A case of hereditary demyelination with conduction blocks in a 13-year old

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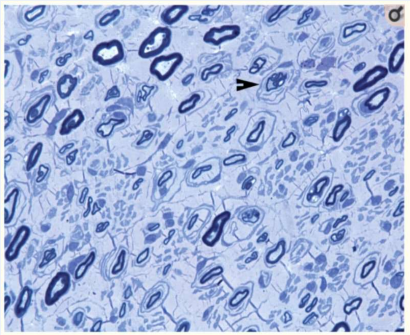
Objective

We describe a case of a rare variant of Charcot-Marie-Tooth (CMT4J) with acquired demyelinating features on electrodiagnosis (EDx), that poses a diagnostic challenge to the neurophysiologist.

Case

A 33 year old patient presenting to clinic reported high arched feet first noticed at the age of 13, with subsequent progressive symmetric distal weakness.
Neurologic examination revealed distal weakness, high arched feet with hammer toes, diffuse areflexia, sensory loss in a glove-stocking distribution, with a high-steppage gait.
NCS revealed non-uniform slowing of nerves with partial motor conduction blocks at compressible, as well as non-compressible sites. Needle EMG examination showed a distal > proximal length-dependent pattern of chronic neurogenic units.
Invitae comprehensive neuropathy panel was performed that revealed homozygous pathogenic variant in FIG4.



Zhang X et al. *Brain*. 2008;131(Pt 8):1990-2001

Loss of myelinated nerve fibres in sural biopsy of a patient with CMT4J. A semithin section with toluidine blue staining was performed on the sural nerve biopsy of the patient 2. The number of myelinated nerve fibres is severely reduced, and there is a large amount of collagen in the extracellular matrix. Arrowhead: onion bulbs and thinly myelinated nerve fibres.

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Lat ms	Peak Lat ms	Amp µV	Segment	Dist mm	CV m/s
Median.R to Digit II (index finger).R						
Wrist	3.5	4.1	13	Wrist-Digit II (index finger)	130	37
Ulnar.R to Digit V (little finger).R						
Wrist	3.1	4.1	16	Digit V (little finger)-Wrist	110	35
Radial.R to Anatomical snuff box.R						
Forearm	3.0	3.6	6	Anatomical snuff box-Forearm	100	33
Sural.R to Ankle.R						
Lower leg	NR	NR	NR	Ankle-Lower leg	140	

Motor Nerve Conduction:

Nerve and Site	Lat ms	Amp mV	Segment	Dist mm	Lat Diff ms	CV m/s
Median.R to Abductor pollicis brevis (C8-T1).R						
Wrist	6.4	12.0	Abductor pollicis brevis (C8-T1)-Wrist	70	6.4	
Elbow	20.1	6.1	Wrist-Elbow	280	13.7	20
Ulnar.R to Abductor digiti minimi m. (C8-T1).R						
Wrist	6.6	7.5	Abductor digiti minimi m. (C8-T1)-Wrist	70	6.6	
Below elbow	17.6	5.2	Wrist-Below elbow	240	11.0	22
Above elbow	26.1	3.0	Below elbow-Above elbow	100	8.5	12
Median Wrist	NR	NR	Above elbow-Median Wrist			
Median Elbow	NR	NR	Median Wrist-Median Elbow	100		
Peroneal.R to Extensor digitorum brevis (L4-S1).R						
Ankle	NR	NR	Extensor digitorum brevis (L4-S1)-Ankle	90		
Fibula (head)	NR	NR	Ankle-Fibula (head)			
Tibial.R to Abductor hallucis (S1-S2).R						
Ankle	NR	NR	Abductor hallucis (S1-S2)-Ankle	90		
Peroneal.R to Tibialis anterior (L4-L5).R						
Fibula (head)	12.1	1.1	Tibialis anterior (L4-L5)-Fibula (head)		12.1	
Popliteal fossa	16.6	0.5	Fibula (head)-Popliteal fossa	95	4.5	21

Needle EMG Examination:

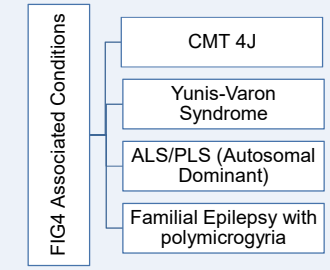
Muscle	Insertion Activity	Spontaneous Activity Fibs	PSW	Fasc	Other	Volitional MUAPs Poly	Amp	Dur	Rate	Pattern	Effort
Tibialis anterior (L4-L5).R	Normal	0	0	0		Few	Incr	Incr	Incr	Reduced	Normal
Gastrocnemius (Medial head) (S1-S2).R	Increased	1+	0	0	CRD	Few	Incr	Incr	Incr	Reduced	Normal
Vastus lateralis (L2-L4).R	Normal	0	0	0		None	Normal	SI Incr	Normal	Min Red	Normal
1st dorsal interosseous (C7-T1).R	Normal	0	0	0		Few	SI Incr	SI Incr	Normal	Min Red	Normal

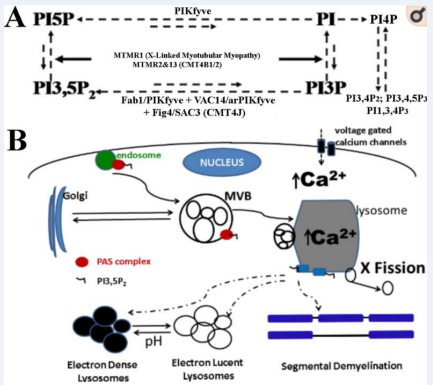
Test Performed
Sequence analysis and deletion/duplication testing of the 72 genes listed in the results section below.
- Invitae Comprehensive Neuropathies Panel

Reason for Testing

Summary

Positive result. Homozygous Pathogenic variant identified in FIG4.





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are marked. Their related diseases are shown in parenthesis. Notice that all pathways involved in 4-phosphate are simplified since they are not relevant to this review. B. A hypothetical mechanism in Fig4 deficiency is illustrated.

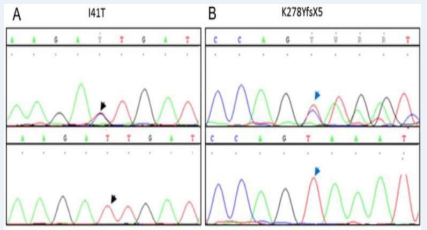

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Fig. 3. Genetics electropherogram. Electropherogram of the I41 I mutation in exon 2 (A-top panel) and K278YfsX5 mutation in exon 8 (B-top panel) of *FIG4* in affected patient and control (bottom panels).

Discussion

CMT4J is a rare variant of CMT with few cases reported in literature so far. It is caused by a mutation of the phosphoinositide phosphatase FIG4 gene in an autosomal recessive pattern. It is characterized by highly variable onset and severity, proximal as well as distal and asymmetric muscle weakness, with a phase of rapid progression. NCS features include nonuniform slowing of conduction velocities, conduction block, and temporal dispersion, resembling those in acquired demyelinating peripheral nerve diseases. EMG may demonstrate denervation in proximal and distal muscles, and frequent progression to severe amyotrophy. FIG4 mutations should be considered in CMT patients especially if found in combination with sporadic or recessive inheritance, childhood onset and a phase of rapid progression.

Conclusion

CMT4J poses a diagnostic challenge with its clinical and EDx features. With wider availability of genetic testing, more cases of CMT4J are expected to be identified, broadening our current knowledge of its clinical features.

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