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Expanding the Phenotypic Spectrum of Vocal Cord and Pharyngeal Weakness With Distal Myopathy due to the p.S85C MATR3 Mutation

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Abstract

Objectives

The c.254C>G (p.S85C) *MATR3* variant causes vocal cord and pharyngeal weakness with distal myopathy (VCPDM), which is characterized by progressive, asymmetric, predominantly distal muscle weakness, dysphonia, dysphagia, and respiratory impairment. Herein, we describe an Italian patient who harbored the p.S85C MATR3 variant and showed a composite phenotype of VCPDM and sensorimotor polyneuropathy.

Methods

The proband underwent neurologic evaluation, muscular MRI of the lower limbs, neurophysiologic assessment, muscle biopsy, and spirometry. After excluding common acquired and genetic causes of sensorimotor polyneuropathy, a larger group of genes involved in inherited forms of neuropathy, distal myopathy, and motor neuron disorders were analyzed by next-generation sequencing targeted panels.

Results

The patient, affected by progressive distal muscle weakness and hypotrophy, myalgias, dysphonia, dysphagia, respiratory impairment, and sensory abnormalities, harbored the heterozygous c.254C>G (p.S85C) *MATR3* substitution. Neurophysiologic assessment revealed a severe sensorimotor polyneuropathy. Variation of fiber size, central nuclei, and nonrimmed vacuoles were evident at muscle biopsy.

Discussion

This finding extends the *MATR3*-associated VCPDM phenotypic spectrum and suggests considering *MATR3* analysis in suspected congenital polyneuropathies with odd features, including dysphonia, dysphagia, and respiratory insufficiency.

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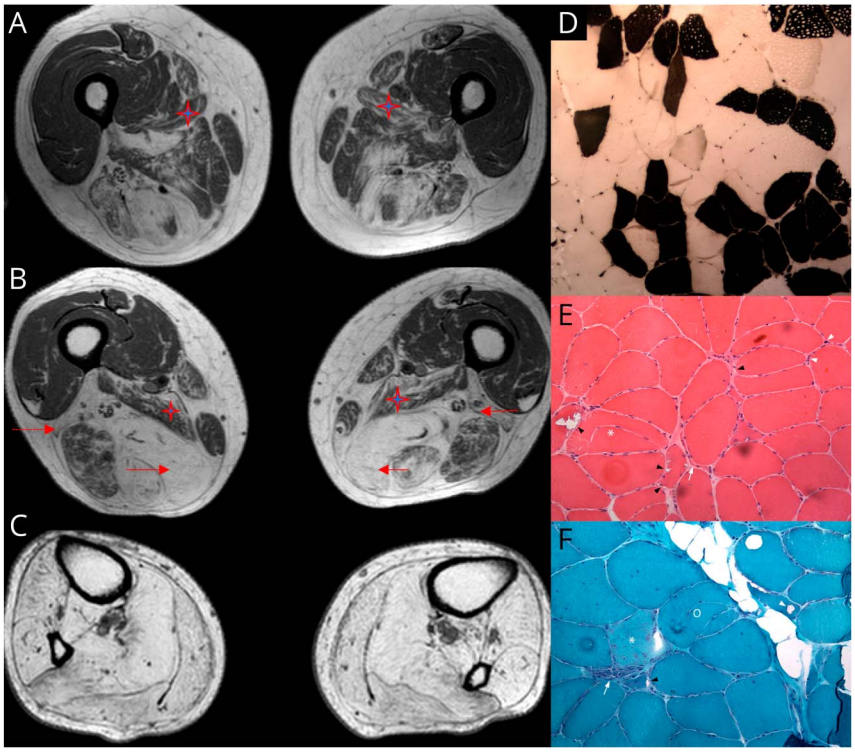
Figure 1 Turbo Spin Echo Axial T1 MRIs From the Thigh (A and B) to the Leg (C), Showing a Remarkable Fatty Degeneration of Muscles, With a Distoproximal Gradient: At the Leg Level, All Muscle Lodges Are Involved, With a Complete Fatty Infiltration Associated With a Less Severe Atrophy



