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Original Articles

The Role of Handheld Point-of-Care Musculoskeletal Ultrasound in Identifying Bone Injury: A Multi-Case Report

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ABSTRACT

Introduction: Ultrasound is not a commonly recommended imaging modality for evaluating bone. The purpose of this report is to illustrate the usefulness of handheld ultrasound in identifying bone injury through the use of three case examples. As handheld ultrasound units are the least expensive imaging equipment, they may be the only option available or may readily complement radiographs.

Cases:
1) 37-year-old male, hit from behind by a trailer while on his bike. Right shoulder dislocation relocated at the hospital. Radiographs confirmed relocation. A Hill-Sachs deformity was identified via handheld ultrasound.
2) 67-year-old woman, reported with a hyperinversion ankle injury, 3 weeks post injury. Initial radiographs concluded there was no fracture. An avulsion was identified via handheld ultrasound.
3) 69-year-old woman presented for a lymphatic massage. The massage therapist called for an urgent consult as her pain with moving was unusual. Pain located at right lateral ribs 7-9. Pain began following a thoracic manipulation a week prior. A rib fracture was identified via handheld ultrasound.

Conclusion: Handheld point-of-care ultrasound can be used to identify a bone injury and can complement radiographs.

Key Words: Hill-Sachs, fracture, avulsion, point-of-care ultrasound, POCUS

INTRODUCTION

When suspecting a bone injury, radiographs are often the first imaging modality that comes to mind due to their low cost and availability compared to computed tomography (CT) or magnetic resonance imaging (MRI). For example, the American Board of Surgeon's imaging guidelines recommend radiographs, then CT/MRI as needed.[1] Musculoskeletal (MSK) ultrasound's use is fairly young, with the Alliance for Physician Certification & Advancement (APCA) and the American Registry for Diagnostic Medical Sonography (ARDMS) only creating a specialty certification (RMSK/RMSKS) in 2012.[2] MSK ultrasound also requires a high frequency linear probe ≥ 12Hz with ideally 196 elements or more.[3] Handheld ultrasound units have improved greatly in recent years with multiple models that meet this criteria such as the Clarius L7/15/22 HD3 and GE Vscan Air CL.[4,5] These units can be purchased for approximately $4,200-$4,900 USD, at the time of this writing, which makes them an affordable imaging modality that requires no special installation, dedicated space, or special considerations due to ionizing radiation.[6,7]

Ultrasound is known for its ability to image soft tissues. In that context, bones are often used as landmarks or are seen as an inconvenience, as the cortex is such a strong reflector that structures behind a bone cannot be imaged. Being such a strong reflector, ultrasound produces a clear outline of the cortex, and can evaluate its form, but is limited to a very narrow window. You are limited by the size of the transducer head and to areas to which you can image. For example, you cannot evaluate the ribs under the scapula or the superior rim of the glenoid due to the scapula and the acromion, respectively, blocking direct access. The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) made a series of evidence-based recommendations for MSK ultrasound use in 2022.[8] These are their recommendations as they apply to bone:[8]

1. Ultrasound (US) should be used to detect peripheral enthesophytes and erosions (Level-of-Evidence(LoE) 1, Strength-of-Recommendation(SoR) strong). Broad consensus (88%).

2. In accessible bone areas, when radiography is negative but clinical suspicion of acute fracture is high, US should be used (LoE 1, SoR strong). Strong consensus (95%).

3. In regions with an acoustic window, US should be used for monitoring fracture healing (LoE 2, SoR strong). Broad consensus (76%).

4. In regions with an acoustic window, US might be used to detect periostitis (LoE 4, SoR weak). Broad consensus (76%).

Note the recommendation with the strongest consensus is to use ultrasound for fractures when radiographs are negative. Ultrasound is reasonably good at identifying fractures: a 2019 meta-analysis examining the use of ultrasound to identify fractures determined a pooled sensitivity and specificity of 0.93 and 0.92 for upper limb fractures and 0.83 and 0.93 for lower limb fractures.[9]

To illustrate the ability of handheld ultrasound in a point-of-care setting for bone injury, three cases are presented: a Hill-Sachs defect, an avulsion, and a rib fracture. Each case features a brief discussion following the case presentation. Ultrasound imaging was performed with a handheld Clarius L15HD3 (Clarius Mobile Health Corp., Vancouver, BC, Canada) by a chiropractor.

CASE PRESENTATION AND DISCUSSION

Case 1: A 37-year-old male was struck by the edge of a trailer from behind while cycling. The right shoulder was dislocated anteriorly and was relocated at the hospital. Relocation was confirmed via radiographs (**Figure 1**). He reported to the clinic 10 days post-injury for treatment and was referred to a physiotherapist for co-management. A partial ultrasound was taken that day examining the most painful sites, but the scan was limited to the regions of pain due to time and the patient's limited range-of-motion (ROM). Myofascial trigger points were identified in the infraspinatus, and the biceps and subscapularis tendons appeared normal. On a check-up approximately 2.5 months later, with increased ROM the supraspinatus was evaluated via ultrasound (**Figure 2**). Decreased echogenicity of the supraspinatus tendon consistent with tendinosis was seen along with a cortical irregularity that, when combined with the patient's history, is consistent with a Hill-Sachs defect. This is not the first one identified via ultrasound though, with the earliest study completed in 1996.[10-12]

A 2021 systematic review of imaging modalities for Hill-Sachs lesions concluded that CT arthrography (CTA) is the most accurate with a median accuracy of 91%.[10] Accuracy is not the only factor and the authors discuss that MRI and ultrasound are both reasonable alternatives. MRI has a similar accuracy but has the added advantage of showing soft tissue injuries (like a capsular defect or bone marrow edema) and ultrasound may be only slightly less accurate (94% when compared with CTA and 91% compared to arthrography in one study).[10,11] Radiographs compared poorly with the other imaging modalities.[10] The authors comment on the gaining popularity of ultrasound: the relative lower cost, less time, and zero radiation exposure to the patient.[10,13] Despite its benefits, ultrasound has some important shortcomings to consider such as: the ROM of the patient might limit the evaluation, the interobserver reliability can be quite low ($\kappa = 0.4$ in one study), and only a fraction of the labrum can be evaluated.[11-13] Lack of exposure to using ultrasound to detect bone injuries might be a factor, even for those trained in MSK ultrasound. The chiropractor who performed the ultrasound study was taken aback by the humeral head's appearance because, despite multiple learning resources, he had never been exposed to the concept of identifying a Hill-Sachs lesion via ultrasound.[14-16] This suggests improvements in ultrasound educational resources may be in order, particularly for POCUS practitioners without access to other forms of imaging.

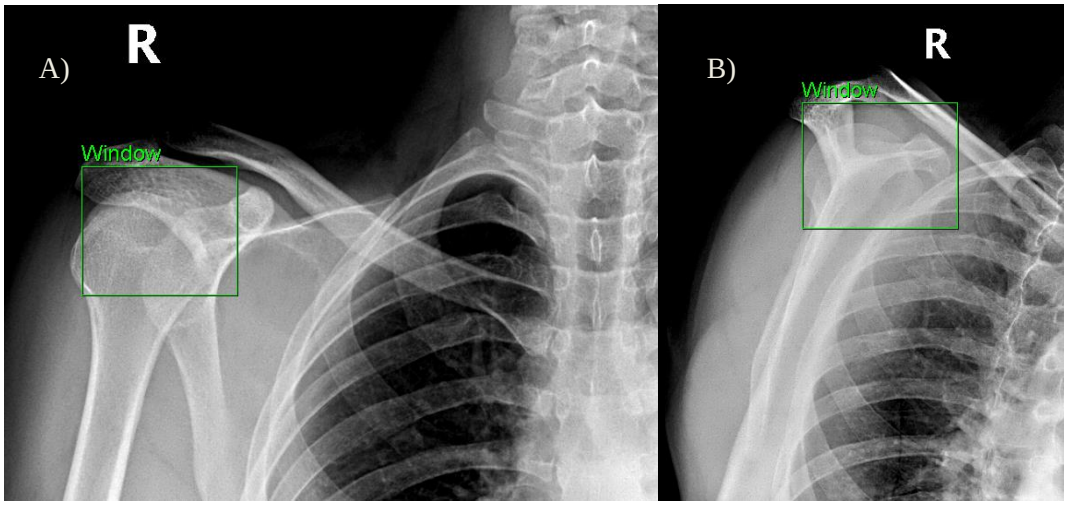

Figure 1: *Patient radiographs of the right shoulder post-relocation: (A) AP with internal rotation and (B) Scapular-Y view. Although not identified on the initial imaging report, a subtle cortical defect is suspected, particularly on the AP with internal rotation view.*

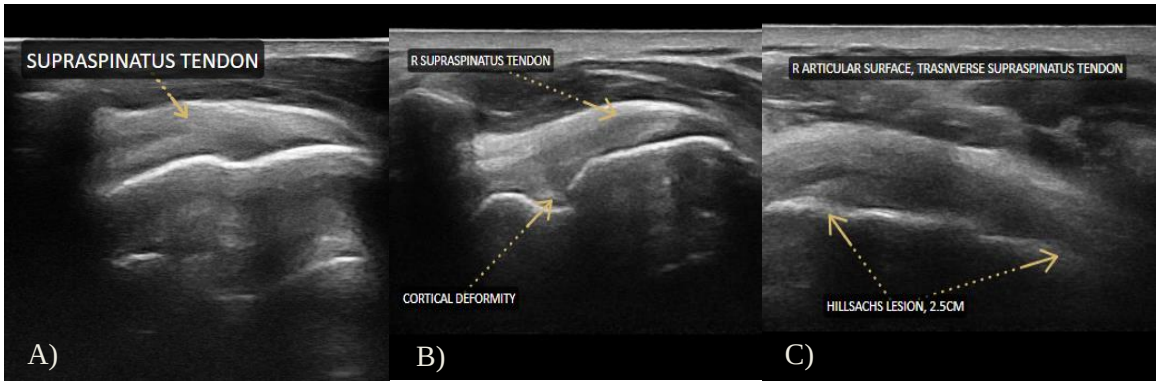

Figure 2: *A) Normal transverse view of the supraspinatus tendon. B) Transverse view of the patient's right supraspinatus tendon. Note the cortical deformity. C) Transverse view of the patient's supraspinatus tendon used to determine the extent of the cortical irregularity.*

Case 2: A 68-year-old female traveler. She had sprained her left ankle via hyperinversion by slipping on a rock in Spain. She was barred from her flight due to the extreme swelling noticed by the flight crew. A radiograph was taken at the hospital ruling out fracture. She reported to our clinic 3 weeks later for acupuncture and lymphatic massage. When she complained that the joint "didn't feel right" she was referred to the chiropractor for evaluation. Some edema was noted, and the anterior talo-fibular ligament (ATFL) region was tender to palpation. An ultrasound was performed showing the bright line of cortex where the ligament should be (**Figure 3**). This was diagnosed as an avulsion injury of the ATFL.

In a study by Takakura et al. comparing radiographs versus ultrasound, it was found that

ultrasound had an increased sensitivity (94% compared with 81%) for detecting avulsions of the ATFL. [17] A meta-analysis in 2019 concluded that ultrasound should be the first-line imaging modality of choice for ATFL evaluation.[18] Although MRI is also fairly accurate, ultrasound performs slightly better when compared with MRI with the added benefit of being more affordable.[19,20]

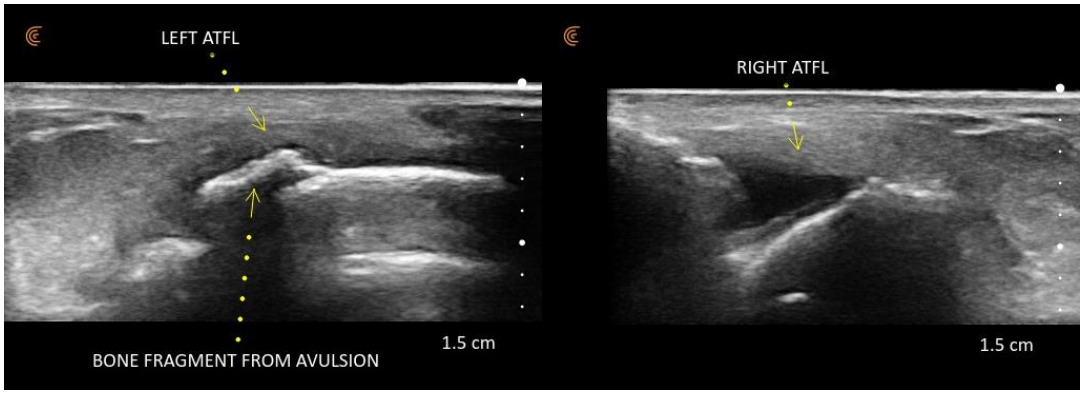

Figure 3: *Split screen view of the left ATFL and right ATFL. Notice the bright line of cortex spanning the majority of the left talo-fibular joint space. Note the lack of signal under the avulsion fragment (posterior acoustic shadowing artifact).*

Case 3: A 69-year-old woman came to the clinic for a massage. The massage therapist noticed her abnormally acute pain with movement and called the chiropractor in for an urgent consult. The pain was located in the right lower posterolateral rib region. Pain was aggravated with trunk movement and deep breathing. The region was tender to palpation. Vibration with a tuning fork against one of her tender ribs increased her pain. An ultrasound scan was performed (**Figure 4**) and there was a sharp discontinuity in the cortex indicating a fracture. She reported that the pain had started one week earlier when a chiropractor had "cracked" her back/ribs. Note that she was later diagnosed with Stage 4 breast cancer so the integrity of her ribs might have been compromised.

A recent retrospective study on the safety of chiropractic spinal manipulative therapy (SMT) found an incidence of severe adverse events was only 2 out of 960,140 SMT sessions.[21] Both recorded events were rib fractures in women >60 years of age with osteoporosis.[21] A rib fracture should be considered in any elderly woman who presents with sharp rib pain following a manipulation. As for diagnosing a rib fracture, ultrasound may be superior to radiographs.[22] In a 2017 study by Pishpin et al. it was found that ultrasound had detected 98% of rib fractures whereas oblique rib view and PA chest radiography detected 46% and 41% of rib fractures, respectively.[22] The authors further noted that ultrasound evaluations were also faster with ultrasounds taking 7-17 min while radiographs took 15-37 min as patients would have to travel to the radiology department and back whereas a portable ultrasound was used in the emergency room.[22]

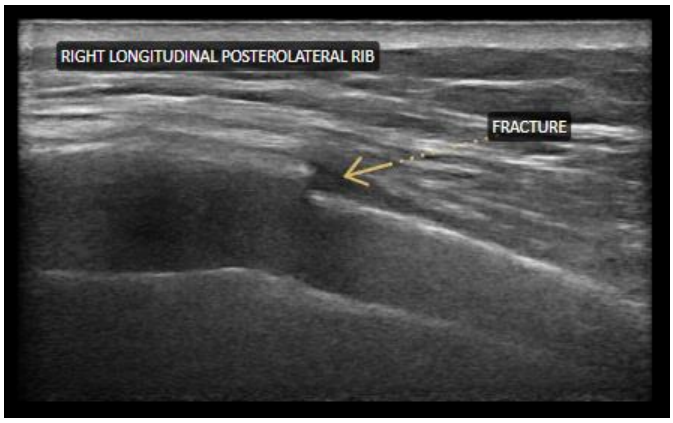

Figure 4: *Longitudinal view of a posterolateral rib. Note the discontinuity of the cortex indicating a fracture. The small hypoechoic region adjacent to the fracture site likely represents a hematoma.*

CONCLUSION

The usefulness of handheld ultrasound to diagnose bone injury was illustrated through three examples: a Hill-Sachs lesion, an avulsion, and a fracture. In two of the cases, radiographs had failed to diagnose the injury. While sonography is limited to regions with direct access, when it is viable, it may perform as well as MRI/CT and can have superior sensitivity to radiographs. Handheld ultrasound is a viable imaging modality for bone and a useful addition to radiographs.

CONSENT

Written consent for publication was obtained from the living patients.

COMPETING INTERESTS

The author offers ultrasound educational courses and consultations. The author declares no other competing interests.

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Undiagnosed Nail Patella Syndrome in an Elderly Chiropractic Patient: A Case Report

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ABSTRACT

Background

Nail-Patella Syndrome is a rare autosomal dominant condition with high penetrance and varied clinical expression, affecting fewer than 20 in 1 million persons. The most common features include nail dysplasia, hypoplastic or absent patella, renal anomalies, and ophthalmological disease.

Case Presentation

A 67-year-old female presented to a chiropractic clinic for symptoms of hip pain with radiation to the knee. The patient's history was remarkable for glaucoma, retinal surgeries, and current cigarette smoking. Physical examination results were remarkable for hypertension, delayed upper and lower extremity capillary refill, cervical and lumbar muscle spasms, and reduced cervical ranges of motion. Radiographic examination revealed osteopenia, diffuse idiopathic skeletal hyperostosis, osteoarthrosis, and iliac horns (bony exostoses) from the posterior ilia.

Results

The patient was diagnosed with Nail-Patella Syndrome, from the radiographic and clinical findings, and with intersegmental dysfunction, hypermyotonicity, osteoarthrosis, and osteopenia. Treatment included chiropractic manipulative therapy, postural exercises,

electrical muscle stimulation, and cryotherapy. The patient's musculoskeletal symptoms fully resolved within 3 weeks. She was referred to nephrology and ophthalmology for evaluation of associated complications of Nail-Patella Syndrome.

Conclusion

An elderly patient with musculoskeletal symptoms experienced pain relief with conservative treatment and was diagnosed with a rare inherited disease not previously recognized by her other physicians or by family members with similar clinical features. The discovery led to specialist consultations in ophthalmology and nephrology for management of possible associated complications of Nail-Patella Syndrome.

Key Words: Nail-Patella Syndrome, Fong Disease, Iliac horns

INTRODUCTION

The atypical patellae and dysplastic nails of the rare hereditary disease known since the 1950s as Nail-Patella Syndrome (NPS) were first described in scientific literature in 1897.[1] Subsequent authors described additional associated features, resulting in several eponymous and descriptive names for NPS, including Turner syndrome, Fong disease, arthro-onychodysplasia, and hereditary osteo-onycho-dysplasia (HOOD).[1]

Nail-Patella Syndrome is a rare hereditary condition of both ectodermal and mesodermal tissues,[2] occurring in approximately 4 to 20 persons per 1 million live births.[3,4] NPS is an autosomal dominant inherited condition with high penetrance and variable expressivity.[4] The condition's inconsistent clinical features may result in delayed diagnoses,[3] even amongst multiple impacted family members, as was the case in the patient described.

