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Case report

Targeted gene approach with biochemical assay confirms *ABCD1* mutation of X-linked adrenoleukodystrophy in a 62-year-old man with gait imbalance

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Abstract

X-linked adrenoleukodystrophy is a peroxisomal disorder caused by a mutation in *ABCD1* gene. The three main phenotypes of X-linked adrenoleukodystrophy include cerebral adrenoleukodystrophy, adrenomyeloneuropathy, and isolated primary adrenal insufficiency. More than 750 non-recurrent mutations exist throughout the coding region of the *ABCD1* gene. We report a 62-year-old man with a 17-year history of progressive gait imbalance and numb feet. He had noted difficulty rising from a chair for 3 years. Examination revealed proximal lower limb weakness and length-dependent sensory loss with preservation of reflexes and unilateral Babinski sign. Electrodiagnostic evaluation confirmed a length-dependent sensorimotor peripheral neuropathy and proximal myopathy. Family history was remarkable for similar symptoms in 6 siblings. A targeted gene approach for 102 known peripheral neuropathy genes led to discovery of *ABCD1* mutation confirmed by kindred evaluation and biochemical assay. This case highlights the importance of combining targeted gene approaches with functional assay confirmation especially for atypical clinical presentations.

Keywords: Adrenoleukodystrophy; Adrenomyeloneuropathy; Peroxisomal disorders; *ABCD1*; Peripheral neuropathy; Myelopathy.

1. Introduction

X-linked adrenoleukodystrophy (X-ALD) is a progressive genetic disorder due to a mutation in X-linked gene *ABCD1* and is the most common peroxisomal disorder. ACBD1 gene codes for an ATP-binding cassette (ABC) transporter located in the peroxisomal membrane, which is necessary for transport of very-long-chain-fatty-acids (VLCFAs) into the peroxisome [1]. Mutations in *ABCD1* gene therefore lead to cellular accumulation of VLCFAs. The three main phenotypes of X-ALD in males include cerebral ALD presenting with leukodystrophy, adrenomyeloneuropathy (AMN) and isolated primary adrenal insufficiency [1]. Age of onset, phenotype and disease severity can vary within families with the same mutation [1,2]. Adrenomyeloneuropathy is a primary axonopathy affecting adults and typically presents in the 3rd decade with a slowly progressive gait disorder due to spastic paraparesis and sensory ataxia with associated neurogenic bladder dysfunction [1,3]. Primary adrenal insufficiency, that can affect both glucocorticoid and mineralocorticoid function, is reported in 70% of AMN patients at time of presentation [4].

We report a 62-year-old man with an atypical clinical presentation of adrenomyeloneuropathy with family history suggesting a genetic cause. A targeted gene approach for

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Table 1
Nerve conduction studies.

Nerve	Stimulation site	Recording site	Distal latency (ms)		Amplitude[a]		Conduction velocity (m/s)		*F*-wave latency (ms)	
				NL		NL		NL		NL
Sensory										
Median	Wrist	Digit II	3.8	<3.6	17	>15	45	>56		
Ulnar	Wrist	Digit V	3.4	<3.1	16	>10	ND	>54		
Sural	Calf	Ankle	4.9	<4.5	8	>6	38	>40		
Motor										
Ulnar	Wrist/AE	ADM	3.7	<3.6	7.8	>6	41	>51	38.7	<32
Fibular	Ankle/AFH	EDB	6.4	<6.6	2.2	>2	33	>41	ND	<58
Tibial	Ankle/Popliteal fossa	AH	6.0	<6.1	6.9	>4	33	>40	69.9	<58

AE, above elbow; AFH, above fibular head; ADM, adductor digiti minimi; AH, abductor hallucis; EDB, extensor digitorum brevis; NL, normal; ND, not performed.
[a] Motor amplitude in mV and sensory amplitude in μV.

102 known peripheral neuropathy genes led to discovery of *ABCD1* mutation confirmed by kindred evaluation and biochemical assay.

2. Case report

A 62-year-old man was evaluated for 17 years of progressive gait imbalance. He had loss of sensation at the feet since symptom onset. He was bothered by upper arm and calf aching. For 2–3 years he had difficulty rising from a seated position. He denied bowel/bladder dysfunction. Discontinuation of rosuvastatin for 3 months and a 3-week trial of moderate doses of prednisone, 8 months prior to evaluation, were not beneficial. Examination demonstrated moderate iliopsoas weakness and difficulty squatting. Reflexes were preserved with left Babinski sign. There was length-dependent loss of all sensory modalities. Casual gait was normal however he had Rombergism and impaired tandem gait. Family history is significant for 4 younger brothers and 2 sisters with symptoms of weakness and/or sensory loss (Fig. 1(A)). Two of the brothers have been evaluated by a neurologist, one with a reported demyelinating neuropathy. The patient's mother also reported lower extremity weakness beginning in the 7th decade and dementia was diagnosed in her 9th decade. She was not formally evaluated. The family history is negative for adrenal insufficiency.