Turbo Spin Echo (TSE) axial T1 MRI images from thigh (A–B) to leg (C), showing a remarkable fatty degeneration of muscles, with a disto-proximal gradient: at leg level all muscle lodges are involved, with a complete fatty infiltration associated with a less severe atrophy. At thigh level there is a selective degeneration of mesial and posterior muscle lodges, in particular semimembranous (red arrow) and biceps femoris short head muscle (dotted red arrow), with a symmetrical pattern. Atrophy and fatty degeneration also of adductor longus (dotted red star) and magnus (red star) and sartorius, with a relative spare of quadriceps, except for rectus femoris, mildly atrophic and infiltrated. (D) ATPase pH 4.3 (magnification: 200x) shows normal sized fibers with fiber type grouping and two hypotrophic angulated fibers (arrows). (E) Hematoxylin and eosin (magnification: 200x) stain showing subsarcolemmal cytoplasmic vacuoles (black arrowheads), small angulated fiber (arrows), splitting fiber (asterisk), small nuclear clumps (white arrowheads). (F) Gomori trichrome stain (magnification: 200x) showing pale degenerating fiber (asterisk) and myophagocytosis (arrow), muscle fiber splitting (circle), subsarcolemmal (black arrowhead) and cytoplasmic vacuoles containing amorphous material (white arrowhead).

Vocal cord and pharyngeal weakness with distal myopathy (VCPDM), due to the c.254C>G, p.S85C *MATR3* variant, is characterized by progressive, asymmetric, predominantly distal muscle weakness, dysphonia, dysphagia, respiratory impairment, and myalgias.[1-7] Although the Achilles deep tendon reflexes (DTRs) are absent, the others can show a slight or brisk response.[2,4] Creatine phosphokinase (CPK) levels are normal to mildly elevated.[1-5] At MRI, the soleus, gastrocnemius, and tibialis anterior and posterior are severely affected, with relative sparing of the quadriceps.[2,4,5] Both needle examination and muscle biopsy mainly show myopathic alterations, with predominant involvement of distal muscles.[1-6] Electron microscopy reveals indentations and segmentation of skeletal muscle and satellite cells' nuclei,[2] small tubular aggregates close to the triads,[1] and autophagic vacuoles in degenerative myofibers.[3,4,6] Previously reported cases are summarized in eTable 1 (links.lww.com/NXG/A534). Herein, we report an Italian patient harboring the p.S85C MATR3 missense change, showing a composite phenotype of VCPDM and sensorimotor polyneuropathy.

Ethics Statement

The Comitato Etico Milano Area 2 Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy) approved the study. Written informed consent was obtained from the patient.

The proband is a 70-year-old man of Italian origin born to nonconsanguineous, asymptomatic parents. The father died at age 65 years of ischemic stroke. The mother died in childbirth at age 33 years together with the proband's brother. His 67-year-old sister is asymptomatic, and he has only 1 adopted son. The complete family pedigree is represented in eFigure 1 (links.lww.com/NXG/A534). At age 40 years, the proband began complaining of myalgias at thighs. In the following years, he developed gait disturbances with recurrent falls, wrist drop, variably flexed fingers, hypophonia, swallowing difficulties, and exertional dyspnea; spirometry performed at 63 years showed a reduced peak expiratory flow rate (PEFR 79%), reduced forced expiratory volume (FEV1) (1.8 L), and forced vital capacity (FVC) (2.2 L), with a preserved FEV1/FVC ratio. Clinical examination revealed marked bilateral muscle weakness, more pronounced distally. DTRs were absent, except for the patellar ones. Vibratory sense was gradually reduced from the knee to the first metatarsal heads. Proprioception was lost at the metatarsophalangeal joint of the great toe. The patient complained of paresthesias bilaterally in feet and ankles. Ambulation was possible only with unilateral support. CPK levels were mildly elevated (274 U/L, normal values 25–200). At 46 years, a gastrocnemius biopsy revealed mixed neurogenic and myopathic changes (Figure 1, D–F). Muscle MRI, performed at 70 years, demonstrated remarkable fatty degeneration and atrophy of muscles, with a distoproximal gradient (Figure 1,

