26(4):376-80.

64: Beer!

Question:
A 63-year-old male with a history of chronic alcohol abuse, alcoholic liver cirrhosis, and chronic obstructive pulmonary disease presented to the emergency room for altered mental status. He complained of weakness and fatigue and was accompanied by his 32-year-old son who said that the patient increased his alcohol intake during the past 2 days. He normally drinks 12-24 beers per day, but he started to binge drink after he found out that his wife had been cheating on him. He tried to quit drinking 4 years ago and experienced alcohol withdrawal seizures and tremors. On examination, he presented with slurred speech and short term memory loss. Serum sodium level was abnormally low at 110 mEq/L using an ion specific electrode. The patient also presented with hypokalemia and low blood urea nitrogen level. Urinalysis, blood tests and a toxicology screen were ordered.

What is the diagnosis and treatment course?

Contributors: Anna Calara, Cassie Kruczek, Neha Mittal

Answer:
The use of an ion specific electrode usually excludes pseudohyponatremia. The patient is most likely suffering from potomania. Symptoms of potomania include weakness, altered mental status, gait disturbance, headache, edema and seizures. Patients with a history of chronic beer drinking tend to also consume a poor diet. Beer contains low protein and electrolyte concentrations and due to the high levels of carbohydrates the body derives energy from non-protein sources (protein/amino acid sparing effect). This results in reduced blood urea nitrogen concentration and urea excretion. In this case, the recent history of binge drinking may have caused hyponatremia which precipitated the altered mental status. The overall low osmolarity intake results in an excess electrolyte-free water that suppresses the activation of anti-diuretic hormone (ADH). Low ADH levels result in diuresis found in these patients when presented with solutes.

Rapid correction of this hyponatremia can lead to osmotic demyelination syndrome. Oligodendrocytes are sensitive to increases in sodium. The rapid increase in osmolarity damages oligodendrocytes, leading to loss of myelin that can cause widespread neurological disturbances. This demyelination reaction leads to central pontine myelinolysis (osmotic demyelination syndrome), a disorder that arises 2-6 days after rapid correction of hyponatremia. This condition clinically presents as dyspnea, dysarthria and ataxia and is best avoided by ensuring that plasma sodium concentration does not rise by more than 8 mmol/L per day. Additionally, patient's fluids should be restricted and their urine output and serum sodium levels should be heavily monitored. Physicians must also keep in mind alcohol withdrawal syndrome which may present as restlessness, headaches, nausea, tremors, anxiety, hallucinations and seizures. Recommended correctional therapy for hyponatremia in beer potomania includes, nothing through the mouth (NPO) for 24 hours, check serum sodium levels every two hours, give intravenous (IV) medications judiciously aiming to increase sodium < 10 mEq/L in the first 24 hours and then <18 mEq/L in the first 48 hours. Additionally, patient education and alcohol use counseling is recommended. Other issues that need attention include hepatic encephalopathy, thiamine and magnesium status.

Take Home Points

- Beer contains low protein and electrolyte concentrations. Its protein sparing effect, referring to the body's use of the beer's carbohydrates as opposed to proteins/amino acids for energy, results in reduced blood urea nitrogen concentration and urea excretion.
- Avoid central pontine myelinosis by ensuring that plasma sodium concentration does not rise by more than 8 mmol/L per day.

References:

1. Lodhi MU, Saleem TS, Kuzel AR, Khan D, Syed IA, Rahim U, Iqal HI, and Rahim M. "Beer Potomania" – A Syndrome of Severe Hyponatremia with Unique Pathophysiology: Case Studies and Literature Review. *Cureus*. 2017;9(12):e2000.
2. Sanghvi SR, Kellerman PS, and Nanovic L. Beer potomania: an unusual cause of hyponatremia at high risk of complications from rapid correction. *Am J Kidney Dis*. 2007;50:673–680.

65: Chronic Cough in Adults

Question:
A 45-year-old man presents to the hospital with complaints of cough and vomiting. The patient states that the cough has been present for the past month and denies fever and changes in appetite. He is accompanied by his wife who confirms that the quality of the cough is unremarkable, but that the cough has been persistent and often precedes the vomiting. The patient is currently not taking any medications and has no past medical history. He denies smoking, alcohol, and drug use. The patient does not recall receiving any vaccinations since reaching adulthood.

What is the most likely diagnosis?

Contributors: Anna Calara, Cassie Kruczek, Alan Peiris

Answer:
Bordetella pertussis is a gram negative coccobacillus. Infection with this organism initially presents as an upper respiratory tract infection followed by the development of a severe persistent cough. *B. pertussis* produces multiple toxins that induce coughing in the patient. Coughing fits are violent and can result in a struggle to regain breath after an episode, described as "whooping cough." This infection spreads via respiratory droplets and can be prevented by the TDaP (tetanus, diphtheria toxoids and acellular pertussis) vaccination (DTaP for children). The CDC recommends that adults receive a TDaP booster every 10 years to prevent immunity from waning.

The clinical manifestation is categorized into 3 phases: catarrhal, paroxysmal and convalescent. The catarrhal phase is clinically similar to an acute viral upper respiratory tract infection and lasts for 1-2 weeks. The progression to paroxysmal phase occurs when coughing episodes are present. These episodes are usually accompanied with swelling, sweats, and post-tussive emesis. The transition to convalescent phase occurs when the persistence and severity of the cough resides after 2-3 months. This infection is commonly found in unvaccinated children. It is recommended that pregnant women during the third trimester, as well as those caring for the child receive a booster TDaP vaccine to prevent transmission to the infant. Treatment consists of supportive and antibiotic therapy with macrolides such as azithromycin.

In adult patients, whooping or post-tussive vomiting should raise pertussis as a potential diagnosis. The lack of a paroxysmal cough or the presence of fever makes pertussis unlikely. Post-tussive vomiting is much less helpful as a clinical diagnostic test in children.

Take Home Points

- The CDC recommends that adults receive a TDaP booster every 10 years to prevent immunity from waning.
- It is recommended that pregnant women during the third trimester, as well as those who will be caring for the child, receive a booster TDaP vaccine to prevent transmission to the infant.

References:

1. Teepe J, Broekhuizen BD, Ieven M, Loens K, Huygen K, Kretzschmar M, de Melker H, Butler CC, Little P, Stuart B, Coenen S, Goossens H, and Vergeij TJ. Prevalence, diagnosis, and disease course of pertussis in adults with acute cough: a prospective, observational study in primary care. The British *Journal of General Practice*. 2015;65(639):e662-e667.
2. Philipson K, Goodyear-Smith F, Grant CC, Chong A, Turner N, and Stewart J. When is acute persistent cough in school-age children and adults whooping cough? A prospective case series study. *Br J Gen Pract*. 2013;63(613):e573-579.

66: Treatment of Chronic Low Back Pain

Question:
A 46-year-old male with a past medical history of migraines presents to the hospital with complaints of chronic lower back pain that started a year ago after heavy lifting. He says that the pain is constant and describes it as a stiff pain that is aggravated by exercise or prolonged immobile periods. On examination, his range of motion was noticeably restricted. His current medications include acetaminophen 500 mg and ibuprofen 400 mg as needed. He has gained 10 pounds since his last visit due to his reduced activity. Patient denies fever, sensory loss and changes in bowel movements. He has been prescribed tramadol and duloxetine in the past but states that they did not provide him any pain relief. Patient has a family history of drug addiction and does not want to be prescribed opioids. His sister is prescribed gabapentin for her fibromyalgia and he was wondering whether this medication might provide him some relief.

What is the next best step?

Contributors: Anna Calara, Jannette M. Dufour, Alan Peiris

Answer:
Chronic back pain is a common presenting symptom to physicians. Patients with chronic back pain should be referred for physiotherapy after exclusion of compressive neurologic manifestations through an initial physical examination. Imaging is generally not required in the presence of a normal examination. Yoga or Pilates may also have a beneficial effect if done under supervision on a carefully selected and monitored basis.

Acute discomfort may merit pharmacological treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), which could be followed by tramadol or duloxetine. Traditionally, opioids are then considered when patients fail to benefit from the first and second line of treatment. In the midst of an opioid epidemic, there has been a recent increase in prescribing gabapentinoids such as pregabalin (Lyrica) and gabapentin (Neurontin) for chronic lower back pain. Pregabalin and gabapentin are medications used to manage postherpetic neuralgia and neuropathic pain. They are neurotransmitter gamma-aminobutyric acid (GABA) analogs that inhibit $\alpha_2\delta$ subunit-containing voltage-dependent calcium channels. While some patient with neuropathic pain may have improvement with these medications gabapentinoids may not be associated with significant improvement in all such patients and may have an increased risk of adverse events.

Take Home Points

- Pregabalin and gabapentin are anticonvulsant medications used to manage chronic pain, postherpetic neuralgia, and neuropathic pain.
- Gabapentinoids that do not result in significant pain improvement should be discontinued over a period of time.

References:

1. Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, Thabane L, Devereaux PJ, and Bhandari M. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2017;14(8):e1002369.

67: Penile Pain

Question:
A 55-year-old male presents to the hospital complaining of penile pain during erection after being administered erectile dysfunction medication. He says that he does not experience pain when his penis is flaccid. He also noticed that his penis deviates to the left. He says that the deviation makes it difficult to penetrate during sexual intercourse and is not sure when the deviation first appeared or what caused it. He denies recent trauma, weight loss, previous pelvic surgeries, and relevant family history. The patient is currently not taking any medications. Physical examination reveals that the testes are soft on palpation. The noted curvature was examined and measured as a 34 degree deviation. The examination was positive for a palpable penile plaque on the dorsal surface at the distal third of the penis. Examination of his extremities was unremarkable.

What is the best course of treatment?

Contributors: Anna Calara, Kandis Wright, Shannon Rice, Alan Peiris

Answer:
Peyronie's disease is a connective tissue disorder in which fibrous scars form in the tunica albuginea on the corpus cavernosum of the dorsal penile surface. This disorder is usually found in men between the ages of 40-60 years and is often described as an abnormal curvature or shortening of the penis with erection. The disorder usually presents as pain both at rest and during erection, impairment of erection, and difficulties with sexual intercourse. Etiologies include autoimmune conditions, trauma, and genetics. Penile scarring and plaque formation are believed to be caused by inflammatory responses including the development of reactive oxygen species, release of transforming growth factor B, and deposition of excess collagen and fibrin. However the underlying pathophysiology warrants further investigation.

The diagnosis is made with clinical findings and can be confirmed by ultrasound. Treatment for Peyronie's disease can be classified into two categories: surgical and nonsurgical. Collagenase Clostridium histolyticum (CCh) is the only Food and Drug Administration (FDA) approved nonsurgical treatment as it is an enzyme capable of degrading interstitial collagen. In a study conducted in 2013, it was found that men treated with CCh and standard penile modeling (gently straightening the penis) showed a 34% penile curvature improvement compared to 18.2% in the placebo group. Additionally, intra-lesional verapamil and interferon-alpha-2B remain off label treatments. Surgical treatments, the gold standard for patients in the chronic phase of the disease, include penile shortening procedures and penile prosthesis implantation.

Take Home Points

- Peyronie's disease is a disorder that is usually found in men between the ages of 40-60 years and is often described as an abnormal curvature or shortening of the penis with erection.
- Collagenase Clostridium histolyticum (CCh) is the only FDA approved nonsurgical treatment. It is an enzyme capable of degrading interstitial collagens.
- The gold standard treatment for patients with chronic peyronie's disease is surgical intervention. However, protracted postoperative rehabilitation can be anticipated and the procedures do carry significant risks.

References:

1. Gelbard M, Goldstein I, Wayne Hellstrom JG, McMahon CG, Smith T, Tursi J, Jones N, Kaufman GJ, and Carson CC. Clinical Efficacy, Safety, Tolerability of Collagenase Clostridium Histolyticum for the treatment of Peyronie Disease in 2 Large Double-Blind, Randomized, Placebo Controlled Phase 3 Studies. *Sexual Function/Infertility*. 2013;190:199-207.
2. Yafi FA, Pinsky R, Sangkum P, and Hellstrom JG. Therapeutic advances in the treatment of Peyronie's disease. *Andrology*. 2015;3:650-660.

68: Recurrent Upper Respiratory Tract Infections

Question:
64-year-old female presents in the ER complaining of recurrent fevers, upper respiratory tract infection and sinusitis. Her fevers have been ongoing for 2 months and usually last 2-3 days. Past medical history is notable for rheumatoid arthritis and anemia, both of which are well-managed. Her current medications include prednisone and sulfasalazine. She has a family history of coronary artery disease and hypertension. She currently works for a plumbing company and has been employed with them for 12 years. Vital signs showed a temperature of 103.3°F. Review of systems was unremarkable, except for those mentioned in the patient history and physical examination. Physical exam revealed tenderness to palpation of lower abdomen, normal active bowel sounds in all four quadrants, and splenomegaly. She was also positive for subcutaneous rheumatoid nodules and negative for synovitis. At admission, the white blood cell count, hemoglobin, and hematocrit were low. Elevated rheumatoid factor, antinuclear antibody, anti-histone, and anti-Granulocyte-Colony Stimulating Factor (GCSF) antibodies were noted. Bone marrow biopsy revealed normal myeloid cellularity. Blood and bone marrow immunophenotyping was unremarkable.

What is the diagnosis and treatment?

Contributors: Anna Calara, Cassie Kruczek, Alan Peiris

Answer:
Felty's Syndrome (FS) is a triad of rheumatoid arthritis, neutropenia and splenomegaly. The pathogenesis of FS is largely unknown, however, studies suggest it may arise due to chronic inflammation in genetically predisposed individuals. While it is unclear if the condition is truly heritable, several familial cases of FS have been observed along with a strong HLA-DR4 allele association. This diagnosis should be considered in patients with complicated rheumatoid arthritis. The complete triad is not required to diagnose FS. However, neutropenia is required for diagnosis and the criteria is an absolute neutrophil count below 2000/μL.The low neutrophil count predisposes patients to developing bacterial infections. Her prednisone use also accentuates the susceptibility to infection.