In 1998, the NPS gene was identified as *LMX1B* on chromosome 9q.[2,5,6] Only 12% of reported NPS cases are due to a spontaneous genetic mutation.[6] The disease is typically diagnosed through a combination of clinical and radiographic features. Genetic testing may be performed if the clinical and radiographic evaluation is equivocal.

Clinical findings of NPS may include:

- **Nail/digit anomalies, pathognomonic** (95.1%)[1,6]: anonychia, hypoplastic (micronychia),[6] or dystrophic fingernails, with the thumb most frequently involved; triangular-shaped lunulae; decreased creases over the distal interphalangeal (DIP) joints; the toenails are less commonly affected
- **Patellar anomalies, pathognomonic (**92.7%)[6]: absent or hypoplastic patellae; superior and lateral patellar dislocations; early osteoarthritis
- **Iliac horns, pathognomonic** (80%)[1,6]: asymptomatic, possibly palpable, posterolateral iliac exostoses at the origin of the gluteus medius, present in approximately 70% of patients, but considered pathognomonic for NPS when identified; iliac horns do not affect the patient's gait or gluteus medius strength[7,8]

- **Elbow anomalies** (92.5%)[6]: reduced flexion, supination, and pronation ranges of motion; possible hypoplastic and posteriorly displaced radius; antecubital webbing (pterygia) of the elbow skin may be present [7]
- **Renal involvement** (26-60%)[6]: proteinuria with or without hematuria, with progression to end-stage renal disease in approximately 5-30%[6,8]; hypertension
- **Ophthalmological disease** (10-16.7%)[1,4]: open-angle glaucoma with optic nerve and visual field damage (peripheral field deficits); ocular hypertension; Lester sign, a cloverleaf hyperpigmented ring in the iris
- **Lower extremity anomalies**: talipes equinovarus, equinovalgus, absence of the fibula[6]

CASE PRESENTATION

A 67-year-old Caucasian female sought chiropractic care for constant sharp left iliofemoral pain with radiculopathy to the left knee. The pain began approximately one-month prior after she lifted several heavy boxes. Her symptoms were worsened by the activities of climbing stairs, walking, crossing her legs, lying on her side, getting in and out of the shower and car, and putting on her shoes. Sitting in a recliner and taking naproxen sodium lessened her pain. Additionally, her pain was worse in the mornings and afternoons and improved in the evening hours.

Examination

The patient was cooperative and attentive during the examination, oriented to person, place, and time, but with pallor, a drawn facial expression, and a forward antalgic posture.

Vital sign examination results were as follows: radial pulse of 64 beats per minute, respiration of 14 breaths per minute, temperature of 98.5 degrees F, and right brachial blood pressure of 138/72 mmHg. The patient's heart sounds were clear and distinct without murmurs, her bowel sounds were present, and her abdomen was soft and non-tender. Bruits of the carotid and subclavian arteries were not detected. Upper and lower extremity capillary refill was delayed with returns greater than 4 seconds. Brachioradialis, biceps, triceps, patellar, and ankle reflexes were brisk and graded at 2+. Upper and lower extremity muscle strength and tone were all 5/5 and light touch and pinprick sensation were intact.

Cervical lateral flexion and rotation were reduced with muscle spasms present. Lumbar extension was reduced, and pain and muscle spasm were noted. Several provocative orthopedic examinations resulted in increased pain lower lumbar pain, including Kemp's test, Seated Straight Leg Raise, Supine Straight Leg Raise, and Fabre-Patrick. Valsalva test did not increase pain. The patient revealed she is a smoker, has glaucoma, and had multiple eye surgeries including selective laser trabeculoplasty. Her mother died at age 67 and her maternal grandfather died at age 91, both due to colon cancer. No additional information regarding her family health history was reported during the initial interview.

Imaging

Radiographic evaluation of the lumbar spine was performed, revealing osteopenia, degenerative disc disease, zygapophyseal facet arthrosis without spondylolisthesis, Diffuse Idiopathic Skeletal Hyperostosis (DISH), and arterial calcifications without aneurysm of the abdominal aorta and iliac arteries. Uncommon and unexpected radiographic findings of large, triangular, bony projections from the bilateral posterolateral ilia were identified. (**Figures 1A and 1B**).

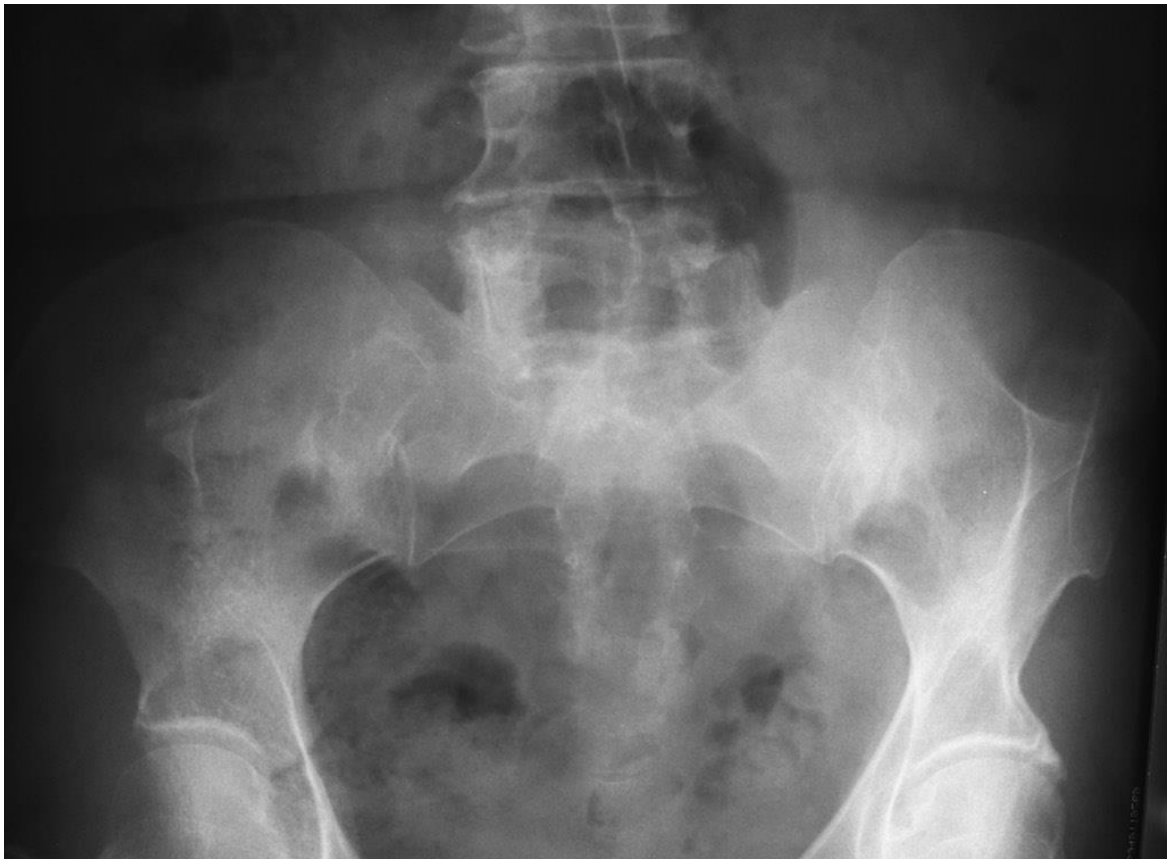

Figure 1A: Bilateral posterolateral iliac exostoses.

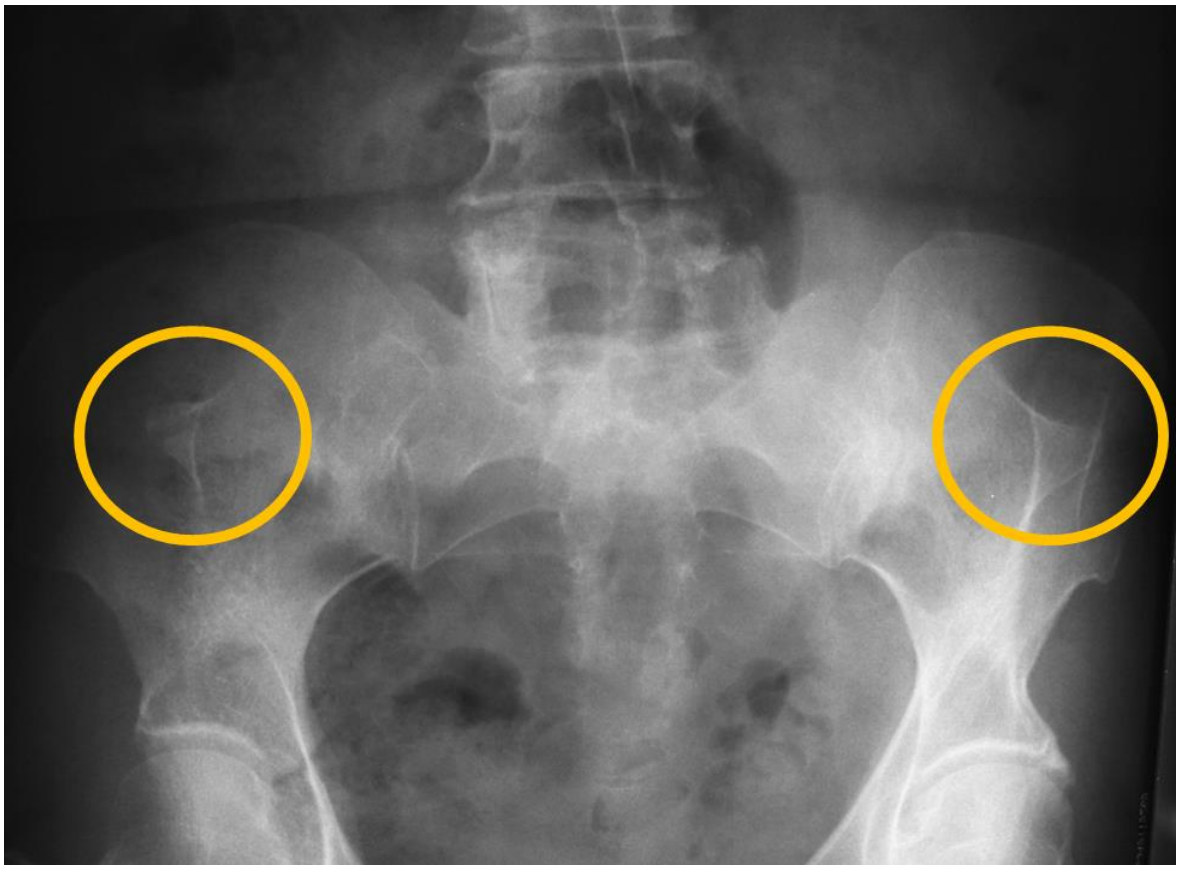

Figure 1B: Bilateral posterolateral iliac exostoses, annotated.

Iliac-based exostoses ("iliac horns") are a pathognomonic finding of Nail-Patella Syndrome (NPS), also known as Hereditary Osteo-Onychodysplasia Disease (HOOD), Turner-Keiser syndrome, and Fong disease. The patient was informed of the diagnosis of NPS, and additional evaluations of the small patellae and hypermobile elbows not identified during the initial examination were performed. The patient subsequently revealed that several family members had "nail problems", including her mother and her son, but no family member had ever received a diagnosis related to the unusual appearance of their nails. (**Figure 2**).

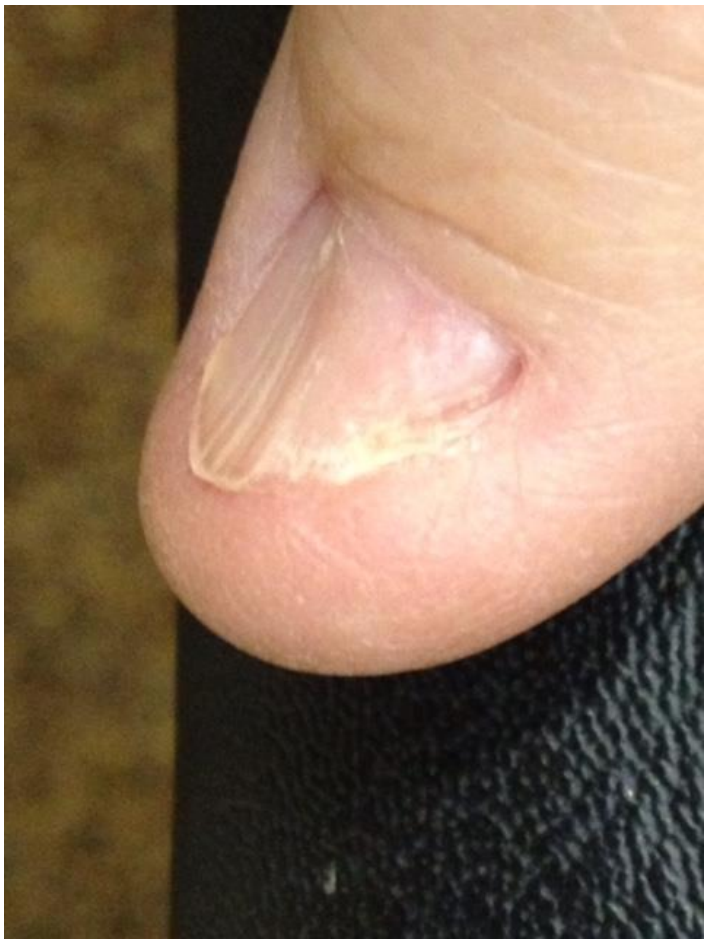

Figure 2: Dysplasia of the patient's thumbnail

Additional diagnoses included osteoarthritis, intersegmental fixation and dysfunction, and hypermyotonicity of the trunk and pelvic musculature. The patient was treated with a combination of chiropractic manipulative therapy, postural exercises, electrical muscle stimulation, and cryotherapy. During the first three weeks of treatment, the patient's pain levels decreased, and muscle spasms were alleviated. She was referred to ophthalmology and nephrology for assessment of complications of the NPS.

DISCUSSION

There is no cure for NPS. The offspring of one parent with NPS have a 50% risk of inheriting this disease.[8] Genetic assessments, prenatal counseling, early diagnostic exams, and surveillance of patients and affected family members are integral to diagnosing the varied expressions of NPS, including the orthopedic, ophthalmological, and renal complications of the disease.[8] Non-steroidal anti-inflammatory medications (as was utilized by the patient in this case report for analgesia) should be avoided due to the detrimental impact on renal function.[9]

CONCLUSION

This is an unusual case of an elderly patient with undiagnosed Nail-Patella Syndrome, despite lifelong signs present in her and multiple family members. This case report emphasizes the importance of early identification of symptoms and signs of NPS to address and reduce the musculoskeletal, ophthalmological, and renal complications associated with this disease.

LIMITATIONS

This is a single-patient case report. Results may not be generalizable to other individuals with similar conditions.

CONSENT

The subject of this case report is deceased, thus she could neither grant nor withhold consent to the use of her de-identified personal information.

COMPETING INTERESTS

The authors declare no competing interests.

ACKNOWLEDGEMENTS

The authors wish to thank the patient and the referring chiropractor for sharing this uncommon clinical presentation.

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Dynamics of Nutrition in the American Prison Complex - Impact of Nutrition on Inmate Health and Response to Chiropractic Care: A Commentary

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INTRODUCTION

Each year, more than 650,000 people are released from state and federal prisons, equating to over 10,000 ex-prisoners entering local communities each week.[1] The number of people incarcerated in the United States was 1.8 million by mid 2020.[2] Considering these statistics it is likely that a chiropractic practitioner will interact with a patient with a history of incarceration, particularly if that practitioner serves an outreach clinic population of financially disadvantaged persons. This demographic of patients is more likely to have histories of physical and psychological trauma, poor sleep quality on steel beds, and inadequate nourishment, which can impact the quality and strength of soft tissues.[3-4] The combination of trauma, inability to access structurally supportive areas to sleep and sit, and lack of access to quality nourishment may lead to slower than expected, or suboptimal response to chiropractic clinical care. Sarcopenia, characterized by the loss of strength and muscle mass that can occur because of poor nutrition[4], was first described in 1989 and categorized as a distinctive ICD-10 coded disease in 2016. The incidences of sarcopenia in chiropractic and allied health settings are likely to rise, commensurate with an aging population and populations with a higher risk of malnutrition.[5] Sarcopenia can decrease the ability for the patient to fully benefit from the chiropractic adjustment and may impact the reduction or elimination of the cycle of pain.[6] Food and nutrition insecurity, a significant determinant of health, impacts people worldwide.[7] Food insecurity is the limited or uncertain availability of nutritionally adequate and safe foods or limited or uncertain ability to acquire acceptable foods in socially acceptable ways, with possible consequences of

malnutrition and sarcopenia.[7] Data is limited, but food insecurity among correctional populations may be among the highest of all populations, with an estimated 70-91% impact level.[7] Providing meals at an institutional level within the justice system is problematic with high reliance on foods that are ultra-processed,[8] a step beyond simple processing through heating, freezing or dicing, to those food products that are mostly or entirely from substances extracted from foods or derived from food constituents with little if any food intact. In addition, food workers exist within the system that lack appropriate food safety training.[8] This commentary describes the nutritional challenges within the American Prison Complex, with respect to the food insecurity within that system,[9] the incidence of preventable disease that results from such a system, and the necessary interventions and considerations to improve chiropractic clinical outcomes in post-incarceration patients.

DISCUSSION

There is a continuum between nourishment intake that is necessary for good health, necessary for survival, and that which creates poor health outcomes. Good health requires the intake of six nutrients for the body to function properly. These nutrients supply the energy, building blocks for repair and growth, and the substances to regulate necessary chemical processes.[10] To more fully understand the impact of poor nutrition in incarcerated persons and its influence on chiropractic clinical care, a brief description of legal requirements to feed the incarcerated, application of the 8th amendment to prison nutrition and examples of prison meals and costs will be given. A concise overview of the basic elements of nutrients is also beneficial to illustrate the potential clinical impact of the poor nutrition common within this population.

