Osteopathic Manipulative Treatment in the Management of Isaacs Syndrome

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Isaacs syndrome is a rare neuromuscular disorder characterized by chronic muscle stiffness, cramping, fasciculations, myokymia, and hyperhidrosis. Pathogenesis includes autoimmunity, paraneoplastic disorders, genetic predisposition, or toxin exposure. There is no known cure for Isaacs syndrome. This case report describes a patient who had been given the diagnosis of Isaacs syndrome and received osteopathic manipulative treatment to manage fascial and cranial dysfunctions and reduce nervous system hyperexcitability. Long-term decrease of myokymia and reduction of severity and frequency of exacerbations resulted.

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Isaacs syndrome was first described in 1961 by neurologist Hyam Isaacs, MD, after he observed 2 patients with persistent muscle activity, hyperhidrosis, and muscle stiffness.[1] Peripheral nerve hyperexcitability (PNH) encompasses involuntary continuous muscle activity that can include muscle cramps, fasciculations, myokymia, and pseudomyotonia, often developing from pathologic changes to voltage-gated potassium channels (VGKCs).[2] Fasciculations are spontaneous discharges of a single motor axon. Group fasciculations at slower rates are called myokymia, where undulating movements of muscles can be seen on the skin surface.[2] Faster rates occur in patients with neuromyotonia.[3] Pathogenesis includes autoimmunity, paraneoplastic disorders, genetic predisposition, or toxin exposure, all of which affect VGKCs.[2] It is recommended that nonmalignant causes be managed symptomatically with carbamazepine, and with phenytoin and gabapentin as second-line treatment.[2] Additional medications include valproic acid, acetazolamide, lamotrigine, clonazepam, and dronabinol.[2] According to the National Institute of Neurological Disorders and Stroke, Isaacs syndrome is considered rare and has no cure.[4] The current case describes a patient with a diagnosis of Isaacs syndrome caused by long-term exposure to toluene.

Report of Case

A 55-year-old-man with Isaacs syndrome presented to the University of Pikeville Kentucky College of Osteopathic Medicine student teaching clinic in August 2014 seeking additional relief of pain and muscle rigidity. He had been undergoing sporadic osteopathic structural examinations (OSEs) and osteopathic manipulative treatment

(OMT) sessions for the past 5 years, since 2009. The patient received a diagnosis of Isaacs syndrome in 2006, 8 years before the current presentation, but irregular OMT sessions and medication at the time of presentation did not relieve his symptoms. He reported that the symptoms began 1 year before diagnosis and included myokymia and total muscle contractions that caused dislocations and muscle tearing. The patient had worked in automotive restoration for more than 20 years before the diagnosis and wore only shorts and a face mask while painting cars. His medical record indicated that the disease was caused by chronic transdermal absorption of toluene, confirmed by muscle biopsy and electromyography, which showed fasciculations and cramping predominantly in proximal muscles. The patient was bedridden at the time of diagnosis. Carbamazepine was prescribed after diagnosis, which restored his mobility, and his medication was later switched to lamotrigine. At the time of presentation to the osteopathic medical school student teaching clinic, disease management included 100 mg of lamotrigine and 10 mg of baclofen twice per day. During severe exacerbations the dose was increased. Hearing loss and muscle atrophy had been observed since the onset of the disease. During that time, he had constant myokymia, neuromyotonia, and peripheral neuropathy. He recollected a baseline pain score of 5 out of 10 using the Numeric Rating Scale. His symptoms increased to incapacitating levels, during which the patient had experienced myocardial infarction due to coronary artery spasm, respiratory failure, muscle tearing, bone fractures, joint dislocations, and severe bruising as a result of muscle cramps and contractures. These exacerbations were worsened by increased activity and cold weather.

Analysis of the patient's response to OMT ranged from August 2014 to September 2015. The patient was scheduled to receive OMT weekly; however, treatment occurrence varied depending on the clinic's schedule and the severity or frequency of exacerbations, which limited his ability to travel. Osteopathic structural examinations and OMT sessions were performed by student teaching fellows and faculty from the Department of Osteopathic Principles and Practices. All providers followed the same OSE process of assessing the cranium and thoracic, lumbar, and pelvic rigidity.

From August to December 2014, the patient underwent 10 OMT sessions. An OSE was performed before and after each treatment session to assess structural and functional improvement. Findings of the OSEs consisted primarily of cervical spine dysfunctions, thoracic and lumbar paraspinal hypertonicity, rib dysfunctions, fascial restrictions of the upper extremity, gait rigidity, pelvic restrictions, and any sequelae related to recent exacerbations. Management included balanced ligamentous tension, direct or indirect myofascial release, functional, facilitated positional release, and articulatory techniques. Techniques that did not use the patient's active muscle contraction and avoided the potential for excessive or rapid stretch were selected. For the first 8 visits, the patient stated that the myofascial release techniques were the most beneficial, as they provided relief of rigidity and pain and decreased hypertonicity in the regions addressed. The relief lasted a few hours. The cranium was not initially a focus of his care owing to consistent findings of soft tissue injury and somatic dysfunction caused by exacerbations, but after finding somatic dysfunctions during the ninth session, osteopathic cranial manipulative medicine (OCMM) was performed. The patient's myokymia resolved for 2 days after the treatment.

From January to September 2015, the patient received 17 OMT sessions with accompanying OSEs. Because the patient had a positive response to OCMM, the cranium was examined and treated first. The majority of findings related to the cranium were sidebending rotations and torsions, but other strain patterns were also observed. Management began with addressing the strain pattern followed by individual sutural restrictions. Techniques used included balanced membranous tension and dural venous sinus release. The fasciculations on the right side of the patient's neck and right eye lacrimation

began during techniques applied to the cranium and ceased when cranial dysfunctions resolved. Total body myokymia improved or resolved immediately after OCMM. Thoracic and lumbar hypertonicity also decreased immediately after OCMM, before any other body region was managed. Sacral dysfunctions were then addressed to improve function of the core link with cranial rhythmic impulse. Rib dysfunctions were addressed to normalize the impact on the sympathetic chain. If the patient tolerated treatment, other remaining somatic dysfunctions were managed using balanced ligamentous tension, direct or indirect myofascial release, and functional techniques. At the end of each session, his gait improved, pain was 3 or less out of 10, and myokymia was consistently reduced or resolved.

Reduction of myokymia was maintained as long as treatment occurred every 1 to 2 weeks. Although they occurred less frequently, the patient still had exacerbations between visits, resulting in substantial pain and myokymia. Treatment sessions subsequent to exacerbations resolved myokymia and decreased self-reported pain levels from 7 or 8 to 3 or less out of 10. When treatment with OCMM occurred weekly, the patient was able to drive independently and return to activities of daily living. The patient continues to receive weekly OMT sessions at the student clinic and his symptoms are well controlled.

Discussion

The definitive mechanism for neurotoxicity from toluene is not fully understood, but interactions with the neurotransmitter are immune and hypothalamic neurohormonal systems are known.[5] The extent of symptoms on exposure can vary depending on genetics, immune function, liver detoxification, and central nervous system hypersensitivity.[5] Most commonly, inhalation is the cause of toluene exposure; however, skin and gastrointestinal absorption can also occur.[5] Other chemical exposures may cause neuromyotonia include penicillamine, sodium aurothiomalate, lead, and silver.[2,6-8]

Our initial hypothesis was that myofascial release was the most effective way to manage the current patient's symptoms, until OCMM was used, which resulted in greater positive effects. Both techniques provided results that were systemic, not only resolving dysfunction in the specific body region addressed, but also dysfunctions in other body regions.

Through systemic connections, fascia has the potential to influence multiple body systems. Fascia is connective tissue consisting of multiple anatomic layers that unite and support the entire body. Highly innervated and vascularized, fascia is involved in metabolic activity and immune surviellance.[9-11] Studies have shown fascia to be a mechanosensitive signaling system with many potential systemic influences.[10] Symptoms related to dysfunction of the deep fascia include disturbance in proprioception, myofascial pain, and muscle cramps.[11] Muscle spindles are connected to the epimysium of deep fascia.[11] Tension in the deep fascia can lengthen the muscle spindles connected to it and activate them by passive stretch.[11] Over-activated muscle spindles cause muscle fibers to contract, which can produce muscle cramps and cause muscular imbalances and an increase in acetylcholine.[11]

One study demonstrated that an independent myofascial force influences the transmission of muscle force.[12] This relationship demonstrates that the adaptability of the fascia can allow muscle spindles to respond appropriately to gamma stimulus, and, when tension occurs in the fascia, it can induce muscle cramps. In the present case, managing the fascia dysfunction benefited our patient by reducing the cramps caused by fascial tension and by reinstating the muscle spindle reflex for protection of muscle fibers in future exacerbations.[12]

Fascia, muscle, and connective tissue surrounding nerves have primary afferent nociceptor innervations, which, when activated, involve facilitation of the spinal dorsal horn.[13] The large fiber system within the primary afferent neurons serves as regulator to the small fiber system in the dorsal horn and prevents

nociceptive information from ascending the spinal cord.[13] Over time, this normal response to tissue injury can become pathologic when under repeated injury and can cause the larger fiber system to amplify nociceptive signals and increase transmission in the spinal cord instead of normally inhibiting them.[13] The small fiber system will also enhance its activity when under repeated stimulus, exasperating chronic pain.[13] The current case demonstrates how OCMM influences this pathologic circuit, reducing its excitatory effects and giving the patient longer relief of symptoms, decreasing the severity of exacerbations, and resolving the myokymia.

Isaacs syndrome is rare and no cure exists.[4] The differential diagnosis includes other PNH disorders (*Table*).[2,14] A case report on stiff person syndrome, a PNH syndrome that causes muscle rigidity and spasms, showed that cranial treatment alone allowed for relaxation of somatic dysfunction throughout the body.[15] The current case and the report by Rajaii et al[15] demonstrate that OMT may be useful in other PNH disorders. Our knowledge of the direct connections between OCMM, central nervous system, and fascia is limited, but future studies examining the use of OMT to manage symptoms in patients with PNH disorders could provide a better understanding of these relationships and the way that OCMM can affect the entire body.

Conclusion

Management of the patient's cranial dysfunction in conjunction with myofascial release was necessary to more effectively address facilitation of the nervous system, although OCMM resolved multiple dysfunctions on its own as a single treatment. Although OMT is not a cure for Isaacs syndrome, it can reduce symptoms, lengthen the time between exacerbations, improve mobility, and enhance the overall quality of life for patients with Isaacs syndrome and, potentially, patients with other PNH disorders.

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Table.
Peripheral Nerve Hyperexcitability Disorders

Disorder	Symptoms and Clinical Evaluation Findings
Isaacs syndrome	Muscle cramps, fasciculations, myokymia, pseudomyotonia, and hyperhidrosis[14]
Morvan syndrome	Similar physical presentation to Isaacs syndrome, in addition to encephalopathy, headaches, drowsiness, and hallucinations[2]
Amyotrophic lateral sclerosis	Weakness, atrophy, and fasciculations[14]
Stiff-person syndrome	Central nervous system hyperexcitability and diffuse stiffness with muscle contraction[14]
Cramp-fasciculation syndrome	Exercise intolerance, muscle cramps, and twitching[2]
Rippling muscle disease	Myotonia and stretch- or percussion-induced episodic rolling movement of muscle[2]

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