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Case Report

Twenty years of misdiagnosis of X-linked adrenoleukodystrophy: a case report

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Abstract: X-linked adrenoleukodystrophies (x-ALDs) constitute a group of rare neurological disorders characterized by both genetic and clinical heterogeneity. The diagnostic process necessitates detecting elevated very long-chain fatty acid concentrations in conjunction with genetic analysis of the ATP-binding cassette transporter D1 (ABCD1) gene. This report presents a case of an atypical manifestation and clinical progression of x-ALD, which was initially misdiagnosed. A 38-year-old male patient with x-ALD exhibited progressively worsening gait disturbances and lower limb weakness. Over two decades of medical intervention, the patient had persistently been diagnosed and treated for hereditary spastic paraplegia. A novel hemizygous mutation in exon 1 (c.356dupC) of the ABCD1 gene was identified. The patient's diagnosis was subsequently revised to x-ALD. This case highlights the necessity of considering x-ALD as a potential differential diagnosis in patients presenting with gradually progressive spastic paraplegia.

Keywords: ABCD1, misdiagnosis, mutation, X-linked adrenoleukodystrophy

Introduction

X-linked adrenoleukodystrophy (X-ALD) is a rare genetic disorder that results from mutations in the ATP-binding cassette transporter D1 (ABCD1) gene, which is situated within the Xq28 region and encodes the ALD protein [1]. Alterations in the ABCD1 gene lead to impaired beta-oxidation reactions, culminating in the excessive accumulation of very long-chain fatty acids (VLCFAs) and their subsequent deposition predominantly in the cerebral white matter, spinal cord, and adrenal cortex [2]. Clinically, X-ALD manifests through a spectrum of phenotypic variations, including cerebral childhood ALD, adrenomyeloneuropathy (AMN), Addison-only, and asymptomatic presentations. Consequently, the likelihood of misdiagnosis remains considerable. In this report, an atypical case of X-ALD is described, characterized primarily by dysarthria, spastic gait, and an initial misdiagnosis as hereditary spastic paraplegia.

Case presentation

A 38-year-old man of Han ethnicity was admitted to the neurology department of PLA Hospital on November 6, 2018, due to a 20-year history of progressively worsening gait disturbances, initially manifested as rigidity and weakness in both legs since 1998. Numbness in the lower limbs was reported by the patient in 2003. Neurological examination revealed impaired cognitive function, mild dysarthria, and spastic paraparesis accompanied by a wide-based spastic gait. Deep tendon reflexes were diffusely brisk, with a bilateral Achilles clonus and a positive Babinski sign. Laboratory evaluations, including full blood counts, electrolytes, liver and renal function tests, thyroid function assessments, ceruloplasm in levels, sex hormones, cortisol levels, and pituitary hormone levels, yielded results within normal ranges. Electrophysiological nerve conduction studies did not indicate any abnormalities. A brain magnetic resonance imaging (MRI) scan exhibited nonspecific white matter changes (white matter hyperintensities), while spinal MRI demonstrated spinal cord atrophy and antero-posterior flattening extending from C1 to T8 (**Figure 1**). The neuropsychological assessment fell within normal parameters. The patient had previously been diagnosed with spinal cord astrocytoma in Guangzhou and had undergone surgical