From a legal standpoint, nutrition standards for the incarcerated are determined at a state and local level, in addition to court precedence and input from The American Correctional Association (ACA), which offers an accreditation process that is voluntary.[9] Another main governing law regulating prison food is the Eighth Amendment that requires that correctional facilities must not deprive those incarcerated from the "basic necessities of life" to prohibit what would be considered cruel and unusual punishment of convicted prisoners.[9] Criticism of prison meals that may cite the Eighth Amendment focus on food items of processed meat, canned fruits and vegetables and packaged bakery items that are devoid of nutritional value and fall short of adequate calorie and/or macro/micronutrient needs[9]. At an average price per meal of $1.77 in the state of Georgia for example, adequate calorie and macro/micronutrient needs become supplemented through fortified drink mixes or other items that may go unconsumed.[9] In addition, the Eighth Amendment is referenced due to deplorable conditions for food preparation and delivery that has led to those incarcerated to be six times more likely to become ill due to foodborne pathogens.[9]

Nutrient needs vary depending on activity level and total energy expenditure and should be separated into two distinct categories: the minimal intake of macronutrients and the flexible intake of additional calories, as needed.[10] Macronutrients (made up of protein, carbohydrates, and fats) and micronutrients (made up of vitamins and minerals) are key providers of energy in the diet and are critical to maintaining health.[10]

Proteins comprise over twenty amino acids and are the most diverse of all macromolecules, with each cell containing several thousand different proteins performing a variety of functions, including: acting as the structural component of the cell and tissues, functioning in the transport and storage of small molecules (such as the transport of oxygen by hemoglobin), transmitting information between cells, and defending against infection through antibodies.[11] The most critical function of proteins is the ability to act as enzymes that catalyze nearly all chemical reactions in a biological system.[11] As a result, proteins direct nearly every activity in the cell.[11] Because the body does not store amino acids, it must create them by modifying existing amino acids, or by obtaining them in the diet.[11] Access to protein is an essential component to health. The National Academy of Medicine recommends adults get a minimum of 0.8 grams of protein for every kilogram of body weight per day, which equates to approximately 7 grams for every 20 pounds of body weight.[12] For a 200-pound person, a minimum of 70 grams of protein is needed per day for good health.[12] Inadequate intake of protein can cause loss of muscle mass, decrease in immune function, and weakening of the heart and respiratory systems.[12]

Carbohydrates are present in several forms, most often sugars, fibers, and starches.[13] The healthiest sources of carbohydrates are unprocessed or minimally processed, such as sweet potatoes, beans, quinoa, and oats.[13] Highly processed or refined foods, such as white bread, packaged cereals, pasta, and sweets, have had the most nutritious components of bran and germ removed, leaving them nearly devoid of beneficial nutrients.[13] These carbohydrates are quick to digest, contribute to weight gain, make it harder to lose weight, and have been shown to contribute to heart disease and diabetes.[13] While carbohydrates are an essential macronutrient, primary sources should be fruits, vegetables, and whole grains.[13]

Dietary fat is an important source of energy and aids in the absorption of specific vitamins and minerals, builds cell membranes, forms the sheath surrounding nerve cells,[14] and is necessary for blood clotting and muscle movement.[14] Some fats, such as olive oil, flaxseed oil, and omega-3 fatty acids, have been shown to lower levels of inflammation.[14] The most readily available, least expensive, and commonly consumed fat in the United States is trans-fat (trans-unsaturated fatty acids).[15] A byproduct of hydrogenation, trans fat converts healthy oils into solids to prevent rancidity. Trans fat has no health benefits or known safe levels of consumption.[16] Consuming trans-fat raises the level of LDL cholesterol in the blood and increases the risk of developing heart disease, the leading cause of death in men and women in the U.S.[16] These fats also create systemic inflammation and increase risk for heart disease, stroke, diabetes, and other chronic conditions.[16]

Micronutrients are vitamins and minerals required by the body for growth and development, disease prevention, and normal functioning of body systems. There are approximately 40 important micronutrients found primarily in fruits and vegetables. Deficiencies of iron, required for oxygen transport in the blood, can cause anemia, consequent fatigue, and reduced physical activity. Vitamin D plays a critical role in decreasing risks of developing chronic illness; persons with a deficiency are at greater risk for low bone density, autoimmune conditions, cancer, and cardiovascular diseases.[9] Few foods contain Vitamin D other than fatty fish and fish liver oils; exposure to sunlight may provide some level of Vitamin D.[9] Vitamin B12 is needed to create nerves, red blood cells, and DNA; deficiencies

of this nutrient can lead to depression, mental illness, joint pain, and many other negative health issues.[17] Deficiency of Vitamin B12 is more common in those that are vegetarian/vegan, as it is primarily in animal products.[17] Diets using soy in place of animal products do not make up for this lack of B12.[18]

The food provided to incarcerated persons in U.S. correctional facilities often fails to meet the nutritional requirements to sustain basic levels of health for its populations. Contributing factors include a lack of national standards for the food served and inconsistencies in correctional food service worker training, which increases foodborne illness, decreases food safety, and does not ensure adequate nutrition for each inmate.[19]

The Marshall Project, a "nonpartisan, nonprofit news organization that seeks to create and sustain a sense of national urgency about the U.S. criminal justice system", discovered that nutritional standards at state and local facilities are governed by a patchwork of state laws, local policies, and inconsistent court mandates.[19] An example of the inconsistencies is a Texas law that requires inmates be fed three times in 24-hours, but this only applies to county jail inmates and not state prisoners.[20] In addition, the American Correctional Association makes only a recommendation, not a requirement, that prisons offer inmates three meals a day, and makes no specifications on nutrient needs.[20] Further, a 2014 investigation by human rights attorneys of inmates at the Gordon County Jail in Calhoun, GA showed the inmates were deemed to be starving with only two meals per day of inadequate caloric levels.[20] Consequently, inmates reportedly resorted to eating toothpaste and toilet paper, licking syrup packets, and drinking excessive amounts of water to combat their hunger.[19] To cut costs, some states have proposed reducing minimum required meals to two per day while others have outsourced food service to private industry companies to further cut associated costs.[19]

Often inmates are underfed or served food that is too high in sodium, sugar, cholesterol, and saturated fat from mostly processed food sources, with levels 2-3 times higher than USDA recommendations.[7] Minimum daily suggested nutrients in the forms of fruits, vegetables, and proteins may not be provided, and when food is delivered, it carries a significant risk of causing food-borne illnesses.[9] A 2017 study from the Centers for Disease Control and Prevention (CDC) determined that people in correctional facilities are approximately 6.4 times more likely to suffer from a food-borne illness than the general population, primarily from Clostridium perfringens and Salmonella.[19] Tainted poultry was the most common single source of illness, followed by raw and undercooked meat, eggs, products made from milk, and seafood.[19] Correctional facilities often lack the ability to properly execute food handling protocols and there are inconsistent processes in place to ensure improvements.[19]

Reporting by the CDC revealed that 80% of the formerly incarcerated said the food served was unappetizing in taste and smell, with 94% reporting they couldn't eat enough to feel full due to the quantity of food available.[19] Sixty-six percent of respondents said they were served food with bugs or portions that were moldy or spoiled, including "weevils in grits, rocks in turnip greens, maggots in meat, a rat tail buried in a day's entrée, and oatmeal containing human hair, pieces of metal, or cockroaches."[8]

Without access to nutritious food, those who are incarcerated are disproportionately at risk for developing chronic diseases, like diabetes and heart disease, or will experience a worsening of existing conditions.[21] A malnourished person is often portrayed as emaciated, but someone can be both malnourished and overweight, even obese, if they consume an excess of calories that lack critical nutrients.[22]

Chiropractic care of a formerly incarcerated person can be complicated by muscle wasting, or sarcopenia, as a consequence of inadequate protein intake, adding to the challenges of providing effective chiropractic interventions for these patients. Sarcopenia occurs in adult tissue when protein degradation rates exceeds protein synthesis.[23] Regulation of muscle mass and fiber size reflects protein turnover, or the balance between protein synthesis and degradation within the muscle fibers.[23] Catabolic conditions that exist include malnourishment/starvation, cancer, fasting, critical illness and forced/chosen caloric restriction.[19] Muscle atrophy in any of the above situations results from shrinkage of myofibers due to a net loss of proteins, organelles, and cytoplasm, with a hyperactivation of cellular degradation pathways, including the ubiquitin-proteasome and autophagy-lysosome pathways.[25] Due to this catabolic process, muscle tissue becomes sinewy and contracted, leading to difficulty with supple and free motion.[23] The chiropractic adjustment may be successfully delivered utilizing a variety of techniques, but due to tissue stiffness and loss of tissue resiliency, change in adjusting technique may be required to accommodate for poor tissue quality.

The diagnosis of sarcopenia is centered on assessment of body composition and physical performance testing, including grip strength with dynamometry, gait speed and sit to stand time[5], with analyses ideally incorporated into portal-of-entry healthcare settings. An additional assessment that may be used in the office is the SARC-F questionnaire (Table 1) that was first published in 2016 as an efficient and economical 5-item screening assessment for clinicians suspecting sarcopenia. Each item (Strength, Assistance, Rise, Climb, Fall) is scored 0-2, with higher cumulative scores (>4) suggesting consequences of sarcopenia. See Table 1.[23] In 2020, the Sarcopenia Definitions and Outcomes Consortium (SDOC) identified grip strength less than 35.5 kg in males and 20 kg in females, and gait speeds less than 0.8 meters/sec as key risk assessment findings tied to likelihood of disability, loss of mobility, falls and fractures and mortality in sarcopenic patients.[25]

SARC-F Component	Question (Patient Response)	Score
Strength	How much difficulty do you have lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or inability = 2
Assistance with walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, uses aids, or inability = 2
Rising from chair/seated	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or inability without help = 2
Climbing stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or inability = 2
Falls	How many times have you fall in the last year?	None = 0 1-3 falls = 1 4 or more falls = 2

Table 1. SARC-F Questionnaire Items[23]
SARC-F scores $\geq$ 4 suggests higher risks of sarcopenia-related complications and the need for more comprehensive examinations.

CONCLUSION

Chiropractic practitioners who may care for formerly incarcerated persons, or other persons at risk for malnutrition or sarcopenia, should be knowledgeable of the unique set of circumstances of nutritional deficit, of the possible poor tissue integrity, and of the psychosocial needs that exist for this demographic. A trauma-informed approach to diagnosis and clinical care that also provides supportive resources to encourage patient nutritional intake should be considered as a model for care. Patient resources may include basic nutritional information, aided by grocery shopping lists, food preparation information, daily food intake goals, and patient weight monitoring, particularly if the patient is cachexic. With these considerations, patients who have been released from a prison system and are seeking a better quality of life, a new life, can be supported and find a valuable resource in their chiropractic office.

COMPETING INTERESTS

The authors declare no competing interests.

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Ankylosing Spondylitis with Undiagnosed Concurrent Diffuse Idiopathic Skeletal Hyperostosis in a 54-year-old Male Seeking Chiropractic Care: A Case Report

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ABSTRACT

Background: Diffuse idiopathic skeletal hyperostosis and ankylosing spondylitis are conditions characterized by ossification of ligament and tendon attachments to bone, mainly impacting the axial skeleton, causing symptoms of spinal stiffness and pain. Sacroiliac joint disease is a prevalent feature of ankylosing spondylitis and has long been used as an exclusion criterion for diffuse idiopathic skeletal hyperostosis.

Case Presentation: A 54-year-old White male with a 16-year history of diagnosed but untreated ankylosing spondylitis sought care at a chiropractic clinic for chronic neck pain and spinal stiffness. Physical examination yielded findings of reduced spinal motion, hypokyphosis, and hypolordosis. Thoracic and lumbosacral radiographs revealed findings of partial sacroiliac joint ankylosis, syndesmophytes, squared vertebrae, and ossified posterior spinal ligaments. The Cervical radiographs demonstrated thick bulky ossification of the cervical anterior longitudinal ligament with minimal disc degeneration.

Results: The patient's prior diagnosis of ankylosing spondylitis was confirmed, along with a new diagnosis of concurrent cervical diffuse idiopathic skeletal hyperostosis. Treatment with spinal manipulation or with adjunctive therapies was deferred, pending rheumatology consultation.

Conclusion: Spinal stiffness, pain, and postural changes are common clinical features of

both ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis. Distinction between the two diseases is aided by evaluation of the radiographic findings. The radiographic evidence of sacroiliitis has historically excluded the diagnosis of diffuse idiopathic skeletal hyperostosis. This case report describes concurrent diagnoses of ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis that have thus far been rarely reported in scientific literature and reviews the clinical features, radiographic findings, and complications of each disease.

Key Words: Ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, HLA-B27, syndesmophytes, spondyloarthropathy

INTRODUCTION

Diffuse idiopathic skeletal hyperostosis (DISH), traditionally considered a non-inflammatory arthropathy, and ankylosing spondylitis (AS), an inflammatory spondyloarthropathy, are the two most common diseases characterized by radiographic evidence of bony proliferation, primarily involving the ligament and tendon attachments (entheses) in the axial skeleton.[1] Both diseases are complex disorders of unknown etiology, marked by distinctive features of ectopic mineralization of soft tissues and eventual ankylosis.[2]

First detailed by Jacques Forrestier and Juane Rotes-Querol in 1950 as ‘senile ankylosing vertebral hyperostosis' and Forrestier disease, DISH was further described in younger patients and in sites beyond the axial skeleton by subsequent researchers.[3] The prevalence of DISH varies significantly between populations, estimated at 2.9% in the Asian population over 50 years of age and 42% in European men older than 65 years. Higher incidences are seen in elderly and obese persons and those with hypertension and type 2 diabetes mellitus.[4,5] The origin and development of DISH is poorly understood; possible etiologies of the disease include low Dickkopf-1(DKK1) protein levels, high vitamin A levels, and metabolic disorders, including diabetes mellitus, dyslipidemia, and hyperuricemia.[5,6]

Ankylosing spondylitis is the most common of the seronegative axial spondyloarthropathies (axSpA), a group of disorders that includes psoriatic arthritis (PsA), inflammatory bowel disease-related arthritis (IBD), and reactive arthritis (ReA).[7] The estimates of AS in the US population range from 0.2%[8] to as high as 1% [9], according to a 2009-2010 National Health and Nutrition Survey. A single population-based study of AS spanning a 30-year period from 1980 to 2009 was conducted in Olmsted County, Minnesota, revealing a 3:1 male to female prevalence in a predominately White population.[9] In 1983, Jumshyd and Khan conducted a longitudinal study in 63 consecutive patients with AS, finding a near equal incidence between female and male patients and more frequent occurrence of the extraspinal sites of hyperostosis in Black patients.[10] In a recent retrospective cohort study of 728,556 US military service members screened for low back pain, Nelson et al. found the incidence of AS was comparable for females and males, challenging the characterization that females are less commonly affected by the disease.[9] The onset of AS symptoms typically manifests between the second and third decades of life.[11] Seronegative spondyloarthropathies have a high association with the prevalence of Human Leukocyte Antigen (HLA)-B27;

approximately 2-8% of the unaffected population are *HLA-B27* positive, while 90% of patients with AS are positive for the *HLA-B27* antigen.[7,11] The presence of *HLA-B27* is linked to sacroiliac joint osteitis and spinal entheseal osteitis (bony inflammation at tendon and ligament insertions), and the classic imaging findings of axial spondyloarthropathies, including bone marrow edema, vertebral body corner erosions (Romanus lesion) and adjacent sclerosis (shiny corner sign), and vertebral body squaring.[12] (**Table 1**)

Both DISH and AS are marked by enthesopathies of primarily the axial skeleton and are radiographically identified by ossification of ligament and tendon attachments to bone and eventual ankylosis.[11,13] In 1976, Resnick and Niyawama evaluated the full spine sectional radiographs of 100 patients with the spinal manifestations of DISH for the purpose of defining "strict radiographic features" as criteria for the diagnosis of DISH and its distinction from other spinal pathologies.[14] Those criteria included: "the presence of 'flowing' calcification and ossification along the anterolateral aspects of at least 4 contiguous vertebral bodies with or without associated localized pointed excrescences (bony projections) at the intervening vertebral body-disc junctions"; "a relative preservation of disc height in the involved areas and the absence of extensive radiographic changes of 'degenerative' disc disease, including vacuum phenomena and vertebral body marginal sclerosis"; and "absence of apophyseal joint bony ankylosis and sacroiliac joint erosion, sclerosis or bony fusion".[14] (**Table 1**)

The sacroiliac articulation is a complex joint, comprising a vertically oriented true synovial joint at the anterior-inferior segment and a horizontally oriented superior-posterior osseous crevice, stabilized by ligaments.[15] Pathological changes to the sacroiliac joint can be assessed based on the site and presence or absence of characteristic radiographic features, such as erosions, sclerosis, and ankylosis. Bilateral and symmetrical sacroiliitis is a hallmark feature of ankylosing spondylitis, seen in most patients eventually diagnosed with AS. Other diseases can mimic the sacroiliitis features of AS, including Paget disease, osteitis condensans ilii (OCI), infections (septic) sacroiliitis, sarcoidosis, and other seronegative spondyloarthropathies. Subchondral sclerosis and joint space narrowing, without erosions, are classic radiographic findings of degenerative arthritis.[15]

The clinical presentations of patients with *advanced* AS and DISH are similar, each exhibiting diminished spinal motion, postural changes, and spinal rigidity.[16] Distinguishing between the radiographic features of AS and DISH is seemingly uncomplicated through application of the 1976 Resnick exclusion criterion of sacroiliac joint erosions radiographs of patients with DISH. With greater availability and increased application of MRI in the diagnosis of joint disorders, significant similarities in the inflammatory characteristics of new bone formation and bone marrow edema in both inflammatory and non-inflammatory diseases have been revealed. Bone marrow edema, classically associated with the inflammatory effects of ankylosing spondylitis, may be seen with MRI in early cases of DISH, despite the disease's categorization as a non-inflammatory arthropathy. Bone marrow edema is identified by decreased (low/dark) signal on T1-weighted images and increased (high/bright) signal on T2-weighted and STIR images.[3,11] The Resnick criterion of the absence of sacroiliac joint disease for a positive diagnosis of DISH excludes the simultaneous presence of AS.[14] (**Table 1**)

We searched 8 databases with combinations of the following search terms: ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, ankylosing hyperostosis, concurrent, simultaneous, and coexistence. We filtered 383 results for case reports and case series, identifying only forty documented cases of concurrent ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis.

