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Letter to the Editor: New Observation

Double trouble: Kennedy Disease and Immune-Mediated Necrotizing Myopathy in a Cree Male

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Genetic neuromuscular disease co-existing with another genetic or acquired neuromuscular disorder in the same individual, termed "double trouble," is uncommon and often presents a diagnostic conundrum.[1] Thorough phenotyping across the neuromuscular clinical and laboratory evaluation is required in atypical neuromuscular disease presentations to ensure co-existing disorders are not overlooked.

Spinal-bulbar muscular atrophy (SBMA), or Kennedy disease, is an X-linked recessive, rare neuromuscular disorder caused by a CAG trinucleotide repeat expansion in the androgen receptor gene.[2–5] The prevalence of SBMA is estimated at 1–2 per 100,000, however, the true prevalence may be underestimated due to under-recognition and the founder effect that the condition exhibits.[2,5] SBMA primarily affects motor neurons, although co-existing sensory neuronopathy is well-recognized.[5] Typical clinical manifestations include bulbar and proximal-predominant limb weakness, prominent perioral fasciculations, areflexia, sensory neuronopathy, creatine kinase (CK) elevation, and androgen insensitivity.[2–5]

Immune-mediated necrotizing myopathy (IMNM) is an acquired inflammatory myopathy sub-categorized by the European Neuromuscular Centre based on the presence of autoantibodies targeting hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) or signal recognition particle, or, if seronegative, occurs in the presence of typical myopathological features of muscle fiber necrosis and regeneration with minimal to no inflammatory infiltrate.[6,7] IMNM accounts for approximately 35% of idiopathic inflammatory myopathies with an estimated global prevalence of 2.4–33.8 per 100,000.[6] The typical clinical presentation is subacute onset of progressive, proximal-predominant weakness with or without bulbar weakness, and significantly elevated CK.[6,7]

Herein, we report a patient presenting with two simultaneous neuromuscular diagnoses, anti-HMGCR IMNM superimposed on undiagnosed SBMA. We highlight the importance of careful characterization of clinical history and examination findings, consideration of local epidemiology relevant to Canadian neuromuscular practice, and correlation of clinical-electrophysiological findings with myopathological and genetic testing results for accurate diagnosis, with treatment implications.

A 72-year-old Indigenous Cree male with dyslipidemia on atorvastatin presented with 8 months of subacute onset, progressive, severe limb weakness, and oropharyngeal dysphagia. He had background history of years of slowly progressive proximal-predominant limb weakness, atrophy, fasciculations, and dysphagia for which he did not seek medical attention. There was no known familial neuromuscular disease.

Neurological examination demonstrated tongue atrophy and fasciculations, perioral fasciculations, bifacial weakness, and flaccid dysarthria. There was atrophy and fasciculations of deltoids and quadriceps, neck flexor weakness (Medical Research Council [MRC] grade 4/5), and proximal, symmetric upper and lower limb weakness (MRC grade 2/5). He had areflexia, flexor plantar responses, and length-dependent large and small fiber sensory loss.

CK was persistently elevated over the preceding 3 months, peaking at 2624 U/L (normal < 250 U/L). Nerve conduction studies demonstrated a length-dependent sensory axonal polyneuropathy. EMG was consistent with a chronic diffuse disorder of lower motor neurons, with a superimposed proximal and axial myopathy with fibrillation potentials and myotonic discharges (Table 1).

With the patient's history of a chronic, progressive lower motor neuron syndrome with examination features suspicious for SBMA, and known high prevalence of SBMA in Indigenous Cree populations,[2] genetic testing was performed, revealing a pathogenic expansion of 40 CAG repeats in the androgen receptor gene, diagnostic of SBMA. The atypical subacute progression of severe weakness, with superimposed myopathic changes and myotonia on EMG, markedly elevated CK, and statin exposure, suggested comorbid anti-HMGCR IMNM. Muscle biopsy findings were consistent with IMNM (Fig. 1). Anti-HMGCR antibodies were positive (Mitogen Labs, Calgary; titer 108.4 CU, normal < 20 CU). CT chest, abdomen, and pelvis were negative for associated malignancy.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1: Summary of needle EMG findings

Muscle	Insertional activity	Spontaneous activity	Voluntary MUP activity
L Genioglossus	Increased	*Fibrillations/PSW:* 1+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Mentalis	Increased	*Fibrillations/PSW:* 2+ *Fasciculations:* 1+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Thoracic paraspinals (T6)	Increased	*Fibrillations/PSW:* 2+	Mixed long duration, high amplitude MUPs and short duration, low amplitude polyphasic MUPs firing with early recruitment
L Deltoid	Increased	*Fibrillations/PSW:* 2+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Biceps	Increased	*Fibrillations/PSW:* 3+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Triceps	Increased	*Fibrillations/PSW:* 3+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L First dorsal interosseous	Increased	*Fibrillations/PSW:* 2+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Vastus lateralis	Increased	*Fibrillations/PSW:* 3+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Tibialis anterior	Increased	*Fibrillations/PSW:* 3+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment
L Gastrocnemius (lateral head)	Increased	*Fibrillations/PSW:* 3+ Myotonic discharges	Long duration, high amplitude MUPs firing with reduced recruitment

L = left; MUPs = motor unit potentials; PSW = positive sharp waves.