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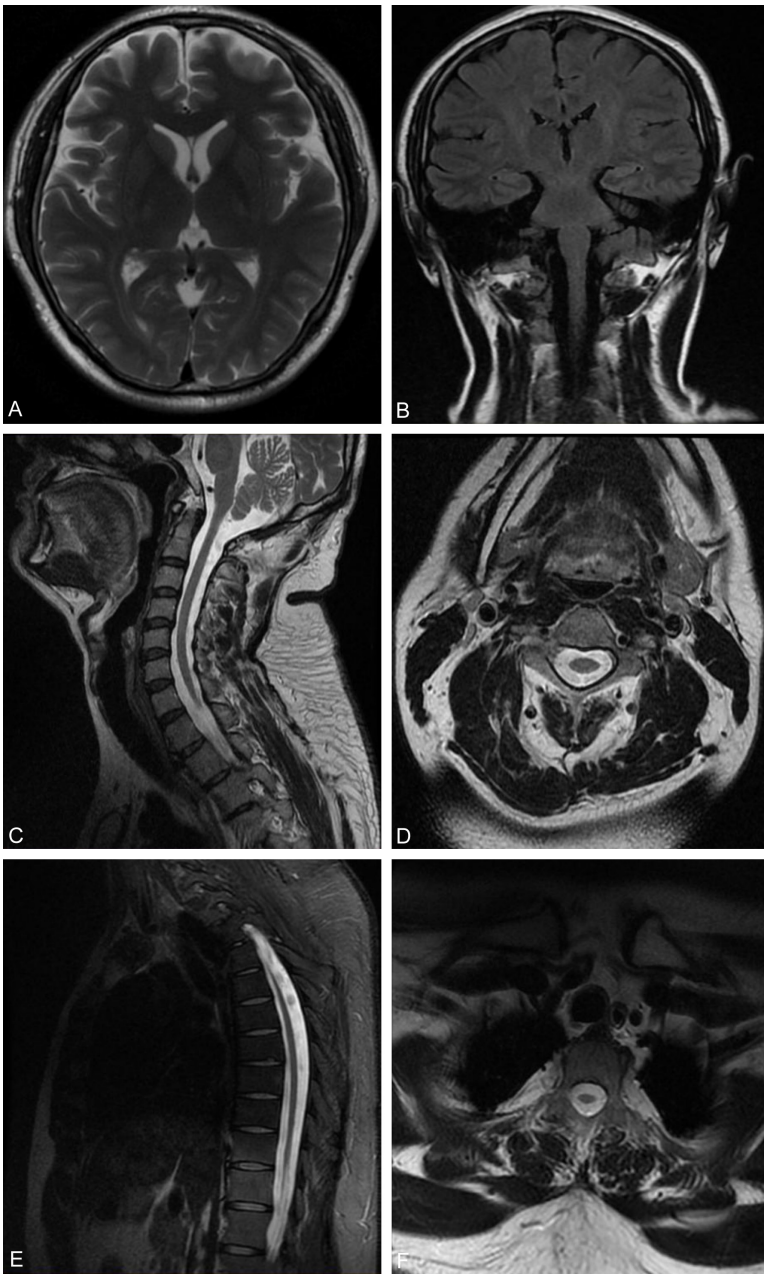

Figure 1. Magnetic resonance imaging scan of a 58-year-old man. No signal changes are seen in axial T2W view (A) and coronal T1W view (B) brain MRI. Sagittal T2W spine MRI (C, E) and axial T2W spine (D, F) showing spinal muscular atrophy.

intervention. However, post-operative pathological examination failed to identify any neoplastic tissue. Following a spinal canal decompression procedure at the thoracic 3/4 segment, symptom progression was observed. Given the presence of progressive spastic paralysis of both lower limbs, gait disturbances, and the exclusion of thoracic spinal tumors, hereditary spastic paraplegia (HSP) was diagnosed. Over the subsequent decade, the patient's gait impairment continued to deteriorate, with a persistent increase in cogwheel muscle tone in both lower limbs, ultimately requiring wheelchair assistance for ambulation. Additional manifestations included asynodia, muscle cramps, and psychiatric conditions such as anxiety, depression, and apathy, alongside sphincter dysfunction. Furthermore, no familial history indicative of gait abnormalities or spasticity was reported.

An inherited disorder was considered due to the absence of abnormalities in prior evaluations, lack of response to treatment, and the multifaceted involvement of brain function. This suspicion was substantiated by the patient's peroxisomal fatty acid profile, and a definitive diagnosis of X-ALD was established following the identification of a pathogenic mutation in the ABCD1 gene. VLCFA analysis indicated elevated plasma ratios of C24/C22 (1.46; reference range: 0.64-0.98) and C26/C22 (0.15; reference range: 0.01-0.07). Genomic DNA was extracted from the patient's peripheral blood. Sanger sequencing detected a novel potentially pathogenic hemizygous mutation (**Figure 2**) at exon 1 (c.356dupC) in the ABCD1 gene. Genetic counseling was provided to the patient's family, and screening of all siblings yielded negative results for the ABCD1 gene mutation.