The first line of treatment for FS is a non-biologic disease modifying antirheumatic drug (DMARD) such as methotrexate. If symptoms do not improve, prednisone is added to the regime. Rituximab is a chimeric monoclonal antibody specific for human CD20 that targets B lymphocytes. It has proven to be effective in increasing the absolute neutrophil count and is considered a second treatment of choice following methotrexate. For patients with low neutrophil counts that frequently acquire infections despite treatment with first line drugs, GCSF has been shown to effectively reduce infection rates. Antibodies to GCSF and IL-3 are rare in patients with FS. The presence of neutralising anti-IL3 antibodies may contribute to the development of cytopenia. It should also be noted sulfasalazine can rarely induce neutropenia or agranulocytosis.

Take Home Points

- FS is a triad of rheumatoid arthritis, neutropenia and splenomegaly.
- Rituximab is a chimeric monoclonal antibody specific for human CD20 that targets B lymphocytes and has proven to be effective in increasing the absolute neutrophil count. It is a second treatment of choice following methotrexate.

References:

1. Owlia MB, Newman K, and Akhtari M. Felty's Syndrome, Insights and Updates. *The Open Rheumatology Journal*. 2014;8:129–136.
2. Campion G, Maddison PJ, Goulding N, James I, Ahern MJ, Watt I, and Sansom D. The Felty syndrome: a case-matched study of clinical manifestations and outcome, serologic features, and immunogenetic associations. *Medicine*. 1990;69(2):69-80.

69: Andropause

Question:
A 66-year-old male with a past medical history of diabetes presents to the clinic with complaints of fatigue, low concentration, and depression. He says that he has not been enjoying activities he used to enjoy as much and finds himself sleeping 10 hours every night. He has been feeling this way for the past month and scheduled an appointment when he realized that he has been displaying low energy and endurance at his job. He is a mechanic and finds himself becoming tired more easily. He has increasing joint pains in his hands which he attributes to his occupation. He also mentions that he has had a decrease in libido and erectile dysfunction. He denies use of opiates, marijuana, alcohol, and steroids. Lab tests were ordered and revealed high luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and low testosterone levels.

What is the next best step?

Contributors: Anna Calara, Kandis Wright, Alan Peiris

Answer:
Andropause is a term used to describe men older than age 65 years with late onset hypogonadism (LOH). LOH pathogenesis is either due to primary testicular failure (low Testosterone [T], high Luteinzing hormone [LH]) or secondary hypothalamic-pituitary axis failure (low T, low or normal LH). The diagnosis is based on the presence of low serum testosterone levels and clinical symptoms. Normal total testosterone levels range from 300 to 1000 ng/dL. Free testosterone levels lower than 220–345 pmol/L are considered abnormal. Caution should be used when interpreting calculated free testosterone levels. Clinical symptoms include both sexual symptoms such as decreased libido and erectile dysfunction, and nonsexual symptoms such as fatigue and poor concentration.. The nonspecific symptoms and the variable testosterone levels can make diagnosing late onset hypogonadism difficult. Some of this patients symptoms may also reflect undiagnosed sleep apnea and vitamin D deficiency. Given history of diabetes and joint pains in his hands it would be worth considering hemochromatosis. Iron can also be deposited in the testes or pituitary giving hypogonadism. Rarely, Peliosis, a lesion characterized by blood-filled cysts, usually in the liver (peliosis hepatis) has been reported with the use of androgenic-anabolic steroids and testosterone.

The European Male Ageing Study recently defined the strict diagnostic criteria for LOH to include the simultaneous presence of reproducibly low serum T and three sexual symptoms (erectile dysfunction, reduced frequency of sexual thoughts, and morning erections). LOH, also referred to as “Low T syndrome” or “Andropause,” is treated with testosterone replacement therapy (TRT). However, the use of TRT is undergoing debate due to limited research on the efficacy and risk in older males. The preferred route of TRT is through transdermal testosterone preparations. Other routes of application include intramuscular injections, transdermal gels/patches and buccal administration. Potential complications include erythrocytosis, subclinical prostate cancer exacerbation, infertility, and male pattern baldness, liver function test abnormalities. TRT is contraindicated in men with prostate cancer. It is important for the patient’s testosterone levels, hematocrit, liver function and prostrate specific antigen to be monitored regularly while on testosterone therapy. Periodic digital rectal examination can also be considered while on testosterone therapy.

Take Home Points

- The European Male Ageing study recently defined the strict diagnostic criteria for LOH to include the simultaneous presence of reproducibly low serum T and three sexual symptoms (erectile dysfunction, reduced frequency of sexual thoughts, and morning erections).
- Use of Testosterone Replacement Therapy (TRT) is undergoing debate due to limited research on the efficacy and risk in older males.
- The testosterone levels, hematocrit, liver function and prostrate specific antigen need to be monitored regularly in men receiving TRT.

References:

1. McBride JA, Carson CC, and Coward RM. Testosterone deficiency in the aging male. Therapeutic *Advances in Urology*. 2016;8(1):47-60.
2. Dimopoulou C, Ceausu I, Depypere H, Lambrinoudaki I, Mueck A, Perez-Lopez FR, Rees M, van der Schouw YT, Senturk LM, Simonsini T, Stevenson JC, Stute P, and Goulis DG. EMAS position statement: Testosterone replacement therapy in the aging male. *Maturitas*. 2016;84:94-9.

70: Chronic Urticaria

Question:
A 34-year-old female presents to the emergency room with pruritic urticarial lesions on her chest, back and abdomen. The lesions are pale pink and are surrounded with erythema. She states that they vary in size and have been present for seven weeks. She does not recall the timing of onset or potential triggers. She says that she has never experienced this before and her past medical history is negative for allergies and inflammatory, autoimmune, and psychiatric disorders. Associated symptoms include joint pain, headache, and fatigue. When asked about her sleep, she reports that since she first noticed the lesions, she has had difficulty falling asleep and frequently gets up in the middle of the night. A complete blood count (CBC), comprehensive metabolic panel, erythrocyte sedimentation rate (ESR), thyroid stimulating hormone (TSH), and C-reactive protein (CRP) were found to be unremarkable. No identifiable causes were found.

What is the next best step in managing this patient?

Contributors: Anna Calara, Kandis Wright, Alan Peiris

Answer:
Chronic urticaria is the presence of recurrent urticaria, an inflammatory disease characterized by the development of angioedema, hives or both, for at least six weeks. It is a self-limiting disorder that usually lasts two to five years. In 80-90% of cases urticaria is idiopathic, otherwise it can be caused by allergens, autoimmune disorders, physical contact, infections, hormonal imbalances, metabolic conditions, neoplastic disorders, and psychological stress. In the dermis of the skin, histamine and other inflammatory mediators from mast cells and basophils are released after being triggered by immunoglobulin E (IgE). Complement activation and proteases from allergens have been proposed as additional non-IgE triggers. This diagnosis is made clinically and laboratory tests are ordered to rule out anaphylaxis. IgE receptor antibodies would be helpful in diagnosis and stopping any precipitating medications such as angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDS), and opiates are appropriate initial measures. Consulting an allergist will likely be beneficial.

The first step in management is avoidance of identified triggers. First line pharmacological treatment for chronic urticaria is second generation H1 antihistamines, including loratadine (Claritin), desloratadine (Clarinex), and cetirizine (Zyrtec). Second generation antihistamines are preferred over first generation antihistamines because they are longer acting, require less frequent dosages, and cause less adverse side effects. If second generation antihistamines provide insufficient control of symptoms, the dosage of the second generation antihistamine could be increased or a different second generation H2 antihistamine added. Leukotriene receptor antagonist may also have a role. If the symptoms remain uncontrolled, the third line of treatment is to add high potency antihistamines such as hydroxyzine or serotonin and norepinephrine reuptake inhibitor (SNRI) with a centrally antagonizing H1 receptor blocker doxepin. Omalizumab or cyclosporine can be tried for refractory urticaria.

Take Home Points

- Chronic urticaria is the recurrent development of angioedema, hives or both, for at least six weeks.
- First line pharmacological treatment for chronic urticaria is second generation H1 antihistamines.
- Add-on therapy with vitamin D3 4000 IU daily maybe an effective and safe immunomodulator and can assist with urticaria management

References:

1. Schaefer, P. Acute and Chronic Urticaria Evaluation and Treatment. *American Family Physician*. 2017; 95(11):717-724.
2. Darlenski R, Kazandjieva J, Zuberbier T, and Tsankov N. Chronic urticaria as a systemic disease. *Clinics in Dermatology*. 2014;32:420-423.

71: Neurological Abnormalities in Celiacs

Question:
A 14-year-old female presents to the emergency room with complaints of ataxia, distal symmetric sensory neuropathy, and migraines. She states that her symptoms have been progressing slowly. She has no relevant past medical history and was not taking any prescribed medications. Patient denies family history of ataxia. Associated symptoms include loose stools and weight loss for the previous 6 months. Patient denies a change in diet and physical activity level. Vital signs are within normal range. Clinical exam findings include loss of proprioception and a positive Romberg test. Pertinent negative clinical signs include lack of chorea and abnormal eye movements. Blood tests revealed elevated serum aminotransferases, but normal levels of calcium, vitamin B and E.

What is the next best step?

Contributors: Anna Calara, Cassie Kruczek, Alan Peiris

Answer:
This patient presents with neurological symptoms along with gastrointestinal symptoms that are suggestive of malabsorption. Patients with elevated serum aminotransferase levels and gastrointestinal symptoms should be assessed for celiac disease. Testing for celiac disease often begins with serological testing of celiac specific antibodies such as IgA anti-tissue transglutaminase antibody. If positive, upper endoscopy is then performed to obtain duodenal mucosal biopsies. Presence of villous atrophy, blunting of the villi, crypt hypertrophy and lymphocytic infiltration of the mucosa confirms the diagnosis of celiac disease. Gluten ataxia is a common neurological disturbance in celiac disease and is not directly correlated with intestinal manifestations or vitamin deficiency. Neurological manifestations can occur in non-celiac gluten sensitivity, a syndrome that is becoming increasingly recognized. Checking B12 levels are generally indicated in many neurological disorders and is especially relevant given malabsorption in this patient. Reversing B12 deficiency may improve neurologic deficits. In some cases of celiac disease, hypocupremia can occur and be associated with myelopathy.

Management for patients with celiac disease include a lifelong recommendation of a gluten free diet. It is recommended that patients avoid wheat, barley, rye, oats, and lactose to prevent adverse reactions. This diet restriction has been associated with decreased adverse gastrointestinal and neurological symptoms.

Take Home Points

- Neurological symptoms in patients with celiac disease are attributed to malabsorption.
- Nutrition complications include deficiencies in iron, folic acid, vitamin D, copper and vitamin B12.

<u>References:</u>

1. Nikpour S. Neurological manifestations, diagnosis, and treatment of celiac disease: A comprehensive review. *Iran J Neurol*. 2012;11(2):59-64.
2. Wierdsma NJ, van Bokhorst-de van der Schueren MA, Berkenpas M, Mulder CJ, and van Bodegraven AA. Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. *Nutrients*. 2013;5(10):3975-3992.

72: Fish Toxins

Question:
An anxious 57-year-old man presents to the emergency room in Key West, Florida feeling very ill. He reports that he is visiting from Oklahoma and has been camping beside the ocean and fishing for his food. Yesterday, he began to have nausea, diarrhea, and abdominal pain, for which he took anti-diarrheal medication. This morning, he woke up confused, and feeling itchiness, tingling, and numbness in his arms and legs. Physical exam shows an anxious, diaphoretic man with blood pressure of 96/57 and respiratory rate of 26. The patient requests diagnosis and treatment.

What diagnosis should the physician consider?

Contributors: Sneha Raju, Kandis Wright, Alan Peiris

Answer:
The patient's combination of gastrointestinal and neurologic symptoms along with history of seafood ingestion should raise clinical suspicion of ciguatera fish poisoning (CFP). Ciguatoxins, which cause this poisoning, are naturally occurring toxins made by the dinoflagellate species *Gambierdiscus* that live in coral reefs. These toxins are eaten along with algae by herbivorous fish, which are consumed by carnivorous fish, which then are eaten by humans. Ingestion of the toxin by fish results in metabolic bio-transformations that make the toxin overly potent, so only low concentrations are required to cause symptoms. Ciguatoxins mediate their effects by activating voltage-gated sodium channels in membranes, causing increased sodium ion permeability and nerve cell depolarization. Ciguatera is the most common marine food-borne illness worldwide. Ciguatera fish poisoning has an approximate incidence of 5.6 cases per 100,000 people. The highest incidence of CFP is in Hispanics, they were more likely to eat barracuda than non-Hispanics. The most common catch locations for CFP were the Bahamas and Florida Keys.

Typically, patients first develop gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain and later develop neurologic symptoms, which can include paresthesias, pruritus, myalgias, anxiety, and hallucinations. Many patients also report a reversal of temperature perception, where they perceive cold objects to be hot and hot objects to be cold. Cold allodynia has been reported with CFP. Fortunately, ciguatera fish poisoning is rarely fatal and patients recover after the initial illness, although they may continue to feel weak for weeks to months afterwards. However, death can occur in cases of cardiovascular shock or respiratory muscle paralysis, particularly in areas remote from medical care. Specifically, bradycardia and hypotension are caused by ciguatoxin inhibition of vasomotor centers innervated by the vagus nerve, which eliminates sympathetic tone needed to maintain normal cardiac rhythm and peripheral vascular resistance.

Many treatments have been tested, but regional differences in toxins and paucity of studies have limited the consensus on effective treatments. Intravenous mannitol is thought to be effective by reducing neuronal edema and possibly acting as a scavenger of free radicals produced by ciguatoxin. Symptomatic relief and supportive treatments are recommended, including fluid resuscitation, respiratory support, and cardiovascular monitoring.