Table 1 Neurophysiologic Findings, Revealing Reduced Conduction Velocities and Low Amplitudes of Bilateral Median and Ulnar Sensory Nerve Action Potentials (SNAPs); Absent Sural SNAPs; Increased Latency and Low Amplitude of the Right Ulnar Compound Muscle Action Potential (CMAP) and of the Left Median CMAP; Low Amplitude of the Right Median CMAP; Reduced Conduction Velocity of the Left Ulnar CMAP; Reduced Nerve Conduction Velocities and Low Amplitudes of Bilateral Tibial CMAPs; Absent CMAPs of Bilateral Peroneal Nerves

Nerve	Stim site	Rec site	Latency	Peak Ampl	Distance	Velocity
Sensory NCS						
R Median						
	Index finger	Wrist	**3.4 ms** (≤2.3)	**3.1 μV** (≥50.0)	15.5 cm	**45.8 m/s** (≥56.0)
L Median						
	Index finger	Wrist	**3.3 ms** (≤2.3)	**2.7 μV** (≥50.0)	16.0 cm	**48.8 m/s** (≥56.0)
R Ulnar						
	Wrist	Little finger	**3.3 ms** (≤3.1)	**1.6 μV** (≥17.0)	15.0 cm	**45.0 m/s** (≥50.0)
L Ulnar						
	Wrist	Little finger	**3.3 ms** (≤3.1)	**1.4 μV** (≥17.0)	13.0 cm	**39.6 m/s** (≥50.0)
Motor NCS						
R Median						
	Wrist	APB	4.3 ms (≤4.4)	**3.3 mV** (≥4.0)		
	Antecubital fossa	APB	9.5 ms	3.0 mV	25.5 cm	49.0 m/s (≥49.0)
L Median						
	Wrist	APB	**5.2 ms** (≤4.4)	**2.7 mV** (≥4.0)		
	Elbow	APB	10.7 ms	2.4 mV	27.0 cm	49.4 m/s (≥49.0)
R Ulnar						
	Wrist	ADM	**3.9 ms** (≤3.3)	**4.8 mV** (≥6.0)		
	Below elbow	ADM	7.3 ms	5.4 mV	23.0 cm	67.9 m/s (≥49.0)
	Above elbow	ADM	9.3 ms	6.3 mV	11.0 cm	55.6 m/s (≥49.0)
L Ulnar						
	Wrist	ADM	3.3 ms (≤3.3)	11.1 mV (≥6.0)		
	Below elbow	ADM	8.07 ms	9.2 mV	25.5 cm	53.2 m/s (≥49.0)
	Above elbow	ADM	10.3 ms	8.4 mV	9.0 cm	**41.1 m/s** (≥49.0)
R Tibial						
	Ankle	AHB	**6.3 ms** (≤5.8)	**0.2 mV** (≥4.0)		
	Popliteal fossa	AHB	19.4 ms	0.1 mV (≥4.0)	45.5 cm	**34.5 m/s** (≥41.0)
L Tibial						
	Ankle	AHB	5.6 ms (≤5.8)	**0.2 mV** (≥4.0)		
	Popliteal fossa	AHB	17.6 ms	0.2 mV (≥4.0)	43.5 cm	**36.3 m/s** (≥41.0)

Abbreviations: ADM = abductor digiti minimi; AH = abductor hallucis brevis; Ampl = amplitude; APB = abductor pollicis brevis; L = left; NCS = nerve conduction study; R = right; Rec = recording; Stim = stimulation.
Abnormal values are in bold; for each variable, normal values are reported in brackets.

