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DPPX-IgG-associated CNS hyperexcitability overlapping with acquired neuromyotonia (Isaacs syndrome): a case report

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Case Report

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Abstract

Background: Dipeptidyl-peptidase-like protein-6 (DPPX/DPP6) autoimmunity is classically associated with central and enteric hyperexcitability, whereas acquired neuromyotonia (Isaacs syndrome) is a peripheral nerve hyperexcitability (PNH) disorder most often linked to CASPR2 but may be seronegative. Objective peripheral nerve abnormalities have only occasionally been documented in anti-DPPX-associated disease.

Case presentation: A 34-year-old man had a 6-year peripheral-predominant course of lower-limb weakness, muscle twitching, hyperhidrosis, distal numbness, gluteal pain, and squatting difficulty, leading to an outside diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy. He later developed exaggerated startle, marked tension, tongue fasciculations, and one paroxysmal generalized tonic-stiffening episode during corticosteroid tapering. Electrophysiology confirmed PNH with fasciculation potentials and triplet discharges. Serum DPPX-IgG was positive at 1:10 by cell-based assay (CBA), whereas cerebrospinal fluid DPPX-IgG, CASPR2, and LGI1 antibodies were negative; VGKC-complex testing was negative on two occasions. Tongue fasciculations disappeared after corticosteroid treatment. At 3 months, repeat serum DPPX-IgG by CBA was negative while residual electrophysiological PNH persisted. A later low-titer P/Q-type VGCC-IgG result was interpreted as associated serology because high-frequency stimulation did not support Lambert-Eaton myasthenic syndrome.

Conclusions: The combined central hyperexcitability features and electrophysiologically confirmed acquired neuromyotonia suggest a DPPX-IgG-associated CNS-PNS hyperexcitability overlap phenotype with predominant peripheral involvement. Previous reports of demyelinating sensorimotor polyneuropathy, active denervation, mixed axonal/demyelinating changes, and a DPPX/CASPR2 double-positive neuromyotonia phenotype support possible peripheral involvement, but direct pathogenicity of DPPX-IgG in peripheral motor axons remains unproven.

Background

Isaacs syndrome, or acquired neuromyotonia, is characterized by persistent peripheral nerve hyperexcitability with muscle twitching, myokymia or neuromyotonic activity, cramps, stiffness, pain, hyperhidrosis, and variable weakness. Diagnosis is clinical and electrophysiological rather than antibody-dependent; VGKC-complex antibodies are detectable in only a subset of acquired PNH, and CASPR2/LGI1-negative cases are well recognized [1-4].

DPPX/DPP6 is an auxiliary subunit of Kv4.2-related A-type potassium channels and regulates channel trafficking, gating, and neuronal excitability [5-9]. Anti-DPPX disease typically includes gastrointestinal symptoms or weight loss, cognitive or psychiatric disturbance, and CNS hyperexcitability, but brainstem dysfunction, exaggerated startle, rigidity, myoclonus, seizures, and incomplete phenotypes are reported [5-7,10-13]. Experimental studies show that patient IgG can reduce surface DPPX/Kv4.2 and increase neuronal excitability in brain and enteric neurons [6-7] (Fig. 1). We report a patient with DPPX-IgG-

associated CNS hyperexcitability features and a long-standing, electrophysiologically confirmed PNH phenotype consistent with acquired neuromyotonia.

Case presentation

A 34-year-old man was admitted with a 6-year history of asymmetric limb weakness, distal numbness, and progressive muscle twitching. Weakness was greater in the lower limbs and accompanied by proximal leg twitching and hyperhidrosis. At another hospital he had been diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and treated with glucocorticoids and neurotrophic therapy, with partial improvement in numbness. The original outside electrophysiological data were unavailable for independent verification; therefore, this history was interpreted as evidence of an early peripheral-predominant syndrome rather than proof of CIDP.

During the 2 years before admission, weakness and twitching worsened, with mobility limitation, difficulty squatting, bilateral gluteal pain, exaggerated startle, and marked tension. He had no documented cognitive decline, prominent psychiatric syndrome, persistent diarrhea, or major weight loss. Before immunotherapy, examination showed mild bilateral tongue atrophy with visible tongue fasciculations, lower-limb weakness, generalized areflexia, and bilateral foot drop. Brain MRI, thoracic spinal MRI, chest CT, and routine laboratory testing were unrevealing.