Take Home Points

- Ingestion of ciguatoxins from ciguatera fish cause gastroinstestinal symptoms first, then neurological symptoms, which incude paresthesias, pruritus, myalgias, anxiety, and hallucinations.
- Ciguatera fish poisoning is rarely fatal.
- Symptomatic relief and supportiave treatments such as fluid resuscitation, respiratory support and cardiovascular monitoring are recommended.

<u>Resources:</u>

1. Friedman MA, Fleming LE, Fernandez M, Bienfang P, Schrank K, Dickey R, Bottein M-Y, Backer L, Ayyar R, Weisman R, Watkins S, Granade R, and Reich A. Ciguatera Fish Poisoning: Treatment, Prevention, and Management. *Mar Drugs*. 2008 Sep:693:456-479.
2. Seymour B, Andreosso A, and Seymour J. Chapter 7- Cardiovascular Toxicity from Marine Envenomation. *Heart and Toxins.* 2015;7.1:203-223.

73: Recurrent Pruritus

Question:
A 47-year-old female presents to your clinic with complaints of sudden, intense itching of her arms and abdomen while showering and occasionally while exercising. She denies any hives or wheals on her skin. She states she has had these symptoms for 3 years, but the antihistamines and topical creams have not helped her. She is extremely distressed and tells you this itching is affecting her life, as she can't enjoy summer activities with her family. She has reduced her daily showers to every other day as a result of her symptoms. She also admits to fatigue, dizziness, headaches and nocturnal sweating.

What is your plan for work-up and possible treatments?

Contributors: Sneha Raju, Cassie Kruczek, Alan Peiris

Answer:
Polycythemia vera (PV) is a myeloproliferative disorder characterized by neoplastic proliferation of primarily red blood cells. A mutation in the JAK2 gene leading to constitutive signaling that is believed to be involved in PV pathogenesis. PV typically has an indolent course with nonspecific symptoms. Aquagenic pruritus (AP) is a characteristic and often presenting symptom, occurring in around 40% of patients with PV. Incidentally, patients with PV presenting with AP are at a decreased risk of developing arterial thrombosis. AP is characterized by an intense itching, stinging, or burning feeling of the skin upon contact with water. In most patients, pruritus occurs on the chest, back, and proximal limbs, and is notably not associated with any visible changes on the skin. Contact with water is the most commonly described trigger for AP, but other triggers have also been reported, including sudden changes in temperature, sweating after exercise, and sitting next to a fire. Other causes of AP in addition to myeloproliferative disorders include hypereosinophilic syndromes, lactose intolerance, xanthogranuloma, hepatitis C and drugs such as clomipramine, bupropion, chloroquine and hydroxychloroquine.

The pathogenesis of AP is still poorly understood, but histamine release from mast cell degranulation is thought to be the cause of pruritus. Patients with both PV and AP tend to have a higher white blood cell count and higher mutated JAK2 allele burden, when compared to PV patients without AP. The workup in clinic must include hematocrit to confirm erythrocytosis.

AP can be a debilitating symptom of PV, causing significant distress and poor quality of life for many patients. Furthermore, treatment of AP is difficult and often ineffective. Management of AP secondary to PV is not agreed upon, with many physicians trying various options until their patients find relief. Efficacious therapies include interferon-alpha, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and fluoxetine, and phototherapy. Antihistamines provided mixed results, while phlebotomy and myelosuppression are less effective. Recently, new therapies that target JAK2 (specifically JAK2 inhibitors) and mTOR have shown clinical benefit and may be efficacious alternatives as more research is conducted.

Take Home Points

- AP is an intense itchiness of the skin that occurs upon contact with water or other triggers. It is usually not associated with any skin rash, but may be a symptom of PV.
- Treatment is unclear, but antihistamines, phlebotomy, or myelosuppression may provide symptomatic relief while new targeted therapies are being further researched.

References:

1. Saini KS, Patnaik MM, and Tefferi A. Polychthemia vera-associated pruritus and its management. *Eur J Clin Invest*. 2010;40(9):828-34.
2. Siegel FP, Tauscher J, and Petrides PE. Aquagenic pruritus in polycythemia vera: characteristics and influence on quality of life in 441 patients. *Am J Hematol*. 2013;88(8):665-669.

74: Intracerebral Hemorrhage

Question:
An 84-year-old man presents to the emergency department with headache, vomiting, and minimal weakness of his right arm and right leg. that began this morning. He has a past medical history of well-controlled hypertension. He is on 325 mg aspirin and amlodipine. Computed tomography (CT) scan of the head shows small microbleeds in the left parietal subcortical region and a lobar hemorrhage in the left temporal area. He states that his family believes his mental function has declined in the last few months.

What might the physician consider in treating this patient?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
Based on imaging, the patient likely has cerebral amyloid angiopathy (CAA). CAA is a notable cause of lobar intracerebral hemorrhage and dementia, resulting from the deposition of beta-amyloid peptide in the leptomeningeal and cortical vessels. Normally, newly synthesized beta-amyloid is cleared from the brain by several different ways: a) uptake and degradation by glial cells, b) degradation by cell-associated and extracellular proteases, c) direct transport across the blood-brain-barrier and d) clearance through the periarterial interstitial fluid (ISF) drainage. Under pathological conditions, the beta-amyloid clearance mechanisms are impaired, which results in slow accumulation of diffuse beta-amyloid plaques. As the majority of beta-amyloid gradient flow is towards the vessels, deposition of these plaques form vessel-related CAA. CT scans show microbleeds and white matter hyperintensities in the cortical or subcortical regions, often sparing the deep brain. There are no specific laboratory findings for diagnosing CAA, although some patients may have cerebrospinal fluid abnormalities such as high protein and low soluble beta-amyloid.

CAA occurs most frequently in elderly males, although rare familial forms can affect younger patients. No treatment guidelines currently exist for CAA, although tight control of blood pressure is recommended to decrease risk of bleeding and corticosteroids have been shown to improve symptoms. On radiographs, CAA can look like vascular dementia, which is caused by hypertension and can be controlled with aspirin and antiplatelet drugs. Notably, aspirin and other antiplatelet drugs are contraindicated in CAA patients, as they are associated with re-bleeding risk and further microbleeds. This salient point indicates the importance of diagnosing CAA, so that appropriate treatment algorithms may be followed. Cognitive decline prior to acute neurologic presentations have been noted in this condition.

Take Home Points

- CAA is a significant cause of intracranial lobar hemorrhage and dementia in older patients, resulting from amyloid deposition in intracranial blood vessels.
- On imaging, CAA may appear like vascular dementia, but while aspirin is a mainstay of treatment in vascular dementia, aspirin and other antiplatelet agents are contraindicated in CAA as they are associated with increased risk of re-bleeding. Aspirin should be stopped in this patient.

References:

1. Tzimou M, Anastasiou A, Katsarou Z, Pyrpasopulou A, and Douma S. Cerebral amyloid angiopathy. *Neuroradiol J*. 2012;25(5):525-527.
2. Kumar-Singh S. Cerebral amyloid angiopathy: pathogenetic mechanisms and link to dense amyloid plaques. *Genes Brain Behav*. 2008;7(Suppl. 1):67-82.

75: Prevention of Chemotherapy-Related Hearing Loss

Question:
A 56-year-old man who has been diagnosed with bladder cancer presents to his oncologist for chemotherapy treatment. He is scheduled to receive a cisplatin-based chemotherapy regimen and understands the possible side effects of these medications. He is particularly concerned about the possibility of cisplatin-induced hearing loss,. Patient states he is a keen pistol marksmen and has already sustained some hearing loss. He asks his physician if there is any way to prevent deteriotation of hearing loss given his impending chemotherapy.

What would you recommend?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
Currently, there are no drugs that are Food and Drug Administration (FDA) approved to prevent or treat drug-induced or noise-induced hearing loss. D-methionine is one agent that shows promise in this capacity. Drug-induced ototoxicity is frequently associated with the chemotherapy drugs cisplatin and carboplatin as well as the antibiotic class of aminoglycosides. D-methionine may also be partially protective against aminoglycoside-induced ototoxicity. Additionally, D-methionine has been shown to protect against permanent noise-induced hearing loss by reducing damage to both inner and outer hair cell loss in animal studies. No data exists to indicate that in humans D-methionine will compromise chemotherapeutic effects. L-methionine may also have a similar effect. However, further studies are needed prior to human use.

There may be multiple ways in which D-methionine exerts its otoprotective effects, but it primarily seems to work as a free radical scavenger and antioxidant, reversing the free radical formation that causes damage in drug-induced and noise-induced hearing loss. Physiologic methionine levels increase intracellular levels of glutathione, also an antioxidant molecule. Additional methionine may prevent the usual efflux of glutathione from injured cells, thereby increasing and protecting intracellular glutathione levels. Furthermore, D-methionine has an excellent safety profile.

Take Home Points

- D-methionine is a drug that shows promise in treating drug-induced hearing loss from drugs such as cisplatin, carboplatin, and aminoglycosides. It may also have a role in preventing noise-induced hearing loss when administered prior to noise exposure.
- There is less data on L-methionine but it may have similar effects without compromising chemotherapeutic efficacy
- The mechanism is not fully known, but the drug may act as a free radical scavenger.

References:

1. Campbell KCM, Meech RP, Klemens JJ, Gerberi MT, Dystad SS, Larsen DL, Mitchell DL, El-Azizi M, Verhulst SJ, and Hughes LF . Prevention of noise- and drug-induced hearing loss with D-methionine. *Hear Res*. 2007;226(1-2):92-103.

76: Sudden Heart Block

Question:
A 31-year-old man was brought to the emergency room by his distraught wife, who reports that her husband fainted just before Thanksgiving dinner. She reports that he was watching football when she suddenly heard him cry out that his heart is racing and that he feels lightheaded. She tells the physician he is healthy and has no past medical conditions. Upon further questioning, she reluctantly admits that her husband drank several beers that afternoon. Physical exam shows a stuporous pale man with a blood pressure 92/59 mmHg, pulse of 113, and respiratory rate of 12. Urine screen for illicit drugs is negative. The physician orders an electrocardiogram (EKG), which reveals first degree atrioventricular (AV) block with a prolonged PR interval of 351 ms and normal QRS and QT intervals.

What may be the cause of this patient's cardiac arrhythmia?

Contributors: Sneha Raju, Jannette M. Dufour, Alan Peiris

Answer:
The patient may be presenting with cardiac arrhythmia caused by acute alcohol intoxication, also known as Holiday Heart Syndrome. The syndrome is related to binge drinking and occurs more frequently over holidays and weekends. It has been rarely reported with marijuana use. Excessive alcohol consumption can cause cardiac arrhythmias, low blood pressure, and sudden cardiac death, even in healthy patients with structurally normal hearts. Atrial fibrillation is the most commonly seen arrhythmia in this context, but atrial flutter, AV block, and premature atrial and ventricular contractions may occur as well.

The mechanism for alcohol-induced dysrhythmias is thought to be due to electrophysiological and autonomic effects. Alcohol and its metabolite acetaldehyde delay cardiac conduction by facilitating re-entry pathways. Alcohol also promotes arrhythmia by activating the sympathetic nervous system by stimulating secretion of adrenaline by the adrenal medulla.

Diagnosis of Holiday Heart Syndrome may be based on new-onset dysrhythmia in the setting of acute alcohol intoxication as well as clinical signs of palpitations, dyspnea, chest pressure, syncope, or near syncope. Cardiac enzymes should be monitored to rule out acute myocardial infarction. Patients may present while intoxicated or within 12-36 hours after alcohol consumption and typically convert back to normal sinus rhythm within a day. However, it can recur and patients should be advised to limit future alcohol intake. Treatment with intravenous fluids to correct an electrolyte imbalance from dehydration may be beneficial. Vital signs and cardiac rhythms should be monitored to detect possible shock and sustained arrhythmias. Persistent dysrhythmias may warrant consideration of other etiologies, anticoagulation and chemical conversion.

Take Home Points

- Acute alcohol intoxication can induce cardiac arrhythmias and sudden cardiac death in a phenomenon called Holiday Heart Syndrome.
- Patients may present while intoxicated or hours after intoxication and typically revert to normal rhythm, although fluid resuscitation and close monitoring of vital signs and cardiac rhythms is warranted.

References:

1. Ghadri JR, Templin C, Duru F, Luscher TF, and Haegeli LM. Holiday heart block: alcohol-induced PR prolongation. *Am J Med.* 2013;126(9):776-777.
2. Sterner KL, and Keough VA. Holiday heart syndrome: a case of cardiac irritability after increased alcohol consumption. *J Emerg Nurs*. 2003;29:570-573.

77: Anisocoria

Question:
A 31-year-old woman visits the emergency room after her husband noticed earlier that day that her left pupil was larger than her right pupil. Her vision was not impaired, except for some difficulty reading. The patient has no past medical history, no visual impairment normally, and takes no medications. She is concerned and presents for evaluation. On physical exam, her left pupil does not constrict to light while her right pupil constricts normally. Upper extremity reflexes are normal, but her left Achilles tendon reflex is diminished.

What might her diagnosis be?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
This patient's pupillary and neurological symptoms point toward a rare neurological disorder known as Holmes-Adie syndrome (HAS). HAS is characterized by unequal size of pupils (anisocoria), a tonic pupil that is poorly reactive to light, and absence of deep tendon reflexes usually in the Achilles tendon. It seems to be more common in women with a peak incidence in the third decade of life. The exact cause of HAS is unknown. However, it is believed that the majority of the time it results from inflammation or damage to the ciliary ganglia or post-ganglionic nerves, which control the pupil's response to light and other stimuli. The absence of deep tendon reflexes in the Achilles tendon is believed to be caused by damage to the dorsal root ganglion.

