CASE REPORT

Adrenomyeloneuropathy: Report of a New Mutation in a French Canadian Female

Annie Dionne, Denis Brunet, Alexander McCampbell, Nicolas Dupré

ABSTRACT: ***Background:*** X-linked adrenoleukodystrophy is a peroxisomial disorder caused by mutations in the *ABCD1* gene. Adrenomyeloneuropathy is the second most frequent phenotype (25-46%) of this disease and classically presents in adulthood with spastic paraparesis. Female heterozygotes can be symptomatic, but they are frequently misdiagnosed as having multiple sclerosis. ***Case report:*** We report a novel missense mutation in the *ABCD1* gene in a 47-year-old French-Canadian female with spastic paraparesis and no confirmed family history of X-linked adrenoleukodystrophy. The mutation is located on exon 1 and causes the amino acid substitution of a valine for an alanine in a region of the protein highly conserved between mouse and man. ***Conclusion:*** Adrenomyeloneuropathy must be considered in the differential diagnosis of spastic paraparesis in men or women. This is an initial report of an *ABCD1* gene mutation in the French-Canadian population, which should lead to the recognition of other cases in the future.

RÉSUMÉ: Adrénomyéloneuropathie : une nouvelle mutation dans le gène ABCD1 chez une femme Canadienne-Française. ***Introduction:*** L'adrénoleucodystrophie liée à l'X est une maladie peroxisomiale causée par une mutation du gène ABCD1. L'adrénomyéloneuropathie en est le deuxième phénotype le plus fréquent (25-46%) et sa manifestation classique à l'âge adulte est une paraparésie spastique. Même les femmes hétérozygotes peuvent être symptomatiques et chez elles un diagnostic erroné de sclérose en plaques est posé fréquemment. ***Observation:*** Nous rapportons une nouvelle mutation faux-sens du gène ABCD1 chez une Canadienne française de 47 ans atteinte de paraparésie spastique, sans histoire familiale confirmée d'adrénoleucodystrophie. La mutation, située dans l'exon 1, est une substitution d'un seul acide aminé, soit d'une valine par une alanine, dans une région de la protéine hautement conservée entre l'homme et la souris. ***Conclusion:*** L'adrénomyéloneuropathie doit être considérée dans le diagnostic différentiel de la paraparésie spastique chez l'homme et chez la femme. Il s'agit de la première fois qu'une mutation dans le gène ABCD1 est rapportée dans la population canadienne-française, ce qui devrait aider à l'identification d'autres cas à l'avenir.

Can. J. Neurol. Sci. 2005; 32: 261-263

X-linked adrenoleukodystrophy (ALD) is a peroxisomial 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.[3] 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

From the Département des Sciences Neurologiques, CHAUQ - Hôpital Enfant-Jésus, (AD, DB, ND); Department of Neurology and Neurosurgery, McGill University, Centre for Research in Neurosciences, Montreal General Hospital, Montreal, QC, Canada(ND); Department of Neurology, Massachusetts General Hospital, Charlestown, MA, USA (AM).

Received October 4, 2004. Accepted in final form January 28, 2005.

Reprint requests to: Nicolas Dupré, Département des Sciences Neurologiques, CHAUQ - Hôpital Enfant-Jésus, 1401, 18e rue, bureau H-346, Québec, QC, Canada, G1J 1Z4

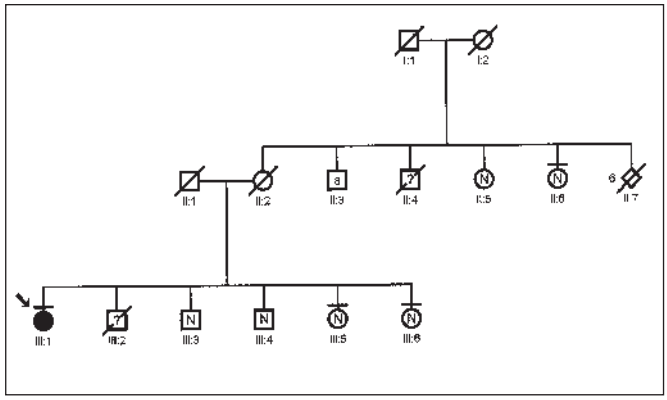

Figure 1: *Family pedigree. N is for normal, ? is for possibly affected, Ø is for examined. Numbers represent the number of individuals.*

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 neurologicaly 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.