Electrophysiology confirmed PNH. Needle EMG of both vastus medialis muscles and the left gluteus medius demonstrated fasciculation potentials and triplet discharges; bilateral tibial F-wave phenomena were recorded, and low-frequency repetitive stimulation of the right tibial nerve showed a decremental response (Fig. 2). Serum DPPX-IgG was positive at 1:10 by CBA, whereas CSF DPPX-IgG was negative (Fig. 3). Serum CASPR2, LGI1, GABABR, NMDAR, and AMPAR antibodies were negative, and VGKC-complex testing was negative on two occasions. The working diagnosis was a DPPX-IgG-associated CNS-PNS hyperexcitability overlap phenotype with acquired neuromyotonia (Isaacs syndrome).

Treatment included methylprednisolone followed by tapering, carbamazepine, and mycophenolate mofetil; two off-label doses of efgartigimod (800 mg) were also administered. Tongue fasciculations disappeared after corticosteroid treatment, suggesting an immune-responsive disturbance involving the bulbar motor system, although this observation cannot anatomically distinguish hypoglossal nuclear from peripheral axonal involvement. During corticosteroid tapering, the patient experienced one paroxysmal episode of generalized tonic stiffening. Because no ictal EEG was obtained, the event was considered compatible with either a tonic seizure or a generalized hyperexcitability-related spasm rather than being classified definitively as epilepsy.

At 3 months, repeat serum DPPX-IgG by CBA was negative, but electrophysiological PNH persisted. A clinical relapse occurred after prednisone had been reduced to 25 mg/day and mycophenolate mofetil had been interrupted for 1 week; weakness and proximal fasciculations improved after intensification of immunotherapy. Pelvic MRI showed bilateral gluteal muscle atrophy with abnormal signal (Fig. 4). Low-titer P/Q-type VGCC-IgG (1:10) was later detected, but high-frequency stimulation showed no

characteristic facilitation; the VGCC result was therefore treated as associated serology rather than a primary pathogenic driver. PET-CT was not performed because of financial constraints, and longitudinal tumor surveillance was recommended. The clinical course is summarized in Table 1.

Table 1
Clinical timeline

Time point	Clinical features	Key investigations	Treatment/outcome
6 years before admission	Lower-limb-predominant weakness, distal numbness, proximal leg twitching, hyperhidrosis	Outside diagnosis of CIDP; original electrodiagnostic data unavailable	Glucocorticoids/neurotrophic therapy; numbness partly improved
2 years before admission	Progressive twitching/weakness, gluteal pain, squatting difficulty, exaggerated startle, marked tension	No cognitive decline or persistent GI syndrome documented	Progressive functional limitation
Admission	Tongue atrophy with visible fasciculations, generalized areflexia, bilateral foot drop	EMG confirmed PNH; serum DPPX-IgG 1:10 by CBA; CSF DPPX-IgG negative; CASPR2/LGI1 negative; VGKC-complex negative twice	Diagnosis reframed as DPPX-IgG-associated CNS-PNS hyperexcitability overlap with acquired neuromyotonia
Initial treatment	Persistent twitching and weakness	Clinical/EMG monitoring	Methylprednisolone, carbamazepine, MMF, two off-label efgartigimod doses; tongue fasciculations disappeared
During steroid taper	One paroxysmal generalized tonic-stiffening episode	No ictal EEG; seizure vs hyperexcitability-related spasm unresolved	Continued immunotherapy; event interpreted cautiously
3-month follow-up	Residual PNH; relapse after prednisone reduction and 1-week MMF interruption	Repeat serum DPPX-IgG negative by CBA; EMG still abnormal	Prednisone intensified and MMF restarted; weakness/fasciculations improved
Reassessment	Persistent gluteal pain and squatting difficulty	Pelvic MRI: bilateral gluteal atrophy; P/Q-type VGCC-IgG 1:10; low-frequency RNS decrement; no high-frequency facilitation	VGCC treated as associated serology; rehabilitation and tumor surveillance advised

Discussion and Conclusions

This case is best interpreted as an overlap between DPPX-IgG-associated CNS hyperexcitability and acquired neuromyotonia with predominant peripheral nerve involvement. Repeated negativity for VGKC-complex, CASPR2, and LGI1 antibodies does not exclude Isaacs syndrome, because acquired PNH is defined by its clinical-electrophysiological phenotype and may be seronegative [4]. The persistent limb twitching, hyperhidrosis, pain, weakness, and electrophysiological PNH therefore support acquired neuromyotonia independently of antibody status.