Typically, the pupillary and deep tendon reflex symptoms begin gradually on one side of the body and progress to the other side over time. Furthermore, the symptoms may not appear at the same time. When excessive sweating or other autonomic dysfunction is also present, the syndrome may be referred to as Ross's syndrome or a variant of HAS. HAS is not life threatening, although loss of deep tendon reflexes is usually permanent. Pupillary symptoms are often improved by reading glasses and pilocarpine drops. Pilocarpine, a cholinomimetic, stimulates pupillary constriction, reversing the anisocoria. Pilocarpine trial can also be used to confirm a suspected diagnosis of HAS. The differential diagnosis of this syndrome includes syphilis, Lyme disease, HIV, and Parvovirus B19 infection

Take Home Points

- HAS is a rare disorder that is characterized by anisocoria and absence of deep tendon reflexes, particularly in the Achilles tendon, and is sometimes accompanied by autonomic dysfunction.
- While the syndrome is not fatal, loss of deep tendon reflexes can be permanent.
- Pilocarpine can be used to treat the anisocoria.

References:

1. Martinelli P. Holmes-Adie Syndrome. *Lancet*. 2000;356(9243):1760-1761.
2. Colak S, Erdogan MO, Senel A, Kibici O, Karaboga T, Afacan MA, and Akdemir HU. A Rare Case in the Emergency Department: Holmes-Adie Syndrome. *Turk J Emerg Med*. 2015;15(1):40-42.

78: Lambert-Eaton vs. Myasthenia Gravis

Question:
A 53-year-old woman presents to her physician complaining of weakness and stiffness for the past 6 months. She reports “seeing double” while reading or watching television, particularly in the morning. She also sometimes has difficulty brushing her hair and rising from a seated position, but this tends to get better as the day goes on. She strives to maintain an active lifestyle, and finds her symptoms to be frustrating. She has a history of smoking 1 pack of cigarettes per day for about 15 years but quit over 20 years ago. She has no skin rashes, and erythrocyte sedimentation rate (ESR) is normal.

What information might the physician consider to reach a diagnosis?

Contributors: Sneha Raju, Kandis Wright, Alan Peiris

Answer:
The patient's complaints may lead the provider to consider myasthenia gravis (MG) or Lambert-Eaton myasthenic syndrome (LEMS), as both have similar clinical presentations of muscle weakness. MG, which is more common than LEMS, occurs due to autoantibodies directed against postsynaptic acetylcholine receptors. Acetylcholine molecules released from vesicles are blocked from binding their receptors by autoantibodies. The complement pathway also destroys the postsynaptic membrane and crosslinking of acetylcholine receptors causing receptor degradation. Eventually the stores of acetylcholine in the nerve terminal are depleted and muscle contractions weaken. Thus, patients will complain of feeling better in the mornings and progressively weaker as the day goes on. Notably, MG can involve respiratory muscles and be life-threatening and both myasthanic and cholinergic crises may occur.Acetylcholinesterase inhibitors are the mainstay of treatment for MG, along with immunosuppressive therapy and thymectomy. Thymomas occur in 10-15% of patients with MG. It is thought that the thymus contains all the components (T-cells, B-cells, plasma cells) needed to elicit immune responses against acetylcholine receptors. Edrophonium tests for diagnosing myasthenia should be done in an intensive care unit with monitoring. Myasthenic patients with muscle-specific tyrosine kinase (muSK) antibodies present differently from the typical presentation of patients with acetylcholine receptor antibodies (AChR). Myopathy, muscle atrophy including facial and tongue muscle atrophy are found in about 23% of muSK patients. Deposition of intramyocellular lipid in the tongue maybe present in about 85% of MuSK but in only 20% of AChR MG patients

LEMS on the other hand, is characterized by muscle weakness that improves with use. This is because the autoantibodies in LEMS are directed against voltage-gated calcium channels on the presynaptic motor nerve terminal, leading to insufficient acetylcholine release. As more effort is applied, calcium accumulates in the nerve terminal and will eventually release acetylcholine vesicles allowing for muscle contraction. About 50% of patients presenting with LEMS have underlying paraneoplastic conditions, so further malignancy workup is necessary, particularly for small cell lung cancer. In people under 50 years with no history of smoking, LEMS often coexists with other autoimmune diseases. Treatment should first target any underlying cause. The drug amifampridine has proven very effective in increasing the release of acetylcholine, from autonomic and motor nerve terminals, with minimal side effects.

Take Home Points

- Myasthenia Gravis and Lambert-Eaton myasthenic syndrome can have similar clinical presentations, but differentiating between the two is important for treatment plans.
- MG is more common, and patients with MG feel progressively weaker as the day goes on.
- Contrarily, LEMS is characterized by muscle weakness that improves with use and may be a sign of underlying malignancy warranting further workup.

References:

1. Sanders DB and Guptill JT. Myasthenia gravis and Lambert-Eaton myasthenic syndrome. *Continuum*. 2014 Oct;20(5 Peripheral Nervous System Disorders):1413-1425.

79: Rash and Eosinophilia

Question:
A 23-year-old woman presents to the clinic with fever, rash on the face and abdomen, and generalized pruritus for the past 2 weeks. She has a past medical history of bipolar disorder, which had been well-controlled on lithium for the past two years. Six weeks ago, the patient's psychiatrist discontinued the lithium in favor of lamotrigine, as the patient could not tolerate the side effects of lithium. On physical exam, the patient is febrile and has excoriations from the pruritus and maculopapular rash on the face and abdomen. Laboratory results show 2486 eosinophils/mm^3 (range 2-500), alanine aminotransferase level of 72 IU/l (normal <40), aspartate aminotransferase level of 98 (normal <40), and alkaline phosphatase of 782 (normal <140). How should the physician proceed?

Contributors: Sneha Raju, Cassie Kruczek, Alan Peiris

Answer:
A careful review of the patient's medication list and physical exam should lead the physician to suspect drug rash, eosinophilia and systemic symptoms (DRESS) syndrome, typically characterized by the symptoms which comprise its name. Diagnostic criteria for DRESS syndrome require the presence of drug-induced skin eruption, eosinophilia $\geq$ 1500 mm^3, and one of the following: lymphadenopathy, hepatitis, interstitial nephropathy, interstitial lung disease, or myocardial involvement. The pathogenesis of the syndrome is unclear, although genetic origin has been proposed. DRESS syndrome is difficult to diagnose due to its nonspecific symptoms, and the mortality rate is estimated to be from 10-20%. Thus, physicians must have high suspicion for DRESS syndrome if given a recent history of a drug that is highly associated with this reaction. These drugs include antiepileptics (valproate, phenytoin, carbamazepine, lamotrigine, and phenobarbital), allopurinol, sulfonamides, and various antibiotics including vancomycin. Symptoms typically present within 1-2 months after drug initiation. Removal of the offending drug is crucial as a life saving measure. Elevated procalcitonin values may indicate bacterial infection and correlate with hepatic enzyme abnormalities. Elevated CRP along with procalcitonin levels may also have utility in suggesting infection or other causes of inflammation.

Treatment of DRESS syndrome begins with immediate withdrawal of the offending drug and administration of corticosteroids. For cases that are resistant to corticosteroids, intravenous immunogobin (IVIG), cyclophosphamide, cyclosporine, and immunosuppressants have shown benefit. Furthermore, for future management of their psychiatric conditions, the patient should avoid the offending drug and other drugs in the same class.

Take Home Points

- DRESS syndrome should be suspected when a patient presents with rash, systemic symptoms, and eosinophilia after starting an antiepileptic, allopurinol, sulfonamide, or antibiotic known for causing DRESS syndrome.
- Treatment involves immediately stopping the drug and administering corticosteroids. Cases that are resistant to corticosteroids may respond to IVIG, cyclophosphamide, cyclosporine, or immunosuppressants.
- The causative drug should be avoided in the future and may be replaced by another drug of the same class.

References:

1. Bocquet H , Bagot M, and Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms:DRESS). *Semin Cutan Med Surg.* 1996;15(4):250-257.
2. Bommersbach TJ, Lapid MI, Leung JG, Cunningham JL, Rummans TA, and Kung S. Management of Psychotropic Drug-Induced DRESS Syndrome: A Systemiatic Reivew. *Mayo Clin Proc*. 2016;91(6):787-801.

80: Paresthesias and Numbness in a Patient with Diabetes

Question:
A 46-year-old Hispanic female presents to her primary care provider complaining of tingling in her distal extremities. She was diagnosed with type 2 diabetes mellitus 6 years ago and has been compliant with her medication regimen of metformin and glipizide. Physical exam shows a well-nourished woman with decreased sensation in her feet. Laboratory studies show a hemoglobin A1C (HbA1C) of 6.3% and fasting blood glucose level of 87 mg/dl.

Why might she be experiencing tingling in her toes, despite adequate diabetes control?

Contributors: Sneha Raju, Jannette M. Dufour, Alan Peiris

Answer:
Metformin, one of the most commonly used drugs to improve insulin sensitivity in type 2 diabetes mellitus, is well-known to cause vitamin B12 deficiency. This is likely due to malabsorption as metformin can interfere with ileal B12 uptake. B12 is important for the nervous system. Both uncontrolled diabetes and vitamin B12 deficiency can cause peripheral neuropathy, and the two causes may be clinically indistinguishable in a patient with type 2 diabetes. In some patients, vitamin B12 deficiency manifests solely as neuropathy without the hematologic sign of macrocytic anemia, although extreme vitamin B12 deficiency can cause subacute combined degeneration of the spinal cord. Therefore, physicians must be cognizant of identifying B12 deficiency as a reversible cause of neuropathy in patients with diabetes.

While it has been assumed that long term metformin use is more likely associated with B12 deficiency, recent evidence suggests that even short term metformin use may be associated with lower B12 levels and a case for prophylactic replacement of B12 has been made. If suspected, patients can be treated with a intramuscular hydroxycobalamin, a natural B12 supplement. Evidence suggests that monitoring B12 levels in chronic metformin users may be useful. In individuals with low normal B12 levels checking methymalonic acid could also be considered to exclude metabolically active B12 deficiency. B12 is necessary for conversion of methylmalonyl CoA to succinyl CoA. Therefore, B12 deficiency leads to increased methylmalonic acid levels. A risk factor for vitamin B12-induced peripheral neuropathy in patients with diabetes is a lower HbA1c, as low HbA1c levels indicate better metformin compliance and increased risk of side effects associated with use of metformin.

Lactic acidosis in extremely rare with metformin use. Metformin remains the drug of choice in type 2 diabetes. It is under investigation for a possible beneficial role in cancer including a reduction in chemotherapy induced nausea.

Take Home Points

- A well-known side effect of metformin is vitamin B12 deficiency, which is characterized by peripheral neuropathy. Uncontrolled diabetes mellitus can also cause peripheral neuropathy.
- The cause of peripheral neuropathy in a patient with diabetes should be identified, as vitamin B12 is easily replenished by intramuscular hydroxycobalamin.

Resources:

1. Ting RZ, Szeto CC, Chan MH, Ma KK, and Chow KM. Risk Factors of Vitamin B12 Deficiency in Patients Receiving Metformin. *Arch Intern Med*. 2006;166:1975-1979.
2. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, and Topoliski R. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med*. 2009;22(5):528-34.

81: Localized Pruritis

Question:
A 61-year-old female presents to her primary care provider for an annual exam. She is in good health and up to date on her vaccinations, but mentions that she has been extremely frustrated by a constant itch under her right shoulder blade that she has a hard time reaching. She reports that this frequently distracts her when she is at work, and wonders if there's anything she can do relieve this. Physical exam shows a well-nourished woman with an erythematous patch in the right T4 dermatomal distribution. Sensation is reduced to monofilament over the site of the lesion. What might be causing this pruritus?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
In the absence of systemic signs indicative of shingles, the physician should consider notalgia paresthetica (NP). NP is a common dermatologic condition that presents as a unilateral pruritus that occurs medial or inferior to the scapula, often in the T2-T6 dermatomes. Patients may describe its location as "just out of reach to scratch", often causing patients frustration and the need to acquire a back scratcher. They may complain of pruritus alone or even pain and hypersensitivity as well. For unknown reasons, NP seems to affect women more frequently than men. Physical exam may show a patch of skin thickening and inflammation-induced hyperpigmentation in the affected area as a result of scratching- lichen amyloidosis. The appearance of this lesion in children may suggest the presence of multiple endocrine neoplasia type 2A.

Although the exact cause of NP is unclear, it is thought that the sensory disturbances are caused by damage to cutaneous branches of the posterior divisions of spinal roots, possibly by muscle spasms or by irritation of the underlying multifidus spinae muscle. Sensation can be reduced or heightened in the affected area. One study suggested that nerve root entrapment could also be responsible as several patients had degenerative changes of the vertebrae corresponding with the affected dermatome. A link also exists between NP and cervical spine degenerative changes. The diagnosis of NP is clinical and while biopsy of the affected skin can show signs of inflammation from scratching, this is not usually indicated. Topical steroids and antihistamines prove ineffective for neuropathic pruritus, but topical capsaicin, gabapentin, botulinum toxin injections, and acupuncture may be effective. There may also be a role for exercises that strengthen the spine, thereby reducing the irritation of T2-T6 cutaneous nerves as they transit the muscles.

Take Home Points

- Notalgia paresthetica is a common condition that presents as an itch just medial to or below the scapula, often described as an itch that is "just out of reach."
- Topical capsaicin, gabapentin, botox injections, or acupuncture may be effective, along with back strengthening exercises that reduce irritation of the affected cutaneous nerves.

References:

1. Ellis C. Notalgia paresthetica: the unreachable itch. *Dermatol Pract Concept*. 2013;3(1):3-6.

82: Low Back Pain in a Young Athlete

Question:
A 21-year-old football player presents to his physician reporting severe pain in his left buttock and the back of his left lower extremity for the past 10 days. He states the pain is excruciating and has impeded his ability to practice football and even sit in his college classes. He complains of worse pain when he tries to sit or squat down to pick up objects. He has never experienced an episode like this before. Further questioning reveals that he fell onto his left buttock during practice about 2 weeks ago. Physical exam shows tenderness to deep palpation in the left gluteal region. Magnetic resonance imaging (MRI) imaging showed no root or spinal nerve compression in the lumbar region.