CASE PRESENTATION

A 54-year-old male laborer sought care as a new patient at a chiropractic clinic for chronic neck pain and spinal stiffness. His history was remarkable for non-traumatic low back pain that began at about age 19 and was first treated successfully with spinal manipulation at a different chiropractic clinic, ibuprofen, and massage. He continued care intermittently for approximately 4 years, ceasing care when he noted his symptoms worsened for several days following each treatment. At age 27, the patient initiated care in an allopathic setting for a workplace injury and was treated over the course of the following 10 years with two lumbar radiofrequency (RF) denervation procedures and ibuprofen. The patient reported his first RF denervation significantly reduced his pain for approximately 5 years; the second RF denervation worsened his symptoms. The patient was referred to a rheumatologist and was prescribed, but refused, an SSRI antidepressant. The patient, at 38 years of age, consulted a second rheumatologist and was diagnosed with ankylosing spondylitis following a positive hematology study for inflammatory markers, including HLA-B27; psoriasis, uveitis, dactylitis (swollen digits), and inflammatory bowel disease were not identified. The patient did not remember undergoing imaging evaluations, and no prior imaging was found in the local hospitals' Picture Archiving and Communication Systems (PACS). In the ensuing years following the diagnosis of AS, the patient engaged in a self-directed regimen of lengthy walking (up to 5 miles per day) and a ketogenic diet. The patient reported he lost excess weight, and his symptoms were remarkably reduced, causing him to question the accuracy of the ankylosing spondylitis diagnosis. Despite the improvements in his symptoms, the patient can work only intermittently due to pain and restricted movements. The patient chose to resume chiropractic care after viewing a Y-strap axial decompression video posted on a social media site; the video was not created, posted, or associated with the chiropractic clinic at which he was examined.

Examination

During physical examination, the physician observed the patient's limited cervical mobility, pronounced thoracic hypokyphosis and lumbar hypolordosis, and rigid posture with inability to stand fully upright. Reflex and muscle strength deficits were not detected. The patient had difficulty rising from a seated position (positive Minor sign), experienced focal pain bilaterally with cervical foraminal compression tests, and bilateral focal cervicothoracic pain with shoulder depressor tests. The patient underwent radiographic evaluation of his cervical, thoracic, and lumbosacral regions.

Imaging

Thoracic Spine Radiographs: Thin marginal bridging syndesmophytes are present from T7 to T12 (ossification of the annular/outer disc fibers, bamboo spine sign); subtle squaring of the T7-12 anterior vertebral body margins is apparent, consistent with the patient's diagnosis of AS. Disc space narrowing with osteophytosis is evident at T5 and T6. The thoracic spine is hyperkyphotic. *These findings are consistent with AS and osteoarthrosis.* (**Figures 1 and 2**)

Lumbar Spine Radiographs: Thin marginal bridging syndesmophytes are present from L1-S1 (bamboo spine sign); subtle squaring of the L1-L5 anterior vertebral body margins is apparent. Disc (nucleus pulposus) calcification is apparent at L1-L5. Ossification of the L1-S2 interspinous and supraspinous ligaments is seen (dagger sign); ossification of the L2-S1 zygapophyseal (facet) capsules is present (railroad track sign; railroad track sign with dagger sign is termed trolley track sign). Calcification of the bilateral iliolumbar ligaments is apparent. The joint spaces of the bilateral sacroiliac articulations are indistinct at the superior and inferior margins; minimal joint space is identified in the middle segment of the bilateral sacroiliac articulations. Zygapophyseal facet arthrosis is identified at L1/L2-L5/S1, without spondylolisthesis. Superior and axial joint space narrowing with femoral head osteophytosis is seen at the bilateral iliofemoral articulations. The lumbar spine is hypolordotic with posterior weight-bearing and a right list. *These findings are consistent with AS and osteoarthrosis*. (**Figures 3 and 4**)

Cervical Spine Radiographs: Dense bulky ossification of the anterior longitudinal ligament is present from C3-C6; ossification of the posterior longitudinal ligament is not apparent. Disc space narrowing with osteophytosis is present at C5 and C6; osteophytosis without appreciable disc space narrowing is evident at C2-C4. Uncinate hypertrophy is noted at C3-C7. Zygapophyseal (facet) arthrosis is identified at C2/C3-C7/T1, without spondylolisthesis. The cervical spine is hypolordotic with anterior weight-bearing. Nuchal ligament ossification is present at C5 and C6. A small round calcification is present within the left carotid artery. *These findings are consistent with DISH, osteoarthrosis, and carotid arterial calcification. Findings of ankylosing spondylitis in the cervical spine are not detected.* (**Figures 5 and 6**)

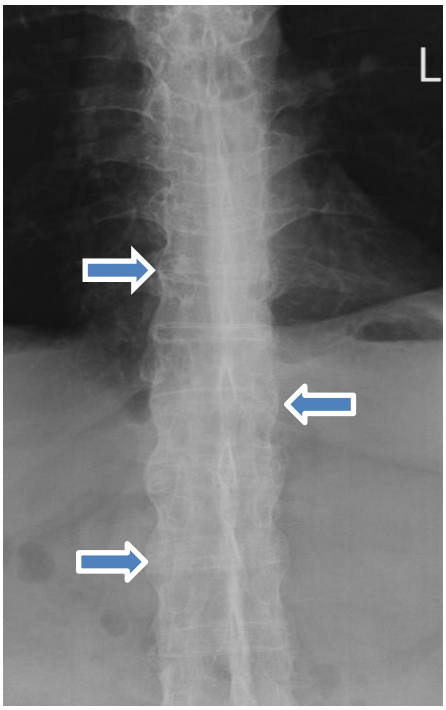

Figure 1: Anteroposterior lower thoracic/upper lumbar radiograph demonstrating multiple levels of thin bridging syndesmophytes at the right and left lateral disc margins (bamboo spine, arrows).

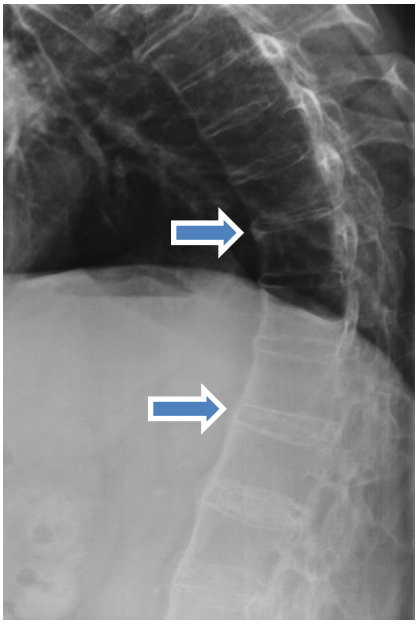

Figure 2: Lateral lower thoracic/upper lumbar radiograph demonstrating multiple levels of thin bridging syndesmophytes at anterior disc margins (arrows) and loss of the anterior concavity of the vertebral bodies (squared vertebrae).

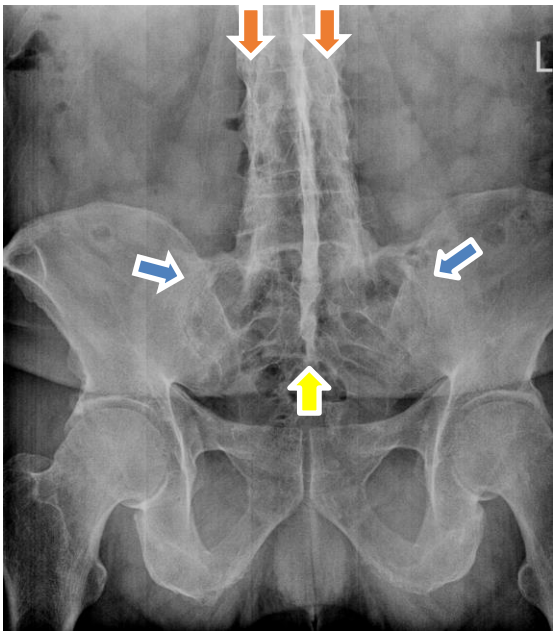

Figure 3: Anteroposterior lumbopelvic radiograph demonstrating ossification of the zygapophyseal (facet) capsules (railroad track sign, orange arrows), ossification of the supraspinous and interspinous ligaments (dagger sign, yellow arrow), and calcification of the bilateral sacroiliac ligaments with partial ankylosis of the sacroiliac joints (blue arrows).

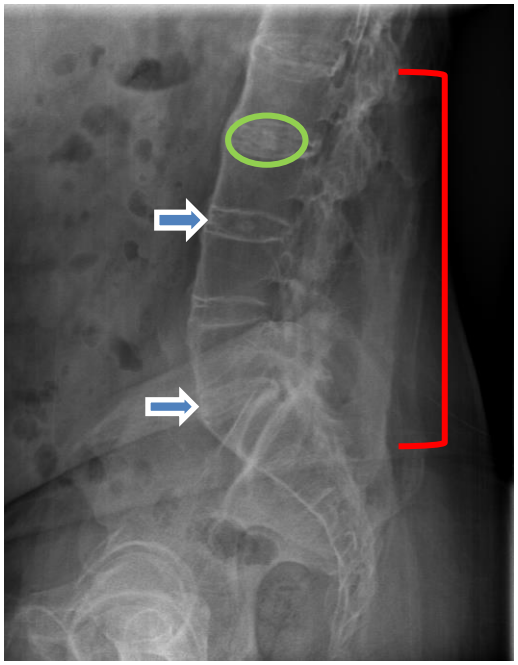

Figure 4: Lateral lumbosacral radiograph demonstrating multiple levels of thin bridging syndesmophytes at anterior disc margins (arrows), loss of the anterior concavity of the vertebral bodies (squared vertebrae), preserved disc spaces, disc (nucleus pulposus) calcifications (L1-L5, green oval), and supraspinous and interspinous ligament ossification (dagger sign on the AP view, red bracket).

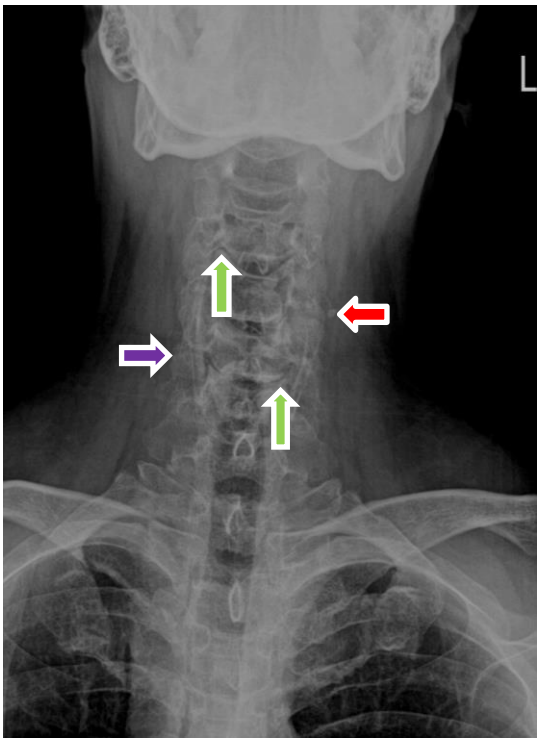

Figure 5: Anteroposterior cervical radiograph demonstrating disc space narrowing, uncinate hypertrophy (green arrows), zygapophyseal (facet) arthrosis (purple arrow), and calcification within the left carotid artery (red arrow).

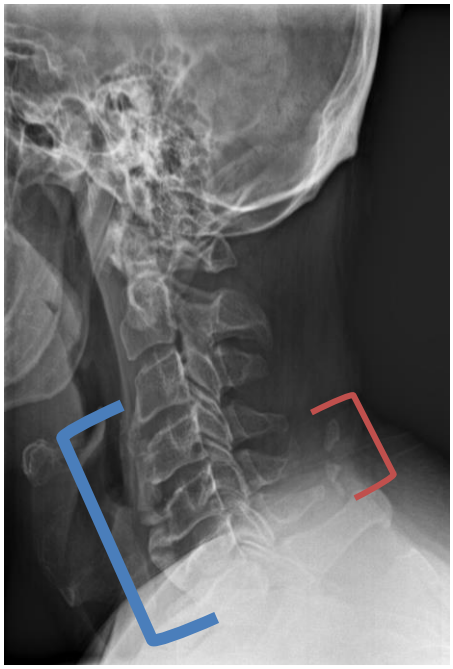

Figure 6: Lateral cervical radiograph demonstrating ossification of the anterior longitudinal ligament from C3-C7 (blue bracket), nuchal ligament ossification at C5 and C6 (orange bracket), relatively preserved disc spaces and osteophytes.

Typical Disease Features	Ankylosing Spondylitis	Diffuse Idiopathic Skeletal Hyperostosis
Age of onset	Adolescence and young adults	Over 45
Population	Males ≥ Females	Males > Females
Symptoms (dependent upon disease progression)	Early onset of back pain, reduced spinal mobility, hyperkyphosis	Asymptomatic early, reduced spinal mobility, hyperkyphosis, dysphagia
Serological Studies	+HLA-B27, +CRP, +ESR	Hyperglycemia, hyperlipidemia, hyperuricemia, excess Vitamin A
Complications	Higher risks of depression, vertebral body fractures, decreased chest expansion, cardiopulmonary compromise	Higher risks of depression, vertebral body fractures
Associated Conditions	Uveitis, inflammatory bowel disease	Diabetes mellitus, obesity, OPLL
Differential Diagnoses	Enteropathic arthritis, early psoriatic arthritis, septic arthritis, OCI	Degenerative disc disease
	Imaging Findings	**Imaging Findings**
	Thin annular disc fiber ossification (syndesmophytes)	Preservation of disc spaces in the early phases
	Squared vertebral bodies	Thick, bulky ossification of the anterior longitudinal ligament over 4 contiguous segments (Resnick criteria)
	Vertebral body corner erosions (Romanus lesion) and sclerosis (shiny corner sign)	
	Ossification of interspinous and supraspinous ligaments (dagger sign)	Extremity enthesal ossifications (whiskering)
	Ossification of zygapophyseal (facet) capsules (railroad sign)	Absence of zygapophyseal (facet) ankylosis
	Sacroiliitis: erosions and eventual ankylosis	Absence of sacroiliac erosions
	MRI: bone marrow edema at entheses	MRI: bone marrow edema at entheses

Table 1: Comparison of typical disease features of ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis.

Treatment

The patient did not undergo any chiropractic or adjunctive therapy during the initial visit, pending additional evaluations. He was referred to his allopathic primary care physician; consultation with rheumatology was recommended. At the time of writing, the patient had not yet consulted with rheumatology and had not returned to the chiropractic clinic.

DISCUSSION

Ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis share several clinical features, including neck pain, spinal stiffness, and changes to spinal sagittal curvatures.[3] The principal symptom of AS is chronic back pain, present in up to 80% of patients with the disease and typically beginning in the late teen or early adult years; uveitis and extremity arthritis are commonly seen.[16,17] By contrast, the symptoms of DISH are uncommonly present prior to age 45 and extremity involvement is infrequent and limited to non-inflammatory enthesopathy in the shoulders and hips.[11] (**Table 1**)

Vertebral fractures occur 4 times more frequently in persons with ankylotic spines than in the general population, with a potential devastating consequence of spinal cord injuries. The reduced flexibility of spines with DISH and AS are less able to dissipate the energy of even seemingly minor low-velocity impacts.[11] Fracture through the atypical stress points of the intervertebral disc can extend to the posterior spinal column, permitting atypical spinal

motion with a higher risk of spinal cord injury.[18,19] Patients with DISH and AS do not demonstrate a greater risk of peripheral fractures.[5]

Patients with DISH may experience complications unseen in AS. The characteristic thick, bulky ossification of cervical anterior longitudinal ligament in DISH can result in dysphagia, hoarseness, and stridor from compression of the posterior pharyngeal and tracheal walls; though dysphagia is rare, it is the most common cervical symptom of DISH.[20] Surgical resection of the bulky anteriorly projecting enthesophytes is effective; changes in food habits and swallowing training may help patients meet nutritional requirements with reduced risks of choking and aspiration.[20] Ossification of the posterior longitudinal ligament (OPLL) is seen as linear ossification immediately posterior to the vertebral bodies, most common in the cervical spine. While OPLL lacks the flowing thickness of anterior longitudinal ligament (ALL) ossification, the space-occupying consequence of OPLL spinal canal stenosis impacting the anterior spinal cord, and early symptoms of numbness, tingling, and reduced muscle strength in the hands; as cord compression worsens, lower extremity neuropathies may result.[20]

Less frequently studied consequences of AS and DISH are the psychological impacts of the diseases. Worldwide, patients with AS have more frequent symptoms of depression than persons without AS; in the United States, one-third of patients with AS experience "significant" symptoms of depression, including helplessness.[21] In 2023, Chung et al. Published a cross-sectional study of 296 patients with axial spondyloarthritis, revealing that high levels of anxiety (13.9% of subjects) and depression (8.4% of subjects) were associated with reduced function and poorer health outcomes. The researchers theorized that functional impairment, pain, and fatigue associated with inflammatory arthritis were at the root of symptoms of psychological distress, impairing the patients' responses to treatment.[22]

Treatment of AS and DISH is complex and focused primarily on preserving mobility and reducing injury risks.[23] Pharmacological treatments include short-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and systemic steroids in symptomatic patients; long-term use is discouraged to avoid associated liver, renal, and gastrointestinal side effects.[23] Disease-modifying antirheumatic drugs (DMARDS), including methotrexate and sulfasalazine, are not typically therapeutic in patients with axial disease, but may aid in reducing symptoms in patients with peripheral arthritis.[23] Tobacco smoking has been associated with an increased risk of AS disease progression; smoking cessation programs should be employed. Physical therapy and exercise programs may be helpful in reducing spinal stiffness and reducing symptoms.[23] Little research is found on the role of spinal manipulation in patients with ankylotic conditions. An unfiltered search of PubMed using search phrases "ankylosing spondylitis" and "spinal manipulation" yielded 4 articles, equally divided in discussions of complications of spinal manipulation and symptom improvement following spinal manipulation. In 2017, Cornelson et al. published a case series of the diagnosis and management of 3 patients with AS in "inactive states", each experiencing improvements in clinical, laboratory, and imaging assessments.[24]

As dynamic thrust is considered an absolute contraindication by the Centers for Medicare and Medicaid Services (CMS) in the regions near sites of "Acute arthropathies characterized by acute inflammation and ligamentous laxity and anatomic subluxation or dislocation;

including acute rheumatoid arthritis and ankylosing spondylitis"[25], the paucity of research of the benefits and risks of spinal manipulation is unsurprising.

