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Case report

# Progressive spastic paraparesis in a young male

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ABSTRACT

Introduction: Adrenoleukodystrophy (ALD) is a hereditary genetic disease linked to the X chromosome. It is caused by mutations in ABCD1, a gene that codes for ALD protein, a peroxisomal membrane protein of unclear function. A very large spectrum of symptoms, as well as different degrees of intensity among the members of the same family may be a serious diagnostic challenge.

Aim: To examine current views with respect to ALD pathogenesis and treatment methods and to present the case of its specific variant: adrenomyeloneuropathy. Additionally, we wish to direct attention to the possibility of such a diagnosis in each patient (including women) with progressive paraparesis.

Case study: We present the case of a 29-year-old male patient with progressive paraparesis. The implemented diagnostics procedures (neuroimaging studies and levels of very long chain fatty acids) led to a correct diagnosis: adrenomyeloneuropathy.

Results and discussion: Symptomatology as well as diagnostic and therapeutic methods implemented for patients with ALD are discussed in detail.

Conclusions: Only a very thorough patient interview and family history as well as a detailed physical examination can provide proper direction for diagnostic procedures. This is important due to the necessity of periodic screening for male children in order to earlier detect the cerebral form of ALD. Early diagnosis is associated with better benefits concerning allogeneic hematopoietic stem cell transplants.

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## 1. INTRODUCTION

Adrenoleukodystrophy (ALD) is a genetically conditioned disease that affects the white matter of the brain, axons, the adrenal cortex and the testes.[1] It leads to progressive demyelination within the central and peripheral nervous system and adrenal failure.[2] The incidence of all phenotypes in hemizygotes (males) and heterozygotes (female carriers) is estimated at approximately 1 : 16 800 births.[3]

The defective gene, ATP binding cassette subfamily D member 1 (ABCD1), that codes for the ALD protein (ALDP), a peroxisomal membrane protein, was mapped on the X chromosome (Xq28).[4,5] ALDP participates in the transportation of very long chain fatty acids C24:0/C26:0-CoA (VLCFA) through the peroxisomal membrane. ALDP mutation prevents VLCFA transport to the peroxisome, and consequently their beta-oxidation. This results in the accumulation of VLCFA in the cytosol.[6] Currently it is postulated that VLCFA may directly damage selected cells (oligodendrocytes and astrocytes) through mitochondrial dysfunction and disturbances of their calcium homeostasis.[7] In the culture of adrenal cortex cells, Whitcomb et al. demonstrated their influence on the microstickiness of the cell membrane and decreased response to the adrenocorticotropic hormone (ACTH). This last effect authors associated with the decreased access to the ACTH receptors.[8] The presence or absence of the cerebral inflammation is a basic feature that differentiates a quickly progressive childhood phenotype from adrenomyeloneuropathy (AMN) and other, milder forms of the disease.[1] In terms of pathology, the standard, initial manifestation of ABCD1 mutation is adrenomyeloneuropathy – a slowly progressing dying back axonopathy that affects both ascending and descending pathways of the spinal cord, and in some cases polyneuropathy. In 60% of male patients, in different periods of life, a conversion to the rapidly progressive cerebral form occurs that is characterized by inflammatory demyelination, histologically similar to that in sclerosis multiplex.[9]

The following clinical phenotypes of ALD have been described:[10,11]

- rapidly progressive childhood phenotype, characterized by progressive demyelination, onset at the age of 5–12 years, which leads to death within a few years,
- adolescent or adult cerebral phenotype,
- AMN, characterized by onset at the age of 15–30 years and slow progression of paraparesis,
- Addison's disease only with no neurological symptoms.

In this paper we present the case of a patient with AMN, and then briefly discuss current knowledge concerning this disease.

## 2. AIM

The aim of this study is to examine current views with respect to ALD pathogenesis and treatment methods and to present the case of its specific variant – AMN. Additionally, we wish to direct attention to the possibility of such a diagnosis in each patient (including women) with progressive paraparesis.