What might be causing this patient's worsening pain?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
In a young athlete with recent history of gluteal trauma and no evidence of disc disease, providers should consider piriformis syndrome, a notable cause of sciatica that does not originate in the spinal cord. The piriformis is a small muscle extending from the sacrum to the greater trochanter that helps with external rotation, abduction, and flexion of the hip. The sciatic nerve is comprised of two nerves, the tibial and common fibular nerves. In as much as 96% of the population, the sciatic nerve exits the greater sciatic foramen inferior to the piriformis muscle. Some individuals, however, have anatomic variations where the sciatic nerve, specifically, common fibular nerve pierces or splits the piriformis muscle, increasing the likelihood that piriformis irritation will cause sciatica. Several etiologies of piriformis syndrome have been proposed. Many studies agree that previous trauma to the buttocks, posttraumatic scarring, and overuse of piriformis muscle can result in soft tissue inflammation or muscle spasm leading to sciatic nerve irritation.

Diagnosis of piriformis syndrome involves excluding other causes of sciatica and performing an extensive physical exam. In piriformis syndrome, sensation, motor strength, and deep tendon reflexes are typically intact. Patients usually experience tenderness to palpation of the piriformis muscle. The straight leg test is not particularly helpful in this case, as it may be positive in many cases of discogenic and non-discogenic sciatica. Several specific tests may be used to stretch the piriformis and diagnose piriformis syndrome. The Freiberg sign is positive when the patient extends and internally rotates the hip and experiences pain when attempting to externally rotate the hip against resistance. The Pace sign is positive when the patient tries to resist abduction and external rotation of the hip while seated. Treatment often begins with nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and drugs for neuropathic pain such as gabapentin. Physical therapy may also play a role in stretching the piriformis and strengthening surrounding muscles. Computed tomography (CT) guided local anesthetic and/or steroid Injections into the pyriformis may help. More recently botulinum toxin type A maybe considered in patients unresponsive to conservative treatment.

Take Home Points

- Piriformis syndrome is an entrapment neuropathy in which the sciatic nerve is compromised by the piriformis muscle or adjacent local structures.
- It can present as sciatica, particularly in cases with a history of gluteal trauma or overuse of the piriformis muscle.
- The diagnosis is made by excluding other causes of sciatica, and by tests that may isolate the piriformis muscle and reproduce the pain.
- Treatment should include nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and gabapentin, and there is often a role for physical therapy.

References:

1. Cass SP. Piriformis Syndrome: a cause of non discogenic sciatica. *Curr Sports Med Rep*. 2015;14(1):41-4.

83: Nosocomial Diarrhea

Question:
A 63-year-old female is transferred to the hospital floor for a severe chronic obstructive pulmonary disease (COPD) exacerbation. She has a past medical history of COPD, for which she uses tiotropium and albuterol rescue inhaler, and well-controlled gastritis. Upon admission, the patient is started on nebulized tiotropium and salmetrol and prophylactic pantoprazole. Four days after admission, her COPD symptoms have reduced significantly but she has begun to have profuse watery diarrhea with abdominal cramping. Physical exam shows her to be dehydrated and fatigued.

What is the likely cause of her diarrhea?

Contributors: Sneha Raju, Cassie Kruczek, Alan Peiris

Answer:
This patient's use of proton pump inhibitors (PPIs) may have predisposed her to develop *Clostridium difficile* (C. *difficile*) diarrhea. The prevalence of *C. difficile* diarrhea in hospitals is associated with significant monetary costs, morbidity, and mortality. Hospitals have established preventative guidelines, including contact precautions, isolation of affected patients, and reduction of risk factors. Due to spore formation, *C. difficile* is extremely hardy within the environment and, once established, proves challenging to eradicate. Infections with toxigenic strains of this organism cause watery diarrhea symptoms and in extreme cases pseudomembranous colitis.

While classically associated with broad spectrum antibiotic administration, recent studies have shown that use of PPIs may also be a risk factor for *C. difficile* diarrhea, even after just 2 days of use. Use of PPIs is also linked to recurrent *C. difficile* infections. It is believed that loss of the highly acidic gastric environment caused by PPIs induces bacterial overgrowth and alters normal gut flora, allowing *C. difficile* bacteria to flourish. PPIs are commonly used in critically ill patients as prophylaxis for stress ulcers, and this practice is likely appropriate in patients with high risk for gastrointestinal bleeding. However, it is possible that many low-risk patients also receive prophylactic PPIs, up to one-third of ICU patients receiving PPIs had no valid indication. It is believed that the risk of *C. difficile* diarrhea is proportional to the level of acid suppression and may even have a stronger predictive factor than the use of high-risk antibiotics. This evidence indicates that hospital providers should utilize the least aggressive acid-suppressive therapy possible and only when indicated. Around 20% of patients with *C. difficile* infection will experience a recurrent infection. Antibiotics such as vancomycin and metronidazole that are commonly used to treat *C. difficile* infections may predispose the patient to recurrent infections. Utilization of fecal transplants has been shown to reduce the risk of recurrent *C. difficile* infection. The implementation of a probiotic bundle when antibiotics are ordered in combination with reduced PPI use may reduce incidence of *C. difficile* in hospitals.

Take Home Points

- PPIs may be a risk factor for *C. difficile* infections, as the loss of the acidic gastric environment may allow *C. difficile* bacteria to flourish.
- PPIs may even be a stronger risk factor for *C. difficile* infections than high risk antibiotics.
- PPIs are frequently administered as prophylactic medication to hospitalized patients. It may be worthwhile for providers to weigh risks and benefits of acid suppression and increased risk of *C. difficile* in these patient
- Probiotic use along with a reduction in PPI may help reduce hospital onset *C. difficile* infections.

References:

1. Barletta JF, El-Ibiary SY, Davis LE, Nguyen B, and Raney CR. Proton Pump Inhibitors and the Risk of Hospital-Acquired Clostrifium difficile Infection. *Mayo Clinic Proceedings*. 2013;88(10):1085-1090.

84: Preoperative Precautions in Rheumatoid Arthritis

Question:
A 32-year-old woman with past medical history of severe rheumatoid arthritis (RA) presents for pre-operative assessment prior to an elective total abdominal hysterectomy. She is prescribed methotrexate for her RA. In addition to standard preoperative measures, what might the surgeon also consider for this patient?

Contributors: Sneha Raju, Gurvinder Kaur

Answer:
The surgeon should be aware that RA involvement of the cervical spine may result in adverse perioperative outcomes for the patient. RA affects the cervical spine, particularly at the C1-C2 level, in up to 80% of cases.

A complex interplay between genetic, environmental and immunological factors are involved in the pathophysiology of RA. These factors activate antigen-presenting cells which in turn activates T cells, specifically CD4 T cells. These CD4 T cells then activate B cells which secrete autoantibodies and anti-cyclic citrullinated peptides, thereby further promoting inflammation. CD4 T cells also activate macrophages which secrete pro-inflammatory cytokines that result in leukocyte influx, fibroblast activation, metalloproteinase secretion, thus causing articular cartilage breakdown. Chronic inflammation of the cervical spine initially leads to proliferation of fibrovascular tissue and pannus formation at the atlas-axis joint (C1-C2). This results in bony erosion and ligamentous laxity, especially of the transverse ligament that aligns the atlas and axis. The subluxation of the odontoid process can result in cranial nerve and brainstem dysfunction including cervical myelopathy. Sudden death due to subluxation of the odontoid process into the medulla oblongata is a rare complication.

Most patients do not have neurological involvement, but any involvement of the brainstem could lead to cardiac arrest, stroke, or obstructive hydrocephalus. In surgery, neck flexion during intubation can result in these adverse outcomes due to pressure on the spinal cord or impaired blood flow through the vertebral arteries. Thus, all patients with RA should receive cervical spine radiographs before undergoing any surgery, due to the risk of neurologic injury during intubation. Magnetic resonance imaging (MRI) is the best imaging modality to visualize early RA, although plain radiographs and computed tomography (CT) scans are acceptable. In the past few decades, the use of disease-modifying antirheumatic drugs and biologic agents has decreased the severity of RA and decreased involvement of the cervical spine.

Take Home Points

- Rheumatoid arthritis can cause laxity and bony erosion of the cervical spine, leading to spinal instability that can be dangerous if the brainstem is affected.
- Patients with rheumatoid arthritis should receive preoperative cervical spine imaging before undergoing surgery, due to the risk of neurologic injury during intubation.

References:

1. Joaquim AF, and Appenzeller S. Cervical spine involvement in rheumatoid arthritis-a systematic review. *Autoimmun Rev*. 2014;13(12):1195-202.
2. Gillick JL, Wainwright J and Das K. Rheumatoid arthritis and the cervical spine: A review on the role of surgery. *Int J Rheumatol*. 2015:252456.

85: Abnormal Sleep Behavior

Question:
A 67-year-old man comes to the clinic reporting sleep disturbances. His wife tells the physician that for the past few months, the patient has been moving a lot in the early hours of the morning, sometimes thrashing about and even yelling. She is worried that he will hurt himself or her with this behavior. She tells the physician that she is always able to wake him up, and he awakens fully within moments. The patient reports he doesn't remember this behavior but states he does dream each night.

What diagnosis may explain the patient's peculiar behavior?

Contributors: Sneha Raju, Gurvinder Kaur, Alan Peiris

Answer:
The patient's history fits the clinical picture of rapid eye movement (REM) sleep behavior disorder. Rodent studies demonstrated that two motor systems, one for generating muscle atonia and one for suppressing locomotor activity are involved in normal REM sleep. Muscle atonia in normal REM sleep occurs via active inhibition of spinal motor neurons along with reduced drive within locomotor generators. Lesions in the brainstem that release the tonic inhibition on spinal motor neurons have been associated with REM sleep behavior disorder. Thus, this disorder is characterized by complex motor activity that occurs during the REM stage of sleep, during which muscles normally have no tone.

Patients with REM sleep behavior disorder appear to act out their dreams, usually in the latter part of the night when REM cycles occur more frequently. They can usually be awakened quickly out of the REM cycle, and although they tend to remember their dreams, they may not recall their movements. These movements may include sleep talking and yelling, limb jerking, walking, and even violent behaviors, and often disturbance or injury to the patient's bed partner which prompts the patient to seek treatment.

REM sleep behavior disorder affects less than 1% of the adults, however, it can be found in up to 25-50% of patients with neuro-degenerative disorders such as Parkinsons' disease (may precede the diagnosis of Parkinson's disease), dementia with Lewy body and multisystem atrophy. Other risk factors for REM sleep behavior disorder are age over 50, male gender, selective serotonin reuptake inhibitors (SSRIs), beta blockers, and narcolepsy. Pharmacologic treatments are effective in up to 90% of the patients, with clonazepam being the most effective followed by melatonin and pramipexole.

Take Home Points

- REM sleep behavior disorder is characterized by patients who appear to act out their dreams, sometimes including violent behavior that may awaken their partners.
- The disorder tends to affect males over 50 years old, and can be an early sign for Parkinson's disease or Lewy body dementia.
- Pharmacotherapy is effective in a majority of patients; clonazepam is most effective, followed by melatonin and pramipexole.

References:

1. Devnani P, and Fernandes R. Management of REM sleep behavior disorder: An evidence based review. *Ann Indian Acad Neurol*. 2015;18(1)1-5.
2. Boeve BF. REM sleep behavior disorder: Updated review of the core features, the RBD-Neurodegenerative disease association, evolving concepts, controversies and future directions. *Ann N Y Acad Sci*. 2010;1184:15-54.

86: Muscle Rigidity and Tremors

Question:
A 44-year-old woman presents to clinic after 12 years of intermittent aches and spasms of her back and leg muscles. She reports that in these episodes, her muscles become rigid and shake uncontrollably. She cannot recall any particular triggers to the episodes, but says they have increased in frequency over the years and now occur almost every day. She is distraught as she no longer leaves her house due to anxiety over her condition. She has been worked up by the neurology department for grand mal seizures, but her electroencephalograms (EEGs) have been negative. Furthermore, treatment with antiepileptic drugs such as phenytoin and levetiracetam have not stopped the episodes. On exam, the patient has a temperature of 102˚F. She is tachycardic and tachypneic, with diffuse back and lower extremity stiffness. Trials of selective serotonin reuptake inhibitors (SSRIs) prove to be unsuccessful in treating the patient.

What might you consider?

Contributors: Sneha Raju, Kandis Wright, Alan Peiris

Answer:
The physician may first consider serotonin syndrome, and neuroleptic malignant syndrome. However, exclusion of these conditions may lead the physician to consider Stiff Person Syndrome (SPS). SPS is a rare autoimmune condition characterized by insidious onset of intermittent muscle tightness that eventually evolves into diffuse rigidity, beginning with the trunk muscles and progressing first to proximal then distal limb muscles. The cause of SPS is thought to be related to antibodies against glutamic acid decarboxylase (GAD), which is the rate-limiting enzyme for the production of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). High titers against the synaptic membrane-associated GAD65 isoform are found in 60-80% of SPS patients. These autoantibodies are also found in some diabetic patients that initially present as type 2 diabetes but later become insulin dependent (latent autoimmune diabetes in adults- LADA). The antibody spectrum linked to stiff person syndrome and related disorders has expanded and includes antibodies against amphiphysin, dipeptidyl-peptidase-like protein-6, gamma-aminobutyric acid type A receptor, glycine receptor and glycine transporter 2. Activated T- and B-cells in the central nervous system (CNS) are also thought to be important in SPS.

