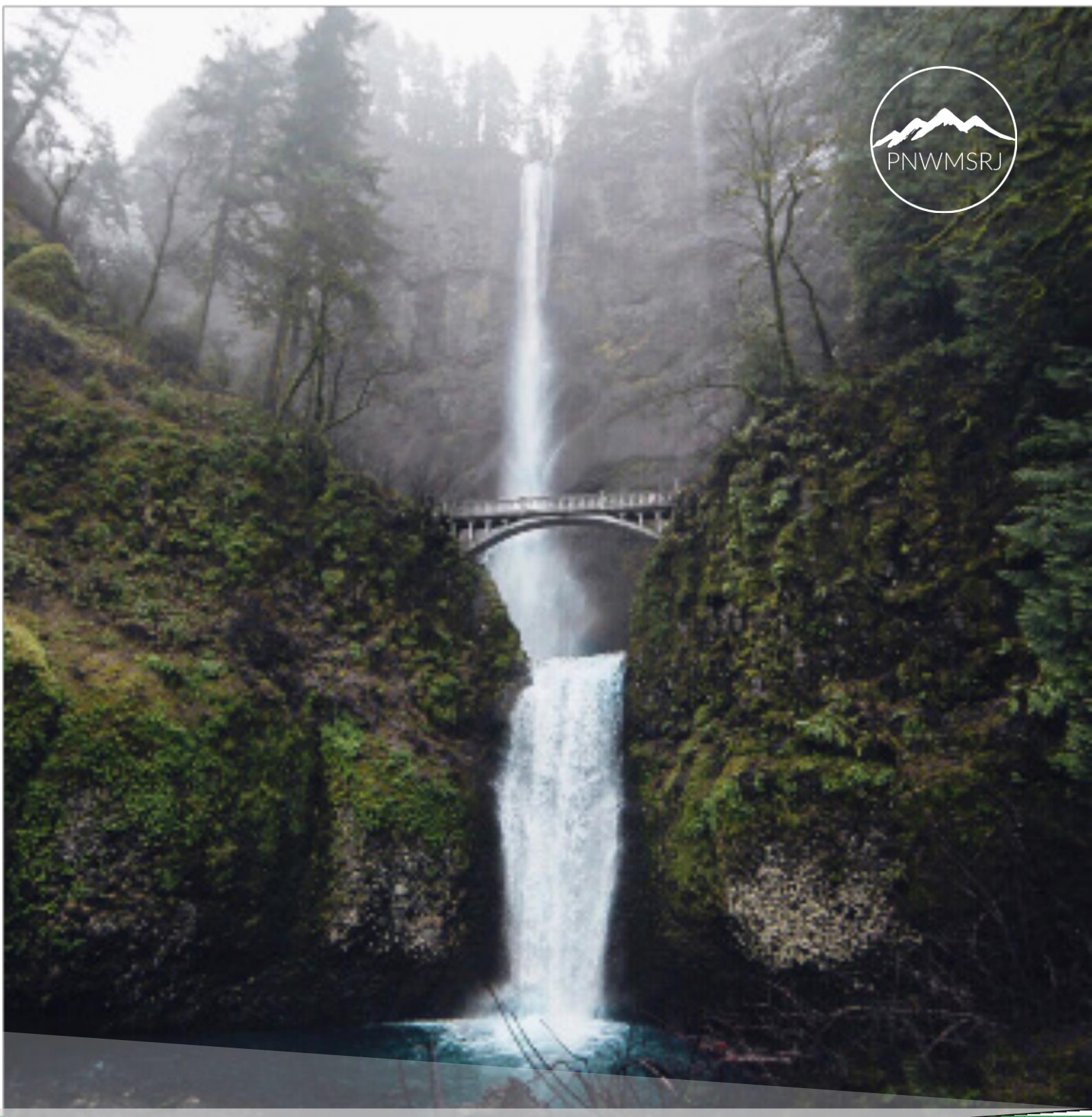

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Featured Artwork - Rockaway Beach

This photo was taken at Rockaway Beach on a clear and starry night. As a ship was passing directly behind the rocks, I was able to capture a 5-second-long exposure. By the time I tried to take a second photo, the ship had already moved too far past the rocks. I got lucky my composure and timing were perfect. Very happy to share the beauty of the pacific northwest.

Photographer: Cory Kim
Cory.kim@westernu.edu

Abstracts selected from the COMP-NW Research Symposium and COMP STRS symposium

1. SOCIAL MEDIA PERSPECTIVES AND QUESTIONS OF LIVING WITH PCOS

Madelaine Towbin, Emerald Chiang, Katherine Ghobrial, Shira Razi

Introduction: This study sought to analyze how women with the hormonal disorder Polycystic Ovarian Syndrome (PCOS) utilize social media, the themes they discuss online, the medical accuracy of the advice they encounter, and if they are aware of their increased risk of anxiety and depression.

Methods: A team of investigators searched for the most viewed social media posts using the keyword "PCOS" between July and December 2019. The criteria for popular posts varied by site: posts in public Facebook PCOS groups, Reddit r/PCOS with 175 upvotes, YouTube videos with 1000 views, Instagram photos with likes and Tweets with 1 interaction were analyzed for mentions of advice, conflicts of interest, and any of the following themes: weight loss, experience with doctors, medication, fertility, acne, abnormal hair growth, anxiety, depression, and/or menstrual irregularity. Advice was classified into categories of "completely accurate" if it was supported by a medical association, "insufficient evidence" if it only was found in peer-reviewed studies, and "inaccurate" if any part was against clinical guidelines or was unsupported. Conflict of interest was noted when it mentioned products from which the poster gained profits.

Results: 376 posts were analyzed with 655 total mentions of the selected themes. Fertility (n=106), weight loss (n=101), and medication (n=100) were the most frequently mentioned, while anxiety (n=28) and depression (n=35) were the least. 100% of Instagram posts contained conflicts of interest (n=47) and 98 were recorded overall.

182 total pieces of advice were recorded: Facebook (54%) and Reddit (49%) had the highest accuracy, while Instagram (20%) had the lowest.

Conclusion: Physicians can create stronger supportive relationships with patients with PCOS by educating more on the themes women most frequently discuss online, such as fertility and weight loss, and by screening for anxiety and depression, as women seem to be largely unaware of those risks.

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2. SIGNAL TRANSDUCTION PATHWAYS INVOLVED IN ANTIMICROBIAL RESISTANCE MECHANISMS OF GRAM-POSITIVE BACTERIA

Neda Amin, Hendrik Szurmant

Project Abstract: Goals of the Study/Hypothesis: Gram-positive pathogens include some of the most formidable human pathogens. Many of these bacteria have evolved resistances to our most important antimicrobials. Bacterial signal transduction systems are heavily involved in mediating these resistances and have been proposed as new drug targets. We conducted a systematic literature review in order to highlight the importance and the diversity of signal transduction systems in antimicrobial resistance of clinical isolates of Gram-positive pathogens.

Materials & Methods: We conducted a systematic literature review by analyzing publications of the past 10 years with a focus on antimicrobial resistance in the Gram-positive pathogens Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes and related species.

Results: Our literature review highlights the diverse mechanisms and the importance of signal transduction in bacterial drug resistance. One prime mechanism involved in these processes is the bacterial two-component system, which has no orthologs in the animal kingdom. Other important mechanisms involved in signal transduction include inducible proteolysis of repressors of transcription of resistance genes. In some instances, mutations in specific native signal transduction systems directly contribute to antimicrobial resistance and this commonly involves the two-component system as well. Conclusions: Our literature review highlights the importance of various signal transduction systems in antimicrobial resistance and thus supports current drug development efforts aimed at targeting these systems

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3. HOW DOES LEISHMANIA VECTOR DISTRIBUTION VARY OVER A GRADIENT OF LAND USE: A REVIEW OF AVAILABLE EVIDENCE

Hannah Cooperman, Thomas Tripolone, Astrid Reyes, Dr. Michelle Steinauer, Dr. Brianna Beechler and Dr. Rhea Hanselmann

Project Abstract: Goals of the Study: Rapid anthropogenic change engenders the spread of infectious pathogens as well as their vectors and carriers. The parasite Leishmania causes debilitating and often deadly disease that

disproportionately affects the poorest populations worldwide. Many environmental factors influence the distribution of sandfly vectors including human-driven habitat modifications and climate change. Our research group has collected vectors in agricultural and wilderness areas in Costa Rica in an effort to understand vector ecology and the influence on Leishmaniasis distribution; however, pandemic restrictions have prevented analysis of the data and further collections. Our aim is to assess the available body of sandfly trapping studies in Central America for a relationship between vector distribution and a land use gradient.

Materials & Methods: Existing sandfly trapping studies were compiled to evaluate for a relationship between vector distribution and land use type. PubMed, Google Scholar, and Web of Science searches combined categories of disease, vector, and location. Relevant studies were screened according to explicit descriptive qualifiers. Only studies with well-defined trap ecotopes were included, then catalogued into domestic, peridomestic, and sylvatic groups.

Results: The preliminary results found a total of 14 full-text articles that met the inclusion criteria. Following a comprehensive categorization of relevant studies, we will complete a statistical analysis of compiled data to describe land use patterns of increased risk for Leishmania transmission.

Conclusions: Evaluation of available studies led to the conclusion that there is an inadequate body of data identifying ecological drivers of Leishmaniasis in Central America. Most studies lacked adequately reproducible site descriptions as well as isolation and identification of Leishmania spp. within trapped vectors. These oversights impede characterization of how parasite distribution varies over geography and time. This knowledge is vital to determine the relationship between disease ecology and human infections. Our findings will inform future experimental design to address these questions on site in Costa Rica.

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4. ARTERIAL LATEX INJECTION FOR MEDICAL STUDENT LEARNING

Christian Shafer, William Merbs, Edie Sperling

Project Abstract: Anatomy lab with patient donors has always been a hallmark of pre-clinical medical school education. While some medical schools choose to explore the option of virtual labs, others continue to look for ways to enhance the learning experience for students within the patient donor anatomy lab. The purpose of this study is to explore the value of adding latex injection of human vasculature as another tool to enhance learning and perspective. Latex injection has been used by specialists and surgeons to study details of arterial trees, and this same model could add to medical student education. As many of these smaller arteries are often discarded and unnoticed as students dissect larger structures, this study is of specific interest in the medical education setting. Red, laboratory grade latex was obtained and injected into the femoral, radial, and ulnar arteries. The latex was allowed three days to set and solidify. Dissection of the structures of interest was then performed and documented photographically. We found clearer visualization of larger arteries in addition to the smaller arteries, specifically those intimate with subcutaneous fat, fascia, and periosteum. Our findings suggest value in utilizing at least one donor patient injected with latex to help students appreciate the smaller and variable arteries that may not typically appear in anatomy textbooks or atlases.

Goals of the Study/Hypothesis: The purpose of this study is to explore the value of observing latex-injected human vasculature as another tool in the dissection lab to enhance learning and perspective in medical education. Latex injection has been used by specialists and surgeons to study details of arterial trees, and this same model could enhance medical students' understanding of the dense concentration and variability of vascular structures. As many of these smaller arteries are often discarded and unnoticed as students dissect larger structures, this study is of particular interest in the health education setting.

Materials & Methods: Red, laboratory grade latex was obtained and injected into radial, and ulnar arteries. The latex was allowed three days to set and solidify. Dissection of the femoral, structures of interest was then performed and documented pnhotograpically.

Results: We found clearer visualization of larger arteries, in addition to many previous non- visualized smaller arteries, specifically those intimate with subcutaneous fat, fascia, and periosteum.

Conclusions: Our findings suggest value in utilizing at least one donor patient injected with latex to help students appreciate the smaller and variable arteries that may not typically appear in anatomy textbooks or atlases.