Nerve conductions demonstrated 5–20% slowing in all motor-sensory nerves with normal amplitudes (Table 1). Needle EMG demonstrated mild neurogenic motor unit potentials in the tibialis anterior and medial gastrocnemius and mild myopathic motor unit potentials in the iliopsoas and thoracic and lumbar paraspinals. No fibrillation potentials were noted. Creatine kinase (79U/L) and B12 were normal. Echocardiogram and pulmonary function testing was normal. MRI of entire spine demonstrated mild degenerative change without central canal stenosis or cord abnormality.

Targeted genetic testing for 102 gene expanded peripheral neuropathy panel (PNPAN, supplemental data) demonstrated an *ABCD1* c.593C>T, p.T198M (transcript NM_000033.3) hemizygous variant as most suspicious in cause. Peroxisomal evaluation by study of VLCFAs revealed elevated C26:0 and C24:0 levels and elevated C26:0/C22:0 and C24:0/C22:0 ratios consistent with hemizygosity for X-linked AMN (Fig. 1(B)). MRI brain did not demonstrate cerebral involvement. Endocrine evaluation was notable for normal total and bioavailable testosterone, aldosterone, ACTH, morning cortisol and renin levels. Dehydroepiandrosterone sulfate was undetectable; therefore a cortrosyn stimulation test was performed and was normal. Targeted Sanger sequencing confirmed four affected brothers and mother carry the identified *ABCD1* variant (Fig. 1(C)). VCLFA analysis by fresh blood sample was abnormal in one of the affected brothers (not performed in other family members). The proband's DNA was also tested using next generation sequencing, including copy number analysis, for 141 gene expanded myopathy panel (MYPAN, supplemental data) and no additional significant finding was detected.

3. Discussion

Targeted genetic approaches are helpful in the evaluation of suspected genetic neuropathies as seen in this case, where AMN was not initially clinically considered. In this case a cause was identified that has potential treatment implications for the family as young boys with cerebral ALD could be candidates for hematopoietic stem cell transplantation [3]. There were a number of atypical clinical features in this case that made diagnosis difficult. The late age at onset and complaints of painful proximal muscle weakness were atypical as was the presence of a proximal myopathy on electromyography. Myopathy has not previously been reported [5]. The myelopathic signs were mild and were limited to preserved reflexes and unilateral Babinski sign. Adrenal insufficiency and its manifestation of hyperpigmentation were absent and are reported in 70% of AMN patients at time of presentation [4].

It has been noted that 43% of kindreds with ALD have a unique mutation; greater than 775 non-recurrent mutations scattered through the coding region have been catalogued in the ALD database [5]. The c.593C>T (p.T198M) variant in