Overall, decreased production of GABA may lead to the over-activation of muscles in SPS despite attempted relaxation. This can manifest as poor balance and frequent falls, mimicking Parkinson-like rigidity. The spasms may be brought on by strong emotional disturbances or by startling stimuli, and usually resolve gradually on their own. Episodes may involve autonomic instability, including hyperthermia, high blood pressure, tachycardia, and diaphoresis. Notably, patients with SPS do not experience muscle weakness or sensory loss. Patients with SPS frequently have comorbid depression, anxiety, agoraphobia, alcohol abuse, and autoimmune diseases, including a 30% chance of developing type 1 diabetes. Their physical symptoms can sometimes be misdiagnosed as somatic manifestations of certain psychiatric illnesses. Symptomatic treatment of SPS can be achieved by a GABA agonist such as diazepam, oral baclofen for muscle relaxation, or the combination of the two drugs. Immunotherapy such as intravenous immunoglobulin (IVIg) and plasmapheresis have also been beneficial to some patients. Unfortunately, the prognosis of SPS is variable and many patients continue to experience symptoms despite multiple therapies. Anesthesia using neuromuscular blockade may pose additional challenges in this group of patients.

Take Home Points

- Stiff Person Syndrome (SPS) is a rare autoimmune condition characterized by slow onset of intermittent muscle tightness beginning with the trunk then moving distally, often triggered by strong emotional disturbances.
- SPS can often be misdiagnosed as other neuromuscular syndromes or somatization of psychiatric disorders.
- The episodes are self-limiting, but diazepam and baclofen can be used for symptomatic relief.

References:

1. Baizabal-Carvallo JF, and Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. *J Neurol Neurosurg Psychiatry*. 2015;86(8):840-8.

87: The Role of Ketogenic Diet in Epilepsy

Question:
A 17-year-old female who has been suffering from epilepsy since childhood presents to her neurologist with intractable seizures, despite several trials of different antiepileptic drugs. Her mother is frustrated by the lack of success with these treatments, and tells the physician that she is exploring possible benefits of a ketogenic diet (KD) in helping her daughter with seizure control. She asks you to shed more light on this topic.

Contributors: Sneha Raju, Jannette M. Dufour, Alan Peiris

Answer:
The KD was used widely in the 1920s and 1930s to control epilepsy. However, its use declined with the advent of antiepileptic drugs. Despite the use of these drugs, up to 30% of people with epilepsy continue to experience seizures. Therefore, the KD is experiencing a revival in popularity. The KD is a high fat, low carbohydrate diet that shifts metabolism from glucose to fat metabolism promoting the production of ketone bodies. The ketone bodies are used by mitochondria in several organs including the brain to produce energy. In spite of the clear benefits of the KD, the reasons for its success are not well understood. This may be due to variability in the causes of epilepsy, as well as the extreme effect the KD diet has on many metabolism parameters.

Currently the proposed mechanism can be divided into two categories, alteration of neurotransmission at synapses and neuroprotection. For instance, seizures are associated with increased neuronal excitability. The KD may change concentrations of neurotransmitters at neuronal synapses, increasing the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and decreasing the excitatory neurotransmitter glutamate. Additionally, ketone bodies are a primary source of energy in utero and infancy. It has been speculated that feeding the brain ketone bodies after infancy creates an environment for brain cells to repair structural damage associated with epilepsy. Moreover, this diet increases the number of mitochondria in neurons and glia, as well as increases the production of other neuroprotective molecules. The KD may be effective in epilepsy related to acquired structural lesions. Randomized controlled trials studying this topic are limited but promising, and further research is required to provide incontrovertible evidence of the benefits of the KD and to elucidate the mechanism(s) of action. It appears that the KD does not alter the serum level of most anti-convulsants apart from possibly valproic acid.

Despite these limitations, the KD is a valid option for people with refractory epilepsy. However, the metabolic acidosis induced by elevated ketone body production can cause adverse events such as nephrolithiasis, osteopenia, fractures, decreased linear growth rate and cardiac effects. Studies are currently underway to modify the KD to improve palatability, decrease metabolic acidosis and still provide the same antiepileptic effects.

Take Home Points

- The KD has been used for decades as a way to control epilepsy that is refractory to antiepileptic drugs.
- Ketone bodies are thought to have several mechanisms of action to reduce epileptic activity, including alteration of neurotransmission at synapses and neuroprotection.
- The benefits of the KD are still being researched and systemic side effects of the induced metabolic acidosis must be weighed against neurologic benefits for epilepsy.

References:

1. Youngson NA, Morris MJ, and Ballard JWO. The mechanisms mediating the antiepileptic effects of the keogenic diet, and potential opportunities for improvement with metabolism-altering drugs. *Seizure*. 2017;52:15-19.
2. Yuen AWC, Walcutt IA, and Sander JW. An acidosis-sparing ketogenic (ASK) diet to improve efficacy and reduce adverse effects in the treatment of refractor epilepsy. *Epilepsy Behav*. 2017;74:15-21.

88: Yellow Nail Syndrome

Question:
A 65-year-old man presents with 1 month of worsening dyspnea on exertion, lower extremity edema and disfiguration of his toenails. The patient has never smoked and maintains an active lifestyle. Physical exam shows decreased breath sounds at left lung base with dullness to percussion, bilateral pitting edema of his lower extremities, and thick, yellow toenails. Chest x-ray shows left sided pleural effusion.

Based on his presentation, what is a likely diagnosis?

Contributors: Sneha Raju, Cassie Kruczek, Alan Peiris

Answer:
Yellow Nail Syndrome (YNS) is a rare triad of nail abnormality, lung involvement, and lymphedema. The nail abnormality is characterized by yellow, thickened, and overly-curved nails. Lung involvement may manifest as chronic cough, sinusitis, bronchiectasis, or pleural effusion, and sputum bacteria follow general epidemiology (*P. aeruginosa, H. influenzae, S. pneumoniae, M. catarrhalis*). Lymphedema is usually bilateral and localized to the lower limbs. In this patient physical examination findings are consistent with a pleural effusion. Refractory pleural effusions in this syndrome can be treated if needed surgically including decortication and/or pleurodesis.

YNS is often isolated but may be associated with malignancies and autoimmune diseases, such as rheumatoid arthritis. The full triad is not always present, with only 40-60% of people having all three characteristic symptoms. Because the symptoms are variable over time and may appear sequentially rather than simultaneously, presence of two of the three symptoms (one of these is usually nail abnormality) is enough to suggest diagnosis of YNS. Fewer than 400 cases of YNS have been published, and prevalence is not known. The syndrome most frequently affects patients over 50 years of age and affects men and women equally.

The etiology of YNS is still unknown but may involve poor lymph drainage due to abnormalities in the lymphatic system, while postulate microvasculopathy associated with protein leakage. Other implicating etiologies may include: thiol compounds (which contains cysteine, a nail component); infections from Candida, Aspergillus, dermatophytes, and Pseudomonas; and planus lichen and psoriasis.

The treatment of YNS is varied and mostly supportive and symptomatic in nature. YNS may spontaneously resolve or may resolve after cancer therapy (if associated with malignancy). Oral vitamin E (alpha-tocopherol) has had some success in treating the nail abnormalities due to its antioxidant properties. Other drugs used with limited efficacy to treat nail abnormalities are: azole antifungals, zinc sulfate supplementation, and local steroid injections. Treatment of pulmonary manifestations may include antibiotic treatment/prophylaxis and octreotide. Finally, lymphedema may improve with lymph drainage, exercises, and low-stretch bandages.

Take Home Points:

- YNS is the rare triad of: 1) thickened, curved, yellow nails, 2) lung involvement, and 3) lymphedema, often bilateral and in the lower extremities, although the full triad is not always present and symptoms may not appear simultaneously.
- Supportive and symptomatic treatment is indicated for this syndrome.

References:

1. Vignes S, and Baran R.Yellow nail syndrome: a review. *Orphanet J Rare Dis*. 2017;12(1):42.
2. Kurin M, Weisen J, and Mehta A. Yellow nail syndrome: as case report and review of treatment options. *Clin Resp J*. 2015;11(4):405-410.

89: Bioavailability of Antimicrobials

Question:
A 31-year-old female has been hospitalized secondary to surgical repair of crush injuries from a motor vehicle accident. She has had an indwelling Foley catheter in place since her admission nine days ago. Recently she has developed costovertebral angle tenderness and suprapubic pain with fever. A urinary culture using a freshly placed catheter results pan-sensitive *Candida albicans* with 10^6 colony forming units/mL. The provider orders fluconazole 200 mg intravenously (IV) daily for 14 days to treat the infection.

What considerations could be made about this patient's regimen?

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
The choice of drug, dose, and duration are all recommended for this patient's catheter associated *Candida* pyelonephritis, however the route of administration could be reconsidered. Fluconazole, a member of a group of antimicrobial agents that have excellent bioavailability, can be given orally instead of IV in most situations. Barring contraindications to oral route, oral (PO) fluconazole would be preferred in this situation for two major reasons: improved cost-effectiveness and prevention of "tying up" or creating an intravenous line. Further, if the patient is reaching discharge status, oral therapy can easily be continued as an outpatient. Other antimicrobial agents that display excellent bioavailability include azithromycin, clindamycin, ciprofloxacin, levofloxacin, moxifloxacin, linezolid, metronidazole, and minocycline. Common disease states that could benefit from initiating bioavailable antimicrobials orally include community acquired pneumonia and urinary tract infections.

Take Home Points

- Barring physiologic gut abnormality, the following antimicrobials have the same bioavailability whether they are administered PO or IV: fluconazole, azithromycin, clindamycin, ciprofloxacin, levofloxacin, moxifloxacin, linezolid, metronidazole, and minocycline.
- IV to PO switches help to reduce line use, are more cost effective, and can be more readily continued at discharge.

References:

1. Cyriac JM, and James E. Switch over from intravenous to oral therapy: A concise overview. *J Pharmacol Pharmacother*. 2014;5(2):83-87.
2. MacGregor RR, and Graziani AL. Oral administration of antibiotics: A rational alternative to the parenteral route. *Clin Infect Dis*. 1997;24:457-467.

90: The Elderly and Diphenhydramine

Question:
An 87-year-old female living at an assisted facility comes into your office for her semi-annual checkup. Her medical history includes depression and Alzheimer's disease for which she takes oral escitalopram 5 mg daily and oral Namzeric (memantine extended release/donepezil) 28 mg/10 mg daily, respectively. Recently she has had problems sleeping at night, reporting that she has difficulty falling asleep. Some of her friends at the facility use ZzzQuil (diphenhydramine) and say it works well, she is wondering if she should buy some on the way home.

What should you reccommend?

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
It would not be recommended to encourage diphenhydramine use in this patient for many reasons that extend beyond the Beers list. Diphenhydramine, a first generation histamine 1 receptor antagonist penetrates the blood brain barrier and can generate both central and systemic anticholinergic side effects. Systemic effects include xerostomia, constipation, urinary retention, blurring of vision, and dizziness; central effects being fatigue or paradoxical excitation, impaired thinking, alterations to memory, and agitation. This can be especially dangerous in a patient with dementia since verbalization may be impaired. Behavioral abnormalities and an increase in falls may occur with an inability to verbalize the adverse effects they experience potentially leading to increased behaviors and risk of fall.

Considering this specific case there is also concern for drug interactions between her cholinergic dementia regimen and diphenhydramine which in combination is the therapeutic equivalent of simultaneously pushing the gas and brake pedal of a car. Further, there is potential for QTc prolongation with the combination diphenhydramine and both of her current medications.

A better starting point for insomnia in the elderly, especially those with preexisting dementia, is to address sleep hygiene and potentially seek cognitive behavior therapy. If this first line therapy fails, then considering pharmacologic intervention either with low dose melatonin or switching the patient's antidepressant to one with drowsiness as a therapeutic side effect, such as mirtazapine, could be considered.

Take Home Points

- In the elderly, 1st generation antihistamines should be avoided as treatment for general seasonal allergies or insomnia due to an undesirable adverse effect profile.
- In those taking cholinergic medications such as donepezil for cognition disorders anticholinergic medications should especially be avoided as they can impair the efficacy of the patient's dementia regimen.

<u>References:</u>

1. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246.
2. Gooneratne NS, and Vitiello MV. Sleep in older adults: Normative changes, sleep disorders, and treatment options. *Clin Geriatr Med*. 2014;30(3):591-627.

91: Creatine Phosphokinase Elevation

Question:
A 52-year-old male recently admitted for native valve right sided endocarditis secondary to intravenous (IV) opioid use. He is started on Cubicin (daptomycin) 8 mg/kg IV daily. His past medical history is significant for depression, hypertension, and hypercholesterolemia for which he is prescribed oral Lexapro (escitalopram) 20 mg daily, oral Zestoretic (lisinopril/hydrochlorothiazide) 20 mg /12.5 mg daily, and oral Crestor (rosuvastatin) 40 mg daily respectively. Five days into his stay his renal function has worsened and he is complaining of lower extremity muscle pain.

What could be the cause for the patient's decline?

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
The patient may be experiencing the effects of elevated creatine phosphokinase (CPK) levels secondary to daptomycin. Daptomycin is a cyclic lipopeptide antibiotic that covers gram positive organisms including methicillin resistant *S. aureus* (MRSA) and vancomycin resistant Enterococcus; it is approved for use in skin and skin structure infections, endocarditis, and bacteremia with off-label uses in osteomyelitis and joint infections. Daptomycin is known to reversibly increase CPK levels via an unknown mechanism; however, this adverse effect is often not therapy limiting. The probability of CPK elevation is directly related to concurrent use of β-Hydroxy β-methylglutarly- CoA (HMG-CoA) reductase inhibitors (statins), the minimum serum concentration of daptomycin, and the duration of therapy. Package labeling recommends monitoring CPK levels at baseline and at least once weekly with consideration for increased frequency in patients that have simultaneous statin regimens, and preexisting renal impairment or myopathy. One could consider holding statins for the duration of daptomycin therapy to reduce the risk of CPK elevation and related complications.