The exaggerated startle, marked tension, paroxysmal generalized tonic stiffening, and steroid-responsive tongue fasciculations are difficult to explain by isolated peripheral neuromyotonia alone and overlap with the recognized DPPX hyperexcitability spectrum [5,7,10–13]. The tongue finding suggests immune-responsive bulbar motor-system involvement, but does not prove direct involvement of the hypoglossal motor nucleus. Likewise, the tonic-stiffening event may represent central hyperexcitability, but the absence of ictal EEG prevents definitive classification as a seizure.

Peripheral nervous system involvement in anti-DPPX disease may be underrecognized (Table 2). Stoeck et al. reported demyelinating sensorimotor polyneuropathy in a patient with DPPX antibody-positive autoimmune encephalitis [14]. Bjerknes et al. described active denervation and mild mixed axonal/demyelinating motor and sensory nerve-conduction abnormalities that normalized after immunotherapy [15]. In the 2024 multicenter cohort, one patient with neuromyotonia had both CSF DPPX and CASPR2 antibodies, making the specific contribution of DPPX uncertain [10]. Our case differs by showing a long-standing, peripheral-predominant PNH phenotype with negative CASPR2/LGI1 and repeated negative VGKC-complex testing. These observations extend, rather than establish de novo, the possible peripheral spectrum of DPPX autoimmunity.

Serological interpretation must remain cautious. The initial DPPX-IgG was low-titer and serum-restricted, and direct functional effects of this patient's IgG on peripheral motor axons were not tested. The negative repeat CBA at 3 months does not necessarily invalidate the original result: temporal fluctuation of DPPX antibodies has been reported [16], and testing occurred after immunotherapy including efgartigimod, an FcRn antagonist that reduces circulating total IgG and IgG autoantibody levels [17]. Persistent electrophysiological PNH after seronegativity may reflect delayed physiological recovery, downstream excitability changes, assay sensitivity, or a contributory rather than exclusive pathogenic role for DPPX-IgG.

The low-titer P/Q-type VGCC-IgG result was deliberately excluded from the core causal model. P/Q-type VGCC antibodies are pathogenic in established Lambert-Eaton myasthenic syndrome, but low-titer positivity outside a compatible electrophysiological phenotype has limited specificity [18–20]. Overall, this case supports a hypothesis-generating DPPX-associated CNS-PNS hyperexcitability continuum with acquired neuromyotonia as the dominant peripheral manifestation. Confirmation requires additional

cases, longitudinal antibody-electrophysiology correlation, and functional studies directly testing DPPX-IgG effects on peripheral nerve excitability.

Table 2
Published anti-DPPX-associated cases with documented peripheral nervous system abnormalities or neuromyotonia

Study	DPPX serology / context	Peripheral phenotype	Neurophysiology	Interpretation
Stoeck et al., 2015 [14]	DPPX-Ab-positive autoimmune encephalitis	Demyelinating sensorimotor polyneuropathy	Nerve-conduction studies documented demyelinating sensorimotor polyneuropathy	Objective PNS involvement; direct DPPX-mediated peripheral pathogenicity not established
Bjerknes et al., 2022 [15]	High-titer DPPX-IgG in serum (10^6) and CSF (10^3)	Severe extremity pain/allodynia with peripheral neurophysiological abnormalities	EMG: active denervation; NCS: slight axonal and demyelinating motor and sensory changes; abnormalities normalized after immunotherapy	Strong prior evidence that objective PNS abnormalities can accompany anti-DPPX disease
Gao et al., 2024, patient 11 [10]	CSF DPPX 1:32 plus CASPR2 1:10	Neuromyotonia with hallucinations and gastrointestinal symptoms	Cohort report; detailed EMG parameters not provided	Relevant CNS-PNS overlap, but coexisting CASPR2 confounds attribution of neuromyotonia to DPPX
Present case	Serum DPPX-IgG 1:10 by CBA; CSF negative; repeat serum negative at 3 months; CASPR2/LGI1 negative; VGKC-complex negative twice	Long-standing peripheral-predominant acquired neuromyotonia/PNH with twitching, hyperhidrosis, pain, weakness, areflexia and foot drop; CNS hyperexcitability features also present	EMG-confirmed PNH with fasciculation potentials and triplet discharges; bilateral tibial F-wave phenomena; low-frequency RNS decrement	Potential DPPX-associated CNS-PNS hyperexcitability overlap; direct peripheral DPPX pathogenicity remains unproven

Patient perspective

The patient reported that lower-limb weakness, persistent twitching, gluteal pain, and difficulty squatting substantially affected daily mobility. After immunotherapy adjustment, weakness, proximal twitching, and tongue fasciculations improved, while gluteal pain and squatting difficulty remained the main residual limitations.