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5. TELEMEDICINE EXPOSURE AND COMFORT AMONG MEDICAL STUDENTS

Josiah Warner,Christian Shafer, Dr. Kathryn Potter

Introduction: The COVID-19 pandemic has required the medical community and medical systems to adapt in numerous ways from working through supply chain logistics and physician shortages to reducing exposure while maintaining patient visits. With mandates to maintain social distancing, it has become increasingly difficult to work within the standard mode of practice of delivering care. As a result, individual physicians, entire

hospital systems, and medical schools have needed to adapt to an online/virtual method of delivery revealing a possible need for more telemedicine education. The survey is focused on medical students and their exposure to telemedicine as well as their levels of comfort with this burgeoning system of delivery. Methods: Given the changes to healthcare delivery and increasing popularity of telemedicine in the face of the COVID-19 pandemic, a survey was designed to better understand students' exposure to, comfort with, and perceptions of telemedicine based on their medical education to date. The 21-question survey polled 213 students—ranging from first to fourth year osteopathic medical students (OMS1-OMS4)—at Western University of Health Sciences College of Osteopathic Medicine of the Pacific and Pacific-Northwest (COMP and COMP-NW). Results: For competency in taking a patient's history via telemedicine, 79% of responses were positive while only 14% responded positively with comfort in performing a physical exam via telemedicine. 78% of student responses indicated thoughts that telemedicine skills should be part of the curriculum. Additionally, 77% of student responses indicated that the current COVID-19 pandemic has increased the desire to learn more about telemedicine. Conclusion: Telemedicine appears to be slowly working its way into medical education as well as into the purview of the osteopathic students; especially among the more recent classes (OMS2 compared to OMS4). Overall, there is a positive attitude towards learning how to conduct and integrate telemedicine visits and an increased interest in learning it due to the COVID-19 pandemic. There remains a large gap both in knowledge of applicability and confidence in carrying out this newer form of patient interview and evaluation. An additional survey may be deployed to compare results and evaluate how faculty have adapted the clinical education curriculum. The survey serves as a small snapshot revealing how telemedicine is perceived and how it may be an important aspect of clinical medical education.

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6. COGNITIVE DEFICITS IN DIFFERENT MOUSE STRESS MODELS

Alexandra Bui and Roshni Jogin

Introduction: Neurocognitive dysfunction has been associated with stress and post-traumatic stress disorder (PTSD). For example, chronic stress results in sustained impairment of cognitive flexibility and synaptic strength in the hippocampus, a brain structure critical for learning and memory. With stress, cytokine-associated inflammation amplifies, and in turn, exacerbates an immune response potentially leading to cognitive defects. We hypothesize that stress leads to changes in chemokine and chemokine receptor (e.g. C-C chemokine receptor 5 (CCR5) and its ligand CCL5) expression, which is involved in the cognitive deficits induced by stress.

Methods: Groups of C57BL/6NTac mice were subjected to no stress (group 1), repeated restraint stress (RRS) for 7 days (group 2) or 14 days (group 3), or single prolonged stress (SPS) (group 4). Afterwards, hippocampal tissue from some mice were collected to measure Ccr5 and Ccl5 expression with quantitative PCR (qPCR), and the remaining mice were tested in behavioral paradigms in the following order: elevated plus maze (EPM), open field (OF), object-place recognition (OPR), novel-object recognition (NOR), and contextual fear conditioning (CFC).

Results: Our preliminary results show that while there was no change in Ccr5 expression, there was an increase in Ccl5 expression in the dorsal hippocampus 24 hours after SPS. Compared to the control group, both 7 days and 14 days RRS groups caused an increase in anxiety and memory deficits.

Conclusion: Compared to the behavioral phenotypes induced by SPS, which was applied in a single day, RRS had a more significant effect on anxiety and memory. Examining the effects of CCR5 and CCL5 expression on learning and memory after exposure to stress will further the understanding of the relationship between chemokine signaling and cognitive deficits after stress.

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7. VEGGIERX: IMPROVING HEALTH THROUGH LOCAL PRODUCE

Hannah Killian, Jewell Roth, Morgan Nichols, Brian Burbidge, and Calder Dorn, Dr. Robyn Dreibelbis, Dr. Heidi Beery, Juliete Palenshus

Introduction: Obesity and diet related illness pose major health challenges in the United States. As of 2018, 42.4% of Americans were obese.1 Additionally, one study noted that Roseburg, OR has 6.5% more obese adults than the state average.2 Today, heart disease, cancer, stroke, and diabetes rank among the leading causes of death.3 The consumption of fruits and vegetables is strongly associated with a reduction in cardiovascular disease factors and all-cause mortality, including cancer.4,5 In general, programs dedicated to increasing the accessibility of farmers' markets to lower income families has been shown to increase fruit and vegetable consumption.5,6,7 In a report published in March 2019, it was noted that Umpqua Valley residents suffered 1.5% greater unemployment rates than those of Oregon at large. With all of this in mind, a 6-month concurrent program was devised to reach individuals experiencing food insecurity and/or chronic illness in and around the Umpqua Valley to increase plant-based food consumption and improve healthy eating habits.

Methods: Inclusion criteria were set to access the most food-insecure patients within the participating clinics.

A total of 50 individuals were enrolled (33 females and 17 males), and baseline health and social statistics were recorded. Participants were given a booklet of VeggieRx vouchers in the equivalent of 10 dollars per single/couple or 20 dollars per family. Vouchers were provided weekly for 6 months to be used at designated farmers' markets and redeemed for fresh produce. Pre- and post-surveys were conducted to evaluate the participants' progress.

Results: Though these data have not been finalized, initial reports have demonstrated an overall increase of 1.19 cups of vegetables consumed in a day and decrease in weight, blood pressure, and BMI over the 6-month period. Additionally, barriers—including but not limited to adherence, accessibility, and affordability—were identified.

Conclusion: There are very few programs that utilize a voucher system prescribed by physicians to increase the exposure of patients to high-quality produce sold at farmers' markets. Given complications from COVID-19 and two of the largest forest fires that Oregon has suffered to date, participation in the program was not as robust as originally intended, and data processing has been delayed. In response to this, we hope to investigate the literature on similar effects during COVID-19 and natural disasters to draw together potential recommendations for the continued pursuit of preventative medical care in such an unprecedented time for our planet. Other questions we hope to investigate include increasing fruit and vegetable consumption in affordable and accessible ways, how to encourage patients to incorporate whole foods into their diet, what motivational interviewing strategies have proven most successful, and what resources should be available to program participants to empower them to succeed. We hope our investigation helps to solidify a framework for other communities to implement similar programs in the future.

PNWMSRJ | Case Report

Erythema nodosum associated with nivolumab therapy in a patient with metastatic melanoma

Joshua Bezecny[1] , Rajan Kulkarni[2], Matthew Hiram Taylor[2], Elizabeth Berry[2]

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Abstract: Introduction and Objective: Erythema nodosum associated with nivolumab therapy is a rare immune-related adverse event. In four previously reported cases, patients had presented with multiple, painful subcutaneous nodules along the lower extremities following nivolumab therapy.

Case Presentation: In this case report, we describe a 36-year-old woman with metastatic melanoma treated with nivolumab, who developed a mildly tender left shin subcutaneous nodule that was discovered incidentally on fluorodeoxyglucose positron emission tomography/computed tomography scanning. Biopsy revealed a septal granulomatous mixed panniculitis consistent with erythema nodosum.

Conclusion: This report differs from previously described cases and highlights the possibility that erythema nodosum secondary to nivolumab therapy can present clinically with mildly symptomatic subcutaneous nodules discovered incidentally on routine surveillance fluorodeoxyglucose positron emission tomography/computed tomography scanning. These findings can increase the clinician's concern for malignancy, prompting further work-up, including biopsy and histopathological assessment of the lesions. Our case report can serve to guide the clinician to identify and manage this rare adverse event.

Introduction: Erythema nodosum (EN) associated with nivolumab therapy is a rare immune-related adverse event (irAE) that has only been described in four prior reports.[1-4] In this case report, we describe a 36-year-old woman with metastatic melanoma on nivolumab who, on routine surveillance fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT), was found to have multiple FDG-avid nodules on her bilateral lower extremities, which led to the discovery of a mildly tender left shin subcutaneous nodule with histopathological findings consistent with EN.

Case Presentation: A 36-year-old woman with a history of metastatic melanoma on nivolumab presented to dermatology clinic after routine imaging identified several FDG-avid nodules on her lower legs. Her past medical history was notable for IV drug use and positive hepatitis C antibody without evidence of active viral infection. In 2011, she was diagnosed with a melanoma of her left thigh (Breslow depth unknown) and was treated with wide local excision and sentinel lymph node biopsy (negative for lymph node involvement).
She remained asymptomatic until Spring 2017 when she developed severe headaches, and imaging revealed a solitary left occipital lobe metastasis. Further imaging revealed nodules in the lungs, right kidney, liver, adrenal glands, and mediastinal lymph nodes. She underwent resection of left occipital brain lesion, and pathology confirmed melanoma. In Summer 2017, she began treatment with ipilimumab (3 mg/kg) + nivolumab (1 mg/kg). Baseline imaging prior to starting immunotherapy showed significant disease progression including 10 new brain metastases and additional involvement of multiple organs. She underwent three gamma knife treatments of the CNS metastases in Fall 2017 and Spring 2018. Following 4 cycles of ipilimumab/nivolumab, restaging CT scans in Fall 2017 showed a mixed interval response with regression of the adrenal and pancreatic metastases and shrinkage or resolution of numerous intracranial masses. She developed immune-mediated colitis that resolved following discontinuation of immunotherapy, and treatment with high dose steroids and a single dose of infliximab. She was restarted on single agent nivolumab 480mg every 4-weeks in Spring 2018. A FDG PET/CT was performed late Winter 2019 which showed dermal-based soft tissue thickening involving the anterior lower legs with associated hypermetabolic activity (Figure 1A). Left leg ultrasound in early Spring 2019 did not demonstrate discrete nodules.

In Spring 2019 she was seen by dermatology, and examination of the left shin revealed a 1 centimeter, solitary, firm but mobile, subcutaneous nodule without a visible punctum or epidermal change (Figure 1B). There were no palpable nodules on the right shin or between the left first and second metatarsal heads, at sites of prior FDG uptake. She reported no preceding illness or infections but noted that she had been diagnosed with hepatitis C in the past (without evidence of current infection). The patient denied new medications exposures prior to the appearance of the nodules. She was not aware of any family history of autoimmune disease. A punch biopsy of the left shin nodule revealed septal granulomatous mixed panniculitis with eosinophils, neutrophils, and plasma cells (Figures 2A and 2B), consistent with EN. There was no evidence

of vasculitis. Gram, Grocott methenamine silver (GMS) and Fite stains for bacterial, fungal, and atypical mycobacterial organisms (respectively) were negative. There was no polarizable foreign material identified. PET/CT performed February 2019 did not reveal enlarged hilar or mediastinal lymph nodes. She continued nivolumab. As she was not symptomatic, she declined treatment for EN. Careful monitoring for development of sarcoidosis on PET/CT imaging was recommended, as EN has been reported as antecedent to development of sarcoidosis.1

Discussion: Immune checkpoint inhibitors (ICIs) have dramatically improved the prognosis for individuals with advanced melanoma (including ipilimumab, nivolumab, and pembrolizumab to date).5 Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to programmed cell death protein 1 (PD-1), inhibiting its interaction with programmed death-ligands 1 and 2 (PD-L1 and PD-L2), thereby helping to reverse T cell exhaustion and facilitate T cell activation. Nivolumab is FDA-approved for treatment of unresectable stage III and stage IV melanoma as well as adjuvant treatment for stage III melanoma at high risk for relapse.6,7

By potentiating T cell activity, nivolumab can also lead to a wide array of deleterious immune-related adverse events (irAEs), most commonly rash or pruritis.8

There have been four patients previously described with histopathologic findings compatible with EN related to single agent nivolumab (Table 1).1-4 EN classically presents with tender, erythematous, subcutaneous nodules and plaques along bilateral lower extremities and occasionally the thighs, arms, trunk, neck and face.9 FDG, a radioactive tracer, concentrates in areas of increased metabolic activity (e.g. cancer cells) on PET/CT, and will also concentrate in EN nodules due to their increased levels of inflammation. Histologically, EN demonstrates a mixed cellular infiltrate of histiocytes, lymphocytes, giant cells, and occasional eosinophils involving the septae of the subcutaneous fat without evidence of vasculitis.9 Described as a type IV delayed hypersensitivity reaction, EN can have a wide array of etiologies including infection (predominantly streptococcal pharyngitis, 28-48%), sarcoidosis (11-25%), drugs (3-10%), pregnancy (2-5%), and inflammatory bowel disease (1-4%).10,11 Up to 55% of cases are idiopathic.11 Hepatitis C has also been reported as a rare cause of erythema nodosum.12 While our patient did have a history of a positive hepatitis C antibody, she did not have evidence of active infection, making hepatitis C an unlikely etiology for her EN.