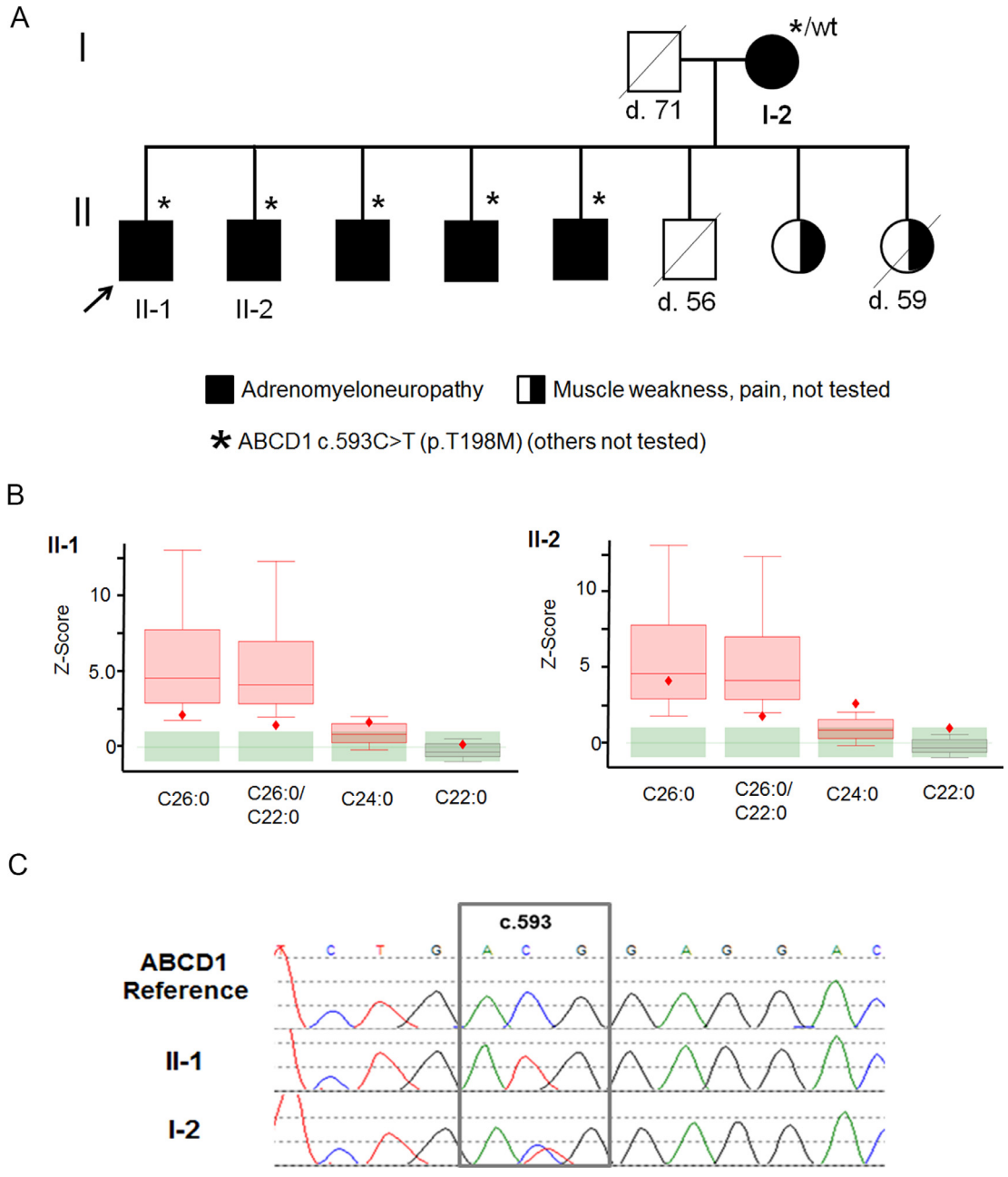

Fig. 1. Clinical history and genetic testing results. (A) The proband and four symptomatic brothers are hemizygous for the *ABCD1* c.593C>T (p.T198M), while the symptomatic mother is heterozygous for this mutation. Arrow indicates the proband (II-1). (B) Very long chain fatty acid (VLCFA) analysis. Values for the proband (II-1) and one affected brother (II-2) are shown (red diamonds, *Z*-scores) demonstrating elevated C26:0 and C24:0 levels and elevated C26:0/C22:0 ratio consistent with hemizygosity for X-linked AMN. Reference ranges are shown as green boxes (display 1st-99th percentile, 19,701 samples) and X-ALD disease range in red as box and whisker plots (display the 99th, 90th,50th,10th and 1st percentiles, respectively, 123 diagnosed cases) generated with Collaborative Laboratory Integrative Reports (CLIR) software (https://clir.mayo.edu/). (C) Sanger sequencing confirmation result of *ABCD1* c.593C>T (p.T198M) of the proband (II-1, hemizygous) and the mother (I-2, heterozygous).

exon 1 of *ABCD1* is listed in the ALD database in one ALD patient with limited clinical information and is unpublished [5]. This variant is absent in Genome Aggregation Database, which includes over 123k exomes and 15k genome data [6]. There are two cases reported with mutation occurring on the same amino acid T198, but with different base pair change (c.593C>G (p.T198R), c.593C>A (p.T198K) [5]. Exon 1 of *ABCD1* appears to be highly susceptible for mutations. As gene panel testing expands and more variants of unclear significance are found, streamlining availability of confirmatory functional assays will be required to confirm the causality of variants, especially where atypical clinical presentations are being evaluated and large kindred evaluations may not be possible. Due to the large number of variants, biochemical testing for X-ALD in males remains the gold standard.

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Dr. Klein – Sits on the therapeutics advisory committee of the CMTA.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.11.007.

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