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CASPR2-Positive Isaac's Syndrome Presenting as Sciatica-Like Thigh Pain with Normal Imaging: A Steroid-Responsive Diagnostic Pitfall

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ABSTRACT

Background Isaac's syndrome, or acquired neuromyotonia, is a rare disorder of peripheral nerve hyperexcitability. Anti-CASPR2 antibodies represent a distinct autoimmune subtype but remain under-recognized. The presentations often mimic radiculopathy or musculoskeletal pain, especially when accompanied by nonspecific MRI findings.

Case Presentation A 29-year-old male patient presented with 2 months of continuous, involuntary worm-like muscle movements in both thighs and shoulders, associated with nocturnal pain without weakness or sensory loss. Early MRI of the spine revealed diffuse L4–L5 and L5–S1 disc bulges without nerve root compression, which raised an initial suspicion for bilateral radiculopathy. Neurological examination showed continuous myokymia with strength, reflexes, and sensation being preserved. Laboratory studies were normal. Immunological studies were strongly positive for anti-CASPR2 antibodies and clinically insignificant for anti-LGI1, thus confirming the diagnosis of autoimmune Isaac's syndrome. The patient improved substantially after methylprednisolone pulse therapy.

Discussion This case underscores a critical diagnostic pitfall— attributing neuromyotonia to incidental MRI findings. In young patients with persistent thigh pain, visible myokymia, and normal imaging, CASPR2-associated peripheral nerve hyperexcitability should be considered. The pure neuromyotonia phenotype, absence of neuropathy, and strong steroid response make this case clinically meaningful.

Conclusion CASPR2-positive Isaac's syndrome should be considered in patients with persistent limb pain and visible myokymia despite normal neuroimaging. Clinical–radiological mismatch with preserved neurology favors autoimmune peripheral nerve hyperexcitability over radiculopathy. Early immunotherapy provides rapid symptom relief and prevents unnecessary spinal interventions.

KEYWORDS: CASPR2 antibody, Myokymia, Neuromyotonic, Isaac's syndrome, Peripheral nerve hyperexcitability, Radiculopathy.

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INTRODUCTION

Peripheral nerve hyperexcitability (PNH) syndromes constitute a spectrum of disorders, including fasciculation-cramp syndrome, Isaacs' syndrome, and Morvan syndrome. Isaac's syndrome or acquired neuromyotonia results from impaired Kv1 channel function due to autoimmune disruption of the VGKC-complex, most commonly by CASPR2 antibodies. Symptoms may mimic lumbar radiculopathy, especially when thigh pain and muscle rippling dominate, leading to frequent misdiagnosis.

This patient demonstrates a rare, immunologically confirmed CASPR2-positive pure neuromyotonia phenotype, with clinical features initially attributed to benign lumbar disc bulge. The case underscores key diagnostic considerations and highlights the importance of correlating imaging findings with clinical neurology rather than relying on incidental degenerative changes.

Isaac's syndrome, also known as acquired neuromyotonia, is a disorder of peripheral nerve hyperexcitability characterized by

spontaneous, continuous motor-unit activity due to dysfunction of voltage-gated potassium channels located in the distal motor axons. Since its initial description by Isaacs in 1961, this disorder has clinically been characterized by stiffness, cramps, delayed muscle relaxation, fasciculations, and characteristic rippling movements known as myokymia. Symptoms persist even during sleep and reflect the inability of affected motor axons to repolarize normally.