CONCLUSION

Spinal stiffness, pain, and postural changes are common clinical features of both ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis. The radiographic evidence of sacroiliitis has historically excluded the diagnosis of diffuse idiopathic skeletal hyperostosis. With greater availability and increased utilization of the advanced imaging techniques of MRI and CT, detection of overlapping features between AS and DISH, such as bone marrow edema and joint ankylosis, will improve and ultimately lead to revisions of the radiographic diagnostic criteria for DISH and axial spondyloarthropathies. Clinicians are advised to assess the clinical and radiographic findings in patients with back pain, spinal stiffness, and altered sagittal spinal curvatures, and consider simultaneous inflammatory and non-inflammatory diseases as possible etiologies.

LIMITATIONS

This is a single-patient case report. Results may not be generalizable to other individuals with similar conditions.

CONSENT

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare no competing interests.

ACKNOWLEDGEMENTS

The authors wish to thank the patient and the referring chiropractor for sharing this uncommon clinical presentation.

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Identification of Freiberg Disease in a Middle-Aged Male with Cerebral Palsy: A Case Report

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ABSTRACT

Objective: This case report will describe the clinical presentation, radiographic examination, diagnosis of Freiberg disease, and appropriate referral in a male patient with non-resolving foot pain.

Clinical Features: A 52-year-old male sought care at a chiropractic college outpatient clinic for low back pain and right foot pain near the head of the second metatarsal. A complicating factor to his care included cerebral palsy creating a scissoring gait with inability to fully extend the right leg during heel strike, and toe walking on the right side. Prior podiatric management of the foot pain included orthotics which the patient believed to have worsened his foot and low back pain. Chiropractic evaluation and manipulation of both feet began at the second treatment visit and evolved over six treatment visits with no resolution of foot pain.

Intervention and Outcome: The patient's low back pain symptoms were successfully reduced and managed with chiropractic care. Upon non-resolution of right foot pain, radiographic examination and identification of a flattening deformity and focal decreased bone density with slightly sclerotic border at the articular surface of the second metatarsal head, consistent with avascular necrosis known as Freiberg disease, was completed. Magnetic resonance imaging examination was advised by the radiologist for further identification of pathological destruction of tissue but has yet to be completed to date. The patient was referred to the treating podiatrist for management.

Conclusion: Freiberg disease is osteonecrosis of one or more metatarsal heads, predominantly seen in adolescent female athletes.[1] The pathophysiology of Freiberg disease is complicated by numerous factors including trauma, altered foot biomechanics, genetic predisposition[2], systemic disorders, and arterial insufficiency.[1] While trauma and vascular compromise are believed to be the most common causes, diabetes mellitus, systemic lupus erythematosus and hypercoagulability are also implicated in metatarsal head osteonecrosis.[3] Early detection and treatment with conservative management to reduce the burden on the joint space can slow or limit progression of osteonecrosis and the need for surgical intervention.[1] While not commonly diagnosed in the chiropractic profession, knowledge of the impact of long-term altered foot biomechanics, as in this case due to cerebral palsy, in the development of Freiburg disease can benefit the patient through early intervention, podiatric referral, and conservative management.

INTRODUCTION

Freiberg disease was first reported in 1914 when Alfred Freiberg identified 6 cases of infarction of the second metatarsal head.[1,3] Diagnosis of the disease is based on patient history, clinical examination findings, and radiographic changes, which in early stages may show widening of the joint space at three to six weeks after onset of symptoms.[4] Minor trauma to the foot is often the triggering event of the disease with subsequent sclerosis and flattening of the distal metatarsal articular surface.[1] There are five stages identified via Smillie's classification system based on surgical findings.[1] (**Figure 1**) Avascular necrosis of the second metatarsal head is the fourth most common osteochondrosis[3] and yet considered a rare disorder.[1] Osteochondroses result from an injury to the epiphysis that alters endochondral ossification and produces irregularity at the joint surface.[3] Most cases of metatarsal osteonecrosis are unilateral, without side dominance.[3] Barefoot walking and wearing shoes with an elevated heel may worsen pain due to increased pressure placed on the metatarsal head.[5] The patient may report a sensation of walking on something hard, such as a stone or marble.[6] The toe may be swollen, ranging in severity from mild thickening around the metatarsophalangeal (MTP) joint to sausage-shaped enlargement that may be pink in appearance.[6] The toe may also extend at the distal metatarsophalangeal joint instead of lying flat.[6]

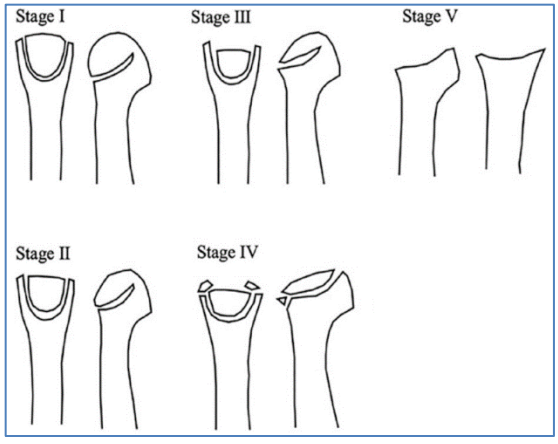


Figure 1: Smillie classification. Stage 1: A narrow fissure fracture in an ischemic epiphysis. Stage II: Absorption of cancellous bone in the metatarsal head with sinking of the articular surface dorsally. Stage III: Further absorption or sinking of the articular surface with larger projections bilaterally. Stage IV: Deeper sinking of the articular surface with peripheral projections/fractures. Stage V: Degenerative arthrosis with flattening/deformity of the metatarsal head.[1] "Smillie Classification" by Ichiro Yoshimura is licensed under CC BY 4.0.

Non-operative treatment of Freiberg disease aims to relieve pain and dysfunction while minimizing metatarsal head deformation.[1] This may include pain medications, activity modification, immobilization, shoe wear modifications and orthotics.[1] Non-operative interventions are most successful in the early stages of disease development with a 60% efficacy rate.[1] If surgical intervention becomes necessary, surgical procedures may be classified as joint-preserving and or joint-sacrificing, dependent upon the level of disease progression.[1] The differential diagnosis of Freiburg disease was not considered when radiographic examination was initiated due to its unusual incidence. The opportunity to identify the pathology assisted in appropriate long-term management of a condition that would have otherwise remained undiscovered.

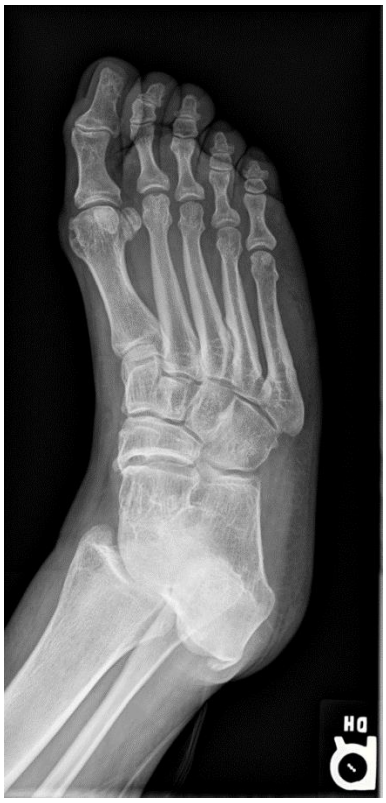
CASE PRESENTATION

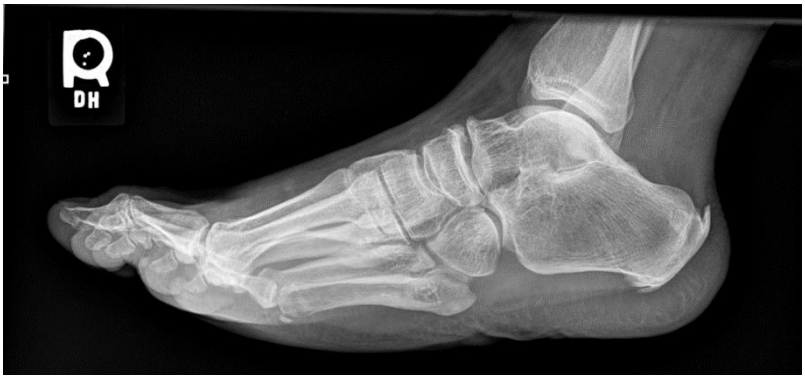
A 52-year-old male sought care at a chiropractic college outpatient clinic for an exacerbation of low back pain and right foot pain near the head of the second metatarsal that started approximately one-year prior and was initially felt after stepping down on the foot and experiencing a tingling sensation in a focal area, leading him to believe he may have stepped on something. The sensation persisted for approximately two weeks, becoming more pronounced in intensity and area of involvement. After six months of intermittent symptoms, the patient was treated by a podiatrist with diclofenac, a nonsteroidal anti-inflammatory typically used to treat arthritic pain. He was advised to take Tylenol in the morning for pain control and given an orthotic for the right shoe. The pain in the right foot worsened with activity, particularly with stair climbing and descent, causing the patient to feel fatigued. The patient was unable to continue treadmill exercises due to pain, described as a consistent dull ache worsened with specific and long-lasting activities requiring weight-bearing posture. The pain did not further alter his gait.

Complicating the assessment of foot pain was the presence of cerebral palsy (CP) with a scissoring gait with right toe walking and inability to fully extend the right leg during heel strike. As a toddler, the patient's crawling and walking were delayed and he had an unusual gait, prompting an evaluation that led to the diagnoses of CP and bilateral subtalar arthrodesis surgeries with autografting of tibial bone, likely performed to correct the orientation of the hindfoot.[7] The patient underwent several years of specialized shoes, orthotics, and physical therapy until age 18, which improved his gait, without the need for additional surgeries, crutches, or walker. He reports his gait has not changed since adolescence.

Initial examination of the foot identified joint restriction and palpatory tenderness of the calcaneus, talus, first metatarsal and phalanx which was treated with chiropractic manipulation on the second and third visit. At the fourth visit, restriction of the cuboid, talus, and calcaneus were treated on the involved lower extremity. At the fifth visit no manipulation of the foot was delivered due to lack of joint restriction or palpatory tenderness although pain continued at the second metatarsal head despite lack of joint restriction or similar palpatory tenderness as with the other joints. Course of care from initiation of treatment focused on reducing pain in the focal area and improving range of motion to the fullest extent possible given the limitations of foot biomechanics due to CP. The lack of pain

resolution prompted further investigation through radiographic examination, not previously performed since onset of foot pain, leading to the discovery of Freiburg disease and referral back to the treating podiatrist with new information that could impact early intervention efforts to preserve joint integrity. (**Figures 2 and 3**)





Figures 2 & 3: Oblique and lateral views of the right foot demonstrate avascular necrosis (Freiberg disease) of the second metatarsal head, subtalar arthrodesis surgery from childhood due to cerebral palsy, talonavicular osteoarthritis, first metatarsal-phalangeal joint degeneration with sesamoid subluxation, hallux valgus, and enthesopathies at the insertions of the plantar fascia and the Achilles tendon. Further examination with MRI of the second metatarsal head was recommended.

DISCUSSION

Freiberg disease is a rare condition with the potential to develop complications that severely impact patient quality of life and activity.[5] It is more common in females than males with a ratio of 5:1 and typical onset between the ages of 11 to 17.[9] The second metatarsal head is the most commonly affected joint at 68% of cases.[3] Its etiology is idiopathic but believed to be most commonly impacted by repeated microtrauma or injuries due to overload.[8] Altered foot mechanics, insufficient blood supply, genetics, and other previously noted factors also contribute to onset.[8] Initial conservative management works to reduce pressure and stress to the joint[6] through orthotics, braces, and footwear modification[8] that can reduce or eliminate the need for surgical intervention.[5] This emphasizes the importance of early identification and intervention to spare further deformation or replacement of the joint, which presents with additional risks and complications.[5] For example, joint debridement procedures alter the anatomical function of the joint and metatarsal osteotomies may disrupt blood supply, causing further development of the necrosis.[6] Surgical intervention becomes necessary when there is persistent pain, deformity, and disability progression, although poor evidence exists to support successful outcomes for this treatment.[9] Spontaneous healing with remodeling may occur in early stages.[2]

CP is a focal traumatic, vascular, or infectious lesion of the white or gray matter[10] in an immature brain that creates a permanent neurological disorder.[11] It occurs in 2-2.5/1000 births with an unchanging rate over the past 40-50 years due to medical advances that allow the survival of smaller and more premature newborn children[11]. Diagnosis is made through observation of abnormal muscle tone or posture, delay in expected motor milestones, and gait abnormalities.[12] If a child is not walking by 2 years of age, only 10% will walk independently by age 7, which highlights the critical importance of early identification and intervention.[12] William Little was the first to label the pathology of cerebral palsy in 1862 as Little's disease.[11] Typically identified in children during their first year of life, a major indicator is lack of developmental skill progression.[11] Once thought to be solely due to lack of oxygen and blood flow to the infant's brain, CP is now known to be a result of multiple potential causes including congenital defect in neural tube closure, premature birth, a brain bleed, ischemia, or postnatal causes like trauma, metabolic encephalopathy or infection. The treatment remains the same regardless of the cause.[9]

This patient has spastic CP, the most common type of CP affecting approximately 80% of people according to the Centers for Disease Control. Spastic CP causes increased muscle tone and awkward movements. There are four types of gaits and motor involvement with spastic CP important to consider with respect to potential development of Freiberg disease: dropped foot (Type I), equinus foot with or without genu recurvatum (Types 2A and 2B, respectively), hamstring and rectus femoral spasticity with equinus foot (Type 3), and the rarest form (Type 4) with equinus foot and spasticity in the gastrosoleus, hamstrings, rectus femoral, psoas, and hip adductors.[11] Assessment of the specific type of gait and interventions to achieve and maintain a functional walking pattern can help patients with CP remain as independent as possible. However, the alteration in gait and biomechanics that result from CP, or any other type of condition whether pathological or created by injury/amputation, must be considered by the practitioner with respect to how the repetitive trauma that results could cause the patient to be at greater risk for avascular necrosis.

CONCLUSION

This case report describes the clinical presentation, radiographic findings, and management through referral of a CP patient presenting with Freiberg disease. The altered gait pattern may have been a primary cause for the development of avascular necrosis in the second metatarsal head. Although the patient was being treated for non-resolving foot pain by a podiatrist, further investigation provided beneficial information to guide management by both the chiropractor and podiatrist. This report also emphasizes the importance of considering that gait alteration, in this case because of CP, may be a contributing factor to the development of a rare disease. Early identification and intervention to avoid further surgical intervention underscores the need for additional investigation when response to care is not as expected. The patient was released following resolution of his low back pain for further management by the podiatrist.

LIMITATIONS

This report describes a single patient's clinical presentation, diagnostic evaluation, and management of Freiberg disease. Generalization of the content of this report to any other individual with a similar clinical presentation is to be avoided.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-In-Chief of this journal.

COMPETING INTERESTS

The authors declare no competing interests.

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Cervical Spine Manipulation, Immediate Stroke, and the Diagnosis of Dissection: A Commentary on Cassidy 2008

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COMMENTARY

Cassidy et al. published a 2008 study entitled, *Risk of Vertebrobasilar Stroke and Chiropractic Care: Results of a Population-Based Case-Control and Case-Crossover Study*.[1] The objective of this study was to investigate the association between doctor of chiropractic (DC) visits and vertebrobasilar (VBA) stroke, while making comparisons to such events after visits with primary care physicians (PCPs). The authors found an increased risk of VBA stroke associated with both DC and PCP visits and concluded, "The increased risks of VBA stroke associated with chiropractic and PCP visits is likely due to patients with headache and neck pain from VBA dissection seeking care before their stroke. We found no evidence of excess risk of VBA stroke associated with chiropractic care compared to primary care."[1]

This study has been referenced to support that cervical spinal manipulation (CSM) does not cause stroke.[2] However, the authors state, "We have not ruled out neck manipulation as a potential cause of some VBA strokes". "It might also be possible that chiropractic manipulation, or even simple range-of-motion examination by any practitioner, could result in a thromboembolic event in a patient with a pre-existing vertebral artery dissection."[1]

This plausible mechanism of causation of stroke from CSM has been noted by multiple chiropractic researchers,[3–6] and there are multiple case reports of immediate post-manipulative stroke.[7–18] However, there are no case reports of a thromboembolic event following cervical spine range-of-motion examination. The sudden neck movement associated with CSM is more likely to dislodge a loosely adherent vertebral artery thrombus

and result in a thromboembolic event.[19]

The chiropractic analysis of this study was designed taking into account that CSM can cause immediate stroke: "For the chiropractic analysis, the index date [the date of the hospital admission for the VBA stroke] was included in the hazard period [the time period between the exposure (DC visit) and the index date], since chiropractic treatment might cause immediate stroke and patients would not normally consult a chiropractor after having a stroke."[1]

However, the 0-1 day PCP visit cohort was excluded from this study. Therefore, the 0-1 day DC visit cohort and the 0-1 day PCP visit cohort could not be compared and contrasted. The 0-1 day cohorts warrant being contrasted, as these are the only cohorts in which an immediate thromboembolic stroke from cervical spine range-of-motion examination or CSM could occur. This lack of direct comparison is a substantial limitation of the study as regards the 0-1 day cohort, and the conclusion of this study as regards the 0-1 day cohort should be interpreted cautiously and put into clinical perspective.

The authors also concluded, "Our population-based case-control and case-crossover study shows an association between chiropractic visits and VBA strokes. However, we found a similar association between primary care physician visits and VBA stroke. This suggests that patients with undiagnosed vertebral artery dissection are seeking clinical care for headache and neck pain before having a VBA stroke."[1] This also suggests that DCs and PCPs fail to diagnose VAD at a similar rate, even when the two most common symptoms of VAD, neck pain and headache, are present.[20] This finding has clinical implications for DCs and PCPs.

COMPETING INTERESTS

The author declares no competing interests.

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Parkinson's Disease and Nutritional Interventions

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ABSTRACT

Objective: Parkinson's Disease (PD) is the second most common neurodegenerative disease process in the world. PD is a progressive neurodegenerative disorder that falls under the category of hypokinetic movement disorders. This literature review underscores the growing interest and potential of nutritional interventions as complementary therapies in the management of PD.