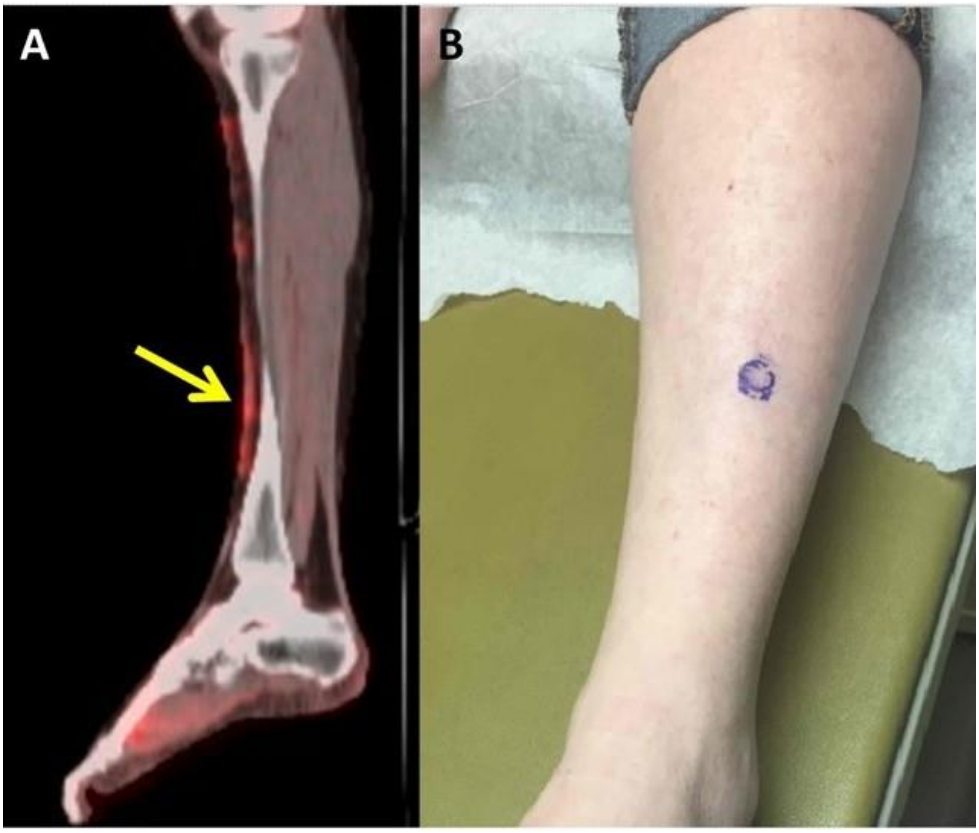

Figure 1. A, FDG PET/CT showing dermal-based soft tissue thickening involving the anterior lower legs with associated hypermetabolic activity, and hypermetabolic focus between first and second metatarsal head. B, Left shin with a 1cm, solitary, firm but mobile subcutaneous nodule without epidermal change.

Table 1: Comparison of previously reported cases of EN secondary to nivolumab. (see appendix)

Conclusion

In contrast to the previously reported patients, multiple FDG-avid nodules were discovered incidentally on routine surveillance PET/CT on our patient prior to any clinical symptoms presenting. Her symptoms were considerably mild in comparison to prior reports, as her only clinical finding consisted of one mildly tender, subcutaneous nodule along her left shin. Despite her subtle presentation, biopsy results revealed significant septal inflammation, which led to the diagnosis of erythema nodosum, an irAE secondary to nivolumab toxicity. As use of nivolumab continues to grow, routine surveillance PET/CT scanning for disease recurrence may reveal new FDG-avid nodules in an increasing number of asymptomatic or mildly symptomatic patients, which can increase the clinician's concern for malignancy, prompting further work-up including biopsy and histopathological assessment of the lesions. The addition of this case to the growing body of literature describing irAEs can further guide clinicians to avoid misdiagnosis and to correctly identify subtle presentations of EN-like panniculitis as an irAE of anti-PD-1 therapy.

Learning points

- In contrast to previous reports, multiple FDG-avid nodules were discovered incidentally on routine surveillance PET/CT on our patient prior to any clinical symptoms presenting.
- Despite her subtle presentation, biopsy results revealed significant septal inflammation, which led to the diagnosis of erythema nodosum, an irAE secondary to nivolumab toxicity.
- As use of nivolumab continues to grow, routine surveillance PET/CT scanning for disease recurrence may reveal new FDG-avid nodules in an increasing number of asymptomatic or mildly symptomatic patients, which can increase the clinician's concern for malignancy, prompting further work-up including biopsy and histopathological assessment of the lesions.

Acknowledgements

I would like to acknowledge and thank doctors Elizabeth Berry, Rajan Kulkarni and Matthew Taylor for sharing this patient's case with me and for their incredible mentorship.

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Table 1: Comparison of previously reported cases of EN secondary to nivolumab.

irAE secondary to nivolumab		
Study	**Clinical Presentation**	**Histopathological findings**
Tetzlaff et al[4]	Numerous painful subcutaneous nodules on bilateral legs and buttocks.	Mixed septal and lobular panniculitis containing lymphocytes, histiocytes, multinucleated giant cells and no evidence of associated vasculitis.
Choi et al[2]	Polyarthralgia and multiple tender nodules along lower legs.	Septal fibrosis and dense lymphohistiocytic infiltrations extending to the surrounding fat lobules.
Laroche et al[1]	Bilateral, tender, pretibial nodules.	Predominantly septal subcutaneous inflammation with mixed infiltrate of mostly lymphocytic, along with histiocytes and multinucleate giant cells.
Jiang et al[3]	Progressively worsening, diffuse. erythematous, nontender, subcutaneous nodules on bilateral lower extremities.	substantial lobular, septal, and paraseptal lymphohistiocytic infiltrate that was primarily granulomatous in areas that had histiocytes present.

PNWMSRJ | Case Report

An Atypical Pain Presentation of Cholecystitis

Steven D. Gay, L.J. S. McKenzie, Christian L. Shafer, Jordan R. Hilton, Dr. S. Kathryn Potter

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Abstract: Introduction: Complicated gallstone diseases like cholecystitis can arise as gallstones block portions of cystic duct systems. Typically, these patients present with severe, constant, several hour postprandial, right upper quadrant pain, accompanied by elevated liver enzymes, leukocytosis, gallbladder thickening and edema on imaging, and a positive Murphy's sign.1-5 Objective: This patient's presentation fell outside these parameters, yet still warranted consideration of cholecystitis as a possible cause for her abdominal and back pain. Conclusion: While cholecystitis pain normally presents with right upper quadrant pain possibly radiating towards the right shoulder, an atypical bilateral location and banding pattern is possible. Early detection and subsequent cholecystectomy can limit time patients suffer from complicated gallstone diseases. However, not all patients with back pain should receive a cholecystitis work up as this presentation is rare and could result in unnecessary testing.

INTRODUCTION

The gallbladder is an organ that receives bile from the liver, stores and concentrates it, and contracts to release it when fatty foods enter the duodenum. In some individuals, concentrated bile can precipitate to form gallstones within the gallbladder—a condition known as cholelithiasis—from undissolved cholesterol or excess bilirubin. Contraction of the gallbladder can cause these stones to dislodge and block the cystic duct or other related bile ducts.

A majority of patients are asymptomatic as the cholelithiasis never causes a blockage. However, a minority of individuals with cholelithiasis will have movement of the stones into their cystic duct, followed by inflammation and significant pain (cholecystitis), ultimately prompting the patient to seek medical treatment.

Typically, a patient with a complicated gallstone disease like cholecystitis will present with right upper quadrant pain (RUQ) that is severe, constant, and lasting several hours following meals, and accompanied by elevated liver enzymes, leukocytosis, gallbladder thickening and edema on imaging, and a positive Murphy's sign.[1-3] The patient presented in this study fell outside some of these parameters yet still warranted consideration of cholecystitis as a possible cause of her abdominal and back pain.

CASE PRESENTATION

An otherwise healthy, 25-year-old Caucasian female, 2-months postpartum, presented to the urgent care clinic with a chief complaint of a 1-week history of achy, bilateral, mid-back pain, in a banding belt-like pattern that was most severe posteriorly, only present at night, and would wake her from sleep. She rated it 7-8/10 with no palliative or provoking factors and it would spontaneously resolve hours later. The patient denied pain while lying down, after meals, or with specific foods. She also denied dysuria, trauma, or previous episodes. Her BMI was normal, she was moderately active, and she ate a diet high in fruits and vegetables and low in fats. Physical exam was unremarkable except for mild tenderness in the RUQ. However, the patient had a negative Murphy's sign. The primary diagnosis at this point was gastroesophageal reflux disease (GERD), with a differential diagnosis of biliary colic.

The patient was then referred to the emergency department (ED) for an ultrasound and laboratory testing. The gallbladder wall appeared normal with ultrasound, but stones were noted [Appendix Figure 1]. At this time, a complete blood count (CBC) and comprehensive metabolic panel (CMP) came back within normal limits except for mildly elevated liver enzymes [Appendix Table 1]. Urinalysis (UA) was unremarkable with the exception of elevated erythrocytes/µL and being positive for leukocyte esterase [Appendix Table 1]. After testing, the patient was sent home, instructed to monitor symptoms, and prescribed the proton pump inhibitor, omeprazole.

Unfortunately, the patient returned to the ED 2-hours later with severe back and stomach pain in a bilateral banding pattern that was equally painful anteriorly

and posteriorly and rated as 10/10. She reported shortness of breath and an inability to get comfortable. Hydromorphone was administered twice, as the first dose was ineffective. A computerized tomography (CT) scan of the abdomen and pelvis with oral contrast identified an edematous gallbladder with no other abnormalities [Appendix Figure 2]. Lab results now showed elevated (compared with the first sample) white blood count (WBC), protein (PROT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [Appendix Table 1]. Upon this second visit, the differential shifted from GERD to acute calculous cholecystitis and the patient was admitted and scheduled for laparoscopic cholecystectomy the next day [Appendix Figure 3]. Postoperatively, the patient's symptoms were completely resolved, and the patient has remained symptom-free.

DISCUSSION

Uncomplicated gallstone diseases such as biliary colic typically present with RUQ pain that can radiate toward the right shoulder blade.1 This pain usually lasts at least 30 minutes and subsides less than six hours later, and is thought to be associated with the gallbladder contracting and coming into contact with gallstones or sludge before relaxing. Laboratory test results are typically normal and abdominal examination typically yields a negative Murphy's sign.

Complicated gallstone diseases like cholecystitis present similarly to biliary colic with the addition of leukocytosis and elevated liver tests and a positive Murphy's sign on exam. Gallbladder thickening and edema as well as a sonographic Murphy's sign are to be expected. The pain in this situation is usually longer in duration, constant, and in the same location as with cholelithiasis.3

The recommended general management for patients presenting with symptoms related to gallstone disease is surgery versus nonsurgical management (such as medication) due to the high recurrence of painful symptoms.1

This patient presented with pain patterns that followed an unexpected, bilateral, mid-back banding pattern that then escalated to include the anterior epigastric area at its peak [Appendix Figure 3]. As such, she was initially prescribed a proton pump inhibitor, omeprazole, with a primary diagnosis of GERD given her symptoms (nightly recurrence and substernal pain radiating to the back).4 The appearance of gallstones on ultrasound was not necessarily an indication that the patient's symptoms were related as a large proportion of the population has stones that are asymptomatic [Appendix Figure 1].[1] Referral to an outpatient surgical clinic and education on the differential of biliary colic were warranted and provided.

Differential diagnoses of cystitis and nephrolithiasis should also be considered given that the UA showed abnormal values for leukocyte esterase and blood [Appendix Table 1]. Leukocyte esterase is typically an indicator for urinary tract infections in the presence of bacteriuria or the presence of nitrite, but this patient's test yielded a negative nitrite result.5 While a urine culture and additional examination are recommended, a negative nitrite result suggests the possibility of a false positive from a contaminated sample. Microscopic hematuria was also noted, which makes nephrolithiasis a possibility given the concurrent severe back pain. Severe back pain could be confused with flank pain, but the bilateral nature and upper abdominal symptoms this patient demonstrated are not consistent with nephrolithiasis [Appendix Figure 3]. Finally, the patient's CT scan more conclusively ruled out the presence of nephrolithiasis [Appendix Figure 2].

While the end result for this patient was resolution of her symptoms post-cholecystectomy, it is of note that the signature pain presentation of biliary colic or cholecystitis can be less localized than to the RUQ as demonstrated in this case. Early consideration of gallstone disease in patients presenting with bilateral back pain could limit the time patients are left suffering from their pain. However, this presentation is extremely uncommon according to the current literature, with no other cases identified by the researchers. In addition, back pain is the second most common patient reported complaint in a systematic review from 2016 that looked at 250,000 patients in 12 countries on 5 continents.6 Testing all patients with bilateral back pain for cholecystitis would lead to many patients enduring unnecessary tests and be costly to providers.

The utility of this case report is to encourage providers to maintain a broad differential in the event that more common causes of back pain are ruled out, especially when patient history, timing, pain patterns, and/or abdominal findings don't fit the expected presentation.