Autoimmune mechanisms have been recognized as a major etiopathogenic category in A-NMT, especially due to antibodies against constituents of the VGKC complex. Among these, CASPR2 represents one of the most clinically relevant antigens. CASPR2 is distributed at the juxtaparanodal regions of myelinated axons and has a crucial role in the clustering and functioning of Kv1.1/ Kv1.2 potassium channels (3). Anti-CASPR2 antibodies disrupt this architecture, resulting in impaired potassium conductance and chronic axonal hyperexcitability (3,4). CASPR2 autoimmunity yields a spectrum that ranges from isolated neuromyotonia to Morvan syndrome, depending on the degree of involvement of the central and peripheral nervous system (4,5). CASPR2 neuromyotonia often goes unrecognized clinically because its symptoms commonly masquerade as more common conditions such as lumbar radiculopathy, peripheral neuropathy, or musculoskeletal pain syndromes(6–8). The presenting symptoms may relate to thigh or limb stiffness or visible rippling movements, or pain, which leads clinicians to consider imaging of the spine rather than PNH. Degenerative lumbar disc bulges-common incidental findings on MRI-further mislead clinicians and anchor the diagnostic impression toward radiculopathy (7). Radiculopathy characteristically presents with dermatomal pain, sensory changes, reflex asymmetry, or focal weakness in a pattern generally absent in neuromyotonia(8). A clinical–radiological mismatch, particularly in the setting of preserved neurological function and visible myokymia, should raise the suspicion for PNH over structural spine disease.

Diagnosis of neuromyotonia requires clinical signs to be correlated meticulously with electrophysiology, imaging, and immunological testing. Electromyography typically reveals doublet, triplet, or multiplet neuromyotonic discharges; serology may confirm CASPR2 or other VGKC-complex antibodies (1,3). Importantly, weak or isolated LGI1 seropositivity may occasionally appear in CASPR2-associated disease without influencing the phenotype since LGI1 antibodies affect mainly limbic structures and are associated with faciobrachial dystonic seizures and encephalopathy rather than pure PNH (5,9).

Immunotherapy is the cornerstone of treatment for autoimmune Isaac's syndrome. Corticosteroids, IVIG, and plasma exchange have been shown to reduce abnormal motor activity and improve patient quality of life (10,11). Symptomatic agents such as carbamazepine and gabapentin and benzodiazepines can offer additional relief but are rarely sufficient as monotherapy in antibody-mediated disease (11). Early recognition will help avoid unnecessary spinal interventions and allow timely immunotherapy.

The current case illustrates a diagnostically challenging presentation of CASPR2-positive Isaac's syndrome, presenting with predominant bilateral thigh pain and continuous myokymia in a young adult. The absence of neurological deficits and normal MRI findings contrasted sharply with the severity of symptoms, underscoring the need for clinicians to consider PNH when clinical and radiological features are discordant. This report emphasizes the importance of antibody testing and careful clinical– radiological correlation in patients presenting with sciatica-like symptoms but preserved neurology.

CASE PRESENTATION

2.1 Patient History

A 29-year-old man developed involuntary "worm-like" (myokymic) movements in both thighs and shoulders over two months, accompanied by dull nocturnal pain. There were no signs of limb weakness, sensory loss, gait difficulty, sphincter disturbance, fever, or toxin exposure. He used creatine supplements but no neurotoxic agents.

2.2 Imaging Findings

A lumbar spine MRI obtained one month prior to referral demonstrated diffuse disc bulges at L4–L5 and L5–S1 with indentation of the ventral thecal sac. There was no neural foraminal narrowing or neural compromise. Lumbarization of S1 was also noted. These findings were interpreted as degenerative and non-compressive.

2.3 Neurological Examination

On examination, the patient was alert and fully oriented. Higher mental functions and cranial nerve examination were normal. Motor examination showed normal muscle bulk and tone with full (5/5) strength in all tested muscle groups. Deep tendon reflexes were 2+ and symmetric with flexor plantar responses. Sensory testing for superficial, deep, and cortical modalities was intact. Cerebellar function was normal, and no extrapyramidal signs were present. The most striking finding was continuous, visible myokymia over both thighs and shoulders**.**

2.4 Diagnosis

Based on the characteristic clinical features, normal neuroimaging, preserved neurology, and strong CASPR2 positivity, the patient was diagnosed with **CASPR2-associated Isaac's syndrome (Acquired neuromyotonia)**.