Abbreviations

AChR
acetylcholine receptor
AMPAR
alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CASPR2
contactin-associated protein-like 2
CBA
cell-based assay
CIDP
chronic inflammatory demyelinating polyradiculoneuropathy
CNS
central nervous system
CSF
cerebrospinal fluid
DPPX/DPP6
dipeptidyl-peptidase-like protein-6
EMG
electromyography
GABABR
gamma-aminobutyric acid type B receptor
LGI1
leucine-rich glioma-inactivated 1
LEMS
Lambert-Eaton myasthenic syndrome
MMF
mycophenolate mofetil
MRI
magnetic resonance imaging
NCS
nerve conduction study
NMDAR
N-methyl-D-aspartate receptor
PNH
peripheral nerve hyperexcitability
PNS
peripheral nervous system
RNS
repetitive nerve stimulation

VGCC
voltage-gated calcium channel
VGKC
voltage-gated potassium channel.

Declarations

Ethics approval and consent to participate

Not applicable for this single de-identified case report.

Consent for publication

Written informed consent for publication of the clinical details and accompanying images was obtained from the patient.

Availability of data and materials

The data supporting the conclusions of this article are included within the article. Additional de-identified clinical data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XW and JS drafted the initial manuscript. JC, YW, and YD collected and interpreted clinical, electrophysiological, imaging, and antibody data. YW supervised the clinical interpretation and manuscript revision. All authors read and approved the final manuscript.

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Reporting guidelines

This case report was prepared in accordance with the CARE guidelines. A completed CARE checklist is provided as an additional file.