Discussion

X-ALD exhibits a broad spectrum of phenotypic expressions, including childhood cerebral, adolescent cerebral, AMN, adult cerebral, olivo-

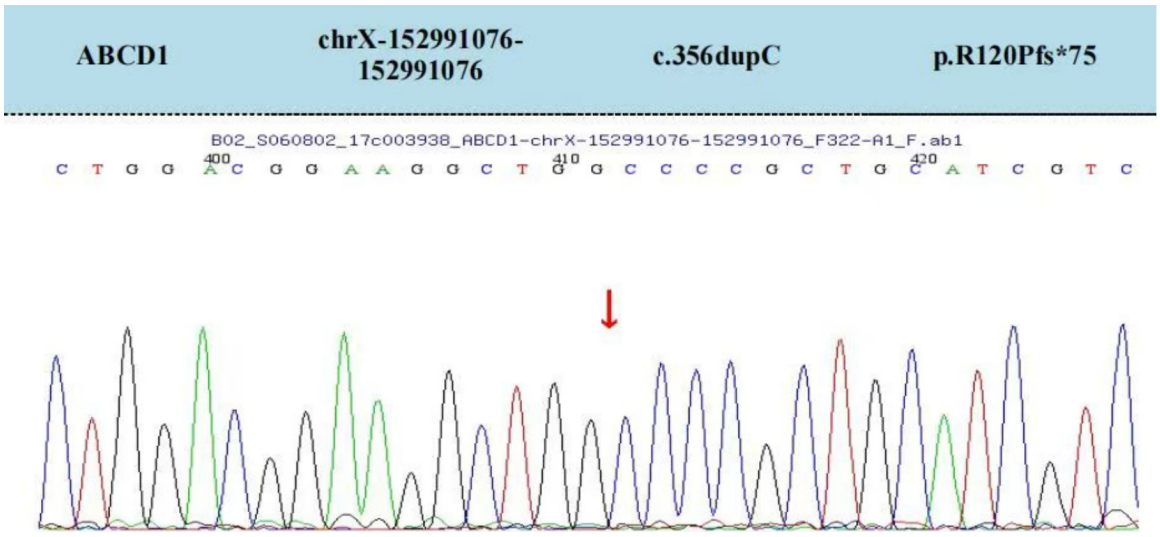

Figure 2. Complementary DNA sequencing with Sanger method of reverse transcription polymerase chain reaction products showing truncation of exon 1 in messenger RNA.

ponto-cerebellar, Addison-only, and asymptomatic forms [3, 4]. AMN occurs more frequently in adult males, characterized by a gradual progression, with onset typically occurring between the ages of 20 and 40 years. The predominant clinical manifestations encompass lower limb weakness and stiffness, gait abnormalities, urinary incontinence or difficulty in urination, and mild cognitive impairment. A marked elevation in serum VLCFA levels is a key diagnostic marker, and identifying a mutation in the ABCD1 gene remains the gold standard for confirming the diagnosis.

The initial symptoms of X-ALD are often nonspecific, which increases the likelihood of misdiagnosis if clinicians do not promptly recognize the condition. Due to the presence of progressive spastic paraparesis, dorsal column dysfunction, sphincter disturbances, and white matter hyperintensities observed on brain MRI, X-ALD is occasionally mistaken for HSP [5]. In cases where clinical suspicion is high, comprehensive plasma VLCFA analysis is essential for diagnosis, particularly in patients presenting with sporadic spastic paraparesis. Elevated plasma VLCFA levels are detected in nearly all affected males and approximately 85% of female carriers [6]. Thus, plasma VLCFA levels serve as a critical diagnostic biomarker for X-ALD.

To date, over 1,000 distinct variants of the ABCD1 gene have been documented, as cataloged in the X-ALD database [7]. To the best of current knowledge, the c.356dupC mutation in the ABCD1 gene identified in this study has not been previously reported. This mutation induces a frameshift alteration, with R120 being the first affected amino acid, leading to a newly formed reading frame that terminates at position 75 (p.R120Pfs*75). This study postulates that the patient carries a novel pathogenic mutation in the ABCD1 gene, which disrupts peroxisomal transport or the catabolism of VLCFAs. Moreover, identifying additional novel mutations in the ABCD1 gene may contribute to an expanded understanding of the genetic spectrum associated with X-ALD.

In conclusion, a case of adult-onset isolated spastic paraparesis without any endocrine abnormalities is reported. This highlights the necessity of considering X-ALD in the differential diagnosis of isolated spastic paraparesis, even in the absence of additional clinical manifestations.

Disclosure of conflict of interest

None.

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