X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder in which accumulation of very long chain fatty acids (VLCFA) leads to cerebral demyelination, peripheral polyneuropathy and adrenocortical insufficiency. At least six different phenotypes can be distinguished, with childhood cerebral ALD (31-57%) and adrenomyeloneuropathy (AMN) (25-46%) being the most frequent.1 Adrenomyeloneuropathy usually presents in the third or fourth decade with spastic paraparesis due to myelopathy. Not only male hemizygotes are affected but approximately 20% of female heterozygotes can also develop moderately severe spastic paraparesis.2 These female heterozygotes are often wrongly diagnosed as having multiple sclerosis. Diagnosis is routinely made by detecting elevated VLCFA in serum, but a 15% false-negative rate is reported in females. Molecular analysis of the ABCD1 gene may be required for certainty. Furthermore, a conclusive genetic result allows for genetic counselling. We report the case of a French-Canadian female who presented with progressive spastic paraparesis in her fourth decade. ABCD1 mutation analysis revealed a missense mutation not previously described.

CASE REPORT

A 47-year-old woman developed progressive gait difficulties with spasms and spasticity in her legs over the past few years. She also
complained of mild hypoesthesia in her distal legs. Her symptoms were not severe enough to require a walking aid. Sphincter function was normal. Physical examination disclosed leg spasticity with normal strength. Fine movements were mildly impaired in the hands. She had hyperreflexia in her arms and legs and Babinski signs were present bilaterally. She had sustained clonus at both ankles. Vibratory sensation was mildly reduced in both legs. Light touch, pain, temperature and position sense were normal. Her gait was moderately spastic. The rest of the neurological examination was normal.

Her family history revealed that her father died at 76 years of lung cancer (see Figure 1 for pedigree). There was no history suggestive of neurological diseases among her father’s brothers and sisters. Her mother died at age 52 from an accident. Her mother had 17 brothers and sisters. One of these brothers died around eight years of age with “paralysis” of uncertain cause, and no medical summary or autopsy were available to us. Six others died in old age of unrelated diseases. Among the ten still alive, eight men are neurologically asymptomatic, one woman has a normal neurological exam, and the other woman could not be examined but has a normal neurological history. Both parents were of French-Canadian origin. The proband has two healthy brothers and two healthy sisters. These two sisters have a normal neurological exam. The neurological history was entirely negative for the two brothers. A third brother died from an unknown disease after a few days of life but no medical summary or autopsy were available. The proband has no children.

Cerebral and whole spine magnetic resonance imaging were normal. Lumbar puncture was normal and there were no oligoclonal bands. Needle electromyography and nerve conduction studies were normal. Vitamin B12, folic acid, venereal disease research laboratories and serum cortisol were all normal. Twice, VLCFA were mildly elevated: C26:0 1.85 (0.24-0.76), C24/C22 1.20 (0.5-0.9), C26/C22 0.046 (0-0.02), C22:0 and C24:0 normal (performed at the Centre hospitalier universitaire de Sherbrooke). DNA sequence analysis demonstrated the substitution of nucleotide C at position 1267 for nucleotide T (Nt1267C>T) in exon 1 of the ABCD1 gene (Kennedy Krieger Institute, Peroxisomial Diseases Laboratory, Baltimore). This causes the substitution of a valine for an alanine at amino acid 294 (A294V) within a highly conserved region of the protein.

**DISCUSSION**

X-linked adrenoleukodystrophy is the most frequent peroxisomial disorder. It is caused by a mutation in the ABCD1 gene (Figure 2a) on chromosome Xq28. This gene contains ten exons and encodes a 745 amino-acid protein (Figure 2b), which is a member of the ATP-binding cassette transporter superfamily. ATP-binding cassette proteins transport a wide range of molecules across cellular membranes. The ALD protein is located on the peroxisomal membrane. Its exact function is unknown, but it is likely involved in transport and/or catabolism of VLCFA. A mutation in the ABCD1 gene leads to the accumulation of VLCFA in the white matter of the brain and spinal cord, in the peripheral nerves, the adrenal glands and the testes, likely impairing the stability of membranes and altering their function. The link between loss of ABCD1 and the elevation of VLCFA is unclear with conflicting reports of impaired peroxisomal β-oxidation of VLCFA and normal peroxisomal function with increased VLCFA synthesis.

![Figure 2a: ABCD1 gene. The gene contains ten exons spanning 20 kbp on chromosome Xq28. The encoded protein has six membrane spanning regions and an ATP-binding domain. The protein is a half-transporter and is thought to require binding to another half-transporter for adequate function. The mutation is on exon 1.](https://www.cambridge.org/core)

![Figure 2b: Adrenoleukodystrophy protein. The mutation reported causes the substitution of valine for alanine at amino acid 294(A294V) within a highly conserved region of the protein. The mutation is circled.](https://www.cambridge.org/core)
Currently, more than 640 mutations have been described (www.X-ald.nl). In a study of 37 kindreds, the majority of mutations (65%) affected a single amino-acid residue. A majority of kindreds (78%) have a unique mutation.8 The most frequent mutation is a two base pair deletion in exon 5 found in approximately 12% of families (www.X-ald.nl). The frequency of de novo mutations is 6.8%.9

There is no correlation between genotype and phenotype or between phenotype and VLCFA level. Even monozygotic twin pairs may have different phenotypes. Consequently, significant phenotypic variability may exist within families, such as a family member presenting the severe form of childhood ALD and another member the mild form of AMN.1 This underlies the importance of an accurate diagnosis since prenatal testing is available. The exception to this phenotypic variability is a large kindred with a highly concordant AMN phenotype that has been published recently.10

The missense mutation described in our patient has never been reported before. It is also the first time that AMN is reported in the French-Canadian population. Elevated VLCFA are strongly in favor of the diagnosis and it would be unlikely that the mutation found represents a polymorphism. Moreover, it does not appear on the database of known ABCD1 polymorphisms (www.X-ald.nl). Since the French-Canadian population is relatively homogenous, it is probably present in several other families of the same ethnic origin. The mutation probably comes from the proband’s mother, since one of her brother’s died at young age, and since her father did not have a neurological illness. Moreover, women may be asymptomatic carriers. Genetic testing was not offered to other family members since they were asymptomatic and did not want other children.

This case underlies the importance of considering X-linked AMN in the differential diagnosis of spastic paraparesis in men and women because 20% of female carriers can present with a slowly progressive myelopathy. The differential diagnosis of spastic paraparesis is reported in Table 1. Approximately 30% of female heterozygotes exhibit subtle neurological abnormalities such as decreased vibration sense or hyperreflexia.2,7 Nervous system involvement in females is different from that in males with AMN and seems confined to the central nervous system. Cerebral magnetic resonance imaging abnormalities have been demonstrated in only 20% of female carriers and peripheral polyneuropathy is rarely present.2 Only one case of adrenoleukodystrophy has been reported in an adult female.11 Prevalence of adrenal insufficiency is low in female carriers.12 Even if therapeutic options are limited, adequate diagnosis is essential as it enables prenatal diagnosis and genetic counselling in women of reproductive age, whose sons could be severely affected.

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