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Figures

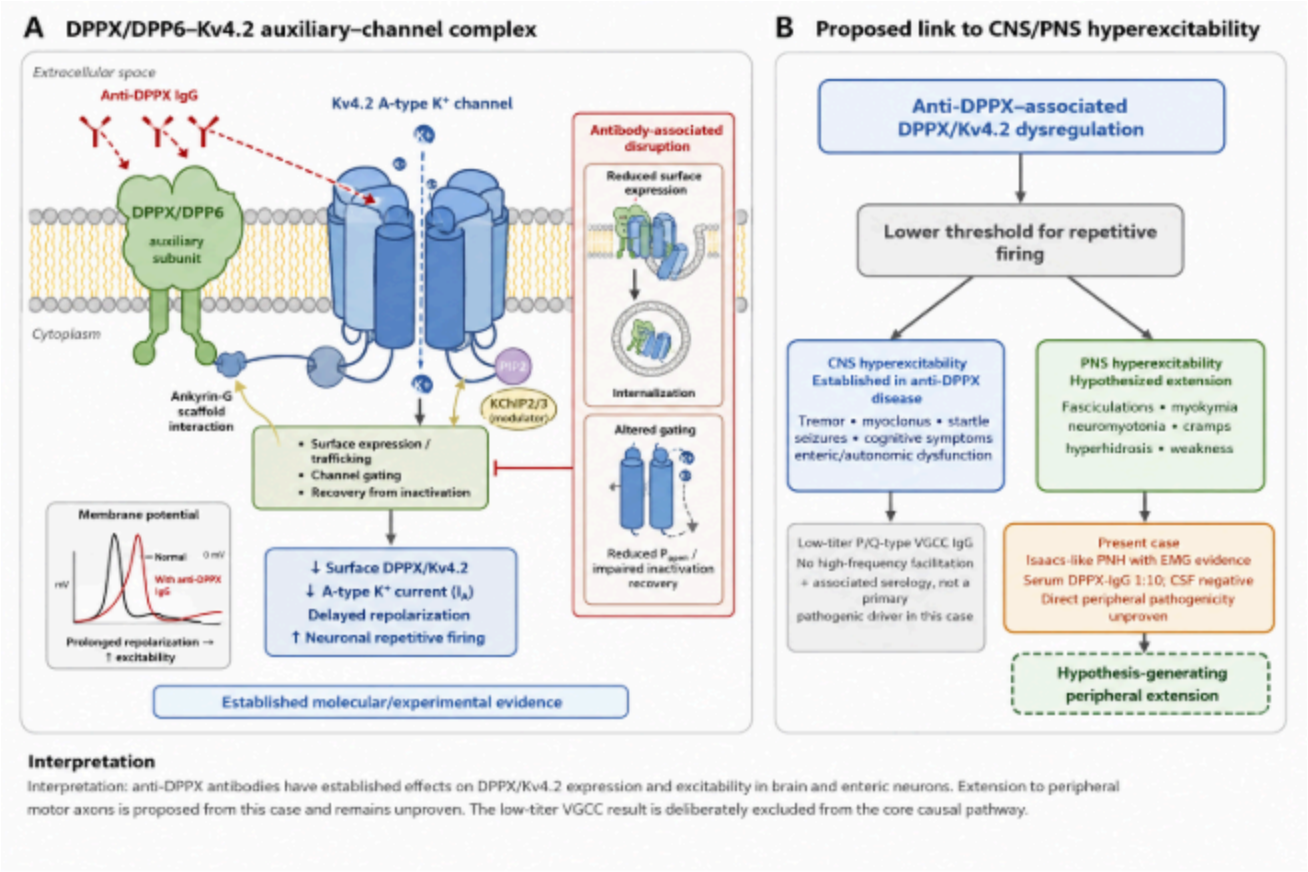


Figure 1

Proposed mechanistic model of anti-DPPX-associated CNS/PNS hyperexcitability. (A) DPPX/DPP6 is an auxiliary subunit of Kv4.2-related A-type K+ channels and modulates surface expression, trafficking, gating, and recovery from inactivation. Anti-DPPX IgG may reduce surface DPPX/Kv4.2 and A-type K+ current, delay repolarization, and increase repetitive neuronal firing [5-11]. (B) This excitability disturbance is established in central and enteric anti-DPPX disease and is hypothesized here to extend to peripheral motor axons, potentially contributing to acquired neuromyotonia. Low-titer P/Q-type VGCC-IgG is shown as associated serology only because the electrophysiological pattern did not support classical LEMS. Direct peripheral pathogenicity remains unproven.