A–C). The results of the last nerve conduction study, performed at 63, were consistent with a severe sensorimotor polyneuropathy (Table 1). Needle examination findings are reported in Table 2. Common genetic (*PMP22*, *MFN2*, *MPZ*, *GJB1*, *NEFL*, *GDAP1*, *TRPV4*, and *HSP22/27*) and acquired (diabetes; alcohol consumption; medications; malnutrition;

Table 2 EMG Summary Table

	Spontaneous					MUAP			Recruitment
	IA fibers	F	PSW	Fasc	HFD	Amp	Dur	PPP	Pattern
Right TA	N	None	None	None	None	N	N	N	No activity
Right GA (Med)	N	None	None	None	None	N	N	N	No activity
Right VL	N	+	+	None	None	+	+	N	Reduced
Left TA	N	None	None	None	None	N	N	N	No activity
Left GA (Med)	N	None	None	None	None	N	N	N	No activity
Left VL	N	None	None	None	None	+	+	+	Reduced
Right FDI	N	+	+	None	None	+	+	+	Reduced
Right ECU	N	+	++	None	+	+	N	N	Single oscillations
Right BB	N	None	None	None	None	+	+	+	Reduced

Abbreviations: Amp = amplitude; BB = biceps brachii; dur = duration; ECU = extensor carpi ulnaris; F = fibrillation potentials; Fasc = fasciculations; FDI = first dorsalis interosseus; GA = gastrocnemius; HFD = high-frequency discharges; Med = medialis; MUAP = motor unit action potential; N = normal; PPP = polyphasic potentials; PSW = positive sharp waves; TA = tibialis anterior; VL = vastus lateralis.
EMG summary table, showing the absence of voluntary activation of distal muscles of lower limbs, and bilateral severe signs of chronic denervation in proximal lower and upper limbs, with active denervation in the bilateral vastus lateralis, right first dorsal interosseous, and right extensor carpi ulnaris.

deficiency of copper and vitamins B12 and E; and monoclonal gammopathy) causes of sensorimotor polyneuropathy were excluded. A targeted next-generation sequencing panel addressing genetic forms of distal myopathy revealed the heterozygous c.254C>G, p.S85C *MATR3* variant (NM_199189), which was absent in the asymptomatic sister (eFigure 2). DNA from other relatives was not available. We also investigated a large group of genes involved in inherited forms of neuropathy and motor neuron disorders without detecting any additional suspicious variant in the proband (eTable 2).

In addition to typical VCPDM features (progressive, mainly distal muscle weakness; distal forearms, hands, and distal legs hypotrophy; dysphonia and dysphagia; and moderate respiratory impairment),[1-6] our patient showed sensory abnormalities, and, intriguingly, neurophysiologic studies and muscle biopsy pointed toward a mixed neuropathic and myopathic process. The presence of a composite phenotype, made of both myopathic and neuropathic alterations, has been previously noticed in 2 Asian patients with VCPDM and sensorimotor polyneuropathy.[4] However, the neuropathic abnormalities described were milder compared with those of our patient. Furthermore, the sensory symptoms developed by the 3 patients were markedly different. The first patient showed impairment of exteroceptive sensations and sparing of vibration and position senses, whereas our proband displayed altered proprioception, accompanied by bilateral paresthesias in feet and ankles. On the other hand, touch, pinprick, vibration, and position sensations were conserved in the second case described and only dysesthesia in the toe tips was described.

Although we cannot exclude the possibility of a double-trouble in the absence of additional unrelated patients with a similar phenotype, the clinical features and the exclusion of other acquired and genetic causes of neuropathy is strongly suggestive for VCPDM. Therefore, our case apparently confirms the clinical, neurophysiologic, and histologic variability of VCPDM and suggests considering *MATR3* analysis in the differential diagnosis of suspected congenital polyneuropathy with odd characteristics, including dysphonia, dysphagia, and respiratory insufficiency.

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Disclosure

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