## 3. CASE STUDY

A 29-year old man, graduate of the Faculty of Pharmacy, father of two healthy daughters, was referred to the Department of Neurology due to progressive lower limb paresis present for 2 years. Moreover, he reported numbness and tingling sensations in distal sections of the lower limbs, particularly following alcohol consumption. The interview revealed: gynecomastia (the patient underwent a surgical procedure due to this, Figure 1) and hypergonadotropic hypogonadism (the patient had been diagnosed by an endocrinologist in an outpatient clinic). The patient's maternal grandfather exhibited very similar symptoms (mother with-

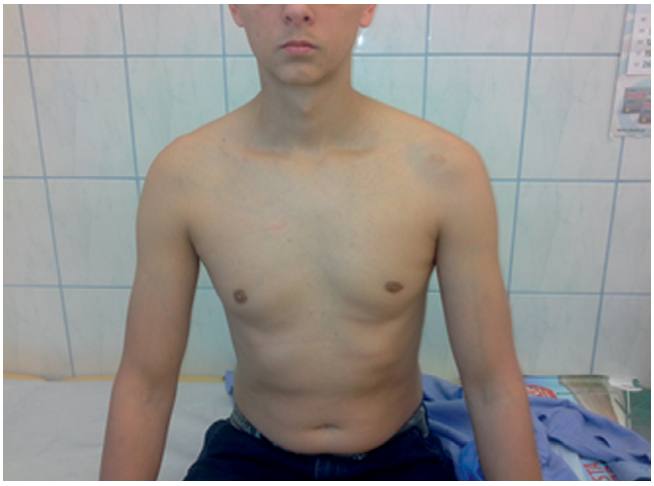

**Figure 1. Residual gynecomastia and absence of male type body hair distribution.**

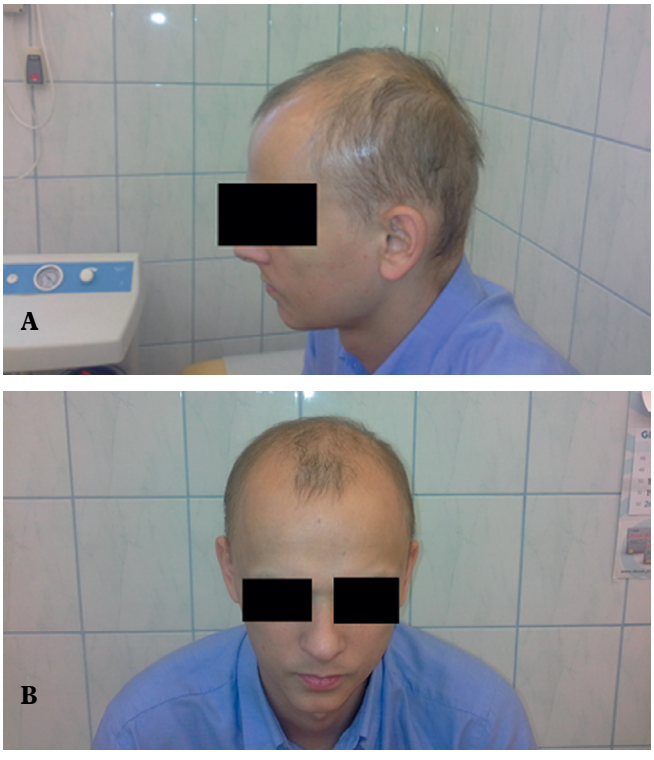


**Figure 2. Very dark complexion, very thin, scarce hair on the scalp.**

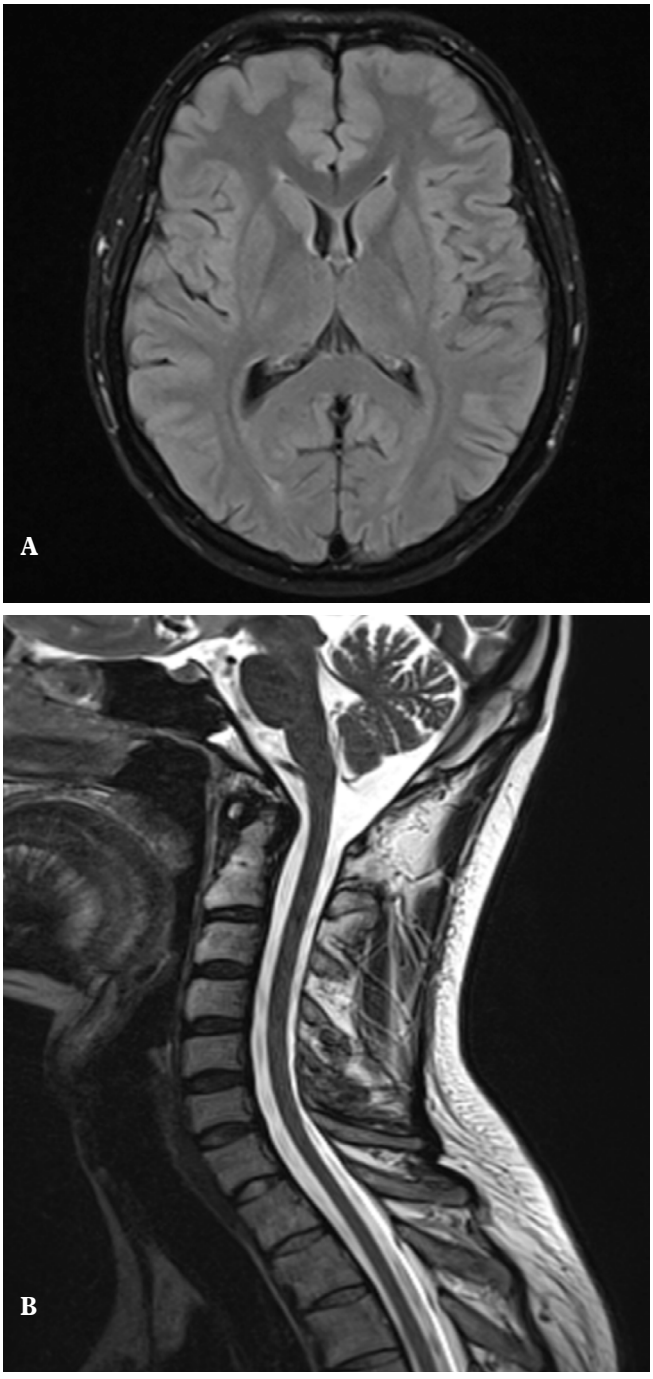


**Figure 3. A complete MRI scan of the brain (A) and spinal cord (B) did not reveal focal lesions and features of atrophy.**

out symptoms). He was diagnosed with sclerosis multiplex, but died at the age of 80 due to other reasons. Many years before his death he had been wheel-chair bound. The physical examination revealed very dark complexion, absence of male type body hair distribution, very thin, scarce hair on the scalp and testicular atrophy (Figures 1 and 2). The neurological examination detected insignificant (4/5 on the Lovett scale) weakness of the lower limbs muscle strength, both sided increased knee and Achilles tendon reflexes, both sided extensor plantar response (Babinski's sign) and weakened vibratory sensibility in distal sections of the lower limbs. The psychological examination did not reveal any cognitive deficits.

A complete MRI scan of the brain and spinal cord (Figure 1) was performed; it did not reveal focal lesions and features of atrophy. Nerve conduction study (NCS) demonstrated features of sensory-motor polyneuropathy, of an axonal-demyelinating type. The level of ACTH in the morning was determined: the result was at the lower norm threshold 25 ng/L (norm 25–80 ng/L). The level of B12 vitamin was normal.

Based on personal interview, family history and the results of additional tests and examinations, AMN was suspected. Differential diagnosis included Kennedy's disease (in our patient bulbar muscles were not affected and he remained fertile) and hereditary spastic paraplegia (hypergonadotropic hypogonadism with no olfactory impairment).