LEARNING POINTS

- While cholecystitis will normally present with right upper quadrant pain that can radiate superiorly and posteriorly towards the right shoulder, an atypical bilateral location and banding pattern is possible as seen in this patient.
- Pain patterns should not be used to rule out diagnoses but should instead be considered a rule in criterion.
- Not all patients with back pain should be met with testing to rule out possible gallbladder etiology as this would neither be in the patient's best interest nor cost effective. However, if no other cause for back pain is found on initial workup, less common

pathologies, such as cholecystitis, should be considered.

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Appendix Table 1. Combined results of laboratory testing from patient's first and second visits. Those highlighted in red were flagged as "HIGH" values by automated systems and were used in understanding the progression of the disease and forming a differential diagnosis

First CBC		Second CBC
WBC	8.76	13.06 (HIGH)
HGB	13.4	13.4
HCT	42.4	40.9
MCV	99	96
PLT	286	352

First CMP		Second CMP
NA	139	141
K	3.7	3.1 (LOW)
Cl	102	101
BUN	10.0	11.0
Creatinine	0.70	0.70
Calcium	9.5	9.9
Protein	8.0	8.6 (HIGH)
BILITOT	0.3	0.5
AST	42 (HIGH)	58 (HIGH)
ALT	78 (HIGH)	78 (HIGH)

Dipstick UA	
Color	Yellow
Clarity	Clear
Specific Gravity	1.015
pH	7.0
Leukocyte Esterase	70 Leu µL (HIGH)
Nitrite	Negative
Protein	Negative
Glucose	Negative
Ketones	Negative
Bilirubin	Negative

Appendix Figure 1. Ultrasound image of the patient's gall-bladder with gallstone (arrow) visible. The stone appears hyperechoic (bright) and causes a hypoechoic (dark) shadow (S).

Appendix Figure 2. CT of the patient's abdomen with oral contrast. Cholelithiasis with a distended gallbladder (yellow box) and a small volume of pericholecystic fluid (red arrow) were found.

Appendix Figure 3. Depictions of the typical pain pattern for gallstone pathology along with those presented by the patient at her initial and second visits (brighter red indicates more severe pain).

PNWMSRJ | Systematic Review

Continuous Glucose Monitor Use and the Pregnancy Outcomes in Mothers with Type I, Type II, and Gestational Diabetes Mellitus: A Systematic Review

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ABSTRACT: Background: The prevalence of diabetes mellitus (DM) in pregnant women is increasing in the US. Diabetes is associated with a higher risk of pregnancy complications such as fetal macrosomia and cesarean sections. Multiple studies have investigated the efficacy of continuous glucose monitor (CGM) use in reducing these complications. Objectives: This study investigates the clinical efficacy of continuous glucose monitor (CGM) use in reducing adverse pregnancy outcomes in mothers diagnosed with type I, type II, or gestational diabetes mellitus. Studied pregnancy outcomes were cesarean delivery rates, fetus large for gestational age (LGA, fetal size >90th percentile in utero), preeclampsia, neonatal hypoglycemia, and prematurity. Average birth weight was also obtained. Methods: A systematic review of primary articles was conducted using nine medical journal search engines. A total of 2,028 cases were gathered from 17 studies between the years 2007 and 2020. Data regarding secondary endpoints, including neonatal outcomes, were also collected. Results were compared using relative risk and Pearson's Chi-square test. Results: The relative risk for cesarean delivery in the CGM group was 0.96 (95% CI: 0.67-1.24) compared to the control, and the relative risk for fetal macrosomia in the CGM group was 0.93 (95% CI: 0.55-1.30). Interestingly, women diagnosed with gestational DM and used CGMs during pregnancy had similar rates of LGA neonates across China, Malaysia, and European countries. However, the rate of cesarean section significantly differed in China and Malaysia compared with European countries. Conclusion: CGM use was not associated with a reduction in diabetes-related pregnancy complications. The cesarean section rate was significantly different depending on the region, which may indicate a difference in clinical practice among those regions. Relevance: To the best of our knowledge, this meta-analysis utilized a larger sample size than any other published literature to explore the impact of CGM use on pregnancy complications.

Introduction

In the US, diabetes during pregnancy is on the rise.1, 2 In 2016, 0.9% of live births were to mothers with preexisting DM (type I and II). 6% of live births involved gestational diabetes. 3

Maternal diabetes is linked to various adverse pregnancy outcomes, including increased preeclampsia, preterm delivery, and cesarean section.4 Infants of mothers with preexisting DM are reported to have a greater risk of perinatal mortality, congenital anomaly, premature birth, being born large for gestational age (LGA), and neonatal hypoglycemia.5, 6 Preexisting diabetic mothers have an increased incidence of elective and emergency cesarean sections.7 Furthermore, preexisting diabetes is linked to perinatal mortality four times higher than non-diabetic pregnancy mothers.8

One of the most crucial factors in diabetes management is optimal glucose control. Several studies show that poor glycemic control, resulting in elevated HbA1C, during early pregnancy is associated with an increased risk of congenital anomalies, stillbirth, and miscarriage.8-10 Also, elevated HbA1C during the third trimester was associated with prematurity, low birth rate, and fetal macrosomia.11 Fetal macrosomia is a common indication for the cesarean section, which has a maternal risk of infections, organ injuries, hysterectomy, chronic pain, and so on.11 When compared to vaginal deliveries, neonates delivered via cesarean section had significantly higher respiratory morbidity.12 For healthy fetal growth, optimal glycemic control is crucial; however, achieving it remains challenging for many mothers with preexisting diabetes.13

CGM was developed in 1999 to enable patients to continuously monitor their blood glucose level throughout the day by detecting the interstitial fluid glucose level through a small device inserted under the skin.14 Depending on the brand, the sensor can be worn for 5-90 days.14, 15 When CGM is worn, finger prick monitoring is only required for occasional calibration. Results can either be read through an at-home monitor or by a provider. Some CGM devices have alarms for when patients are either hyperglycemic or hypoglycemic.14 While CGM is more expensive than finger prick monitoring, CGM has high patient satisfaction.16

Multiple studies have shown that incidence of LGA, cesarean sections, and preeclampsia did not improve with use of CGM during pregnacy.17, 18 One study found that CGM is a worthwhile pursuit for mothers with type 1 diabetes because of lower HbA1C (-0.19%) and increased time in target glucose range when compared to mothers using finger prick monitoring.19 Another benefit was that infants of mothers with CGM required fewer treatments for hypoglycemia.18, 19 This review aims to analyze the up-to-date literature to further investigate the clinical efficacy of CGM use for the management of diabetes during pregnancy. Additionally, the regional pregnancy outcomes among the CGM use group were analyzed to understand the impact.

Methods:

Data about the pregnancy outcomes of mothers with type I, type II, or gestational DM who have used a CGM during pregnancy was obtained through the following nine major medical literature search engines: Pubmed,

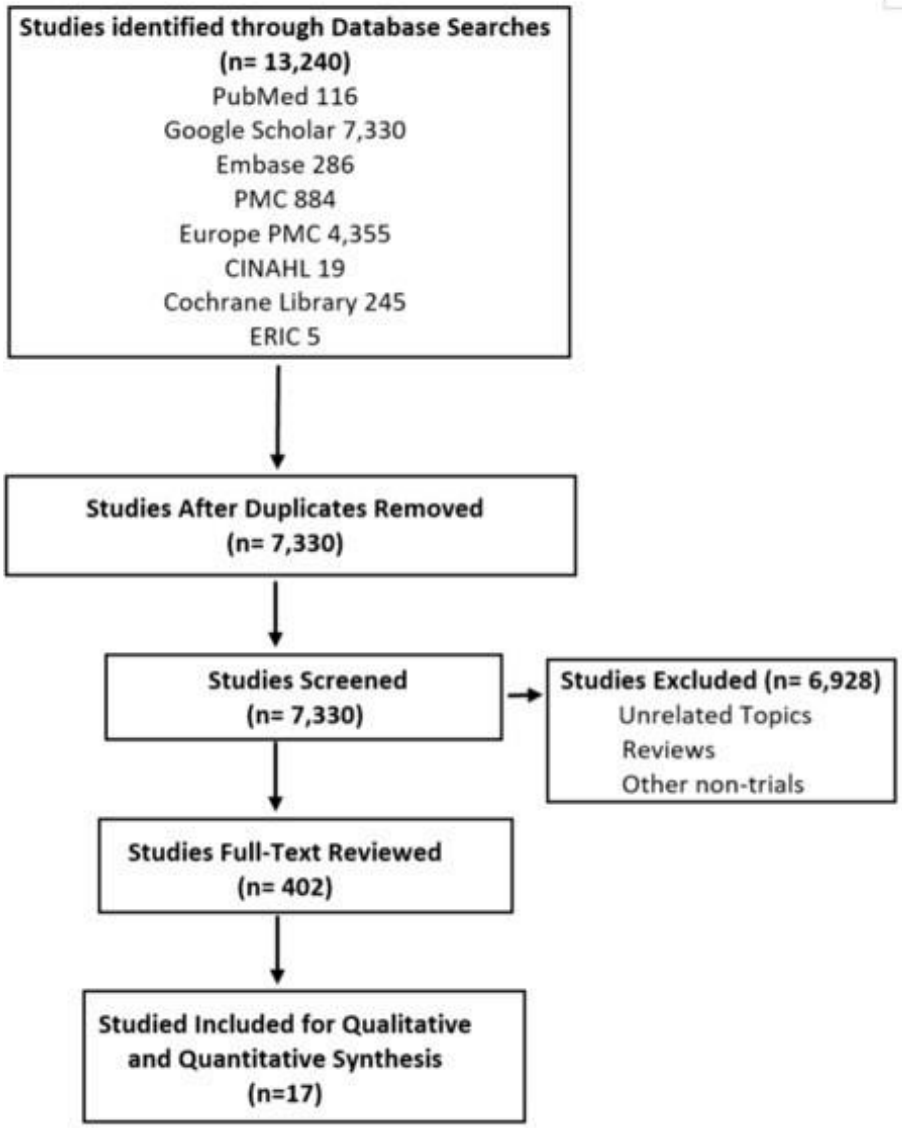

Figure 1: Information about the following factors was also collected: country where research was conducted, patient diagnosis of type I or type II DM, patient diagnosis of gestational DM, average maternal ages and BMI, manufacturer of CBGM device, insulin administration route, frequency of data collection of the CBGM device, rates of miscarriage, and rates of cesarean delivery. Neonatal endpoints include incidence of neonatal hypoglycemia, the incidence of severe neonatal hypoglycemia, the incidence of severe congenital deformity, average birth weight, rates of macrosomia defined as birth weight over 4000g, premature birth, and incidence shoulder dystocias during delivery were also recorded. Further data recorded include the following pregnancy complications: the incidence of gestational hypertension, preeclampsia, and HELLP syndrome.

The information about above complications were considered soft inclusion criteria, and the lack of available data regarding these endpoints was not necessarily exclusionary. For statistical analysis, the SAS University program was used to calculate the relative risk and Pearson's Chi-square test. The relative risk analysis was conducted to determine the correlation of having specific pregnancy outcomes such as cesarean delivery, LGA, neonatal hypoglycemia, prematurity, and preeclampsia in the CGM use group in contrast with the control group. Similarly, the Chi-square test was used for the analysis of four different correlations: 1) CGM use (user vs. non-user) and pregnancy complications, 2) region in the world (Asia vs. Europe, Asia vs. the Middle East vs. Europe), and cesarean section frequency in mothers who used CGM, 3) region in the world (Asia vs. Europe) and LGA frequency in mothers who used CGM, and 4) type of diabetes (Type I vs. GDM) and pregnancy complication frequency.

Google Scholar, Embase, PMC, Europe PMC, CINAHL, Cochrane Library, MeSHMEDLINE, and ERIC. The articles published from inception to May 10th, 2020, were included.

Articles were included if the study subjects were pregnant, had a diagnosis of type I or type II DM before pregnancy, or had a diagnosis of gestational DM during their current pregnancy, and monitored their blood glucose with CGM at some point during pregnancy. Also, we required the paper to include data about the rate of cesarean delivery or the rate of neonates LGA, which is defined as greater than the 90th percentile.

Exclusion criteria were the followings: nonpregnant patients, no history of type I or type II DM, no diagnosis of gestational DM during the current pregnancy, blood glucose monitoring with methods other than a CGM, or research that did not include data regarding fetus LGA, or rate of cesarean delivery. After the selection, 17 articles were included. The selection process is summarized in image 1.

Results:

This review comprises 17 studies with 2,028 patients from Asia (East, Southeast, and Middle), US, Canada, and Europe, diagnosed with type I, type II, or gestational diabetes. Among these, 1,292 cases used CGM for a certain period during pregnancy, and 736 patients used the finger-prick method exclusively to monitor their blood glucose throughout pregnancy. CGMs were primarily used as an educational tool to improve glycemic control during pregnancy, and the pregnancy outcomes were measured.