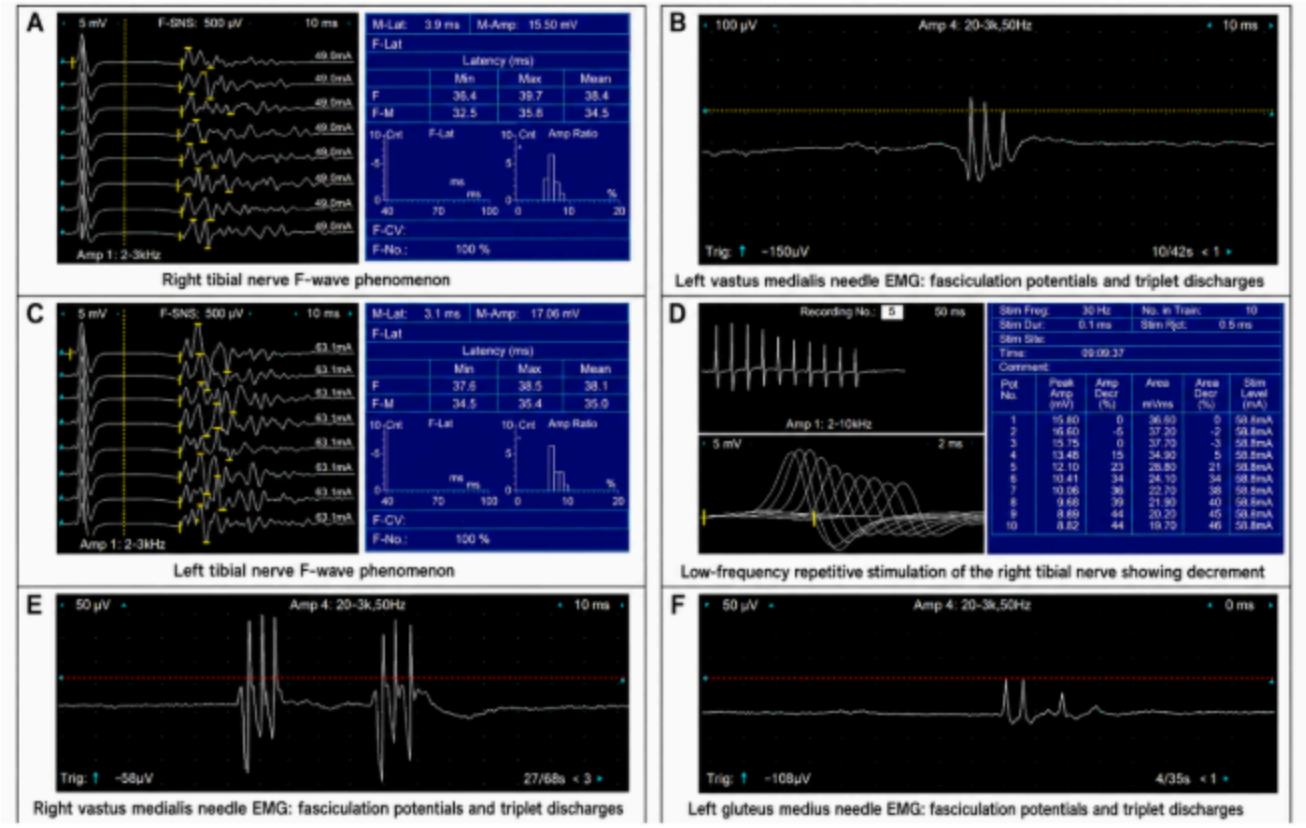


Figure 2

Electrophysiological findings. (A, C) Right and left tibial nerve F-wave phenomena. (B, E) Needle EMG of the left and right vastus medialis showing fasciculation potentials and triplet discharges. (F) Needle EMG of the left gluteus medius showing fasciculation potentials and triplet discharges. (D) Low-frequency repetitive stimulation of the right tibial nerve showing a decremental response. Together, these findings support a peripheral nerve hyperexcitability phenotype.