Blood serum was taken to determine VLCFA levels – the ratio of C24:0/C22:0 = 1.565 was obtained (reference range less than 0.960), and C26:0/C22 = 0.044 (reference range less than 0.030). The result confirmed the values of VLCFA associated with X-ALD. Six months later this patient went to the Mayo Clinic for neurological consultation, where diagnosis based on VLCFA profile was confirmed. Performed genetic examinations revealed mutation p. Gln 157(c.469C>T) in ABCD1 gene. The patient started therapy with Lorenzo's Oil and low C26:0 diet, but he ceased it because of high cost and lack of effect (constant disability progression). Because our patient had two sons (4 and 1 year old), 3 asymptomatic sisters with multiple offspring (9 males) VLCFA profile and subsequent genetic testing for all family members mentioned above was urgently recommended.

## 4. RESULTS AND DISCUSSION

The clinical picture of AMN includes: progressive paraparesis (upper limbs are not affected at all, or affected insignificantly) with increased tendon reflexes, pyramidal signs, axonal polyneuropathy (panmodal abnormalities, mainly concerning proprioception), features of neurogenic bladder, adrenal failure (loss of body mass, nausea, vomiting, skin hyperpigmentation). Moreover, testicular atrophy, gynecomastia, impotence and reduced scalp hair were observed.[12,13] Testicular dysfunction involving a decreased ratio of the testosterone level to the luteinizing hormone (LH) and/or elevated gonadotropines levels were detected in 81.6%, and adrenal failure in 70% of patients.[14,15] The influence of this disease on baldness seems logical due to the confirmed expression of ABCD1 in the hair follicles.[16] Cognitive disorders, although typical of the cerebral ALD, were revealed in lesser intensity even up to 60% of patients with the AMN phenotype and were manifested as subcortical dementia.[17]

There is no correlation whatsoever between the type of ABCD1 gene mutation and the disease phenotype. In the same family cerebral phenotypes of ALD and AMN may occur.[5,18] AMN is probably the most commonly found phenotype of ALD.[19] AMN may transform itself to the cerebral form of ALD. The risk of such a transformation to occur is

approximately 20% within 10 years 21 and is associated with poor prognosis.