10 studies were from Europe,17, 19-27 4 studies were from the US,19, 28-30 2 studies were from China,31, 32 one study was from Malaysia,33 and one study was from Saudi Arabia.34 One of those studies was conducted in the US, Canada, and European countries.19 The primary outcomes of this study are summarized in Table 1.

The CGM group consists of women who used CGMs during pregnancy and were diagnosed with either type I, II, or gestational DM. The Control group consists of women who used finger prick exclusively for monitoring their blood glucose level throughout pregnancy. Some studies did not specify the number of patients with each type of diabetes. 379 patients who used CGM without specification of their diabetes type (type I vs. type II vs. gestational) are included in the CGM group. The chi-square results and relative risk (RR) for pregnancy-related complications among the CGM user vs. non-user are also summarized in Table 1. None of those have statistically significant outcomes.

The secondary outcomes are summarized in Table 2. The type I DM group consists of women diagnosed with type I diabetes and used CGM during pregnancy. The gestational DM group consists of women diagnosed with gestational diabetes and used CGM during pregnancy. For calculating the duration of diabetes, 0.4 years was used for the duration of gestational diabetes uniformly as gestational diabetes is routinely screened between 24th and 28th gestational weeks. Type II DM patients were not included due to a small sample size. Additionally, patients with unspecified types of DM were not included.

The type of diabetes (type I vs. gestational) among mothers who used CGM showed a strong correlation with the frequency of pregnancy-related complications such as preeclampsia, cesarean delivery, LGA, neonatal hypoglycemia, and prematurity. In other words, CGM use did not close the gap between the pregnancy-related complication rate between type I GM and gestational GM patients. The results are summarized in Table 2.

The demographics of the patients who used CGM during pregnancy based on the regions in the world are summarized in Table 3. The East/Southeast Asia group consists of women from China and Malaysia. The Middle East Asia group consists of women from Saudi Arabia. The European group consists of women from Belgium, Denmark, England, Finland, France, Ireland, Italy, Netherland, Scotland, Spain, and Sweden.

Chi-square test results are summarized in Table 4. A P-value of <0.05 was considered statistically significant. The Chi-square test revealed a statistically significant association between the region in the world (East and Southeast Asia vs. Middle East Asia vs. Europe) and the rate of cesarean section in mothers with gestational diabetes who used CGM during their pregnancy. The Chi-square value was 12.82 with a degree of freedom (df) of 2, and the p-value was 0.001644. Also, the statistically significant difference in the cesarean section rate between East/Southeast Asia and Europe was found based on the Chi-square value of 11.95, df of 1, and the p-value of 0.000548. However, the association between the region (East and Southeast Asia vs. Europe) and the rate of LGA in mothers with gestational diabetes was statistically insignificant based on the Chi-square value of 2.576 with df of 1 and the p-value of 0.1085. These results reveal that even though the rate of LGA among mothers diagnosed with gestational diabetes and used CGM in Asia and Europe was comparable, the cesarean section rate was not.

Discussion:

Our primary outcome agrees with previous research that the periodical CGM use during pregnancy did not have a significant impact on the pregnancy outcomes compared with the group who used the finger-prick method to monitor their blood glucose level.18, 35 While

a randomized control trial conducted by Voormolen et al. included all three types of diabetes mellitus, Murphy et al., Secher et al., and Law et al. only focused on type I and II diabetes.20, 21, 23, 24 Two small studies conducted by Taslimi et al. and Dalfra et al. included both type I diabetes and gestational diabetes.26,30 In contrast, multiple studies limited the study population to women diagnosed with one specific type of diabetes mellitus. The studies conducted by Feig et al., Polsky et al., Kristensen et al., and Mulla et al. focused on type I diabetes.17, 19, 28, 29 Whereas Franck et al., Kestila et al., Yu et al., Alfadhli et al., Paramasivam et al., Law et al., and Wei et al., solely focused on the women with gestational diabetes.22, 25, 27, 31, 32, 33, 34 Regardless of these differences, all studies conclude that CGM use did not improve the glycemic control which translated to no significant difference in pregnancy outcomes.

One possible explanation for the non-significant effect of CGM use during pregnancy compared to finger prick would be CGMs compliance and frequency of use throughout pregnancy. In the DIAMOND randomized clinical trial, type I diabetic patients used CGMs for 24 consecutive weeks, and the HbA1C level, blood glucose level target in range time, and the duration of hypoglycemia in the CGM group decreased significantly.36 In contrast, in many studies included in this review, the women were required to wear a CGM 5 to 7 days every 4 to 6 weeks.20, 23, 24, 26, 29, 32, 33 Other studies required women to wear CGMs once during pregnancy for two days to 1 month. 22, 31, 34

In the CONCEPTT trial, 325 women with Type I DM were enrolled and randomly assigned to the CGM group with finger prick monitoring or the control group with the finger prick monitoring only. The study group wore the CGM throughout the pregnancy and the neonatal outcomes showed statistically significant improvement with a lower rate of LGA, NICU admission, and neonatal hypoglycemic episodes. On average, the CGM group had one shorter day of hospital stay.19 In the sub-analysis of the CONCEPTT trial, the progressive improvement in the time in glucose target range among the CGM group was found as the pregnancy progressed: 7.7 % during the first trimester, 10.2% during the second trimester, and 35.5% during the third trimester. This would explain why the study found lower neonatal complications associated with poor glucose control in later trimesters such as LGA.44 This suggests that wearing CGM throughout pregnancy would be overall beneficial for this population.

Our secondary outcomes highlighted some important facts to consider for future studies measuring pregnancy outcomes. The Chi-square tests for women diagnosed with gestational DM and used CGMs during pregnancy showed similar rates of LGA neonates across East/ Southeast Asia and European countries. However, the rate of cesarean section was significantly higher in Asia compared with European countries. This may indicate a difference in clinical practice by region and country. In fact, in a study of 121 countries, the cesarean section rate in Asia was 15.1%, while that of Europe was 13.8%, which is higher than the world average of 12.4%.37

This difference in the threshold for cesarean section based on the region in the world is interesting and almost contra-intuitive considering that higher BMI is one of the risk factors for cesarean section. In our study, the average BMI of East/Southeast Asian mothers was 23.6 kg/m2, which is within the normal range, while European mothers were 29.3 kg/m2, which falls in the overweight category.38 Multiple large studies, including the HAPO study, indicate a strong association between the increase in the rate of cesarean section and the maternal BMI.39,40 This suggests that the variability in clinical practice may have a stronger impact in the rate of cesarean section than maternal BMI.

Some of the confounding variables of this study include the use of different brands of CGMs, the difference in duration and the timing of the CGM use, the variation in viewing options of the CGM reports, women having different types of diabetes mellitus, and non-standardized care for each patient.

The types of continuous CGMs used in each study varied. Some of the CGMs used in the studies included Guardian Real-time CGM, Minimed Medtronic, Freestyle Libre, and iPro2 Professional CGM.17, 24, 31, 32 Additionally, the duration and the timing of the CGM use were not identical across the studies.

As mentioned above, most of the studies included had patients use CGMs for less than a week for multiple non-consecutive weeks.20, 23, 24, 26, 29, 32, 33 Some studies had the mothers wear CGMs once for a variety of periods.22, 31, 34 For the most accurate results, having an identical period and duration of CGM use across participants would be beneficial.

While most studies allowed patients to view their blood glucose level in real-time, some studies only had glucose level reviewing during office visits.17 CGM is advantageous because it gives patients immediate feedback about the effect of diet, medications, exercise, and insulin injections on their blood glucose levels.41 Thus, having different modes of viewing may affect the study outcomes indefinitely.

In our study, pregnant women with all types of diabetes mellitus were included similarly to a previous study by Voormolen et al.20 While this approach increases statistical power, including all types of maternal diabetes is a confounding variable. As previous studies showed, preexisting maternal type I or type II DM is strongly associated with pregnancy-related complications such

a s premature birth, LGA, and neonatal hypoglycemia compared to no maternal DM or gestational DM.5, 6 Therefore, the impact of those should be analyzed in the future studies.

The care and appointment time for each patient were not standardized within each study and across the studies. The standard treatments for diabetes are lifestyle change (diet and exercise), medications such as metformin and glyburide, and insulin therapy.42

Lifestyle medicine is an emerging field, and its benefits on chronic conditions are promising. Mothers of gestational diabetes who received lifestyle medicine intervention had lower rates of postnatal depression and neonates large for gestational age.43 One study, included in this systematic review, reported an outstandingly lower LGA rate compared to other studies. While the rate of LGA for other studies fell in the range of 13% to 63%, with the median value of 34.8%, the study by Law et al. reported only 9.2% of neonates classified as LGA. Interestingly, their primary intervention was lifestyle modification. Therefore, providing standardized care would be beneficial to assess the true effectiveness of CGMs in future studies.22

Conclusion:

This study included two thousand twenty-eight pregnant wome n with a history of type I, type II, and gestational DM from 17 studies. The evidence suggests that intermittent CGM use has no significant impact on improving pregnancy outcomes, including the rates of preeclampsia, cesarean section, large for gestational age fetus, prematurity, and neonatal hypoglycemia. Secondary findings suggest that country/ region may affect the rate of cesarean section, but not LGA. Additionally, the rate of cesarean section and LGA fetuses in type I diabetes mothers with CGM use were significantly higher than those of gestational diabetes mothers. Further study is indicated to investigate the efficacy of continuous CGM use with various viewing options for the diabetes-associated complication risk reduction in pregnant patients.

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Table 1. Pregnancy Complication Outcomes in Patients (CGM use vs. non-CGM use)

	Control: Finger Prick without CGM	CGM (Total)	Relative Risk	Confidence Interval
Sample Size	736	1292	-	-
Mean Age (years)	31.4	31.9	-	-
Mean BMI (kg/m2)	25.5	26.6	-	-
Mean Duration of Diagnosis (years)	8	7.8	-	-
Birth weight (g)	3391	3406	-	-
Preeclampsia (%)	10.8	9.2	0.85	0.017 - 1.7
Cesarean delivery (%)	49.7	47.6	0.96	0.67 -1.2
LGA (%)	36.6	33.9	0.93	0.55 - 1.3
Neonatal hypoglycemia (%)	27.6	25.8	0.94	0.48 - 1.4
Prematurity (%)	22.4	24.4	1.07	0.59 - 1.6

Table 2. Pregnancy Complication Outcomes in CGM use Patients (Type I DM vs. Gestational DM)

	Type I DM with CGM	Gestational DM with CGM	Relative Risk	Confidence Interval
Sample Size	398	515	-	-
Mean Age (years)	31	32.3	-	-
Mean BMI (kg/m2)	26	27.3	-	-
Mean Duration of Diagnosis (years)	16.1	0.4	-	-
Birth weight (g)	3667	3176	-	-
Preeclampsia (%)	14.7	3.4	1.4	1.3 – 1.6
Cesarean delivery (%)	57.5	49.3	1.7	1.3 – 2.1
LGA (%)	49.5	14.5	2.1	1.9 – 2.4
Neonatal hypoglycemia (%)	25.6	8.8	1.6	1.4 – 1.8
Prematurity (%)	30.6	15.3	1.2	1.1 – 1.3

Table 3. Pregnancy Outcome of Gestational Diabetes Mothers with Intermittent CGM Use per Region

	East, Southeast Asia	Middle East Asia	Europe
Sample Size	223	60	232
Mean Age (years)	31.6	32.9	32.7
Mean BMI (kg/m^2)	23.6	-	29.3
Cesarean delivery (%)	54.2	55	31.6
LGA (%)	17.0	-	11.4
Birth weight (g)	3022	2870	3292

Table 4. Gestational DM Mothers Pregnancy Complication vs. Region in the world

	East, Southeast Asia	Middle East Asia	Europe
Sample Size	223	60	232
Mean Age (years)	31.6	32.9	32.7
Mean BMI (kg/m^2)	23.6	-	29.3
Cesarean delivery (%)	54.2	55	31.6
LGA (%)	17.0	-	11.4
Birth weight (g)	3022	2870	3292

PNWMSRJ | Original Research

The Effects of the COVID-19 Pandemic on the Mental Health of First Responders: A review of the Lebanon Fire Department

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Abstract: COVID-19 first was discovered in the United States in January 2020 and has since changed the way we live. From donning PPE to social distancing to virtual workplaces, we have all been affected by this pandemic. Those working on the front lines have been particularly impacted. The goal of this study is to assess the changes in mental health status among first responders as a result of COVID-19, thus allowing organizations to implement systemic changes as needed to help their employees. Using the Lebanon Fire Department (LFD) – a fire and EMS service in Linn County Oregon – as a model, anxiety and depression levels were assessed both pre- and post- pandemic onset. Data was collected during November 2020 and used recall to access pre-pandemic scores. Full time paramedics, EMTs, and firefighters were assessed using the standardized General Anxiety Disorder 7 (GAD-7) questionnaire and Patient Health Questionnaire 2 (PHQ-2). Results were analyzed using a Wilcoxon Rank Sum test with a significance level of 0.05. Average anxiety levels increased significantly from 1.8 to 4.9 ($p = 0.019$) following the onset of the pandemic on February 28, 2020, correlating to a clinical anxiety level rise from mild to moderate. Depression levels increased significantly from 0 to 1.3 ($p = 0.037$), however this does not correlate to a clinically significant screening as depression scores remained in the no depression range. From this data, we can conclude that COVID-19 has negatively impacted the mental health of first responders within LFD – especially regarding anxiety levels. However, more data is recommended due to the small sample size. From this knowledge, first responders and their employers should implement changes to increase mental health care and wellness as mental health disorders can lead to lower life expectancies and poorer physical health outcomes.