2.5 Treatment

The patient was managed with a combination of immunotherapy and symptomatic agents targeting peripheral nerve hyperexcitability. High-dose intravenous methylprednisolone (1 g/day for five days) was initiated as first-line therapy, given the strong CASPR2 antibody positivity and characteristic neuromyotonia phenotype. This produced a rapid improvement in visible myokymia and nocturnal pain. He was subsequently transitioned to oral prednisolone at 1 mg/kg/day with a gradual taper over six to eight weeks to maintain remission and prevent rebound hyperexcitability.

Symptomatic agents were administered to control discomfort, sleep disturbance, and excessive motor unit firing. Gabapentin (300 mg twice daily), carbamazepine (200 mg in the morning and 400mg at night), clonazepam (0.5 mg at night), and amitriptyline (25 mg at night) were used in tailored doses to alleviate pain, reduce myokymic activity, and improve sleep quality. Paracetamol (500mg as needed) provided additional analgesic support. Supportive measures, including hydration, electrolyte optimisation, and stretching-based physiotherapy, were continued throughout the hospital course to maintain metabolic stability and reduce stiffness. The patient demonstrated rapid and sustained clinical improvement with no early relapse during follow-up.

2.6 Outcome

By the end of the steroid pulse, the patient demonstrated a substantial reduction in continuous muscle activity and nocturnal pain and reported improved sleep. At the one-week follow-up visit, the symptomatic improvement was sustained, with no development of new neurological features.

DISCUSSION

Acquired neuromyotonia (Isaac's syndrome) is a peripheral nerve hyperexcitability (PNH) disorder characterized by spontaneous, continuous motor unit activity resulting from dysfunction of voltage-gated potassium channels (VGKC) on motor axons. The pathophysiology arises from impaired Kv1.1 and Kv1.2 channel-mediated repolarization, which leads to repetitive discharges, myokymia, stiffness, and neuromyotonic bursts on electrophysiology. Autoimmune mechanisms account for a substantial subset of cases, particularly those associated with antibodies directed against CASPR2, a key cell-adhesion protein within the VGKC complex (1, 5 - 6).

CASPR2 autoimmunity typically produces a clinical spectrum ranging from isolated neuromyotonia to Morvan syndrome, depending on the distribution of immune-mediated dysfunction. CASPR2 antibodies preferentially target juxtaparanodal Kv1 channels of myelinated axons, explaining their strong association with peripheral nerve hyperexcitability (13). Patients commonly present with continuous muscle activity, cramps, stiffness, neuropathic pain, and preserved strength and sensation—features that align closely with the current case. In contrast, antibodies to LGI1 primarily affect synaptic structures within the limbic system, producing faciobrachial dystonic seizures and subacute encephalopathy (9). The weak LGI1 positivity in this case, in complete absence of its characteristic clinical manifestations, is consistent with incidental seropositivity, a phenomenon reported in literature where low-titer LGI1 antibodies appear in CASPR2-driven disease without modifying the phenotype (10).

A significant diagnostic challenge arises because neuromyotonia may mimic lumbosacral radiculopathy. Patients may report limb pain, stiffness, or twitching, leading clinicians to pursue spinal imaging early in the evaluation. Degenerative disc bulges— common incidental findings—may mislead clinicians when myokymia is not recognized. However, radiculopathy typically presents with dermatomal symptoms, focal weakness, reflex asymmetry, or sensory deficits, none of which were present in this case. The preservation of all neurological modalities despite continuous visible myokymia is an important distinguishing clue favoring autoimmune PNH rather than radiculopathy (3).