Although ALD mainly affects males, at least half of women, X-ALD heterozygotes, develop symptoms similar to those of AMN, and in approximately 1% symptoms of adrenal failure will occur.[1,18] It should be remembered that neurological symptoms in females appear later in life (65% by the age of 60 years).[18] Moderately severe paraparesis develops in 15% of heterozygotes.[15] Due to considerable differences in the intensity of signs and symptoms in patients with AMN, and also the possibility of transformation to the severe inflammatory form, prognosis is impossible to determine. Each patient is at risk of developing adrenal failure.

Presently, the most recognized diagnostic method for ALD is the biochemical serum analysis. As Moser et al. demonstrated in hemizygotes elevated levels of C26, C25, C24, and C23 fatty acids were present, while the levels of C20 and C22 remained normal.[21] Currently, the basic method is to determine levels of C26 and the ratio of C26/C22 and C24/C22.[18] In heterozygotes, biochemical tests yield negatively false results in approximately 15% of cases. Consequently, in this group, the examination of choice is the analysis of the ABCD1 gene mutation.[10]

MRI techniques serve mainly for differential diagnosis. The MRI scan of the brain of a patient with AMN may not demonstrate abnormalities or may detect a moderately increased signal within pyramidal tracts (internal capsule, brain stem, including the pons) in T2-FLAIR sequences, which is reflected by Wallerian degeneration. The MRI scan of the spinal cord may occasionally reveal its atrophy. The presence of contrast-enhanced lesions or ones that transgress the borders of pyramidal tracts suggests the transformation of AMN into cerebral X- ALD.[13]

In differential diagnostics for AMN, sclerosis multiplex, myelopathy of a different etiology, Kennedy's disease and hereditary spastic paraplegia should always be considered. Kennedy's disease demonstrates some common features with some AMN phenotypes, such as: X-chromosome inheritance, gynecomastia, impotence, features of androgen insufficiency (in this case caused by the androgen insensitivity syndrome). It should be remembered that in Kennedy's disease weakness and atrophy of bulbar and proximal limb muscles dominate. Patients are generally infertile.[22] In the case of hereditary spastic paraplegia, only the coexistence of paraparesis with Kallmann syndrome has been reported (olfactory impairment and hypogonadotropic hypogonadism), and not the presence of hypergonadotropic hypogonadism, which in the case of our patient allowed us to exclude preliminarily this group of diseases.[23]

AMN/ ALD remains an incurable disease. Administration of Lorenzo Oil along with eliminating VLCFA from the diet normalizes their level within a month, but this does not prevent progression of earlier neurological symptoms.[21] This treatment may benefit young boys without neurological symptoms.[24] Despite earlier studies reporting the reduction of VLCFA levels by lovastatin, more current research suggests that this is the effect of reducing the LDL levels that VLCFA are associated with. Hence, currently this drug is not recommended.[25] Allogeneic haematopoietic cell transplantation is recommended for children in an early stage of cerebral ALD.[26] Such treatment may also be effective in adults with an early stage of cerebral ALD, but no studies and reports on this subject exist. Symptomatic treatment is used in AMN. Moreover, periodic check-ups of adrenal function should be performed in order to detect their insufficiency and introduce substitutive therapy[13].

Due to a significant range in the intensity of symptoms among patients with AMN, and also the possibility of transformation into a severe inflammatory form, it is not possible to determine prognosis for any particular patient.

## 5. CONCLUSIONS

X-ALD is a heterogeneous disease in terms of its phenotypes. Its specific form, AMN, should be always considered in differential diagnosis when symptoms of myelopathy are present, especially in young males. Only a thorough personal interview and family history, as well as searching for discreet clinical features of adrenal dysfunction, testicular dysfunction and other characteristic phenotype features may enable a correct diagnosis. Despite the lack of targeted treatment for adult patients with AMN, correct diagnosis may benefit their sons who, following proper screening, may be candidates for allogeneic haematopoietic cell transplantation.

## Conflict of interest

None declared.

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