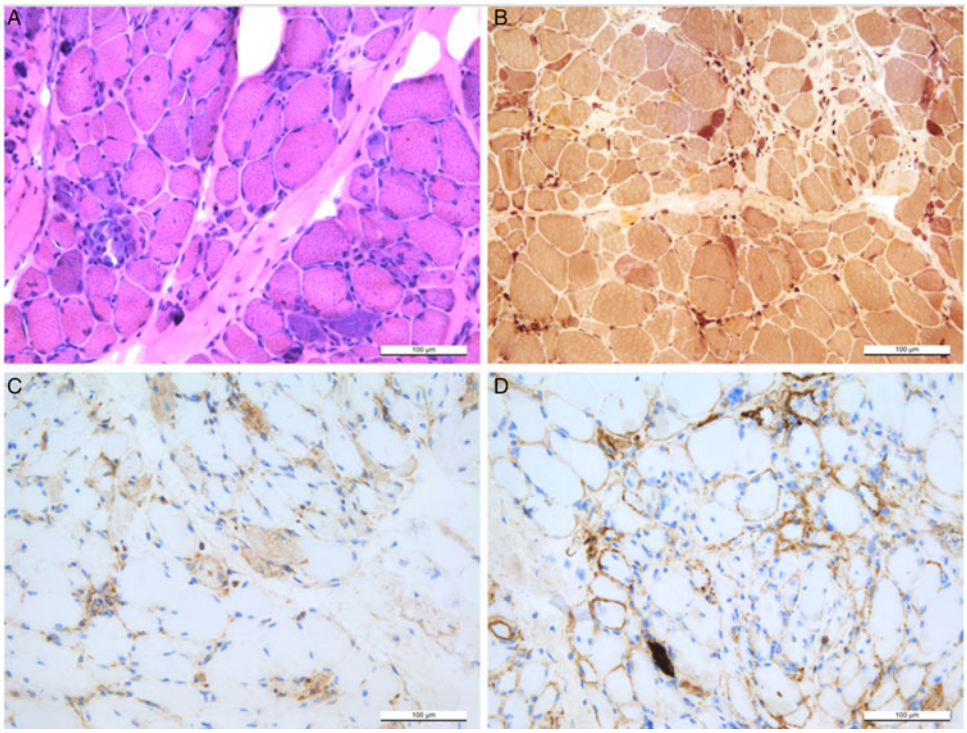

Figure 1: Right biceps brachii myopathological findings. Hematoxylin and eosin-stained section (A) demonstrates muscle fiber size variability, mildly increased internalized nuclei, scattered atrophic fibers and pyknotic nuclear clumps, necrotic and regenerating fibers, and increased endomysial fibrous connective tissue, in keeping with an active and chronic myopathy with associated denervation. The atrophic fibers are of either histochemical fiber type and overreact for nonspecific esterase (B), in keeping with denervation atrophy. Scattered necrotic and non-necrotic fibers demonstrate sarcolemmal positivity of MHC-I (C) and C5b-9 (membrane attack complex, D) in keeping with an immune-mediated myopathy.

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He underwent treatment for IMNM with methylprednisolone 1g IV daily for 5 days and intravenous immunoglobulin (IVIG) 2g/kg over 5 days, followed by maintenance IVIG 1g/kg monthly and prednisone 60 mg daily with a taper. CK normalized within 3 weeks. At 6-month follow-up, he was ambulating independently with residual mild weakness secondary to SBMA.

This patient, diagnosed concurrently with SBMA and anti-HMGCR IMNM, highlights important considerations when evaluating suspected neuromuscular double trouble.

First, consideration of local epidemiological factors and disease prevalence rates in specific patient populations can expedite appropriate genetic testing. This is relevant here, given the patient is of Cree First Nations ancestry, which is associated with highly increased prevalence of SBMA (14.7 per 100,000) due to a founder effect,[2] compared to the generally estimated prevalence of 1–2 per 100,000.[3] The increased prevalence seen in Western Canadian Indigenous communities is likely still underestimated, however, owing to the relative preservation of functional independence in SBMA[2,3] and thus, patient under-recognition of symptoms, unless there is a concomitant, more severe disease process, as in this case. Additionally, longstanding social barriers to accessing the health-care system within this population suggest that many patients may not have access to or present to specialty neuromuscular clinics.[2]

Second, awareness of the natural history and expected progression of the underlying genetic neuromuscular disorder helps prevent premature diagnostic closure and here, facilitated recognition of a disease course atypical for SBMA. While bulbar and proximal-predominant weakness occurs in SBMA,[2–5] this is slowly progressive and patients often remain functionally independent for most activities of daily living.[3] Therefore, the subacute, progressive, and severe weakness prompted evaluation for comorbid diagnoses including IMNM.

Identification of atypical laboratory and electrodiagnostic features for SBMA further assisted recognition of superimposed IMNM. The degree of CK elevation (peak 2624 U/L), while rarely observed in SBMA, was greater than the mean CK (939 ± 590 U/L) reported amongst patients with a mean disease duration of 8 years.[4] Decline in CK and improvement in strength after immunotherapy supported CK elevation being predominantly referable to IMNM than SBMA alone. EMG was key to identifying a myopathic process superimposed upon chronic neurogenic changes and reiterated the importance, in this clinical context, of recognizing associated myotonic discharges, which are validated as a diagnostic feature and biomarker of treatment response in IMNM.[8]

Lastly, the patient's myopathological findings further supported dual pathology, owing to the presence of an active immune-mediated myopathy with sarcolemmal positivity of MHC-I and C5b-9 on both necrotic and non-necrotic fibers, consistent with IMNM, and denervation atrophy likely referable to SBMA.

Most importantly, identification of double trouble can positively impact patient outcomes. Anti-HMGCR IMNM is treatable with immunotherapy[6,7] as demonstrated by our patient's significant improvement, while no disease-modifying therapy exists for SBMA.[2–5]

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Competing interests. None.

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