In asymptomatic patients with stable renal function, there is no evidence suggesting that daptomycin must be discontinued secondary to CPK elevation alone. There are scattered reports demonstrating withholding a single dose of daptomycin plateaued further CPK elevations, allowing patients to complete an extended 6 week course without consequence. In symptomatic patients or those exhibiting worsening renal function it is advised to discontinue daptomycin and switch to another antibiotic agent.

Take Home Points

- Daptomycin (Cubicin) is known to cause reversible increases in CPK levels.
- The rate of occurrence is directly related to concurrent statin use and the duration of antibiotic therapy.
- If the patient is having symptomatic CPK elevations with it is advisable to hold statin therapy and consider switching to a different antimicrobial if possible.

References:

1. Bhavnani SM, Rubino CM, Ambrose PG, and Drusano GL. Daptomcin exposure and the probability of elevations in the creatine phosphokinase level: Data from a randomized trial of patients with bacteremia and endocarditis. *Clin Infect Dis*. 2010;50(12):1568-1574.
2. Burdette SD, Oleson F, McDaneld PM, Benziger D, and Patel HN. Dosing strategy to allow continued therapy with daptomycin after asymptomatic increases in creatine kinase levels. *Am J Health Syst Pharm*. 2014;71(13):1101-1107.

92: Fluticasone and Cytochrome 3A4 Inhibitors

Question:
A 57-year old female presents to the primary care clinic with complaints of severe seasonal allergies. She reports copious nasal drainage and sneezing. Her past medical history is significant for HIV-1 diagnosed 12 years ago and hypertension. She is currently taking lisinopril 40 mg daily and combination preparation containing elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide (Genvoya)- one tablet daily. Given the propensity for HIV treatment regimens regimens for drug interactions, the provider is considering localized with an intranasal corticosteroid spray such as fluticasone.

What considerations should be made before prescribing intranasal fluticasone for this patient and what are examples of preferred alternatives?

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
While the provider approaches this case with a thoughtful mindset, fluticasone would not be the preferred agent to relieve the patient's symptoms considering the patient's current HIV regimen. Genvoya includes cobicistat, a cytochrome 3A4 inhibitor, used as a pharmacokinetic enhancer to increase the systemic availability of antiretroviral 3A4 substrates such as atazanavir, darunavir, and elvitegravir. Fluticasone, a 3A4 substrate, interacts with cobicistat to increase the serum concentration of the corticosteroid potentially leading to serious adrenal suppression secondary to drug induced Cushing's syndrome. This interaction can also occur with ritonavir, a 3A4 inhibitor also used as a pharmacokinetic booster, and fluticasone resulting in more than a 100-fold increase in plasma steroid exposure. Most electronic prescribing systems will alert the prescriber on this drug interaction and recommend an alternative choice. However, fluticasone is now available over the counter without a prescription. This availability combined with the widespread endorsement to utilize intranasal corticosteroids for seasonal allergies could lead to a direct patient recommendation, not prescription, which is not checked through a computerized order entry system.

Alternatives to fluticasone to treat allergic rhinitis in this patient population include intranasal beclomethasone, intranasal triamcinolone, or an oral second generation H_1 antagonist such as loratadine or cetirizine. Mometasone and budesonide are both substrates of 3A4, although to a lesser extent than fluticasone; mometasone could be utilized, however monitoring of adrenal function would be encouraged.

Take Home Points

- Fluticasone, a 3A4 substrate, can be affected by major 3A4 inhibitors often used in antiretroviral therapy such as cobicistat and ritonavir, leading to systemic adrenal suppression.
- Fluticasone nasal spray is available over-the-counter, thus all patients on 3A4 inhibitors should be counseled to avoid Fluticasone and offered alternative treatment for seasonal allergies.

References:

1. Saberi Parya, Phengrasamy T, and Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: A review of pharmacokinetics, case reports, and clinical management. *HIV Med*. 2013;14(9):519-529.

93: Hydrochlorothiazide Ceiling

Question:
An 83-year-old female presents to establish care in a cardiology clinic. She has a past medical history significant for reduced ejection fraction heart failure (HFrEF) and chronic kidney disease (CKD) stage 4 with a current regimen including oral Entresto (sacubitril/valsartan) 200 mg daily, Toprol XL (metoprolol succinate) 100 mg daily, and Maxzide (triamterene/hydrochlorothiazide) 75/50 mg 1-2 tablets daily as needed for edema. She states that on average she utilizes Maxzide two tablets three times weekly in attempts to control her edema, however, as of late it does not seem to be reducing the swelling as it used to. In clinic today she is normotensive and reports no prior history of hypertension; bilateral lower extremity 3+ pitting edema is noted upon physical exam.

What optimizations could be made to her congestive heart failure regimen?

Contributors: Shannon Rice, Rebecca Sleeper, Alan Peiris

Answer:
As needed Maxzide (triamterene/hydrochlorothiazide) would not be the preferred agent for symptomatic management of this patient's HFrEF. The 2013 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines include the recommendation of thiazide diuretics for mild fluid retention in hypertensive patients with a maximum hydrochlorothiazide dose of 200 mg daily. However, it has been documented that at doses greater than 50 mg/day, hydrochlorothiazide demonstrates minimal response escalation with increased incidence of electrolyte disturbance. At doses greater than 50 mg daily the risk of hypokalemia, hypomagnesemia and hyponatremia outweighs the questionable benefit of increased diuresis. Further, this ceiling effect is intensified in those with a creatinine clearance less than 30 mL/minute.

Mechanistically, the thiazide class is dependent on reaching the distal convoluted tubule of the nephron. In those with severe renal dysfunction the ability to distribute these agents to their site of action is impaired, thus rendering them inefficacious. It is possible that using thiazide-like diuretics such as indapamide and chlorthalidone maybe superior to hydrochlorothiazide in reducing blood pressure without elevating serum cholesterol or reducing sodium and potassium concentrations.

Considering a patient that lacks a hypertensive history and has a creatinine clearance less than 30 mL/minute, a loop diuretic would then definitively become the preferred agent for controlling fluid retention associated with systolic heart failure. Loop diuretics allow for dose titration in CKD patients with retained efficacy and possess reduced antihypertensive properties as compared to the thiazide class.

Take Home Points

- Hydrochlorothiazide has a documented plateau of efficacy at 50 mg/day.
- The efficacy of hydrochlorothiazide is dependent on the patient's ability to filter the agent to the site of action at the distal convoluted tubule. As such, their efficacy is impaired with renal impairment.
- If fluid retention or hypertension is not controlled with a hydrochlorothiazide dose of 50 mg/day, switch to another class of medication or addition of another agent should be considered.

<u>References:</u>

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Sevenson LW, and Westlake C. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2013;128:e240-e327.
2. Peterzan MA, Hardy R, Chaturvedi N, and Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension*. 2012;59(6):1104-1109.

94: Tenofovir Formulation Change

Question:
A 24-year-old Hispanic male presents to establish care at the HIV clinic. He was diagnosed one week ago at the public health department following routine screening. He has no significant medical history outside his recent diagnosis. Upon speaking with him, he identifies as homosexual and does report having casual sexual encounters. Towards the end of the conversation he mentions a HIV positive friend of his recently switched medication to a new agent called Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) that is much better.

He asks for more information on Genvoya and what makes it better than other HIV medications?

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
Genvoya is a combination antiretroviral agent that includes tenofovir alafenamide, a nucleoside reverse transcriptase inhibitor, emtricitabine, a nucleotide reverse transcriptase inhibitor, elvitegravir, an integrase inhibitor, and cobicistat, a cytochrome 3A4 inhibitor. Genvoya is very similar to Stribild, differing only by the formulation of tenofovir present; tenofovir alafenamide (TAF) is a prodrug used in Genvoya while tenofovir disoproxil fumarate (TDF) is used in Stribild. TAF is the preferred formulation of tenofovir in the treatment of HIV-1 and hepatitis B virus (HBV) infections because it has demonstrated non-inferior efficacy compared to TDF with a clinically significant improvement in safety. Specifically, TAF shows significantly less incidence of proteinuria and glomerular filtrate rate (GFR) reduction as well as fewer alterations of bone mineral density in the spine and hip compared to TDF.

TAF achieves this adverse effect reduction secondary to reduced serum concentrations; TAF concentrates intracellularly rather than remaining in circulation like TDF. This is especially important for patients who will be taking antiretroviral agents for extended durations, such as in the case described above. As patients with HIV live longer, it is important to minimize the incidence of preventable drug-induced chronic conditions such as renal dysfunction and bone mineral changes. Further, TAF has fewer interactions with cytochrome P450 enzymes when compared to TDF. While TAF still has its own side effects and interactions that should be reviewed with patients before treatment initiation, it is now the preferred tenofovir formulation.

Take Home Points

- Tenofovir alafenamide (TAF) is a prodrug of tenofovir that has less adverse effects compared to tenofovir disoproxil fumarate (TDF), specifically less renal toxicity and bone mineral density impairment.
- Ideally, all patients on an antiretroviral regimen that includes tenofovir should be transitioned to the TAF formulation over TDF.

References:

1. Mills A, Ortiz R, Crofoot G, et al. 48 week study of the first PI-based single tablet-regimen (STR) darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) vs darunavir (DRV) boosted by cobicistat (COBI) and emtricitabine/tenofovir disoproxil fumarate (TVD) in HIV-infected treatmentnaïve adults; 54th ICAAC; Washington, USA: 2014. Abstract H-647c.
2. Wang H, Lu X, Yang X, and Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. *Medicine*. 2016;95(41):e5146.

95: Ketorolac Duration

Question:
A 42-year-old male presents to the emergency department complaining of stiff neck, photophobia, headache, fever, chills and malaise. He is initiated on ketorolac 30 mg intravenously (IV) every 6 hours as needed for pain. He is admitted for a work up and is later diagnosed with aseptic meningitis; supportive care is initiated. The patient's pain is well controlled with the ketorolac and on average he uses three doses per day. On the fifth day of hospitalization the provider informs the patient they will be discontinuing the ketorolac and the patient becomes upset. He does not understand why the agent must be stopped if it's working.

Offer an explanation to this patient for the proposed action regarding ketorolac.

Contributors: Shannon Rice, Rebecca Sleeper

Answer:
Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) used for moderate to severe pain. The mechanism of ketorolac is cyclooxygenase (COX) enzyme inhibition with a slightly greater affinity for COX1. While COX inhibition reduces prostaglandin production and secondary nociception, it also prevents the formation of a protective mucus layer in the stomach. Without this barrier, corrosive acid can contact the stomach lining, potentially inducing serious adverse effects such as gastrointestinal (GI) ulceration and perforation. Similar to other NSAIDs, ketorolac also can impair renal function through inhibition of vasodilation of the glomerulus afferent arteriole and increase the risk of bleeding via inhibition of platelet aggregation. Reducing the duration of the agent to less than or equal to five days and utilizing the lowest effective dose helps to reduce the incidence of serious adverse events. Most studies suggest doses over 90 mg/day are associated with the greatest risk.

An example of explanation to the patient could be as follows. While ketorolac is helping your pain, there are risks to its long-term use including possible stomach ulcers, increasing your risk of bleeding, and kidney problems. After five days, these potential risks now are larger than the benefit of pain relief; however, we will start a new medication to make sure your pain is effectively managed.

Take Home Points

- Ketorolac is a strong NSAID used for moderate to severe pain.
- Risk for adverse effects, including GI bleeding and renal dysfunction, increase directly with the dose and duration of ketorolac.
- It is advisable to keep doses as low as possible and limit duration to 5 days.

References:

1. Gillis JC, and Brogoden RN. Ketorolac: A reappraisal of its pharmacodynamics and pharmacokinetic properties and therapeutic use in pain management. *Drugs*. 1997;53(1):139-188.
2. Vadivelu N, Chang D, Helander EM, Bordelon GJ, Kai A, Kaye AD, Hsu D, Bang D, and Julka I. Ketorolac, oxymorphone, tapentadol, and tramadol: A comprehensive review. *Anesthesiol Clin*. 2017;35(2):e1-e20.

96: Pseudoephedrine Use in Pregnancy

Question:
A 30-year-old pregnant woman comes to the pharmacy counter, and is inquiring about what type of over-the-counter (OTC) medication would be best for her congested nose. She is in her first trimester of pregnancy.

She has heard that using Sudafed (pseudoephedrine) during pregnancy is not recommended and she wants to know why.

Contributors: Jessica Agrimor, Rebecca Sleeper

Answer:
The use of pseudoephedrine especially during the first trimester of pregnancy would not be recommended. The American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI) recommend the use of oral pseudoephedrine as decongestants in the second and third trimester of pregnancy but not in the first trimester. Previous case control studies have shown there is a possible risk of gastroschisis (birth defect of the abdominal wall), small intestinal atresia, or hemifacial microsomia associated with oral pseudoephedrine use in the first trimester of pregnancy. During the second and third trimesters, pseudoephedrine 30 to 60 mg every 4 to 6 hours may be used in pregnant women with no underlying cardiac diseases.

Nasal decongestants such as oxymetazoline and xylometazoline are also not preferred decongestant agents due to their 5-hydroxytryptamine (serotonin) receptor agonistic activity that could potentially affect fetal development, and in addition to this, there have been case reports with adverse fetal/neonatal events. Use of intranasal triamcinolone during pregnancy has been shown to be associated with increased risk of respiratory system defects. On the other hand, first generation antihistamines such as diphenhydramine, chlorpheniramine, and clemastine and second generation antihistamines (loratadine and cetirizine) are associated with no adverse effects to the fetus.

In this case, the best choice of intervention for rhinitis would be to try nonpharmacological approaches first such as controlling the environment, avoiding allergens, using saline lavage and to suggest lying in the supine position as this increases nasal resistance to passage of air or elevating head of the bed. Another approach would be the use of isotonic saline products or external nasal dilators.