Background: Early research conducted on mental health within the scope of COVID-19 in China found that 54% of health care workers reported the psychological impacts of the pandemic to be moderate or severe with 29% reporting moderate to severe anxiety as a result2. This is significant because people with an established mental health disorder have lower life expectancies and poorer physical health outcomes when compared to the general public3.

First responders are faced with additional mental health challenges as the first people on scene. They see the full impacts of trauma before any medical care can be rendered and often are faced with severe triage situations, having to prioritize the lives of those that can be saved given their resources. This can further contribute to mental health disorders – something that was brought to light following the September 11, 2001 terrorist attacks in New York.

For the firefighters and EMS personnel on scene immediately following 9/11, individuals were found to have post-traumatic stress disorder, anxiety, depression, survivor guilt, insomnia, risk taking behavior, and other mental health conditions in the months and years following4. PTSD was reported at a rate at least twice as high as that expected by the general population4 and was found to increase alcohol consumption and tobacco smoking among those affected. Thus, we can conclude that mental health concerns are prevalent among first responders and increase when exposed to traumatic events.

The goal of this study was to analyze the effects of COVID-19 on the mental health of firefighters and EMS workers within the Lebanon Fire Department – a rural fire and EMS service consisting of approximately 35 full time employees and 80 volunteers. Using questions from the General Anxiety Disorder 7 (GAD-7) questionnaire and Patient Health Questionnaire 2 (PHQ-2), first responders were asked to assess their mental health both before and after the COVID-19 outbreak in Oregon. This allowed us to quantify the changes in mental health status among first responders thus allowing organizations to implement systemic changes as needed to help their employees. We hypothesized that COVID-19 negatively impacted mental health among first responders correlating with increasing scored on the GAD-7 and PHQ-2 screening tools.

Materials and Methods: An anonymous online survey was administered to first responders – defined as firefighters, EMTs, and paramedics – within the Lebanon Fire Department. Participants were asked to access their mental health using GAD7 and PHQ2 screening tools both pre- and post-the onset of COVID-19 in Oregon, defined as February 28th, 2020. Data was collected during November 2020 and used recall to access pre-pandemic scores. Previous mental health disorders and deliberate wellness activity participation – including counseling, support groups, exercise, etc. – were also investigated. Pre- and post-pandemic GAD7 and PHQ2 scores were analyzed using Wilcoxon rank sum tests for non-parametric data with a significance level of 0.05. All analysis was performed in R version 4.0.3.

Results: Average anxiety increased significantly from 1.8 to 4.9 (p value = 0.019) following the onset of the pandemic on February 28, 2020 (Fig. 2). This correlates to a clinical anxiety level rise from mild to moderate. For 11 of the 13 individuals assessed in this study, GAD7 scores increased with the most significant being a jump from a GAD7 score of 0, corresponding to no anxiety, to a GAD7 score of 15, corresponding to severe anxiety (Fig. 1).

On average, those participating in deliberate wellness activities – including counseling, support groups, exercise, etc. – had a smaller increase in GAD7 score pre- versus post- pandemic compared to those who did not (Table 1). However, this result was not statistically significant with a p-value of 0.3367. Depression levels increased significantly from 0 to 1.3 (p value = 0.037), however this does not correlate to a clinically significant screening as 0 and 1.3 correspond to no depression on PHQ2 screenings (Fig. 3).

Discussion: Anxiety and depression have significant impacts on the overall health of those affected, correlating to lower life expectancies and poorer physical outcomes3. Therefore, it is important that we evaluate the impacts of mental health on those around us. It was found that first responders had increases in both anxiety and depression screening tools in response to the COVID-19 pandemic. From this information, we can conclude that COVID-19 has had a negative impact on the mental health of first responders.

The treatment of depression and anxiety is complicated, but their effects can be mitigated by the participation of wellness activities. Physical activity and exercise have been shown to reduce the severity

of anxiety and depression1. This is consistent with results from this study showing that the participation in wellness activates including counseling and exercise correlated with smaller increases in anxiety levels in response to COVID-19. Thus, exercise can be utilized to lessen the negative impacts of COVID-19 on mental health. In addition, treatment by mental health professionals including the use of psychotherapy and medications are important factors in addressing mental health and reducing the long-term negative impacts of COVID-19.

Depression levels, while increased among first responders post-pandemic onset, did not show a clinically significant increase as levels remained at no depression. However, the sample size of this study was small (n=13) and repetition on a larger scale may show different results. This study has the potential for recall bias when assessing pre-pandemic anxiety and depression levels as participants were asked to access their pre-pandemic levels many months after the onset of COVID-19. Additionally, this study was conducted in the first few months following the onset on COVID-19 and results obtained now may show more significant impacts.

Conclusion: As many as 18% of adults in the United States demonstrate some form of anxiety or depression1 – diseases which can be amplified by acute stressors such as COVID-19. For those working as first responders, it is important that we are not only aware of mental health disorders but help provide those affected with resources to lessen the burden. Though this study only assessed the Lebanon Fire Department, it is likely that other departments would yield similar results in response to anxiety and depression levels. From this knowledge, first responders and their employers should implement changes to increase mental health care and wellness during this particularly stressful time.

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Participation in Wellness Activities	Average Pre-Pandemic GAD7 Score	Average Post Pandemic GAD7 Score	Average Change in GAD7 Score
Yes	1.14	3.67	2.53
No	1.00	6.00	5.00

Table 1. Effects of participation in deliberate wellness activities– including counseling, support groups, exercise, etc. – on average GAD7 scores pre-pandemic, post-pandemic, and the change in these scores. Average change in GAD7 score p-value = 0.3367 (alpha = 0.05), n=13.

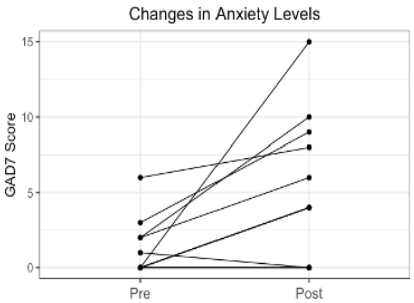

Figure 1. Changes in GAD7 scores pre- and post-pandemic onset.

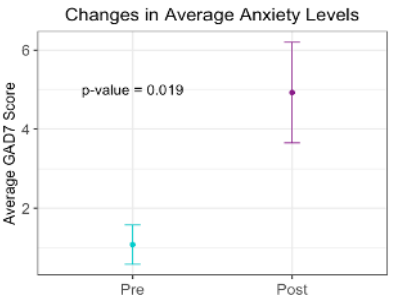

Figure 2. Comparison of average GAD7 score for first responders within LFD pre- and post- pandemic. P value = 0.019 (alpha = 0.05), n=13.

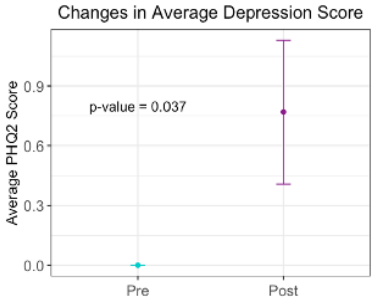

Figure 3. Comparison of average PHQ2 score for first responders within LFD pre- and post- pandemic. P value = 0.037 (alpha = 0.05), n=13.

PNWMSRJ | Case Report

The Benefits of Dietary Modification in Hashimoto's Thyroiditis: A Case Report

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Abstract: Introduction: Autoimmune diseases have been increasing in incidence in the Western world over the last few decades at a faster rate than expected through genetic variation alone. This is suggestive of a correlation between the worsening American diet and inflammatory mediated autoimmunity. Several studies have proposed mechanisms for this correlation including the relationship between the gut microbiome and autoimmune disease, as well as the role of diet composition and the activation of the immune system. Our case report highlights the proposed relationship between dietary choices and clinical severity of Hashimoto's Thyroiditis (HT).Objective: The relationship between diet and autoimmune disease has been well studied in inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes. The literature on the role of diet in HT however, has been considerably lacking. This case report intends to stimulate research interest in the role of diet in HT as a supplement to pharmaceutical intervention. Case Presentation: A 54-year-old patient with past medical history of HT and leaky gut syndrome presented to her primary care physician for extreme fatigue, rosacea, facial edema, and irregular bowel movements. At the time of presentation, the patient had baseline laboratory tests drawn including lipid panel, thyroid panel, thyroperoxidase (TPO) antibody level, and inflammatory markers. Following six months of diet modification, the patient reported clinical resolution of her symptoms with concordant improvement of her lab values at her six-month evaluation. Conclusion: Elimination of gluten, dairy, and red meat with the increased consumption of fiber and omega 3 fatty acids was correlated with improved laboratory values from this patient's baseline lab values. The patient had a decrease of her inflammatory markers including TPO antibody and hs-CRP, with an increase of cardioprotective fatty acids including omega-3 and hs-omega 3 after six months.

INTRODUCTION

Autoimmune disease plays a major role in patient wellness and health care, currently affecting more than 8% of the US population.1 The incidence of autoimmune disease has continued to rise over the last 30 years for unknown reasons, with a stable prevalence of the autoimmune genetic pool.2 This suggests that the increase in autoimmune incidence has largely been influenced by environmental factors.

Some known environmental factors that increase the incidence of autoimmunity include smoking, UV light exposure, infections, and, most importantly, diet.3,4 Multiple clinical trials have found that a vegetarian diet high in fiber, fruits, and vegetables has led to decreases in inflammatory markers such as human serum C-reactive protein (hsCRP) as well as interleukin-6 (IL-6) cytokine.5 In addition, diet has a large influence on the composition of gut microbiome which has been shown to modulate GI homeostasis and immune function. The disruption of this symbiotic relationship between gut microbiome and immune system is known as dysbiosis and has been shown to cause an imbalance in the Th1 and Th2 differentiation pathway leading to the initiation of autoimmune disease.6,7,8

HT is a complex autoimmune disease that leads to symptoms of decreased thyroid function such as fatigue, constipation, hair loss, and weight gain.9,10 Clinically, patients present with an enlarged thyroid, a decrease in free T4, and elevated levels of thyroid-stimulating hormone (TSH) and TPO-ab. In addition, patients with HT have been found to have elevated serum proinflammatory cytokines, especially IL-6 which plays an essential role in both acute phase immune response and chronic inflammation.11

Case Presentation:

We present a 54-year-old moderately obese female with a past medical history of HT and leaky gut syndrome presented in January 2019 complaining of extreme fatigue, rosacea, facial edema, diarrhea and constipation, bilateral knee pain, excessive hair loss, and weight gain of 25lb. She was diagnosed with HT in 2018 and was prescribed levothyroxine 50 mcg daily. Her diet was high in carbohydrates, animal fat and protein, and high salt intake in the form of fast food, and her symptoms worsened when eating wheat products, refined sugars, and red meat. Pertinent social history included the patient admitting to high stress having to take care of her autistic child. Past medical history and family history was negative for autoimmune disease. Physical exam included rosacea and facial edema with no other significant findings. Her baseline labs included fatty acids, thyroid panel, TPO antibody, and hsCRP (column A, Table 1). She was started on a dietary plan including the reduction of high salt and high fat intake, reduction of omega 6 rich foods and the elimination of dairy products, gluten, red meat, wheat, glyphosate. The patient was also advised to increase consumption of omega 3 rich foods such as avocado and salmon. Fiber intake was increased to 5 cups per day in the form of lentils, beans, nuts, and seeds. She was assigned a personal trainer to manage her weight as well.

After 6 months of following her strict diet and exercise plan, the patient lost 37 lbs with resolution of her facial edema and rosacea. The patient reported no improvement in her bilateral pain in her knees or hair loss. Labs including fatty acids, thyroid panel, TPO, and hsCRP were redrawn and compared to her baseline values (See column B, Table 1.)