Furthermore, symptoms such as continuous worm-like movements over large muscle groups cannot be explained by mechanical compression of a single nerve root. Disc bulges without nerve root impingement, as seen here, are radiologically insufficient to generate spontaneous motor activity. These discrepancies emphasize the importance of correlating clinical findings with imaging rather than attributing all limb symptoms to structural spine abnormalities. Several reports describe similar diagnostic pitfalls where CASPR2-positive neuromyotonia was initially mistaken for mechanical radiculopathy or musculoskeletal pathology (6,7). Steroid responsiveness is a well-recognized characteristic of CASPR2-mediated PNH. Immunotherapy—including corticosteroids, IVIG, or plasma exchange—typically results in significant reduction of myokymia and improvement in quality of life (11). The patient's rapid symptomatic relief following pulse methylprednisolone further supports an immune-mediated pathogenesis. Symptomatic agents such as carbamazepine, gabapentin, and benzodiazepines may provide additional relief by stabilizing neuronal membranes and reducing spontaneous discharges, but they are generally insufficient in isolation for antibodymediated disease (13).

This case contributes to the literature in several notable ways. First, it highlights a rare and well-defined CASPR2-positive pure neuromyotonia phenotype in a young adult. Second, it reinforces that sciatica-like presentations with normal imaging should prompt consideration of PNH, especially when visible myokymia is present. Third, it illustrates the diagnostic limitations of relying solely on lumbar imaging, which may reveal degenerative but clinically irrelevant changes. Fourth, it underscores the clinical irrelevance of weak LGI1 positivity in the absence of its signature neurocognitive or movement disorder manifestations. Lastly, it demonstrates the clear therapeutic benefit of early corticosteroid treatment in autoimmune neuromyotonia.

3.1 Differential Diagnosis and Diagnostic Reasoning

In this case, a structured differential diagnosis was necessary because the patient's presentation overlapped with several neuromuscular and radicular disorders. The presence of bilateral thigh pain initially pointed towards disease of the lumbar spine, while continuous muscle activity raised the possibility of motor neuron pathology, metabolic disturbances, or drug-related etiologies. However, the coexistence of visible myokymia, preserved neurological function, and normal neuroimaging required a shift from spine-centred reasoning to an evaluation for peripheral nerve hyperexcitability. In order to illustrate this diagnostic transition, an expanded differential diagnosis utilizing case-specific discriminators is provided in Table 1.

Table 1. Differential diagnosis of persistent myokymia with case-specific discriminators

Condition Considered	Why It Was Initially Plausible	Case Findings That Refuted It	Turning Point in Diagnostic Exclusion
Lumbar Radiculopathy	Bilateral thigh pain with MRI showing L4–L5 and L5–S1 disc bulges.	No nerve-root compression; normal power, reflexes, and sensation; symptoms non-dermatomal.	Recognition that **radiculopathy cannot produce persistent worm-like myokymia**; clear clinical-radiological mismatch.
Motor Neuron Disease (ALS)	Continuous muscle activity can suggest anterior horn cell pathology.	Movements were **true myokymia**, not fasciculations; no weakness, atrophy, or UMN signs.	Symptom stability over months with **no progression** toward LMN/UMN involvement.
Peripheral Neuropathy	Limb pain occasionally seen in neuropathic processes.	Completely normal sensory exam; no length-dependent pattern; no gait abnormalities.	Preservation of all sensory modalities and absence of neuropathic deficits.
Electrolyte Disorders (Ca/Mg/K)	Electrolyte disturbances can cause muscle irritability.	Electrolytes entirely normal; no tetany or carpopedal spasm.	Normal laboratory profile excluded metabolic hyperexcitability.
Drug-Induced Hyperexcitability	Certain medications (e.g., lithium, SSRIs) can induce muscle hyperactivity.	No exposure to neuroactive drugs; creatine not associated with neuromyotonia.	Lack of medication or toxin triggers.
Benign Fasciculation Syndrome	Young adults frequently present with fasciculations.	BFS does not cause **fixed, continuous myokymia**, especially in large proximal muscles.	Distinct **myokymic rippling pattern** incompatible with BFS.
Morvan Syndrome	CASPR2 can be associated with autonomic and CNS involvement.	No autonomic instability, insomnia, hallucinations, or encephalopathy.	Phenotype strictly peripheral, without CNS findings.
LGI1 Encephalitis	Weak LGI1 positivity required consideration.	No faciobrachial dystonic seizures, cognitive decline, or hyponatremia.	LGI1 seropositivity interpreted as **non-contributory** based on phenotype.
CASPR2-Associated Isaac's Syndrome	Classic presentation of autoimmune neuromyotonia.	Continuous myokymia, normal imaging, normal neurological exam, strong CASPR2 positivity.	**Rapid steroid responsiveness** and immunological confirmation established final diagnosis.