Methods: A literature review was performed relevant to therapeutic applications of dietary interventions and nutritional supplementation for PD.

Results: The evidence gathered highlights the intricate relationship between diet, nutrient supplementation, and the pathophysiological mechanisms of PD.

Conclusion: Nutritional interventions for PD or parkinsonism symptoms may be beneficial. The review identifies a gap in the understanding of the long-term effects of therapeutic interventions and their interactions with standard PD medications. Future research should aim to fill these gaps, providing a more comprehensive understanding of how nutrition can be optimally used in PD management.

Keywords: Parkinson's Disease, Diet, Supplements, Nutraceuticals, Ketogenic Diet

INTRODUCTION

Parkinson's Disease is the second most common neurodegenerative disease process in the world. The process is characterized by alpha-synuclein misfolding affecting dopamine signaling of the direct pathway of the basal nuclei at the substantia nigra pars compacta. Symptoms experienced negatively impact patients cognitively, socially, emotionally, and physically. A literature review was performed relevant to the behavioral effects of PD and symptomatology. Nutritional interventions with evidence were analyzed and reviewed. Studies indicated that intestinal dysbiosis, the Western diet, inadequacies in omega3 fatty acids, vitamin D, vitamin B6, environmental toxin exposure, elevated homocysteine, and previous traumatic brain injury are linked to symptomatology associated with PD. Dietary and nutraceutical support may improve symptoms associated with this condition.

Parkinson's disease (PD) is a progressive neurodegenerative disorder that falls under the category of hypokinetic movement disorders. It is clinically manifested by cardinal features such as a resting tremor, muscular rigidity, bradykinesia (slowed movement), and postural instability, often accompanied by a characteristic shuffling gait. While there are various hypokinetic conditions, including Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Multiple Systems Atrophy (MSA), and Lewy Body Dementia (LBD), idiopathic Parkinson's disease emerges as the most prevalent form. Notably, PD is the second-most diagnosed neurodegenerative condition, trailing only Alzheimer's Disease in frequency.[1]

Epidemiologically speaking, the overall prevalence of hypokinetic movement disorders is not precisely determined; however, Parkinson's disease specifically is estimated to affect about 0.3% of the population in industrialized nations—a figure that increases to 1% among those aged 60 and older.[2] There is evidence to suggest ethnic disparities in the prevalence of PD, with higher rates observed in Caucasian populations compared to African or Asian groups. Nevertheless, this data is potentially skewed by factors such as diagnostic accuracy and variability in response rates. Additionally, some studies indicate a higher susceptibility in males, potentially due to the neuroprotective effects of estrogen, though the evidence is not conclusive. The incidence of Parkinson's disease is reported at 8-18 cases per 100,000 person-years, with a significant rise after the age of sixty.[2]

It is crucial to acknowledge the variability in reported prevalence and incidence of PD, which is largely dependent on the methodologies used in the studies and the case-finding strategies employed. Liberal diagnostic criteria can inflate reported figures, while the mode of study—whether in-person assessments or record-based investigations—also influences the reported rates, with in-person approaches generally revealing higher prevalence (by 24% to 42%) and incidence (by 39% to 53%) rates.[1]

The etiology of Parkinson's Disease (PD) lies in its classification as a proteopathy, characterized by the aberrant aggregation of misfolded proteins. More specifically, PD is an alpha-synucleinopathy, which denotes the accumulation of alpha-synuclein protein within certain neural structures. The aggregation predominantly occurs within the basal ganglia, a subcortical brain region integral to motor control. The basal ganglia comprise several interconnected nuclei, including the substantia nigra (pars compacta and reticulata) and the

neostriatum (encompassing the globus pallidus internus and externus, caudate nucleus, and putamen). Within this network, the direct and indirect pathways orchestrate movement, with dopaminergic synapses featuring D1 and D2 receptors being essential for signaling. Parkinsonian syndromes like PD, PSP, CBD, MSA, and LBD result from impaired signaling in the direct pathway, while the indirect pathway's dysfunction leads to hyperkinetic disorders.

PD specifically involves the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), impacting both pathways due to alpha-synuclein accumulation and subsequent Lewy body formation, though it is primarily characterized as a disorder of the direct pathway. This interruption in dopaminergic signaling is the genesis of the motor deficits typical of PD.

In terms of risk factors, PD is influenced by both genetic and environmental components. A significant non-genetic contributor is exposure to environmental toxins, such as those encountered in certain occupations. Notably, the 1983 discovery that MPTP (4-phenyl-1,2,3,6-tetrahydropyridine) selectively targets and damages dopaminergic neurons in the SNpc highlighted the vulnerability of this region to environmental agents. Various herbicides and pesticides, notably Paraquat and Rotenone, have been implicated in striatal dopamine depletion. Additionally, heavy metal accumulation may foster PD pathogenesis by promoting alpha-synuclein aggregation in the SNpc.

Interestingly, lifestyle factors such as smoking, alcohol intake, and caffeine consumption have been inversely correlated with PD incidence, suggesting a protective mechanism that will be explored further in the context of nutritional interventions. Elevated homocysteine levels have also been identified as a potential risk factor.

Common to many of these risk factors is the induction of systemic inflammation, which subsequently impairs mitochondrial function through ATP synthase inhibition. This inflammation triggers a cascade characterized by heightened cytokine activity in the brain and cerebrospinal fluid, which has been documented in individuals with PD. Post-mortem examinations often reveal activated microglia within the brains of PD patients, indicative of an inflammatory response or possibly autoimmune reactions, as these cells attempt to clear the pathogenic protein accumulations. Additionally, various genetic factors contribute to both the causation and susceptibility of the disease.

Diagnosis of Parkinson’s Disease (PD) is inherently challenging, as definitive confirmation is traditionally achieved post-mortem via neuropathological examination. Despite advancements in clinical assessments, such as the Unified Parkinson’s Disease Rating Scale (UPDRS), there remains an absence of a singular conclusive diagnostic test for PD during a patient's life. Clinicians currently rely on the manifestation of cardinal motor symptoms—resting tremor, bradykinesia, rigidity, and postural instability—to substantiate a clinical diagnosis.

Additional prodromal features, such as anosmia, may herald the onset of motor symptoms, often decades in advance, and are becoming increasingly recognized in the early identification of PD. Certain signs are more specifically suggestive of PD, including the

classic 'pill-rolling' tremor and the distinctive rigidity patterns described as 'cogwheel' or 'lead-pipe'. Oculomotor abnormalities, such as impaired vertical saccades and compromised optokinetic reflexes, along with a stooped posture known as camptocormia, contribute to the clinical picture. Non-motor symptoms, including facial hypomimia, constipation, micrographia, and hypophonia, also inform the clinical diagnosis.

When a comprehensive clinical evaluation yields a pattern of these findings, a provisional diagnosis of PD is typically established. However, the inherent complexity of PD symptomatology underscores the necessity for high precision and caution in clinical judgment.

This review article aims to synthesize the existing body of literature on nutritional interventions for PD, reflecting the growing interest in dietary measures as potential modifiers of neurodegenerative processes. Recent research has begun to unravel the intricate relationships between nutrition, systemic health, and neurodegeneration, offering insights into how dietary practices and targeted nutrient administration may influence the course of PD. There is an emerging emphasis on the gut-brain axis, particularly the role of the intestinal microbiome, in modulating PD pathology. By exploring these associations, this review seeks to elucidate nutritional strategies that could potentially contribute to the management, and conceivably the prevention, of PD.

METHODS

In conducting this comprehensive review, we systematically searched electronic databases for scholarly articles addressing the intersection of Parkinson’s Disease (PD) and nutritional interventions. We utilized PubMed, Google Scholar, and CINAHL as the primary repositories for sourcing the literature. Our search strategy employed a combination of terms tailored to each database to optimize relevance and specificity: 'Parkinson’s Disease' paired with 'nutritional supplements' for PubMed, 'Parkinson’s Disease' with 'nutraceuticals' for Google Scholar, and 'Parkinson’s Disease' in conjunction with 'Ketogenic Diet' for CINAHL.

The inclusion criteria were confined to studies published in the English language, thereby streamlining the scope of our review. We selectively extracted studies that primarily examined the therapeutic applications of nutrition in PD or explored nutrition-related systemic alterations amenable to dietary interventions, excluding those that primarily focused on the pathogenic underpinnings of the disease. This selection criterion significantly narrowed the field of relevant research, as literature on PD pathophysiology substantially outweighs that on therapeutic nutritional strategies.

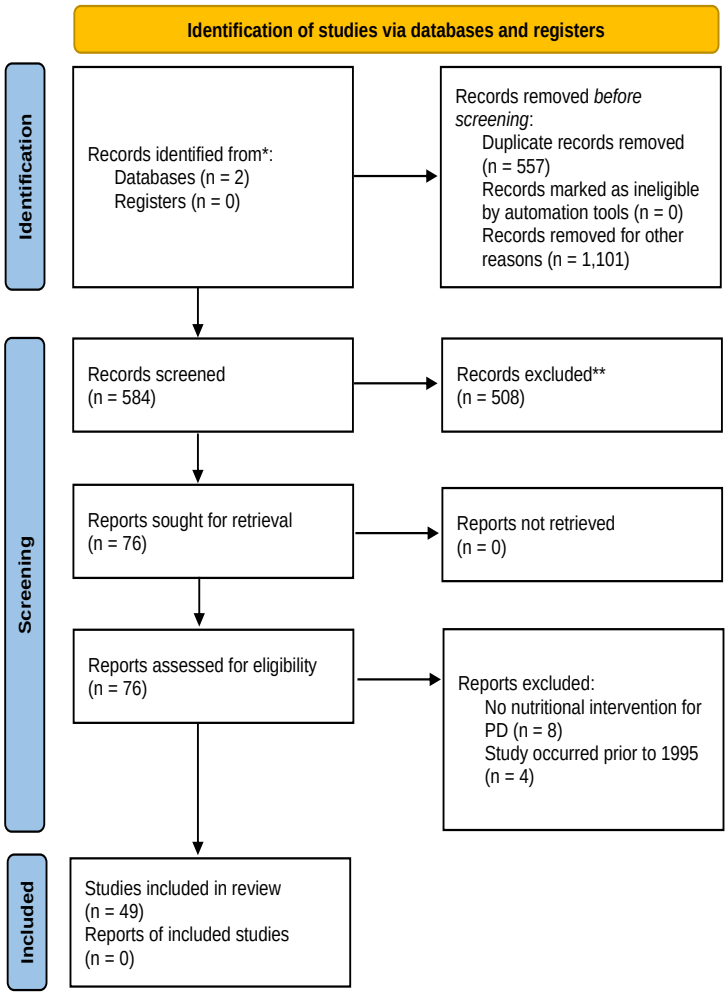
From the chosen studies, we extracted content that explicitly or implicitly related to therapeutic nutritional strategies or interventions in the context of PD or broader neurodegenerative processes. Our synthesis of the data involved a qualitative analysis of the proposed nutritional interventions for PD and related neurodegenerative conditions.

We applied filters to include a range of robust study designs: clinical trials, meta-analyses, randomized controlled trials (RCTs), and systematic reviews. In our review, we

encompassed cohort studies, epidemiological research, RCTs, meta-analyses, and systematic reviews that were published with full texts available from 1995 through 2022. Any studies that did not directly pertain to Parkinson's Disease were meticulously excluded to maintain a clear focus on the review's objectives.

RESULTS

A database search for this review resulted in 2242 abstracts. After accounting for duplicates and abstracts that did not meet inclusion criteria, 584 papers remained. Based on the title and abstract provided, 76 papers were considered relevant. After a full text review, 63 papers were included in this review. Included studies were papers involving nutraceutical and dietary interventions for treating Parkinson's Disease, as well as etiology reviews and population studies discussing current perspectives on Parkinson's Disease treatment.



DISCUSSION

Neuronal Resting Membrane Potential: Mitochondrial Requirements and Interventional Considerations

Within the realm of neurophysiology, the integrity of neuronal resting membrane potential is paramount for proper neural function and is intricately linked to mitochondrial health. The fundamental determinants for the maintenance of a stable resting membrane potential encompass a constellation of requirements: adequate oxygen supply, glucose, neuronal stimulation, and a robust mechanism for mitochondrial uncoupling during oxidative stress conditions. Collectively, these factors facilitate an enhanced synthesis of adenosine triphosphate (ATP), bolstering neuronal resilience and sustaining the activity of the sodium-potassium ATPase, a critical ion pump that regulates intracellular sodium levels.

A critical analysis reveals that impediments to these vital components can stem from various physiological dysfunctions. Compromised blood flow and anemic conditions can attenuate oxygen delivery to neurons. Dysglycemia—a hallmark of metabolic disorders—can disrupt glucose availability, while inadequate physical or cognitive activity can result in suboptimal neuronal stimulation. Moreover, inflammatory processes, autoimmune reactions, and the bioaccumulation of environmental toxins may inhibit the essential process of mitochondrial uncoupling, a protective mechanism against oxidative stress.

Such disruptions can precipitate a cascade of detrimental effects including a significant reduction in ATP generation. This deficit in energy production undermines neuronal stamina, precipitating a precipitous onset of fatigue. Additionally, it impedes the sodium-potassium pump's function, leading to an aberrant accumulation of intracellular sodium. Addressing these underlying conditions is paramount in restoring and maintaining the delicate equilibrium required for optimal neuronal function.

Nutritional Interventions in Neurodegenerative Disorders: Insights and Evidence

Nutritional strategies present a multifaceted and increasingly recognized approach for therapeutic intervention in the spectrum of neurodegenerative diseases, with PD being a prime candidate for such interventions. The complexity of PD, characterized by the progressive degeneration of dopaminergic neurons and the presence of alpha-synuclein aggregates,[1] necessitates a comprehensive approach that includes, but is not limited to, dietary modifications, targeted nutraceutical supplementation, and a potential reevaluation of gastrointestinal health. Dietary patterns, such as the ketogenic diet and caloric restriction, have been posited to exert neuroprotective effects, potentially through the modulation of energy metabolism and the enhancement of mitochondrial function.[3] Concurrently, specific nutrients such as omega-3 fatty acids, Coenzyme Q10, and various B vitamins have been implicated in mitigating oxidative stress and supporting mitochondrial biogenesis, suggesting a synergistic role in stalling or possibly reversing the pathophysiological processes of PD.[24,32,60] Collectively, these nutritional interventions embody a promising therapeutic adjunct, offering a non-pharmacological arsenal against the debilitating progression of neurodegenerative disorders.

Dietary Interventions in PD: Ketogenic Diet and Intermittent Fasting

This review synthesizes current research on dietary interventions that hold promise for modifying the disease process and providing symptomatic relief. Among these, the ketogenic diet (KD) and intermittent fasting (IF) have garnered attention. Uncontrolled clinical trials and animal studies suggest that such diets could confer both symptomatic and disease-modifying benefits across a spectrum of neurodegenerative diseases, such as Alzheimer's and Parkinson's, and even in conditions like traumatic brain injury and stroke.[3] The mechanisms posited include the stimulation of mitophagy and mitochondrial biogenesis during dietary restriction, which could act as a quality control mechanism, enhancing mitochondrial turnover.[4]

Intermittent Fasting

IF in particular has shown promise in mouse models where it has been demonstrated that fasting every other day increases the levels of brain-derived neurotrophic factor and glial-derived neurotrophic factor in the nigrostriatal pathway and attenuates MPTP-induced dopaminergic neuronal loss and astroglial activation in the substantia nigra and the striatum.[5] Dysfunction in mitochondria, excessive oxidative stress, and the targeted demise of specific neurons are recognized as underlying factors in the development of PD. This complex pathology gives rise to symptoms that encompass difficulties with motor function, mood disorders such as depression and anxiety, and cognitive deficits.[6,7,8] Studies have indicated that a Fasting Mimicking Diet (FMD) has been shown to modify gut microbiota composition, reestablish astrocyte and microglia equilibrium in the substantia nigra via metabolic signaling, and reduce inflammatory reactions in these PD models.[9] Additionally, research involving an animal model that simulates early-onset autonomic dysfunction in PD found that Alternate-day Fasting (ADF) enhanced cardiac autonomic regulation, ameliorated elevated resting heart rates, and rectified impaired cardiovascular reactivity, which were correlated with a decrease in parasympathetic function and a buildup of alpha-synuclein within the brainstem.[10]

Ketogenic Diet

In a preliminary investigation by VanItallie et al.[11] with a small cohort (n = 7), the impact of a KD on individuals with Parkinson's Disease (PD) was explored. Out of seven participants, five successfully adhered to the diet regimen, each exhibiting enhanced scores on the Unified Parkinson's Disease Rating Scale (UPDRS), including motor function improvements. Notably, the most compliant three participants achieved a mean serum β-hydroxybutyrate (β-HB) level of 6.6 mmol/L, indicating substantial ketosis. A subsequent, more extensive study by Phillips et al.[12] in 2018 involved 47 PD patients in a randomized setup to compare a modified ketogenic diet to a low-fat diet over eight weeks. The average serum β-HB in the ketogenic diet group reached 1.15 mmol/L. Notably, this group experienced a 41% improvement in the UPDRS I scores, which assess non-motor aspects of daily living, in stark contrast to the 11% improvement observed in the control group. This improvement was particularly evident in symptoms such as fatigue, daytime sleepiness, pain, urinary problems, and cognitive impairments. Further, a pilot trial by Krikorian et al.[13] assessed the KD's effects in 14 participants with mild cognitive impairment (MCI)

secondary to PD. The KD group showed an average increase in serum β-HB to 0.31 mmol/L and significant memory enhancements compared to the control diet group, although no notable changes in motor symptoms were detected.

In a recent study, Norwitz et al.[14] conducted a double-blind, placebo-controlled, crossover trial involving 14 individuals with PD, to evaluate the impact of an acute ketone ester supplementation against a carbohydrate placebo equivalent on exercise endurance. The ketone supplement significantly increased the mean β-hydroxybutyrate (β-HB) levels to 3.5 mmol/L within a half-hour of ingestion. This increase correlated with a notable 24% enhancement in the participants' capacity for endurance exercise relative to the carbohydrate placebo. These findings indicate that ketone ester intake may positively affect motor capabilities in PD.