Discussion

This patient with a past medical history of HT presented with clinical symptoms of hypothyroidism including fatigue, rosacea, facial edema, alternating diarrhea and constipation, weight gain, bilateral knee arthralgias, and hair loss. These symptoms persisted despite original treatment with levothyroxine 50mcg daily and TSH within normal range12. By eliminating dairy products, gluten, red meat, wheat, and glyphosate she reported clinical improvements in weight loss of 37lb, reduction of facial edema, and decreased rosacea in a 6-month span. The patient also demonstrated marked improvement from her baseline labs specifically in TPO antibody levels (189 to 117), hsCRP (9.1 to 6.5), and fatty acid levels (hs omega 3 4.0% to 7.4%).

HT (and several other autoimmune diseases) have largely been implicated as a systemic inflammatory disorder due to increases in acute phase reactants such as ESR and CRP.13 While it is unclear which specific molecules are the cause for an increase in the proinflammatory state, the TPO antibody has been a target of investigation. Some studies suggest that higher TPO levels also elicit a proinflammatory state by triggering the production of known inflammatory cytokines such as TNF-α, IFN- γ, and IL-6 in a dose-dependent manner.14

In contrast, polyunsaturated fatty acids (PUFAs) including omega 3s and omega 6s (in moderation) have a strong protective effect against circulating inflammatory markers. PUFAs are responsible for the modulation of systemic inflammation via the downregulation of transcription of key inflammatory cytokines such as TNF-α, IL-1, and IL-6, and the upregulation of anti-inflammatory markers such as IL-10 and TGF-β.14 Its potent effects on gene regulation of both proinflammatory and anti-inflammatory cytokines exponentiate the overall reduction in systemic inflammation.

Several mechanisms connecting diet with autoimmune disease have been proposed15. Gut microbiota has been a major area of research in recent years in the pathogenesis and progression of autoimmune disease. Dysbiosis in HT is found in the form of molecular mimicry and the distribution of epitopes to activate the immune system and induce the loss of self-tolerance. Morphological changes in enterocytes of the duodenum have been observed in patients with HT including increased thickness and increased space between adjacent microvilli. These microscopic changes are consistent with increased intestinal permeability leading to a leaky gut syndrome. The proposed loss of self-tolerance and loss of protective barrier caused by dysbiosis is a major trigger that could contribute to the development of HT.8,13

Another possible mechanism involves a high fat diet modulating autoimmune disease. Increased fatty acids induces Th17 responses resulting in increased levels of IL-17, a pro-inflammatory cytokine linked to autoimmunity. In addition, a high salt diet intake causes immune activation at the level of T cells which also increases the number of Th17 population and ultimately the upregulation of proinflammatory cytokines.15
Limitations of our case presentation include the inability to isolate factors that contributed to the improvement of her clinical symptoms and her reduction of inflammation markers. Our patient was started on both a dietary and an exercise intervention simultaneously, which implies that her reduction in inflammation is likely multifactorial. The persistence in her bilateral knee pain suggests a lack of association with a systemic inflammatory process. However, it is also possible that the pain improved passed the 6-month span.

Genetic testing was not performed on our patient, and as a result we do not have any information regarding the possible genetic predisposition such as HLA haplotype. Furthermore, the patient did not have a repeat lipid panel to compare to her baseline labs. Trending the lipid panel could have either supported or rejected the theory that lipid regulation played a role in reducing the severity of the patient's autoimmune disease.

Learning Points

• Elimination of gluten, dairy, red meat, and other known inflammatory foods along with increased consumption of fiber and omega 3 fatty acids led to a reported improvement in rosacea and fatigue, and an improvement in TPO antibody levels and hs-CRP from baseline in this patient.

• An increase in this patient's hs-omega 3 index and omega 3 levels from baseline suggests that the mechanism of reduced systemic inflammation could be due to the protective effects of PUFAs against proinflammatory markers.

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Table 1: Summary of Laboratory tests

Item	Baseline Labs[1]	6 Month Evaluation[2]
Fatty Acid Index		
hs-Omega 3 Index	4% (4-8% intermediate risk)	7.4%
Omega 3 Total	6% (0.1% - 14%)	11%
Omega 6 Total	36.1% (28.6% - 44.5%)	34.3%
cis-Monounsaturated Fat Total	16.2% (11.5% - 20.5%)	16.8%
Saturated Fat Total	40.4% (36.6% - 42.0%)	37.4%
Trans fat total	0.7% (<0.1% - 1.8%)	0.5%
Thyroid Panel		
TSH	0.78 (0.27 - 4.2)	1.12
T4 free	1.82 (0.93 – 1.7)	1.84
T3 free	3.1 (2 – 4.4)	3.2
Thyroid Autoimmune		
TPO antibody	189 (<34)	117
Inflammation		
hsCRP	9.1 (<5.0)	6.5

[1] *Column A*
[2] *Column B*

Source: Chan 2020

PNWMSRJ | Research Commentary

"Adipose tissue is a critical regulator of osteoarthritis" Proceedings of the National Academy of Sciences of the United States of America

A commentary written by Cory Kim[1], Mentored by Brian Johnstone Ph.D[2]

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Introduction: Osteoarthritis (OA) is a highly prevalent disease characterized by the degeneration of joint articular cartilage. It is by far the most common form of arthritis. Obesity has been linked with an increased risk for OA. It was previously thought that this is due to the increased mechanical loading on joints that accelerate the wear and tear of the cartilage. However, Collins et al. have recently shown otherwise. They have shed light on how adipose tissue signaling, through the release of adipokines is a key mediator of joint degeneration. In their study, a mouse model with lipodystrophy (LD), or an absence of fat, was used to directly observe the effects of adipose signaling on OA.

Importance: This study challenges the long-held dogma that the major influence of adipose tissue on joint degeneration is through the burden of excess weight on the joint tissues. The researchers did so by utilizing transgenic LD mice that cannot store fat. This allowed for the direct measurement of the influences that both adipose tissue and a high fat diet can have on OA. Discovering that paracrine signaling from fat tissue plays a major role in the progression of OA opens up potential avenues of research in the development of therapeutic targets for this joint disease.

Observation: The study revealed that knee joints from LD mice that were lacking fat were more protected from spontaneous or trauma-induced OA. It was found that LD mice were also protected from OA even when fed a high fat diet, which has otherwise been shown to induce cartilage damage. Furthermore, the researchers implanted adipose tissue from wild type WT mice into LD mice (WT fat-rescue mice) or injected mouse embryonic fibroblasts from WT wild type mice (MEF-rescue mice) and found the protective LD effects were reversed; there was a restored susceptibility to OA. These findings indicate that adipose tissue has a significant impact on joint disease independent of its role in increasing body weight.

Conclusions and Relevance: Previously, it was believed that being overweight or obese caused osteoarthritis due to the increased mechanical forces on joints. This new study has challenged this belief and has shown that there are more complex mechanisms by which adipose tissue influences OA. By use of LD mice, the researchers eliminated weight as a variable and were able to directly study the paracrine influences of adipose tissue on joint degeneration in mice. This research paves the way for new OA therapeutics. Once we know how the signaling influences the progression of the disease, we can then create disease-modifying agents to target these pathways and potentially prevent osteoarthritis, the commonest debilitating joint disease.

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PNWMSRJ | Meta Analysis

An Unusual Presentation of Hypoglossal Nerve Palsy in a Young Woman

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Abstract

Hypoglossal nerve palsy can be seen under various emergent or chronic disease scenarios. It is commonly due to mass effects from a tumor, and other causes include neck trauma, operative injury, gunshot wound, stroke, or infections . However, it is relatively rare to see these symptoms without an apparent mass causing compression of the caudal medulla or a vascular lesion such as vertebral artery dissection. We describe a patient with a history of thyroid cancer who initially presented with left tongue deviation and atrophy. Other cranial nerve symptoms then showed up as various lesions were discovered in her internal jugular vein, spinal cord, and brain.

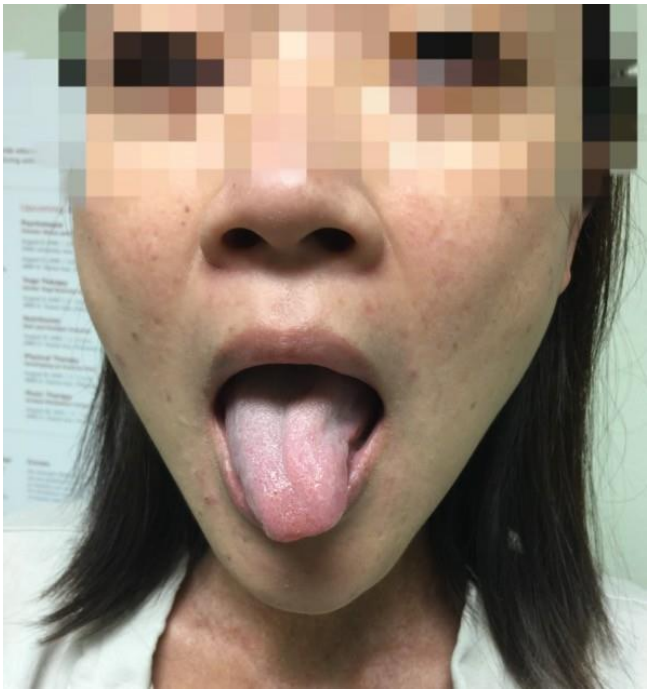

Figure 1:Initial Presentation of Left Tongue Deviation

Introduction

Hypoglossal nerve is the 12th cranial nerve that arises from the hypoglossal nucleus in the medulla oblongata of the brainstem. It exits the cranium via the hypoglossal canal and passes inferiorly to the angle of the mandible. It travels over the common carotid artery and internal carotid artery and eventually innervates the majority of the muscles of the tongue except for palatoglossus . The hypoglossal nerve controls all tongue movements, and an isolated hypoglossal nerve palsy is relatively uncommon. Space-occupying lesions are the most common cause of hypoglossal nerve palsy, followed by traumatic, vascular, and inflammatory lesions . Nuclear or infranuclear lesions lead to paralysis, atrophy, and fasciculation of the tongue on the affected side; supranuclear lesions produce weakness on the contralateral side . Hypoglossal nerve palsy also presents with other cranial nerve symptoms such as facial paralysis and vision changes due to mass effect .

Report of case

In April 2019, a 38 year old Asian female with a history of thyroid cancer and breast cancer presented with left neck and shoulder stiffness, tongue deviation, and left side tongue atrophy. She also complained of hoarseness of her voice since 2017. Her medications included levothyroxine and vitamin D. Family history revealed that her mother had brain cancer and passed away at the age of 60. Physical exam was unremarkable except for the neck stiffness and left tongue deviation. MRI of the brain with and without contrast was generally unremarkable except for fatty replacement of the posterior right parotid gland, which was consistent with MRI record from a year ago.

Figure 1:Initial Presentation of Left Tongue Deviation

Four months later, her previous symptoms had persisted and she now complained of dysphagia and left scalp numbness for two months. Physical exam still showed left tongue deviation and decreased sensation in the

head and neck region. Laboratory tests of MuSK, Ach receptor, and striational antibodies were all negative; Serum thyroid stimulating hormone (TSH) and myoglobin level was low. An Magnetic resonance imaging (MRI) of the cervical spine without contrast revealed a left internal jugular vein thrombus at level C1-C2 measuring approximately 45mm in length, which was also confirmed by Duplex ultrasound. Pt was prescribed Eliquis as treatment for internal jugular vein thrombus. She was put on anticoagulant medication for eight months, but she did not report improvement of symptoms. We were suspecting that the tongue deviation towards the left was due to compressive neuropathy by the internal jugular vein thrombosis. She underwent magnetic resonance angiography (MRA) of the head and neck and another MRI of the brain, which were all normal. She was then referred to a vascular surgeon, but no intervention was suggested.

In January 2020, which was 8 months after her initial visit, she developed left facial twitching, facial numbness, facial weakness with slurred speech, and blurry vision in her left eye. An MRI of the brain still showed no abnormality. She underwent mastectomy in February 2020 and was put on hormone therapy after being diagnosed with breast cancer in the end of 2019. Patient was wondering if acupuncture and physical therapy could help with her current symptoms of stiffness and weakness in the upper body. She visited several traditional Chinese medicine practitioners and had acupuncture sessions. Patient reported slight relief of symptoms after treatments.