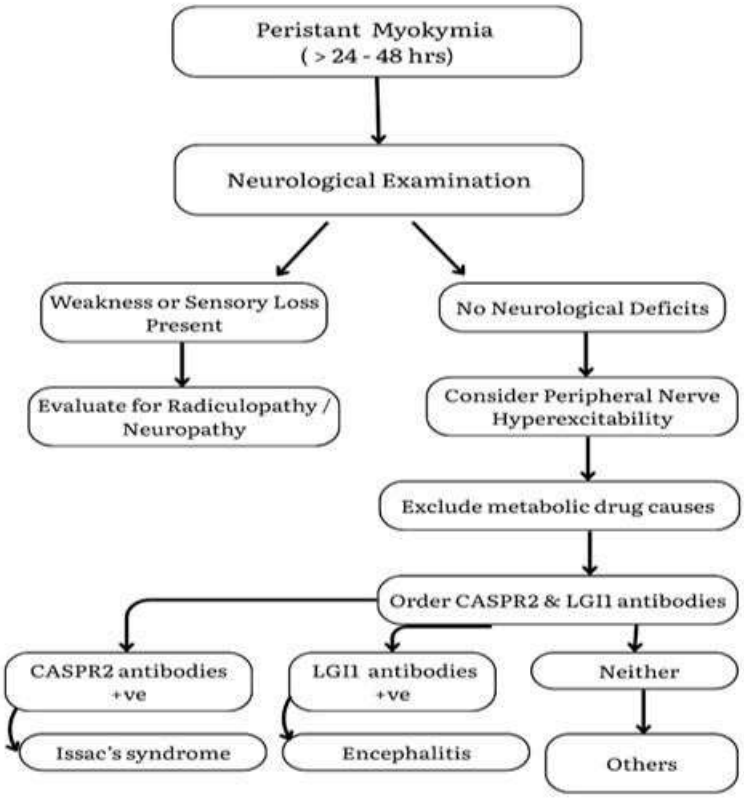

Figure 1. Diagnostic Workflow

Figure 1 shows Algorithm outlining evaluation of sustained myokymia with normal neuroimaging. Persistent visible myokymia, intact neurological examination, and absence of metabolic or drug triggers guided testing for autoimmune peripheral nerve hyperexcitability. Strong CASPR2 positivity confirmed CASPR2-associated Isaac's syndrome.

CONCLUSION

CASPR2-positive Isaac's syndrome should be considered in patients presenting with chronic limb pain and involuntary rippling movements, even in cases when lumbar spine imaging only reveals minor degenerative changes. This case illustrates how visible myokymia, normal neurological examination, and non-compressive neuroimaging should point diagnostic efforts away from spinal etiologies toward autoimmune peripheral nerve hyperexcitability. Early recognition of autoimmune neuromyotonia enables early immunotherapy, with significant symptomatic improvement.

Weak LGI1 seropositivity must be interpreted with caution and in strict correlation with the clinical features. If encephalitic, cognitive, or faciobrachial phenomena are not present, then antibodies against LGI1 are unlikely to play a role in the clinical picture.

This case underlines the importance of neuromyotonia as a potential mimicker of sciatica and emphasizes the need for proper clinical–radiological correlation. Early immunotherapy results in good clinical recovery and prevents long-term morbidity. A high degree of awareness of this presentation among clinicians could avoid diagnostic delay and mismanagement, including unnecessary spinal interventions.

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