Further investigation is warranted to clarify how ketogenic methods may ameliorate the motor symptoms associated with PD, given the varying levels of ketosis induced by different protocols. Preliminary evidence suggests that stronger ketone-producing agents and higher resultant β-HB concentrations may be required to exert a considerable impact on motor symptoms. Additionally, it is conceivable that a comprehensive treatment strategy, incorporating therapeutic ketosis as one facet, might be necessary to fully address the multifaceted nature of PD's pathophysiology.[15] According to the American Academy of Neurology (AAN) standards, the current body of research yields a "C" rating (potentially effective) for addressing non-motor symptoms and a "U" rating (evidence insufficient or conflicting) for motor symptoms in PD. Nonetheless, with optimistic initial results and numerous ongoing studies, these recommendations could potentially change in the near future.

A particular focus has been on the intersection between PD and metabolic disorders such as Type 2 Diabetes Mellitus. Research indicates shared pathophysiological mechanisms, chiefly perturbations in glucose metabolism, which may exacerbate PD.[16] Insulin and Insulin-like Growth Factor-1 (IGF-1) signaling pathways, involved in PD, highlight the potential exacerbating role of metabolic abnormalities and peripheral inflammation in the progression of nigrostriatal dopaminergic system degeneration.[16] This insight also suggests that targeting peripheral inflammation with dietary strategies like the KD could yield therapeutic benefits.

Gut Dysbiosis

Furthermore, the gut-brain axis has emerged as a significant area of interest in understanding PD etiopathogenesis. The gut microbiota’s role is increasingly acknowledged, where dysbiosis and small intestinal bacterial overgrowth could trigger systemic inflammation, potentially initiating pathogenic processes such as alpha-synuclein misfolding.[17] Early Lewy body pathology affecting the enteric nervous system and the dorsal motor nucleus of the vagus provides insights into the gastrointestinal dysmotility observed in PD, implicating both central and peripheral pathogenetic mechanisms.[18,19]

Experimental evidence underscores that various forms of alpha-synuclein can propagate from the gut to the brain, with microtubule-associated transport being implicated in the

neuronal translocation of aggregated alpha-synuclein.[20] The discovery of abnormal intestinal permeability in PD subjects and its correlation with intestinal alpha-synuclein accumulation — a PD hallmark — further accentuates the relevance of the gut in the disease process.[21] This body of evidence substantiates the rationale for supporting gut health to potentially mitigate alpha-synuclein misfolding and its consequences.

In summary, the current literature indicates a potential role for nutritional interventions influencing systemic inflammation and gut health in the therapeutic landscape of PD and related neurodegenerative disorders.

Nasal Dysbiosis

Impairment of the sense of smell is an early non-motor indication of PD, manifesting long before the clinical diagnosis, and it can have a detrimental impact on the life quality of individuals with PD. It has been suggested that alterations in the microbial populations in the deep nasal passages, in close proximity to the olfactory bulb, may initiate a neuroinflammatory process in the olfactory bulb, which could contribute to the depletion of dopamine typically seen in PD. Recent research has demonstrated that PD patients can possess notable differences in the prevalence of certain microorganisms, including a higher presence of potentially harmful species like *Moraxella catarrhalis*.[22] Notably, significant associations have been found between the presence of *M. catarrhalis* and more pronounced motor symptoms in those with PD. This research points to the possibility that certain pathogens can be identified in the olfactory bulb and that specific alterations in the microbial community of PD patients may stem from environmental factors uniquely associated with living with the disease. This opens the door to novel treatment avenues such as the potential for intranasal probiotic therapy.

Methylation and Hyperhomocysteinemia

Within the context of PD, hyperhomocysteinemia has garnered interest due to its potential contributory role in neurodegenerative processes. Recent studies suggest that deviations in homocysteine metabolism could influence the pathophysiological landscape of PD.[23] Notably, elevated homocysteine levels have been observed in PD patients, a phenomenon predominantly attributed to the methylated degradation of L-Dopa, a cornerstone in PD management.[23] The relationship between L-Dopa treatment and increased homocysteine concentrations has been substantiated through meta-analytical evidence.

Methylcobalamin, L-5-Methyltetrahydrofolate, and Pyridoxine

Vitamins, particularly of the B complex, have been recognized for their role in modulating homocysteine levels and serving as methyl donors, which may support neurological health in PD. Data indicates that PD patients often exhibit lower levels of vitamin B12 and comparable folate levels relative to control subjects.[24] Additionally, high dietary intake of vitamin B6 has been inversely associated with PD risk.[24] This seems to be due to the fact that chronic administration of levodopa is frequently associated with the development of peripheral neuropathy. Research indicates that the cumulative exposure to levodopa, coupled with insufficiencies in B-complex vitamins such as B6, B9, and B12, as well as genetic

predispositions, are significant contributors to the onset of neuropathy. This condition is further characterized by increased levels of methylmalonic acid (MMA) and homocysteine. The spectrum of neuropathic manifestations ranges from acute presentations, resembling Guillain–Barré syndrome, to more subacute and chronic forms.[25] Particularly at risk are patients subjected to daily doses of levodopa exceeding 2,000 mg or those whose dosage is escalated swiftly, such as during the commencement of Levodopa-Carbidopa Intestinal Gel (LCIG) therapy.[26] Elevated homocysteine levels combined with diminished pyridoxine are primarily implicated in the development of this adverse effect.

Thiamine and PD

Notably, serum thiamine levels have been found to be significantly lower in PD patients, with supplementation yielding promising clinical outcomes.[27] Thiamine has been shown to play a beneficial role in PD by promoting dopamine release and alleviating symptoms related to the condition. Advances in genetic research have shed light on specific proteins that serve as links between thiamine and PD pathogenesis. Moreover, thiamine impacts PD through both genomic and nongenomic pathways. Several elements implicated in PD and influenced by thiamine include the DJ-1 gene, excitatory amino acid transporters, the α-ketoglutarate dehydrogenase complex, coenzyme Q10, lipoamide dehydrogenase, genes located on chromosome 7, transcription factor p53, components of the renin–angiotensin system, heme oxygenase-1, and poly(ADP-ribose) polymerase-1.[28]

Additionally, gastrointestinal issues are prevalent among PD patients, potentially interfering with treatment efficacy.[29] Delays in gastric emptying are commonly observed in those with PD.[30] Furthermore, a reduction in passive absorption through the enterocyte brush border has been noted in PD patients, complicating the efficient uptake of therapeutics and nutrients.[31]

Cell Membranes

In the evolving landscape of PD therapeutics, the potential role of fatty acid supplementation has garnered considerable interest. Omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are increasingly recognized for their neuroprotective properties. Mechanistically, these PUFAs are thought to modulate neuroinflammation, a key component of PD pathophysiology, by influencing the inflammatory cytokine milieu and enhancing the resolution of neuroinflammatory responses. Furthermore, DHA and EPA are integral to maintaining neuronal membrane fluidity and integrity, which could be crucial in countering the dopaminergic neuronal loss characteristic of PD. Additionally, the role of monounsaturated fatty acids (MUFAs) such as oleic acid, typically abundant in the Mediterranean diet, is being explored for its potential anti-inflammatory and antioxidant effects. Emerging evidence suggests a beneficial impact on mitochondrial dysfunction and oxidative stress, both of which are pivotal in the progression of PD. However, the optimal dosages, formulations, and specific fatty acid profiles for maximal therapeutic benefit in PD remain to be conclusively determined, necessitating further robust clinical trials to elucidate these aspects. Nonetheless, the incorporation of specific fatty acids into the dietary regimen of PD patients could represent a promising adjunct to current pharmacological interventions, potentially mitigating disease progression

and improving quality of life.

DHA

In the realm of nutraceutical interventions, the impact of DHA on brain function presents a compelling avenue for research. Animal studies have demonstrated that oral DHA administration can modulate brain DHA levels, suggesting potential modifications in brain functionality relevant to disorders such as Alzheimer's and PD.[32] Further, brain levels of essential n-3 PUFAs, which are reliant on dietary sources, have been shown to influence elements critical to dopaminergic synapses. For instance, a deficiency in n-3 PUFAs in rats leads to decreased expression of brain-derived neurotrophic factor (BDNF) through a p38 MAPK-dependent pathway.[33] Considering the observed reduction of BDNF in PD post-mortem analyses, n-3 PUFA supplementation could represent a viable strategy to enhance BDNF production in the cerebral context.

EPA

Phospholipids enriched with Eicosapentaenoic acid (EPA-PL), commonly found in marine sources, have garnered attention for their potential neuroprotective effects. While the combined impact of EPA and DHA on PD has been documented, the specific influence of EPA alone remains less clear. Recent research has focused on EPA-PL derived from the sea cucumber (*Cucumaria frondosa*) and compared its effects against commercially available EPA in ethyl ester form (EPA-EE) in a mouse model of PD induced by the neurotoxin MPTP.[34] The results indicate that dietary supplementation with EPA-PL, rather than EPA-EE, significantly ameliorated behavioral deficits induced by MPTP. Further investigations have revealed that EPA-PL effectively mitigated oxidative stress and apoptotic processes triggered by MPTP, contributing to the preservation of dopaminergic neurons. This neuroprotection was mediated through the mitochondrial pathway and the mitogen-activated protein kinase pathway. Thia serves to demonstrate that EPA-PL can positively impact the symptoms and pathological progression of PD induced by MPTP, offering valuable insights for future preventive and therapeutic strategies against neurodegenerative disorders.

DGLA

Interestingly, recent research has found plasma levels of α-linolenic acid (ALA), linoleic acid (LA), and arachidonic acid (AA) to be reduced in the PD patients.[35] There was no substantial link between the dietary intake of PUFAs and their plasma levels in the PD cohort. Notably, in the PD patients, plasma levels of ALA and LA showed an inverse association with motor symptom severity, whereas docosahexaenoic acid and AA levels exhibited a positive correlation with non-motor symptoms, factoring in age and sex adjustments. This suggests a potential for supplemental Dihomo-y-linolenic acid supplementation to be administered in PD patients as direct precursor to arachidonic acid. Although, other research has shown DGLA to contribute to cellular ferroptosis.[36] While this has been a novel discovery for the targeting of senescent[37] and cancerous cells, research also suggests that externally sourced DGLA predominantly induces neurodegenerative effects in dopaminergic neurons via ferroptosis through its metabolite formed by cytochrome P450-epoxide hydrolase (CYP-EH), known as dihydroxyeicosadienoic acid (DHED) and is

actually pronounced in PD patients due to their potential for iron accumulation.[38]

The role of AA in Parkinson's Disease PD is a topic of ongoing debate. There is research suggesting that metabolites of AA, known as epoxyeicosatrienoic acids (EETs), might be beneficial in treating PD.[39] These compounds are found throughout the brain and are known for their anti-inflammatory and antioxidant properties. The same research team found that EETs could boost antioxidant enzyme levels and reduce oxidative stress and inflammation in a fruit fly model of PD. However, there's another side to this story. In PD, α-synuclein plays a critical role. Normally, in healthy neurons, this protein exists in the less harmful, a-helical form. There is data showing that AA can encourage α-synuclein to assemble a-helically, suggesting that AA might reduce neuronal damage in PD.[40]

Yet, the situation is more complex. AA interacts with a protein called fatty acid-binding protein 3 (FABP3), known to be an early marker of dementia and PD and prevalent in dopaminergic neurons.[41] When AA binds to FABP3, it seems to promote the harmful aggregation of α-synuclein in certain cell types. Supporting this, a study by Julien et al. in 2006 found higher levels of AA in the brains of PD patients upon postmortem examination.[42] Furthermore, a 2019 meta-analysis concluded that diets high in cholesterol and AA could increase the risk of developing PD.[43]

In summary, both AA and precursor dietary DGLA have contradictory evidence regarding their role in PD.

Neuroprotection and Neuroinflammation

Flavonoids

Flavonoids, a substantial family of phenolic compounds derived from plants, are commonly found in various plant-based foods and drinks. Structurally, these compounds are characterized by a 15-carbon framework that comprises two benzene rings, labeled A and B, linked through a heterocyclic pyrone ring known as the C ring. They are categorized into six primary subgroups - flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanins. This classification is based on the specific attachment point of the B ring to the C ring, alongside the level of oxidation and the pattern of substitution that occurs on the C ring.[44] Numerous research studies have indicated that flavonoids, despite having limited bioavailability, offer a variety of health advantages, including the potential to lower the risk of PD. These benefits are attributed to the biological activities of flavonoids, such as their antioxidant, anti-inflammatory, anti-apoptotic, and lipid-reducing properties.[45]

Apigenin

Apigenin (AGN), a non-mutagenic flavone present in many fruits and vegetables, demonstrates a range of biological activities. These include its ability to prevent cell death (anti-apoptotic), reduce inflammation (anti-inflammatory), and neutralize free radicals. Recent research demonstrate data which indicate that AGN confers neuroprotection against dopaminergic neuronal degradation in the nigrostriatum in a rotenone-induced mouse model of PD,[46] wherein it mitigated mitochondrial dysfunction, a-synuclein accumulation and

motor deficits.

Quercetin

Quercetin is a flavonoid known for its neuroprotective and antioxidant effects and has been shown in rotenone-induced a mouse model of PD to significantly mitigate behavioral impairment while simultaneously augmenting autophagy and ameliorating endoplasmic reticulum stress-induced apoptosis.[46]

Luteolin

Luteolin, a polyphenolic compound found in foods like celery, green peppers, perilla leaves, and chamomile tea, has been recognized for its anti-mutagenic, anti-tumorigenic, antioxidant, and anti-inflammatory properties and recent research has demonstrated that luteolin not only reduces oxidative stress, but also delays the loss of climbing ability of PD model flies that express human alpha synuclein in their brains.[47]

Rutin

Rutin is a flavonoid that is found abundantly in many plants, such as Eucalyptus, passionflower, buckwheat, tea, and apple that may prevent neuroinflammation. It is thought to be antioxidant and a free radical scavenger. Rutin is hydrolyzed in the gastrointestinal tract to release another flavonoid, quercetin, which is ultimately responsible for many of the primary actions of rutin. It has been demonstrated previously to protect dopaminergic neurons from oxidative stress in an animal model of PD.[48]

Catechin/Epigallocatechin and Proanthocyanidin

Tea ranks among the top beverages consumed globally. The three main varieties, green, black, and oolong tea, all originate from the *Camellia sinensis* (L.) O. Kuntze plant. Of these, green tea has received the most attention in research for its potential health benefits, including its impact on conditions like cancer, obesity, diabetes, as well as inflammatory and neurodegenerative diseases. Green tea contains flavonoids known as green tea catechins (GTC)s.

In a study involving over 129,000 people, researchers found a link between eating flavonoid-rich foods and a lower chance of developing PD. Specifically, they noticed that those who consumed more epicatechin (EC) and proanthocyanidin dimers, both found in certain foods, seemed to have a reduced risk of PD.[49] The researchers suggest that EC might help by activating a specific protein that supports brain cell health and learning processes, and by reducing the activity of a certain enzyme. Similarly, proanthocyanidins could help by increasing dopamine levels in the brain, slowing down another enzyme's activity, and protecting against certain types of brain cell damage. This study suggests that compounds found in tea, particularly catechin derivatives, might contribute to its potential benefits in preventing PD.

Naringenin

Naringenin is a major citrus flavonoid that is widely distributed in oranges, grapes, and tomatoes that has a bioactive effect on human health. It has several anti-inflammatory properties and has been demonstrated to decrease a-synuclein expression and neuroinflammation in MPTP-induced PD model in mice.[50]

Turmeric

There's growing evidence that problems with mitochondria and oxidative damage may contribute to the development of PD. This idea has gained support from animal studies, where the use of a specific inhibitor that targets part of the cell's energy production system closely reproduced the biochemical and tissue characteristics seen in PD. Various compounds have been identified that could potentially improve cellular energy processes and offer antioxidant benefits. One such compound is turmeric (*Curcuma longa* L.), a widely used medicinal plant in traditional practices like Ayurveda, Unani, and Siddha. It's commonly used as a home remedy for various ailments. Data from as far back as 2011 suggests that regular dietary intake of turmeric may boost the brain's antioxidant capacity and shield it from oxidative and nitrosative stress, thereby helping to prevent neurodegenerative damage.[51] Current research highlight the need for a deeper examination of turmeric and its constituents that may influence neuronal health and guard against neurotoxic effects.[52] These insights could aid in refining dietary habits and creating therapies with minimal side effects for in vivo applications.

Resveratrol

Resveratrol is a polyphenol most often recognized for its presence in red wine. A 2021 review encompassing 18 studies assessed the protective efficacy of resveratrol in animal models of PD. These studies were meticulously selected from three different databases. The findings from the analysis demonstrate that resveratrol exhibits significant neuroprotective properties across various PD models, as determined through quantitative methods.[53]

Silymarin

Silymarin, composed of flavonolignans like silybin, isosilybin, and silychristin, along with minor quantities of flavonoids (like taxifolin), fatty acids, and other polyphenolic substances, is derived from the dried fruit of the *Silybum marianum* plant. Historically, it has been used in clinical settings for its liver-protecting properties. Its potential for neuroprotection has been explored in different models of neurological conditions, including Alzheimer’s disease, PD, and cerebral ischemia. A review conducted in 2018 looking at in vitro and in vivo studies of silymarin’s anti-parkinsonian effects concluded that silymarin was a beneficial therapeutic choice in the treatment of PD due to its mitigation of dopaminergic neuron apoptosis in the substantia nigra, but also discusses silymarin’s poor bioavailability.[54]

Baicalein

For many years, mitochondrial dysfunction has been associated with the development of PD. Recently, it's been discovered that issues with mitochondrial biogenesis (mitobiogenesis) are frequently observed in PD cases. Baicalein, a primary active component found in *Scutellaria baicalensis Georgi*, has shown neuroprotective properties in various PD experimental models. Recent research findings demonstrate that baicalein alleviates behavioral issues and loss of dopaminergic neurons caused by rotenone in a rat model.[55] Additionally, baicalein was effective in restoring mitochondrial health and improving mitobiogenesis measured via mitochondrial density in the rotenone-induced parkinsonian rats.