Three months later, the patient returned to the clinic for a follow-up, and reported that all of her previous symptoms have persisted and now the numbness of the head and neck had expanded to the left upper chest. She underwent another spine MRI, which revealed abnormal 14mm x 15mm nodular dural enhancement at C2 associated with paraspinal region soft tissue mass and heterogeneous marrow signal. She then went to see her oncologist for possible cancer metastasis. A positron emission tomography (PET) scan of the cervical spine later ruled out metastasis.

A follow-up appointment in July 2020 revealed persistence of previous symptoms and now atrophy of the left trapezius and left ear hearing loss. A repeated MRI revealed a 2.3 x 1.6 x 1.2 cm mass in the left cerebellopontine angle region extending to the internal auditory canal, suspicious for an acoustic schwannoma. Later, a brainstem auditory evoked response (BAER) test confirmed peripheral left acoustic neuropathy. A visually evoked response (VER) test showed normal primary visual cortex response. Patient was referred to neurosurgery for the likely acoustic schwannoma.

Discussion

Cranial nerve XII is proximal to carotid and vertebral arteries, and vascular lesions are reported to affect cranial nerve XII function. After discovering the internal jugular vein thrombosis, a compressive neuropathy was suspected due to its proximity to the hypoglossal nerve. Internal jugular vein thrombosis is commonly found in patients with a history of malignancy or hypercoagulable state , which was consistent with the patient's history of thyroid cancer and breast cancer. It is possible that the thrombosis presented soon after the thyroidectomy patient had 20 years ago and eventually compressed her hypoglossal nerve. However, most patients with internal jugular vein thrombosis typically present with facial swelling and upper extremity pain . This patient's symptom of hypoglossal nerve palsy is not a usual presentation of internal jugular vein thrombosis.

Hypoglossal nerve palsy is also caused by primary cancer metastasized to the base of skull or primary malignancy such as hypoglossal schwannoma . However, the patient's hypoglossal nerve palsy has persisted for more than a year before the cerebellopontine angle mass showed up on brain MRI. She initially presented with hypoglossal nerve palsy and neck stiffness without significant imaging findings in the brain and she had multiple imaging of the brain with normal impressions during the next 10 months. Therefore, this mass in particular is unlikely to have been the cause of her left tongue deviation.

Mass at the cerebellopontine angle, on the other hand, does produce symptoms that relate to compression of cranial nerve V, VII, and VIII. The patient later developed Bell's palsy, which can be explained by the suspected acoustic schwannoma. The weakness of her left facial muscles caused chronic incomplete closure of her left eyes, which could have lead to unilateral blurry vision. However, the lesion was not proximal to the hypoglossal canal and presented later than the initial hypoglossal nerve palsy. The tongue deviation, therefore, is unlikely to have been caused by the suspected acoustic schwannoma.

The patient's scalp, neck, and upper trapezius tingling and numbness can be correlated to the later discovered C2 nodular dural lesion, which was suspected to be a meningioma of the spinal cord. This specific lesion will be closely monitored.

Patient has reported improvement of symptoms after Chinese acupuncture session. Although this method has not been well accepted as clinically effective, other approaches are possible to help with our patient's symptoms and improve her quality of life, especially after

a series of malignancy-related treatments.

Learning Points

- In general, hypoglossal nerve palsy presenting with other cranial signs is not uncommon in patients with ongoing malignancy due to mass effect on hypoglossal nerve.
- It is important to keep internal jugular vein thrombosis as a differential diagnosis of tongue deviation and atrophy when a patient presents with a history of cancer and cranial nerve lesions.
- Compression ultrasonography with Doppler is an effective and economical means of confirming upper extremity and neck deep vein thrombosis .

Acknowledgement

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Concerns and Recommendations for Magnetic Resonance Imaging in Patients with Spinal Cord Stimulators

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Abstract:
A literature review of the current recommendation for spinal cord stimulators (SCS) compatibility with magnetic resonance imaging (MRI) and a review of the Food and Drug Administration (FDA) approved spinal cord stimulation systems were performed. The current recommendations of an MRI with a 1.5T magnet and a mean total body specific absorption rate (SAR) of 0.9 W/kg or below have shown increase in patient safety and satisfaction despite the variability between SCS manufacturers. Measurements of safety included tearing of tissues due to rotational force generated by the magnetic field, acceleration of the device towards the bore of the magnet ("missile effect"), and burns caused by overheating of the device.

Questions being addressed:
Is the usage of MRI safe in patients with spinal cord stimulators (SCS) and does usage of MRI interfere with picture quality compared to those patients who do not have spinal cord stimulators?

Introduction:Clinical application of Magnetic Resonance Imaging (MRI) has increased dramatically in the setting of various cerebral, musculoskeletal, cardiovascular disorders. MRI is particularly relevant in patients with chronic pain who have spinal cord stimulators (SCS), needing MRI for consistent evaluation of the underlying disease. While the potential benefits of MRI are numerous, there are precautions that must be considered especially in the setting of a patient with a SCS (Table 1).

Thermal changes of the device are minimal when generated by the variable magnetic fields and pulsed radiofrequency fields elicited by MRI signals. A specific absorption rate (SAR) of less than 1.4 W/kg has produced no significant thermal changes at the leads where the maximum temperature is reached at the lead tip. Studies by Jose de Andres et al. and Lubenow T et al. have also reached similar findings that MRI exposure does not lead to SCS device malfunction or inactivation.

The current recommendations reveal close adherence of an MRI with a 1.5T magnet and a mean total body SAR of 0.9 W/kg or below can promote safety for the patient, despite the variability between different SCS manufacturers.1 The FDA is responsible for approving SCS compatibility with MRI.2 Magnetic Resonance (MR) conditions of two commonly used SCS, Senza Omnia Spinal Cord Stimulation System (Nevro) and Precision™ Montage™ MRI Spinal Cord Stimulator System, are included in Table 1.3,4

Adherence to these MR conditions specific to SCS device manufacturer optimizes patient safety index and image quality. Case report by Mansfield et al. on the patient safety and utility of MRI in patients with high frequency SCS shows well tolerated results without any complication while image quality was sufficient and not distorted.5 An example of MRI with SCS that is of sufficient quality for neuroradiologist reading is shown in Figure 1.

Importance: Major referral centers have been acquiring MRIs with a magnetic bore core of 3T. It remains uncertain whether SCS manufacturers can develop SCS that are compatible with 3T magnets without compromising SCS quality.

Conclusions: Strict adherence to an MRI with a 1.5T magnetic bore core and a SAR of 0.9 W/kg or below can promote patient safety despite the various SCS developed by manufacturers. Providers and technicians should be encouraged to seek specific SAR and Slew Rate and Field Strength conditions found on the manufacturers' website to yield the highest safety index and optimal image quality.

Future research may be necessary to expand on the recommendations for MR imaging in patients with SCS. Further expansion on MR recommendations for patients with SCS from different manufacturers than those mentioned in this review may be useful in medical decision-making processes. Additionally, although the image quality in patients with vs. without SCS are shown to not be statistically significant, it may be useful to review rates of diagnostic errors in medical decision making between the two groups to revisit and reaffirm possible implications on patient safety.

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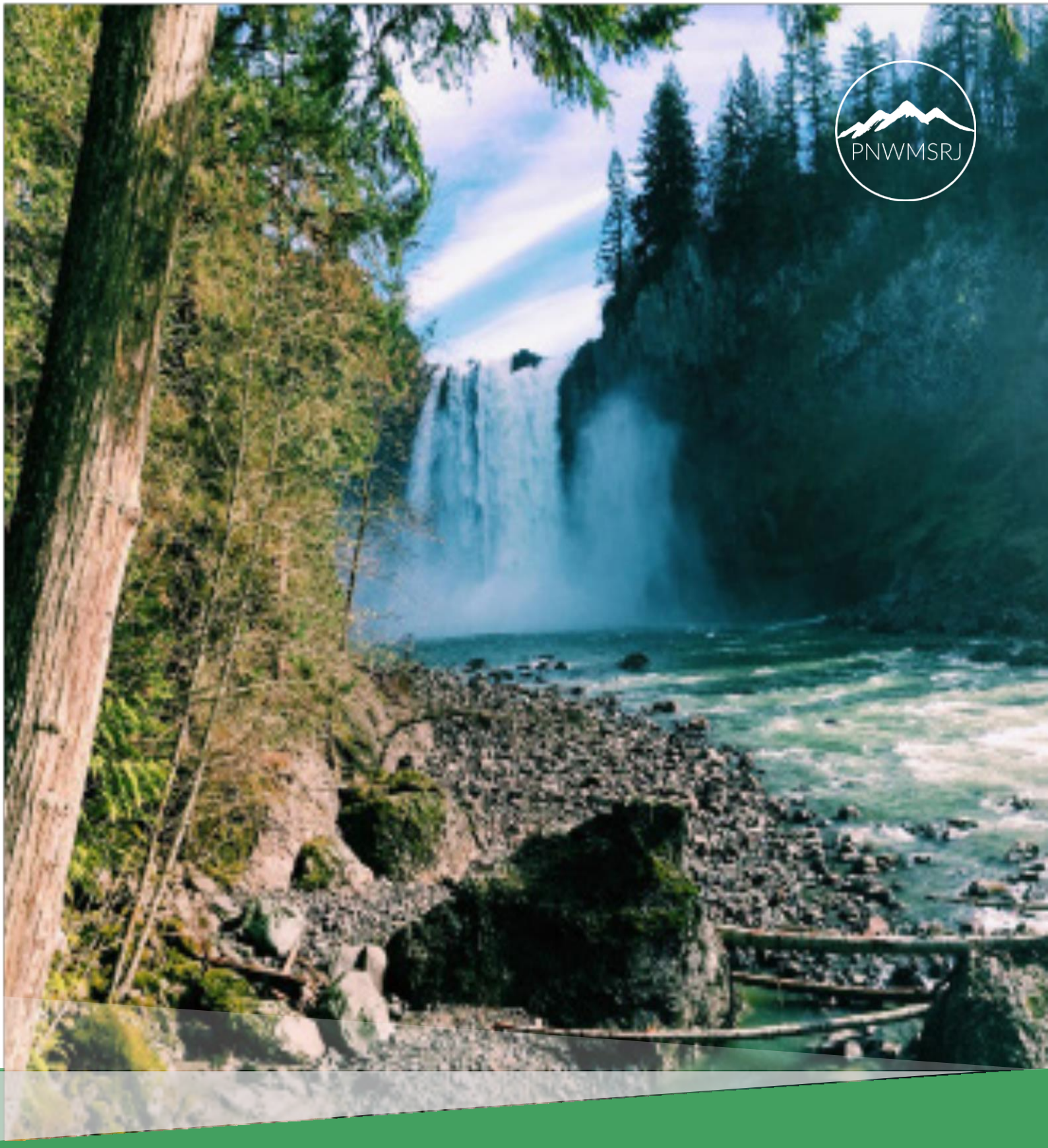
Figure 1. Sagittal T2-weighted MR imaging demonstrating signal drop-out imaging artifact from epidural leads. Although representation of inferior imaging settings for SCS were not accounted for, the image quality was sufficient for the reporting neuroradiologist to answer the clinical question posed5.

Table 1. MR conditions of two FDA approved SCS that must be fulfilled to achieve highest patient safety.

Spinal Cord Stimulator	MR Conditions*
The Senza Omnia™ Spinal Cord Stimulation System (Nevro)[3]	General requirements • Do not perform an MRI if the patient has a device or device component from a different manufacturer attached to the Nevro IPG. • Do not perform an MRI if impedance on any of the conductor path on the lead is greater than 10 kΩ. • Body Temperature – If a body coil is used (transmit only or transmit/receive), do not perform a scan if the patient's body temperature is greater than 37° C. Elevated body temperature in conjunction with tissue heating caused by an MRI scan increases the risk of excessive tissue heating, which could cause tissue damage. MRI requirements • Only use MR scanners with maximum spatial field gradient of 1900 gauss/cm (19 T/m) or less. • Only use MR scanners which limit gradient slew rate to 200T/m/sec per axis or less
Precision™ Montage™ MRI Spinal Cord Stimulator System[4]	MRI systems must meet following criteria • MRI magnet strength of 1.5T only • Gradient slew rate per axis less than or equal to 200 T/m/s. • Maximum spatial field gradient less than or equal to 40 T/m. • Scanner operation at or below normal operating ode limits for RF and gradient exposure: Whole body SAR must be < 2.0 W/kg, Head SAR must be < 3.2 W/kg.
*MRI examinations can be safely conducted if all the instructions provided in the table are followed. Further requirements may be found on the manufacturer's website.	

Figure 1. Sagittal T2-weighted MR imaging demonstrating signal drop-out imaging artifact from epidural leads. Although representation of inferior imaging settings for SCS were not accounted for, the image quality was sufficient for the reporting neuroradiologist to answer the clinical question posed5.



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