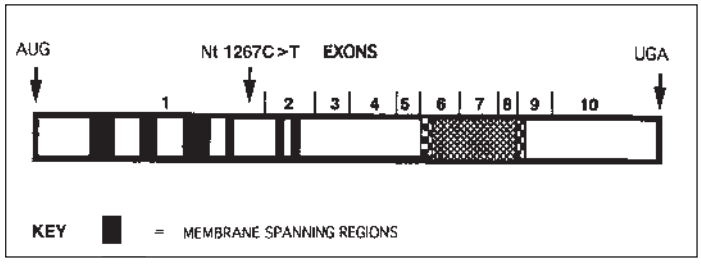

Figure 2a: *ABCD1 gene. The gene contains ten exons spanning 20 kB on chromosome Xq28. The encoded protein has six membrane spanning regions and an ATP-binding domain. The protein is a half-transporter and is thought to require binding to another half-transporter for adequate function. The mutation is on exon 1.*

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.[4] 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 peroxisomial membrane. Its exact function is unknown, but it is likely involved in transport and/or catabolism of VLCFA.[5] 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.[6] The link between loss of *ABCD1* and the elevation of VLCFA is unclear with conflicting reports of impaired peroxisomial β-oxidation of VLCFA and normal peroxisomial function with increased VLCFA synthesis.[7]

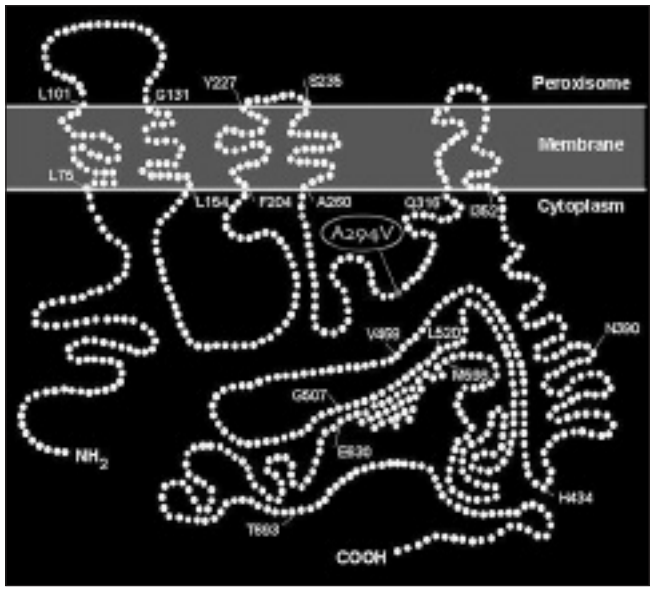

Figure 2b: *Adrenoleukodystrophy protein. The mutation reported causes the substitution of valine for alanine at amino acid 294(A294V) within a highly conserved region of the protein. The mutation is circled.*

https://doi.org/10.1017/S0317167100004091 Published online by Cambridge University Press

Table 1: Differential diagnosis of spastic paraparesis

Cervical spondylosis or neoplasm
Spinal cord arteriovenous malformation
Arnold Chiari malformation
Diplegic cerebral palsy
Hereditary spastic paraparesis
Spinocerebellar ataxias
X-linked adrenomyeloneuropathy
Metachromatic leucodystrophy
Krabbe leukodystrophy
Arginase deficiency
Abetalipoproteinemia
Vitamin E deficiency
Vitamin B12 deficiency
Neurolathyrism
Neurosyphilis
Human T-cell lymphoma virus
Acquired immune deficiency syndrome
Multiple sclerosis
Motor neuron disease
Dopa responsive dystonia

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 50% 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.

Acknowledgements

The authors thank the audiovisual department of CHA for technical assistance with figures and the Kennedy Krieger Institute for DNA testing.

References

1. van Geel BM, Assies J, Wanders RJ, Barth PG. X-linked adrenoleukodystrophy: clinical presentation, diagnosis, and therapy. J Neurol Neurosurg Psychiatry 1997;63:4-14.
2. Schmidt S, Traber F, Block W, et al. Phenotype assignment in symptomatic female carriers of X-linked adrenoleukodystrophy. J Neurol 2001;248:36-44.
3. van Geel BM, Assies J, Haverkort EB, et al. Delay in diagnosis of X-linked adrenoleukodystrophy. Clin Neurol Neurosurg 1993;95: 115-120.
4. Sarde CO, Mosser J, Kioschis P, et al. Genomic organization of the adrenoleukodystrophy gene. Genomics 1994;22:13-20.
5. Valle D, Gartner J. Human genetics. Penetrating the peroxisome. Nature 1993;361:682-683.
6. Moser H, Dubey P, Fatemi A. Progress in X-linked adrenoleukodystrophy. Curr Opin Neurol 2004;17:263-269.
7. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain 1997;120 (Pt 8):1485-1508.
8. Ligtenberg MJ, Kemp S, Sarde CO, et al. Spectrum of mutations in the gene encoding the adrenoleukodystrophy protein. Am J Hum Genet 1995;56:44-50.
9. Feigenbaum V, Lombard-Platet G, Guidoux S, et al. Mutational and protein analysis of patients and heterozygous women with X-linked adrenoleukodystrophy. Am J Hum Genet 1996;58:1135-1144.
10. O'Neill GN, Aoki M, Brown RH, Jr. ABCD1 translation-initiator mutation demonstrates genotype-phenotype correlation for AMN. Neurology 2001;57:1956-1962.
11. Schlote W, Molzer B, Peiffer J, et al. Adrenoleukodystrophy in an adult female. A clinical, morphological, and neurochemical study. J Neurol 1987;235:1-9.
12. el-Deiry SS, Naidu S, Blevins LS, Ladenson PW. Assessment of adrenal function in women heterozygous for adrenoleukodystrophy. J Clin Endocrinol Metab 1997;82:856-860.