Ginkgo Biloba

Ginkgo is one of the oldest living tree species and extracts of this tree have been used to treat memory problems and are thought to serve as natural cholinesterase inhibitors. The neuroprotective effects of EGb 761, a type of Ginkgo extract, particularly against MPTP-induced neurotoxicity, have been associated with the modulation of dopamine-related gene expression and transcription factors like Nurr1, essential for the preservation of dopaminergic neuron functionality.[56]

Tobacco and Caffeine

Prevailing epidemiological data suggests an intriguing inverse association between the incidence of PD and the consumption of tobacco and caffeine.[57] Two prevailing hypotheses exist to explain this phenomenon: the first posits that individuals predisposed to PD may inherently exhibit an aversion to substances like coffee and nicotine; the second suggests that these substances might exert a neuroprotective effect. Beyond these hypotheses, it has been suggested that the consumption of coffee and cigarettes may influence gut microbiota composition in a manner that reduces intestinal inflammation. This alteration could potentially attenuate the misfolding of alpha-synuclein, a protein implicated in PD pathology.[57]

Magnesium

Magnesium intake has demonstrated neuroprotective properties in models of neurotoxicant-induced PD as well.[58] Numerous investigations have demonstrated a decrease in magnesium (Mg) levels in individuals with PD. Experimentation has shown that in rats aged one year, which were fed a diet with Mg levels reduced to one-fifth of the normal intake over several generations, there was a pronounced loss of dopaminergic neurons specifically in the substantia nigra. Research has uncovered a notable and impactful role of Mg in safeguarding against damage to neurites and neurons.[58]

Glutathione

Glutathione is the human organism’s master antioxidant. While an exhaustive exploration of all the ways glutathione is neuroprotective exceeds the scope of this paper, it is noteworthy to mention the observed correlation between depleted glutathione levels and PD.[59]

Considering glutathione's role in cellular antioxidant defense mechanisms, its fortification in clinical settings warrants consideration as a therapeutic adjunct in PD management.

Mitochondrial Support Coenzyme Q10, Carnitine, Riboflavin, Niacin, Alpha-Lipoic Acid, and Magnesium, methylene blue

Various hypotheses have been proposed regarding the underlying causes of PD, with mitochondrial dysfunction being a key factor in both its sporadic and hereditary variants. This dysfunction is characterized by a range of issues including bioenergetic flaws, mutations in mitochondrial DNA, mutations in nuclear DNA genes associated with mitochondria, and alterations in mitochondrial dynamics, such as fusion or fission processes. Additionally, changes in mitochondrial size and shape, modifications in trafficking or transport mechanisms, impaired mitochondrial movement, transcriptional dysregulation, and the presence of mutated mitochondrial-associated proteins are also implicated in the pathogenesis of PD. There are various nutritional interventions that have been studied to treat these dysfunctions.

Coenzyme Q10 and Riboflavin

Coenzyme Q10 (CoQ10) has garnered significant interest as a nutritional intervention in PD due to its role in mitochondrial function and antioxidant properties. In PD, mitochondrial dysfunction is a well-documented phenomenon, and CoQ10, a key component in the mitochondrial electron transport chain, could potentially counteract this dysfunction. Earlier research delved into the neuroprotective mechanisms of CoQ10. Researchers found that combining CoQ10 with riboflavin significantly improved mitochondrial function and had a protective effect against neurodegeneration in PD models.[60] This highlights the potential of CoQ10 not just as a standalone treatment, but in combination with other vitamins.

Acetyl-L-Carnitine and A-Lipoic Acid

Acetyl-L-carnitine (ALC) and alpha-lipoic acid (ALA) are two compounds that have been explored as potential treatment strategies for PD due to their roles in cellular metabolism and antioxidant protection. Research in this area is focused on how these compounds might mitigate the mitochondrial dysfunction and oxidative stress often associated with PD. Research conducted in 2013 suggests that these compounds could protect dopaminergic neurons and improve mitochondrial function and emphasizes the importance of mitochondrial health in PD and proposes ALC and ALA as potential agents to counteract mitochondrial-related neurodegeneration.[61]

Niacin

Niacin, also known as Vitamin B3, has been explored in the context of treating PD due to its potential role in cellular metabolism and neuroprotection. Research in this area primarily focuses on how niacin might influence the health and function of neurons, particularly in the brain regions affected by PD. One significant angle of investigation is niacin's ability to activate specific receptors in the brain, known as PPAR receptors. These receptors play a crucial role in managing oxidative stress and inflammation, both of which are prominent

features in the pathogenesis of PD. By stimulating these receptors, niacin could potentially offer neuroprotective effects, reducing the damage to dopaminergic neurons, which are critically affected in PD.[62] Moreover, niacin is known to be involved in energy metabolism, a vital aspect considering the mitochondrial dysfunction observed in PD. Enhancing mitochondrial function and energy production in brain cells might be another way through which niacin contributes to neuroprotection in PD.

Iron

Iron supplementation is generally contraindicated in PD treatment due to several reasons. Iron can exacerbate oxidative stress, a key factor in PD pathogenesis. The involvement of iron in Fenton reactions leads to the production of harmful hydroxyl radicals. Additionally, the substantia nigra naturally has high iron levels. In PD, there's an abnormal iron accumulation in this area, which can worsen dopaminergic neuron degeneration.[63] Iron is also thought to promote the aggregation of alpha-synuclein. This protein forms Lewy bodies, characteristic of PD.[63]

CONCLUSION

In conclusion, this literature review underscores the growing interest and potential of nutritional interventions as complementary therapies in the management of PD. The evidence gathered from various studies highlights the intricate relationship between diet, nutrient supplementation, and the pathophysiological mechanisms of PD.

However, it's also evident from the review that the field is still in its nascent stages. While preliminary studies are promising, there is a need for more extensive, well-designed clinical trials to establish the efficacy, safety, and appropriate dosages of these nutritional interventions. It is also crucial to recognize the individual variability in response to these interventions, highlighting the need for personalized dietary plans for PD patients.

Moreover, the review identifies a gap in the understanding of the long-term effects of these interventions and their interactions with standard PD medications. Future research should aim to fill these gaps, providing a more comprehensive understanding of how nutrition can be optimally used in PD management.

In essence, this review points towards a hopeful direction where nutrition interventions may be beneficial for those with PD or managing parkinsonism symptoms. However, it also calls for cautious optimism and a balanced approach, integrating scientific evidence with clinical prudence to harness the full potential of nutritional interventions in PD.

LIMITATIONS

There were limitations for this review. Due to the large number of preliminary studies this review is limited by a lack of more extensive, larger scale, and well-designed clinical trials to establish the efficacy, safety, and appropriate dosages of these nutritional interventions for PD. The research highlighted variability between individuals in response to dietary and nutritional interventions for PD. Future research is needed to identify the potential benefits

of nutritional interventions with limited research identified in this review.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Diagnosing Vertebral Artery Dissection: Commentary on the 2014 Mattox Case Report

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INTRODUCTION

In 2014, Mattox et al. published the case report Recognition of Spontaneous Vertebral Artery Dissection Preempting Spinal Manipulative Therapy: A Patient Presenting With Neck Pain and Headache for Chiropractic Care.[1] Although this case report was published ten years ago, it is still referenced today as an example of chiropractic clinical competency. A critical analysis of this case report yields insights into the history, examination, differential diagnosis, and advanced imaging required to diagnose vertebral artery dissection (VAD).

This study is historically important as it was one of the first case reports of VAD published by the chiropractic profession. Other important early case reports of this nature were Kier (2006),[2] Liebich (2014),[3] Tarola (2015),[4] and Futch (2015).[5]

VAD and stroke were discussed in the literature as early as 1947.[6–17] Notably, this topic has been discussed by chiropractic researchers: Haldeman (1999),[18] Haldeman (2002),[12,19] Tuchin (2013),[20] and Brown (2024).[21] The IFOMPT (International Federation of Orthopedic Manual Physical Therapists) Cervical Framework Document, a resource for examination of the cervical region for potential vascular pathology, was first published in 2012.[22] Chaibi and Russell published a risk assessment strategy to exclude VAD in 2019.[23]

DISCUSSION

The Case

Upon subjective examination, the 45-year-old female patient presented with "…upper back/neck pain and stiffness as well as headache and pain in the posterior portion of the right arm down to the elbow of 3 days duration. Her level of discomfort progressed in severity in the 24 hours prior to presentation".

Unilateral neck pain and headache are one of the most common symptoms of VAD. Episodic stress/tension headaches and migraines will normally improve after 72 hours or less, whereas this patient's headache was progressing after 72 hours.[24,25] Cervical spine radicular symptoms can also be a symptom of VAD as vessel wall hematoma in the V2 segment can compress the cervical spine nerve roots.[26] Radicular symptoms can also be caused by cervical spine disc herniation and cervical spine nerve root compression.[27]

The subjective examination indicated the patient had no history of trauma. However, there was no other information provided about the patient's past medical history or risk factors for dissection or stroke. It is unknown if the patient took medications, was a smoker, or used oral contraceptives. It is unknown if the patient's pain was non-responsive to over-the-counter or prescription medications. It is unknown if the patient had a recent acute infection.[28] The report states the patient was "well-nourished", but the patient's BMI (body mass index) was not recorded. A low BMI is a risk factor for dissection, a high BMI is a risk factor for ischemic stroke.

The objective examination consisted of active range of motion, done visually, and palpation. No vital signs, not even blood pressure, were recorded. No orthopedic testing was done. No neurological testing was performed. No reflexes, myotomes, or dermatomes were evaluated. No cranial nerve testing was done. No auscultation for carotid artery bruits was performed. Apparently, no imaging was considered or ordered. Minus neurological examination, it cannot be determined if any of the 5 Ds, 2 Ns, and an A of cerebral ischemia were present (diplopia, dizziness, drop attacks, dysarthria, dysphagia, nausea, numbness, nystagmus, and ataxia).

The assessment was "myofascial pain syndrome." A differential diagnosis including other causes of neck pain, headache, and radicular symptoms was not formulated. Treatment consisted of 4 minutes of therapeutic ultrasound over the suboccipital and posterior cervical musculature, and massage therapy to the same area.

An exact time lapse from treatment to the onset of ischemic symptoms was not noted. However, "within minutes" of treatment the patient became dizzy, reported visual and cognitive disturbances, and had difficulty speaking. She proceeded to lose control of her right leg, which spontaneously assumed a flexion contracture. At this point, the DC suspected vascular etiology and paramedics were summoned.

Right VAD in the V2 segment was noted on CT angiography examination. The case report stated that "Hospital records described transient ischemic attack, but imaging showed no evidence of stroke." Anticoagulation therapy was administered and the patient was discharged without complications after 5 days in the hospital.

According to Easton and Johnston, "TIAs are minor ischemic strokes. These events should be named such, and the term TIA should be retired."[29] Therefore, this author will refer to the cerebrovascular ischemic event that occurred in this case as a stroke.

Weakness of Case Report: Informed Consent

There was no documentation that the DC obtained written or verbal informed consent concerning the risks of physical medicine modalities such as massage therapy and therapeutic ultrasound.[30] While informed consent may have been obtained it was not documented in the case report. In medicolegal settings, this would be tantamount to consent not having been obtained. Such information is relevant to a case report on the clinical management of VAD and should have been included and discussed.

Weakness of Case Report: Misdiagnosis

There was no acknowledgement that the DC misdiagnosed the patient with "myofascial pain syndrome." It cannot be ruled out that this misdiagnosis was the result of inadequate history and physical examination. This patient may have had myofascial pain syndrome, but it was not the primary cause of their symptoms.

Weakness of Case Report: Failure to Diagnose & Refer

There was no acknowledgement that the DC failed to suspect right VAD and refer the patient to medical emergency prior to the occurrence of the stroke.[23] The authors state that it was, "…not possible to distinguish her musculoskeletal symptoms from the those of the VAD". This is incorrect. The symptoms she presented with were the symptoms of the VAD. Headache, neck pain, and radicular pain can be symptoms of many types of conditions, including vascular conditions.

A DC is required to determine the nature of a patient's symptoms. They cannot assume the presence of musculoskeletal symptoms; this is beneath the standard of care. The standard of care requires a thorough history, examination, and differential diagnosis be performed to exclude VAD before performing any treatment.[23] The DC failed in their duty to do so.

The differential diagnosis for the patient's symptoms includes, but is not limited to, cervical spine radiculopathy, cervical spine disc herniation, cervical spine nerve root compression, vertebral artery dissection, and carotid artery dissection. There was no differential diagnosis considering any of these conditions. Had the DC suspected VAD and referred the patient for emergency medical treatment prior to administering massage therapy and therapeutic ultrasound, which may have been contributory, the stroke could have been prevented.

Weakness of Case Report: Causation

There was no acknowledgement that the physical medicine modalities performed by the DC more likely than not caused the stroke. Causation can be established as more likely than not if plausibility, temporality, and lack of a more probable alternative explanation are present.[31] These three criteria are met in this case to establish causation of stroke by these physical medicine modalities:

1. It is plausible that therapeutic ultrasound and massage therapy could exacerbate VAD and cause stroke by a thromboembolic mechanism. Both therapies are contraindicated in the presence of symptoms of potential VAD.[32,33] Bombarding an existing VAD with therapeutic ultrasound for four minutes could putatively dislodge a loosely adherent blood clot causing a thromboembolic stroke.

Neck and head movement associated with seated massage therapy could do the same. The use of a seated massage chair to stabilize the cervical spine and head was not noted. Since the type of massage therapy performed was not documented, it cannot be ruled out that stretching associated with massage therapy treatment may have exacerbated the patient's condition. There are several case reports of a causal association between massage therapy and cervical artery dissection and/or stroke.[34,35,36]

2. There was a close temporal relationship (documented as minutes) between the physical medicine modalities and the stroke. The temporal proximity of the physical medicine treatments and the worsening signs and symptoms was not considered by the authors.

3. There is not a more probable explanation for the cause of the stroke. The VAD had been present and stable for at least 72 hours and only progressed into a stroke within minutes of contraindicated therapies.[31]

Further Analysis

Since we cannot rule out that many readers will fail to go on to the full text article after reading the abstract, especially if they are prone to confirmation bias along the lines that chiropractic care almost never causes stroke, we must comment on the dangerous disinformation provided by the abstract. It states: "A 45-year-old otherwise healthy female presented for evaluation and treatment of neck pain and headache. Within minutes, non-specific musculoskeletal symptoms progressed to neurological deficits, including limb ataxia and cognitive disturbances." The authors fail to mention that the neurological deficits began after the subjective and objective examination and "within minutes" of contraindicated therapies. The abstract implicitly, without stating as such, suggests the neurological deficits began before any evaluation or treatment was provided. It is unfortunate that the treating doctor did not properly examine the patient for a condition that could lead to such deficits.

The abstract states: “We suggest that early recognition and emergent referral for this patient avoided potential exacerbation of an evolving pre-existing condition and resulted in timely anticoagulation treatment.” However, the “early” recognition and emergent referral was not early enough to avoid the stroke. Exacerbation of a pre-existing condition is actually what happened, rather than avoided. Stroke following contraindicated therapies is as concerning as stroke following contraindicated spinal manipulation.

The authors state: “Neck pain and headache in such a case could easily be mistaken as musculoskeletal in origin, such as the myofascial pain syndrome.” This is misleading. This patient presented with more than simply non-specific neck pain and headache. Three days of progressively worsening unilateral neck pain, headache, and radicular symptoms is a different clinical picture than “neck pain and headache”. Chiropractic students are taught to consider that a headache different from previous headaches, such as a headache worsening after several days, is a red flag warning against treatment without proper evaluation.

The authors state: “Most clinicians, whether medical or practitioners using SMT [spinal manipulative therapy], when faced with VAD in progress aren’t aware that non-specific symptoms such as neck pain and headache may be the only symptoms.” However, as accredited medical and chiropractic graduate and postgraduate programs teach that non-specific symptoms such as neck pain and headache may be the only symptoms of VAD, this statement lacks plausibility.

The authors state, “Awareness of the non-specific symptoms of VAD is important because SMT could exacerbate the condition and lead to complications such as stroke.” This is true.[21] However, it is also true that therapeutic ultrasound and massage therapy could exacerbate the condition and lead to complications such as stroke. The VAD may have been present but stable for at least three days prior to the therapeutic ultrasound and massage therapy treatment, and only developed into a stroke within minutes of those treatments. Had the authors not provided therapy, the patient had an excellent chance of healing on his or her own: “Most dissections of the vertebral arteries heal spontaneously and especially, extracranial VADs generally carry a good prognosis.[37]

The title of the case report is misleading and factually incorrect. The treating doctor of chiropractic did not recognize the would-be spontaneous VAD. They recognized the stroke and neurological deficits the patient had within minutes of contraindicated therapies. Spinal manipulation was not somehow preempted by astute recognition of “spontaneous” VAD. SMT was preempted by recognition of iatrogenic stroke following contraindicated therapies performed after inadequate patient evaluation.

Bias Against Cervical Spine Manipulation

If this patient had suffered the same neurological deficits within minutes of cervical spine manipulation, as opposed to within minutes of therapeutic ultrasound and massage therapy, there would likely have been a lawsuit against the DC and this case report would not have been published due to the malpractice case. The treating doctor was fortunate that the patient did not appreciate the likely causal connection between the stroke and the treatment.

Strength of Case Report

A strength of this case report is that it was published in the first place. The chiropractic profession does not normally publish case reports of clinical case management resulting in stroke. This report is useful in an academic setting to teach the importance of a thorough history, examination, differential diagnosis, and advanced imaging. Other professions, such as physical therapy, have published case reports of clinical case management resulting in stroke.[38]

CONCLUSION

According to the information presented in the case report, the DC may have breached the standard of care for the chiropractic profession on four counts. The DC could have been held liable for:

1. Failure to obtain informed consent to the risks of physical medicine modalities.

2. Mistaking right VAD as myofascial pain syndrome.

3. Failure to diagnose and refer a right VAD for concurrent medical evaluation.

4. Causation of thromboembolic stroke by contraindicated therapies performed in the presence of a right VAD.

This case report shows it is essential for DCs to form a differential diagnosis and order the proper advanced imaging when indicated. DCs are under a duty to diagnose and refer out non-neuromusculoskeletal conditions such as VAD lest a cerebrovascular accident occur.

Very few DCs encounter VAD in their clinical internship during their graduate education. Chiropractic post-graduate residency opportunities in the area of vascular disorders are also limited.[39,40] However, patients do present to DC's with neck pain, headache, and radicular symptoms as a result of vascular conditions. Thus, it is essential that DCs take post-graduate continuing education in the diagnosis of vascular disorders. In order to train for the diagnosis and referral of non-neuromusculoskeletal conditions, hospital-based residencies for DCs have been recommended.[39,40]

COMPETING INTERESTS

The author declares no competing interests.

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