Take Home Points

- Use of pseudoephedrine in the first trimester is contraindicated due to risk of birth defects, but may be used during the second and third trimester of pregnancy.
- Nonpharmacological treatments are recommended first to alleviate pregnancy rhinitis.
- A relatively safe option of OTC product for pregnant women in their first trimester would be - isotonic saline products and first or second generation antihistamines.

<u>References:</u>

1. The use of newer asthma and allergy medications during pregnancy. Position Statement. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). *Ann Allergy Asthma Immunol*. 2000;84:475-480.
2. Pray WS, Pray GE. Self-Care of Rhinitis During Pregnancy. *US Pharm*. 2014;39(9):16-23

97: Panic Disorder

Question:
A 28-year-old male has been having incidences of increased fear with symptoms of shaking, sweating, increased heartbeat, and a choking feeling that just suddenly comes and goes. After seeing a psychologist, he was diagnosed with panic disorder without agoraphobia. He was prescribed oral alprazolam 0.75 mg 1 tablet three times a day which has been controlling his panic attacks.

What other therapeutic considerations would be optimal for the overall care for this patient?

Contributors: Jessica Agrimor, Rebecca Sleeper, Alan Peiris

Answer:
The four pharmacological modalities to treat panic disorders with comparable efficacy are tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines. The choice of treatment is based on adverse side effects and costs associated with each drug class. This patient's treatment regimen of alprazolam to control his panic attacks is appropriate.

Benzodiazepines provide rapid response by working centrally in the nervous system and act as a positive allosteric modulator on the gamma aminobutyric acid (GABA)-A receptor. However, the use of benzodiazepines such as alprazolam should be considered a short-term treatment. The risks of developing dependence or recurrent/rebound withdrawal symptoms upon discontinuation of alprazolam are high. The American Psychiatric Association recommends SSRIs or SNRIs as first line agents for the chronic treatment of panic disorders. The patient would benefit more from the addition of an SSRI or SNRI with tapering of the alprazolam. Antidepressants take at least four to six weeks to take effect and alprazolam should not be discontinued prematurely. TCAs are considered last line agents because of their unfavorable side effects of anticholinergic symptoms, sexual dysfunction, weight gain, orthostatic hypotension and potential for lethal cardiotoxicity. It should be noted that that SSRIs and SNRIs may have many adverse effects including loss of libido and hyponatremia. Another cornerstone therapeutic intervention that is recommended as an adjunctive therapy is cognitive-behavioral therapy (CBT).

Take Home Points

- First line agents for treatment of chronic panic disorders are serotonin reuptake inhibitors (SSRIs) with the short-term use of benzodiazepines.
- Tricyclic antidepressants (TCAs) are last line agents for treatment of chronic panic disorders due to adverse effects.
- Adjunctive therapy with CBT is also recommended.

References:

1. Stein MB, Goin MK, Pollack MH, et al. Practice Guideline for the Treatment of Patients with Panic Disorder, 2nd edition. Work Group on Panic Disorder. *Am J Psychiatry*. 2009:1-90.

98: Management of Statin Intolerance

Question:
A 53-year-old patient states that he has missed multiple doses of his atorvastatin 40 mg daily secondary to new onset muscle pain. Patient is on his statin for coronary artery disease and has had 2 cardiac stents placed in the last 3 years. The patient has no history of diabetes and smoking, but is on anti-hypertensives (HCTZ 25 mg daily). The patient would like to discontinue his atorvastatin and requests your input. He states there is a string family history of cardiac disease and his father died suddenly at age 54 years.

Recent additions for his dyslipidemia include gemfibrozil 600 mg twice a day. Labs 3 months ago: Cholesterol: 235 mg/dL, LDL: 188 mg/dL, HDL: 47 mg/dL, TG: 268 mg/dL. Labs today: Cholesterol: 230 mg/dL, LDL: 180 mg/dL, HDL: 44 mg/dL, TG: 225 mg/dL and moderate CK elevation. His blood pressure is elevated at 150/89 mmHg.

What advice would be given to the patient at this point?

Contributors: Jessica Agrimor, Rebecca Sleeper, Alan Peiris

Answer:
There are multiple therapeutic options. First, it would be recommended to discontinue his gemfibrozil therapy as combination with atorvastatin is associated with increased risk of rhabdomyolysis (defined as creatinine kinase, CK, >10 times upper limit of normal). Other agents to avoid or use with caution if on a statin due to increased risk of rhabdomyolysis would be amiodarone, cyclosporine, verapamil, antifungals such as ketoconazole, or any CYP3A4 inhibitor agents (depending on the statin). Switching him to fish oil instead would be better for his hypertriglycemia. This would most likely eliminate the muscle pain symptoms associated with the patient, however, if he continues to have muscle pain, then the next step is to discontinue atorvastatin for two weeks or until symptoms resolve and rechallenge with the same statin regimen with a reduction in dose and then increase as tolerated.

Another option would be to do a trial of intermittent dosages (alternate-day therapy or several times a week) using longer half-life statins such as atorvastatin and rosuvastatin. If symptoms continue, the patient may switch to the less lipophilic statins (pravastatin, fluvastatin, and rosuvastatin) with the same high intensity goal. When other statins are not tolerated, then switching to non-statin therapy such as ezetimibe, bile acid sequestrants or niacin could be considered. These agents do not generally have the magnitude of LDL reduction seen with statins. Newer agents such PCSK9 inhibitors asalirocumab, evolocumab, could be considered but they are expensive and evidence to support these therapies in reducing cardiovascular outcomes compared to statins is less well established. Statins not only lower LDL, but also have anti-inflammatory effects to stabilize and regress atherosclerotic plaques and so dechallenging/rechallenging with statins would be recommended first before switching to other non-statin therapies.

Take Home Points

- Combining a statin and fenofibrate is contraindicated due to increased risk of rhabdomyolysis.
- Other agents that could increase the risk of rhabdomyolysis with a statin are amiodarone, cyclosporine, verapamil, antifungals, or CYP3A4 inhibitors.
- Ways to manage statin intolerance is by discontinuing and rechallenging statins, reducing the dose, switching to less lipophilic statins using intermittent dosing of statins with a longer half-life or switching to non-statin therapy as last line of therapy.

References:

1. Fischer S, and Julius U. Management of patients with statin intolerance. *Atheroscler Suppl*. 2017;30:33-37.
2. Bitzur R, Cohen H, Kamari Y, and Harats D. Intolerance to statins: mechanisms and management. *Diabetes Care*. 2013;36(Suppl 2):S325-S330.

99: Empagliflozin and Cardiovascular Benefits

Question:
A 64-year-old male presents to clinic for a diabetes follow-up The patient has a past medical history of type 2 diabetes, hypertension, mixed hyperlipidemia, and cardiovascular disease requiring a cardiac stent. He is currently on metformin 500 mg extended release 2 tablets twice daily for his diabetes. Patient states he is compliant with metformin with no issues and has been gradually working on lifestyle modifications particularly incorporating more physical activity as he wishes to lose weight. He is afraid of needles and wants to stay on oral diabetic medications as much as possible. Most recent A1c of 8.8% and elevated home blood glucose readings show poor glycemic control.

What is the next recommended oral diabetic agent for this particular patient?

Contributors: Jessica Agrimor, Neha Mittal

Answer:
The patient's wish to avoid injections does limit some options and should be explored further. It does limit some therapies such as Liraglutide. There is considerable variation among specialists regarding the choice of anti-diabetic agents. One group of agents that could be considered are the SGLT-2 inhibitors such as empagliflozin because of his past medical history of vascular disease. Recent clinical studies have shown that empagliflozin may provide additional cardiovascular benefits with lower mortality in certain high-risk patients with diabetes. Empagliflozin may possibly also aid weight loss. It should be noted that this group of agents have been used over a relatively short period in clinical practice. An increased risk of amputations in the lower limbs (below knee) have been reported with this group of agents.

Empagliflozin decreases plasma glucose concentration through inhibition of sodium-glucose cotransporter 2 in the proximal renal tubules which in turn reduces renal reabsorption of glucose resulting in increased urinary excretion of glucose. Because of this indirect mechanism of decreasing hyperglycemia, empagliflozin's ability to lower A1c and blood sugar levels are moderate compared to metformin. In this case, keeping metformin would be advisable as tolerated. Also, with the loss of salts comes polyuria, and so patients on empagliflozin should be advised to keep themselves hydrated. Other side effects with empagliflozin include genitourinary infections (due to increased glucose in urine) and ketoacidosis.

Take Home Points

- Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor may provide additional cardiovascular benefits and could be considered in diabetic patients with established cardiovascular disease.
- Most common side effects of empagliflozin are polyuria and genitourinary infections, therefore counsel patients to stay hydrated.
- Increased risk of amputations in the lower limbs have been reported with the use of these agents

References:

1. Sonne DP, and Hemmingsen B. American Diabetes Association: Standards of medical care in diabetes 2017. *Diabetes Care*. 2017;40(Suppl. 1):S1–S2.
2. Zinman B, Wanner C, Lachin JM, Fitchett D, Bulhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, and Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373:2117-2128.

100: Drug Induced QT Prolongation

Question:
A 50-year-old male patient comes into the pharmacy to pick up his medications. The pharmacy technician approaches you, the intern, for a new counsel on citalopram 40 mg daily for depression. Upon reviewing his medication list, you notice that he is on omeprazole 20 mg daily for his gastroesophagel reflux disease (GERD).

What drug-drug interaction and self-monitoring side effects would you counsel the patient on between these two medications?

Contributors: Jessica Agrimor, Rebecca Sleeper, Neha Mittal

Answer:
The drug-drug interaction seen between citalopram and omeprazole is a potential drug-induced QT prolongation. Citalopram is metabolized by CYP2C19 and omeprazole is a moderate inhibitor of this enzyme. As a result, omeprazole increases the drug serum levels of citalopram predisposing the patient to QT prolongation syndrome of serious arrhythmias, fainting, seizures, or sudden death. Patients on citalopram and omeprazole should be counseled to monitor closely for increased adverse effects associated with citalopram such as hyperthermia, agitation, hyperreflexia, tremor, sweating, dilated pupils, and diarrhea. This interactions could be seen with several PPIs (esomeprazole, lansoprazole, and pantoprazole) and other SSRIs such as escitalopram and sertraline.

The use of omeprazole and citalopram would be considerably safer at a dose of 40 mg daily of omeprazole or less and 20 mg daily of citalopram respectively, according to the US Food and Drug Administration (FDA). The combination of these two medications warrant specific monitoring and documentation due to drug-induced QT prolongation. Arrythmias such as torsades de pointes and sudden cardiac arrest could occur. This makes it crucial to assess these patients for a history of structural heart disease and personal/family history of QT prolongation syndrome. Such a history could increase the risk of QT prolongation and require EKG and electrolyte monitoring. This maximum dose of citalopram could be limited to 20 mg per day depending on whether a patient is a poor metabolizer of CYP2C19, age >60 years old, or those who have hepatic dysfunction or are currently on another CYP2C19 inhibitor.

Take Home Points

- QT prolongation syndrome include serious arrhythmias, fainting, seizures, and sudden death.
- The QT prolongation risk between citalopram and omeprazole is increased at doses of citalopram of 40 mg per day.
- The citalopram dose should be limited to 20 mg per day in patients who are poor metabolizers of CYP2C19, are currently on a CYP2C19 inhibitor, greater than 60 years old, or have hepatic dysfunction.

References:

1. Sheeler, RD, Ackerman MJ, Richelson E, Nelson TK, Staab JP, Tangalos EG, Dieser LM, and Cunninghamd JL. Considerations on safety concerns about citalopram prescribing. *Mayo Clin Proc*. 2012;87(11):1042–1045.
2. Gjestad C, Westin, AA, Skogvoll E, and Spigset O. Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors citalopram, escitalopram, and sertraline. *Ther Drug Monit*. 2015;37(1):90–97.

101: Disulfiram-like Reaction with Metronidazole

Question:
A 48-year-old female was rushed to the emergency room (ER) for facial flushing and tachycardia. Upon review of her medication list, you notice that she is on metronidazole 500 mg 1 tablet three times daily for 10 days. The patient's daughter reports that her mother is currently on her 7th day of antibiotic course, and upon further interviewing find out that the patient ingested a glass of wine prior to ER admission.

What would you tell the patient's daughter on what could have caused the symptoms to develop?

Contributors: Jessica Agrimor, Neha Mittal

Answer:
The patient experienced what is called disulfiram-like reaction, antabuse effects, or acetaldehyde syndrome which was caused by the interaction between metronidazole and alcohol. Other symptoms associated with disulfiram-like reaction include abdominal cramps, headache, nausea, vomiting, hypotension, and may even lead to myocardial infarction and shock in severe cases. These symptoms occur due to the inhibition of acetaldehyde dehydrogenase and further inhibition with coadministration of alcohol produces increased acetaldehyde levels in the blood. There has been conflicting evidence on the exact mechanism on how and why metronidazole and alcohol interact to cause disulfiram-like reactions in some individuals but not in others. However, it is evident that there have been case reports of disulfiram-like reactions and even death as a result of concurrent ethanol and metronidazole intake.

It is important to note as well that it takes approximately 48 hours for metronidazole and other nitroimidazole agents to be cleared from the body system in healthy subjects. FDA recommendations state it is advisable to abstain from alcohol within 3 days of therapy discontinuation. Due to the incidences (even though rare) and severity of symptoms related with disulfiram-like reaction, patients on metronidazole should always be counseled to avoid concomitant alcohol products during therapy and at least after 72 hours of therapy discontinuation.

Take Home Points

- Disulfiram-like reaction symptoms present as abdominal cramps, headache, nausea, vomiting, and hypotension.
- Avoid alcohol during and at least 72 hours after discontinuation of metronidazole therapy.

References:

1. Borja-Oliveira CR. Alcohol-medication interactions: the acetaldehyde syndrome. *J Pharmacovigilance*. 2014;2:145.
2. Williams CS, and Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother*. 2000;34:255-7.


TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER