Isaac Syndrome with Intractable Neuropathic Pain Features: A Case Report

Mustafa Al-Chalabi, Nicholas R. DelCimmuto, Pratyush Pavan Devarasetty, Jayasai Jeyarajan, Blair N. Baumle, Noor Pirzada

Department of Neurology, University of Toledo, Toledo, OH, USA; College of Medicine and Life Sciences, University of Toledo, Toledo, OH, USA

Keywords
Isaac syndrome · Neuropathic pain · Voltage-gated potassium channel · Peripheral nerve hyperexcitability

Abstract
Isaac syndrome (IS) is a peripheral nerve hyperexcitability state associated with voltage-gated potassium channel (VGKC) complex antibodies. Major manifestations are muscle twitching, stiffness, hypertrophy, and dysautonomic features such as hyperhidrosis [Ahmed and Simmons. Muscle Nerve. 2015;52(1):5–12]. Neuropathic pain is a rare manifestation. We describe a case of IS characterized by muscle twitching and intractable neuropathic pain. Diagnostic workup included elevated VGKC complex antibodies and EMG/NC that showed neuromyotonic discharges. Neuropathic pain was initially difficult to relieve even after using multiple medications, including opiates, benzodiazepines, anticonvulsants, and intravenous immunoglobulin (IVIg). Moderate pain control was eventually achieved with long-term use of carbamazepine and subcutaneous immunoglobulin (SCIg). Common manifestations of IS are muscle twitching, stiffness hypertrophy, and dysautonomia [Ahmed and Simmons. Muscle Nerve. 2015;52(1):5–12]. Sensory manifestations such as neuropathic pain are rare, but, as illustrated by our patient, can be the most distressing symptom. In our patient, not only was neuropathic pain disabling but it also showed the least response to IVIg. The use of 200 mg of long-acting carbamazepine twice daily with weekly SCIg demonstrated the best response. This case highlights an uncommon but potentially resistant symptom of IS.

Correspondence to:
Mustafa Al-Chalabi, mustafa.alchalabi@utoledo.edu
Introduction

Isaac syndrome (IS) is an acquired peripheral nerve hyperexcitability (PNH) state that presents as diffuse, rapid, asynchronous muscle contractions [1]. This is an autoimmune syndrome and is associated with autoantibodies of the voltage-gated potassium channel (VGKC) complex. Elevated VGKC antibody titers are seen in PNH disorders, such as IS, Morvan syndrome, and cramp-fasciculation syndrome (CFS) [2]. These autoantibodies have been associated with neoplastic tumors such as thymoma and small-cell carcinoma. Studies have shown that 21–25% of patients diagnosed with IS have some form of underlying neoplasm. Thymomas are cited to be present in 20% of patients with a CASPR2 antibody [3].

We present a case of a middle-aged male who came to the emergency department with a 4-week history of generalized myalgia, intractable neuropathic pain, and muscle cramping. Further investigation revealed an elevated titer of VGKC complex antibodies and EMG showed neuromyotonic discharges, leading to the diagnosis of IS with a rare presentation of intractable neuropathic pain.

Case Presentation

A 45-year-old male presented a 4-week history of muscle twitching, severe generalized burning pain, and episodic sweating in the extremities. He had no history of weakness, dysphagia, or dysarthria. He received Vicodin and muscle relaxants with no relief.

On examination, positive findings included persistent muscle fasciculations over the deltoids, triceps, forearm, thighs, and calf muscles (video-1). Muscle atrophy or hypertrophy was not observed and strength was grade 4+ in all muscles. These fasciculations were observed to be asynchronous resting contractions that involved the proximal and distal musculature. Visible asynchronous contractions were also observed in the abdominal musculature. He also complained of constant burning pain in his distal extremities bilaterally. The patient was started on a 5-day course of intravenous immunoglobulin (IVIg). Burning pain in the extremities required high doses of Dilaudid and then morphine with only mild relief. After starting IVIg, muscle fasciculations improved and soon resolved with only a minor improvement in pain, and the patient was transitioned to oral Percocet and gabapentin without significant pain relief. Average pain was rated 9/10 on the pain assessment scale.

The complete blood count and the basic metabolic panel revealed elevated creatine kinase 620 U/L and white blood cell count of 9.2 × 10^9/L. Autoimmune studies revealed negative ANA and anti-dsDNA, negative GAD antibodies, negative ACH receptor antibody, negative extractable nuclear antigen panels that include anti-Jo, antiscleroderma scl-70, anti-RNP, anti-Smith, anti-ro, and anti-la, and TSH within normal levels and Lyme antibodies were negative.

Electromyography and nerve conduction studies revealed spontaneous activity in the form of grouped +3 discharges as well as neuromyotonic discharges in the right medial gastrocnemius and left deltoid muscles. Motor unit potentials were normal (Fig. 1). VGKC antibody levels were elevated at 63 pmol/L (normal 0–31), confirming the diagnosis of IS. The chest CT scan was negative for thymoma. The whole-body PET scan was negative for malignancy.

His neuropathic pain persisted despite using IVIg, carbamazepine, gabapentin, opiates, phenytoin, dantrolene, and benzodiazepines. Moderate pain relief was achieved with the combination of carbamazepine and subcutaneous immunoglobulin (SC Ig) at the 1-year follow-up visit. Moderate pain relief was translated to 5/10 on average.
Discussion

The clinical presentation of IS involves a gradual stiffening of the generalized musculature, with frequent cramping and slow movement. Other common manifestations include hyperhidrosis, sialorrhea, piloerection, and abdominal pain. Neuropathic pain is a rare finding in patients with IS [4]. In our case, neuropathic pain was the dominant symptom of IS. This is likely due to an elevation in peripheral neuron hyperexcitability. From EMG reports, spontaneous depolarization of these nerves is the mechanism for the myotonias seen in the clinical picture [5]. We believe that these hyperexcitable nerves may also elicit a peripheral neuropathic pain syndrome, as seen in this case. Elevated VGKC antibody titers are observed in PNH disorders, such as IS, Morvan syndrome, limbic encephalitis, and CFS [4]. These autoantibodies have been associated with neoplastic tumors such as thymoma and small-cell carcinoma [3]. There was no evidence of malignancy in our case despite an extensive oncological workup. Electrodiagnostic studies remain the gold standard in the diagnosis of IS by demonstrating myokymic and neuromyotonic discharges when performing needle electromyography [6]. The differential diagnosis of suspected IS includes Morvan syndrome, limbic encephalitis, Stiff-Man syndrome, rippling muscle syndrome, CFS, and Schwartz-Jampel syndrome (Table 1).

Although the pathophysiology of IS involves the dysfunction of VGKCs by autoantibodies resulting in potassium-ion imbalance that leads to symptoms of muscular hyperexcitability, this case highlights the question of how neuropathic pain can accompany the typical presentation [4]. One possibility is that the potassium-ion imbalance occurring in IS extends to a similar hyperexcitability in sensory neurons. Although there are many theories regarding the mechanism of neuropathic pain, some studies have shown that hyperexcitable neurons leading to excessive discharge can cause neuropathic pain while also triggering central sensitization [7]. Furthermore, studies have shown that neuropathic pain is complex and can involve the dysfunction of multiple ion channels along sensory axons, but the disruption of one channel, such as VGKC, can result in further disorganization of the function of other ion channels causing excessive afferent signals and/or failed inhibitory pain signals [3]. Thus, VGKC autoantibodies of IS could lead to an imbalance of various sensory axon ion channels, leading to a sensation of neuropathic pain [1]. In this case, quantitative sensory testing (QST) was not used, which may have been helpful in identifying detection, pain thresholds, and stimulus-response
curves. Immense standardization is not required for this test to have reliability. Studies have found that detection of neuropathic pain was possible using QST, especially in cases such as small, isolated fiber neuropathy. This case describes a systemic neuropathy and thus QST was not performed [8]. Although this form of testing is a widely accepted tool for detecting neurosensory and somatic pain, further evaluation and validation of its ability to form more comprehensive and focused treatment is needed [9].

Table 1. Differential diagnosis of IS

| Isaac’s Syndrome Differential | clinical Features | etiology |
|-------------------------------|------------------|---------|
| Myotonia congenita (Thomsen/Becker disease) | Myotonia, transient muscle weakness, stiffness, warming-up effect, muscular hypertrophy, delayed release phenomenon | Autosomal dominant, CLCN deletion |
| CFS | Fasciculations, myoclonus | Unknown |
| Morvan syndrome | Autonomic features (hyperhidrosis, fever pruritus), CNS features (encephalopathy, delirium, confusion), PNS features (fasciculations, neuropathic pain, areflexia) | Poorly understood, potentially autoimmune anti-VGKC |
| Limbic encephalitis | Memory impairment, seizures, confusion, psychiatric disturbance | Immune reactions from malignancy, infection, autoimmune |
| Stiff-Man syndrome | Skeletal muscle rigidity, hyperhidrosis, painful muscle spasms triggered by noise or internal psychiatric stimuli (stress), falls, and fractures | Autoimmune (Anti-GAD/Anti-amphiphysin), araneoplastic (lung, breast, lymphoma), idiopathic |
| Rippling muscle syndrome | Adult-onset exercise-induced muscle cramping, elevated creatine kinase, muscle hypertrophy, tiptoeing | Autosomal dominant CAV3 mutation |
| Schwartz-Jampel syndrome | Early-onset myotonia, mask-like facies, chondrodysplasia, pectus carinatum, platyspondyly, joint restriction, abnormal blinking, muscle spasms | Autosomal recessive mutation in HSPG2 |
| Amyotrophic lateral sclerosis | UMN/LMN signs, asymmetric limb weakness, fasciculations, cramps, muscle stiffness, dysarthria, dysphagia, weight loss | SOD1, TARDBP, C9orf72, FUS, head trauma, environmental exposure |
| Progressive spinal muscle atrophy | Hypotonia, muscle weakness, paralysis, atrophy and tongue fasciculations, tremor, muscle cramps, joint pain | Autosomal recessive SMN1 gene |
| Intoxication (mercury, toluene, organophosphates) | Mercury: GI/Renal dysfunction, ataxia, erethism mercurialis, polyneuropathy, buccal inflammation Toluene: hallucination, euphoria, tremors, seizure, coma | Toxic exposure, intentional ingestion |
Carbamazepine has been reported to show the greatest success in symptomatic treatment [1]. Gabapentin, phenytoin, and mexiletine are other options with variable success [1]. Less frequently used medications in symptomatic management include valproic acid, acetazolamide, lamotrigine, clonazepam, and dronabinol [1]. Immunotherapy such as plasma exchange has been shown to control neuromyotonia [1]. Our case of neuropathic pain associated with IS was resistant to many anticonvulsants and analgesic medications in addition to IVIg. Carbamazepine 200 mg twice daily with weekly SCIG managed pain to a tolerable level.

In conclusion, our case illustrates a patient with IS who had intractable generalized neuropathic pain. This pain was resistant to various classes of medications, but ultimately the patient reported improvement with the combination of carbamazepine and SCIG. More studies are needed to better understand the pathogenesis of neuropathic pain in IS and to identify the best management strategy.

Acknowledgment

The authors thank the patient who generously agreed to participate in this medical report.

Statement of Ethics

The paper is exempt from Ethical Committee approval in accordance with University of Toledo policy regarding case reports. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This case report has not received any funding.

Author Contributions

M.A., J.J., and N.P. were responsible for the clinical management of the patient. N.D., P.D., and B.B. participated in drafting of the manuscript and acquisition of data. M. Al-Chalabi and N.D. participated in analyzing and interpretation of data. N.P. revised the final manuscript for intellectual content. All authors read and approved the final manuscript.

Data Availability Statement

All the data supporting our findings are contained within the manuscript.
References

1. Ahmed A, Simmons Z. Isaacs syndrome: a review. Muscle Nerve. 2015 Jul;52(1):5–12.
2. Katirji B. Peripheral nerve hyperexcitability. Handb Clin Neurol. 2019 Jan 1;161:281–90.
3. Ratté S, Prescott SA. Afferent hyperexcitability in neuropathic pain and the inconvenient truth about its degeneracy. Curr Opin Neurobiol. 2016 Feb 1;36:31–7.
4. Park SB, Thurbon R, Kiernan MC. Isaacs syndrome: the frontier of neurology, psychiatry, immunology and cancer. J Neurol Neurosurg Psychiatry. 2020 Dec 1;91(12):1243–4.
5. Kanmaz S, Özcan M, Şimşek E, Serin HM, Gökben S, et al. A rare case of peripheral nerve hyperexcitability in childhood: Isaacs syndrome. J Pediatr Neurosci. 2020 Apr;15(2):153.
6. Song J, Jing S, Quan C, Lu J, Qiao X, Qiao K, et al. Isaacs syndrome with CASPR2 antibody: a series of three cases. J Clin Neurosci. 2017 Jul 1;41:63–6.
7. Misawa S. Pathophysiology of neuropathic pain: Na⁺ channel and hyperexcitability of primary afferents. Brain Nerve. 2012 Nov 1;64(11):1249–53.
8. Krumova EK, Geber C, Westermann A, Maier C. Neuropathic pain: is quantitative sensory testing helpful? Curr Diab Rep. 2012 Aug;12(4):393–402.
9. Pfau DB, Geber C, Birklein F, Treede RD. Quantitative sensory testing of neuropathic pain patients: potential mechanistic and therapeutic implications. Curr Pain Headache Rep. 2012 Jun;16(3):199–206.