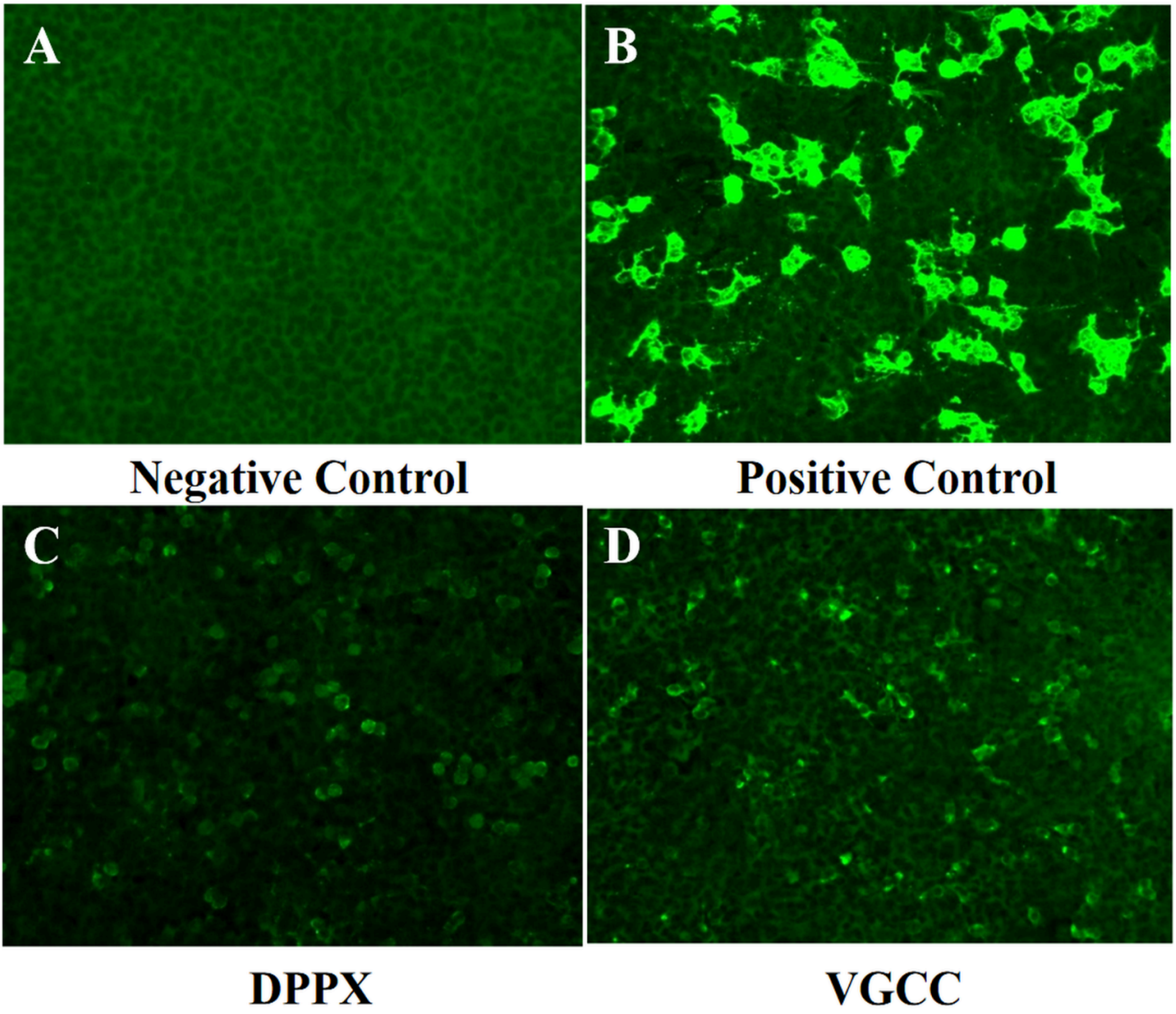


Figure 3

Cell-based antibody assays. (A) Negative control. (B) Positive control. (C) Patient serum DPPX-IgG positivity at 1:10. (D) Low-titer P/Q-type VGCC-IgG positivity at 1:10. Repeat serum DPPX-IgG by CBA was negative at 3 months; VGCC-IgG was interpreted as associated serology rather than diagnostic evidence of LEMS.

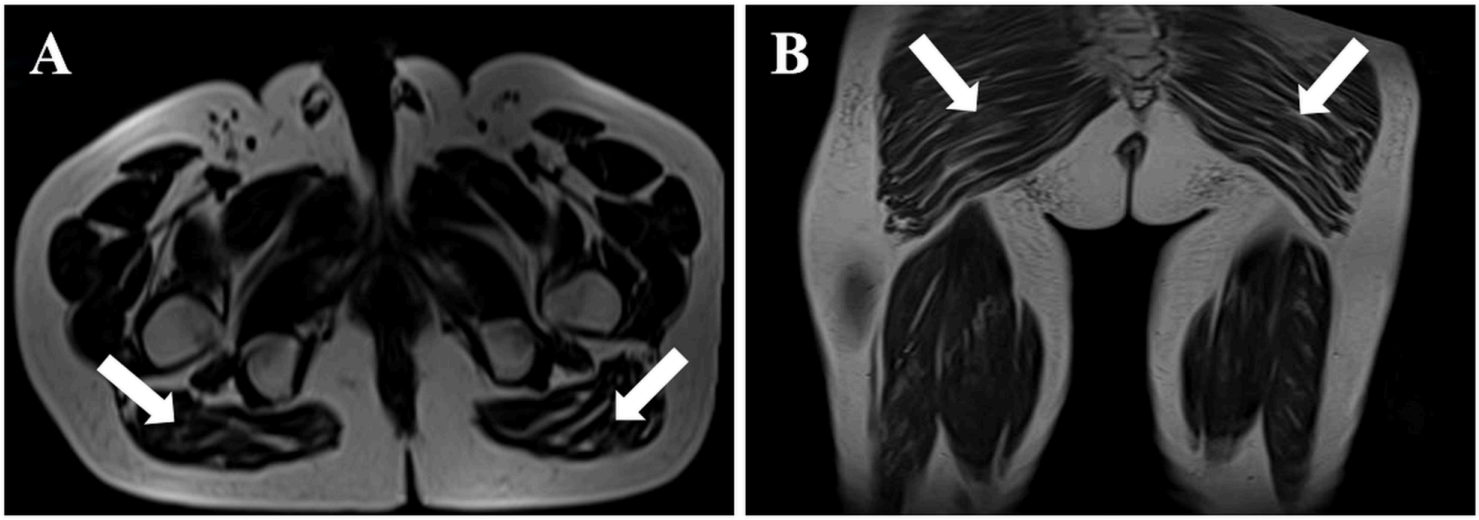


Figure 4

Pelvic MRI showing bilateral gluteal muscle atrophy with abnormal signal (arrows). The mechanism remains uncertain and may include chronic denervation, disuse, or prolonged abnormal motor-unit activity.