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X-Linked Adrenoleukodystrophy in an 11 Years Old Child: A Case Report

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Abstract **Case Report**

An 11-year-old boy was referred to the pediatric ward for regression in school performance and behavioral problems. The clinic has been evolving for two years. Given the clinical deterioration, the patient is treated at the pediatrician. A somatic assessment is performed and highlights lesions of the white matter evoking the diagnosis of X-linked adrenoleukodystrophy (X-ALD), confirmed by the metabolic assessment. No curative treatment will be proposed given the stage of the disease; the patient dies less than two years later. The X-ALD is a degenerative disease of the white matter having a prevalence estimated at 1/20.000 cases worldwide. The mutated gene, located on the long arm of chromosome X, encodes a peroxisomal membrane protein. Over 500 mutations are known and cause a disorder of fatty acids b-oxidation. Several phenotypes exist without phenotype-genotype relationship. The diagnosis of X-ALD is mainly based on brain magnetic resonance and blood very long chain fatty acids (VLCFA) blood level. Allogenic hematopoietic stem cell transplanta-tion, only known cure can be achieved in patients with asymptomatic (from screening) or early stage. Without treatment, the survival prognosis at diagnosis is an average of 3 years. Genetic counseling and screenings (pre-natal, neo-natal and family) are essentials to improve this diagnosis.

Keywords: Adrenoleukodystrophy, genetic disease, Brain MRI, pediatric, Genetic counseling.

INTRODUCTION

The X-ALD is a rare progressive peroxisomal disorder characterized by endocrine dysfunction (adrenal failure and sometimes testicular insufficiency), progressive myelopathy, peripheral neuropathy and, variably, progressive leukodystrophy. The diagnosis is mainly based on brain magnetic resonance and blood very long chain fatty acids (VLCFA) blood level.

Allogenic hematopoietic stem cell transplantation, only known cure can be achieved in patients with asymptomatic (from screening) or early stage. Without treatment, the survival prognosis at diagnosis is an average of 3 years. Genetic counseling and screenings (pre-natal, neo-natal and family) are essentials to improve this diagnosis.

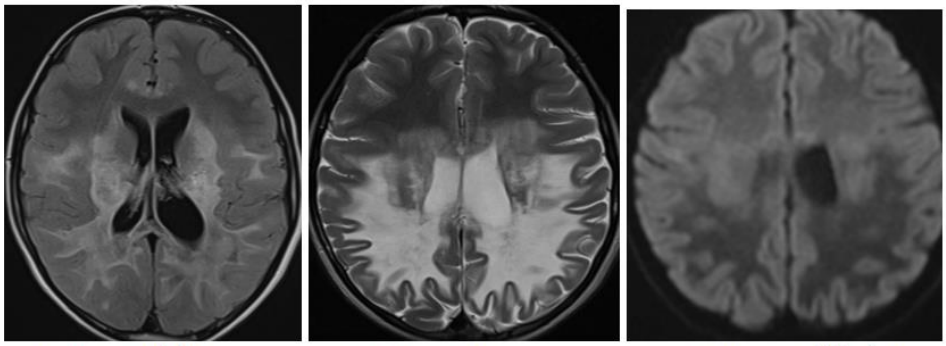
CASE REPORT

An 11-year-old boy was referred to the pediatric service for behavioral disorders and psycho-cognitive regression.

The patient's history was unremarkable, except for a 2-year-old head injury. He is the only child of healthy parents. There is no psychiatric or neurological pathology in his family history.

The regression in school performance began the following year. A paramedical follow-up was instituted. This spectacular regression in learning and the increase in behavioral problems led to a child psychiatric opinion and an organic adjustment.

On admission, the patient presented with right hemiparesis and dysarthria. Signs of psycho-cognitive deterioration were evident.



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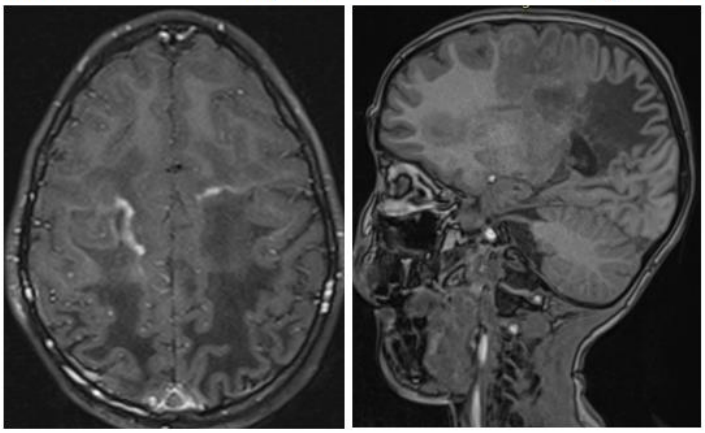

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Diffuse bilateral and symmetrical signal abnormalities of the white matter extended to the thalami, internal capsules and cortical-spinal bundle of the midbrain.

DISCUSSION

Adrenoleukodystrophy is an X-linked peroxisomal neurodegenerative disease. It affects the central and peripheral nervous systems as well as the adrenal and testicular functions. Its incidence is estimated at approximately 1/20,000 births (1/17,000 to 1/21,000) including hemizygotes and symptomatic forms in heterozygous women [2-4].

The mutated gene (ABCD1) located on the long arm of the X chromosome (q28) codes for a peroxisomal protein called ALD (AdrenoLeucoDystrophy Protein). More than 500 different mutations have been described without any relationship between phenotype and genotype. Several clinical forms are found in patients with the same mutation and who are related to each other [5].

ALD protein is a peroxisomal wall hemitransporter: its mutation leads to altered beta-oxidation of fatty acids, and cellular and extracellular accumulation of very long chain fatty acids (VLCFA/AGTLC). The pathophysiological mechanism linking VLCFA accumulation and cellular destruction is not elucidated [2, 3].

There are several phenotypes of X-ALD, their classification is clinically based and varies between authors. Seven clinical forms have been described: childhood cerebral ALD (5-10 years; 31-35% of cases), adolescent ALD (also called non-inflammatory ALD; 10-15 years; 4-7%), adult cerebral ALD (2% of cases), adrenomyeloneuropathy with demyelinating brain involvement (20-45 years; 10-12% of cases), simple adrenomyeloneuropathy (20-60 years; 25-30%), isolated adrenal insufficiency (Addison's disease, 5-40 years) and gonadotropic insufficiency (>20 years) [2-6].

Some hemizygous patients have symptoms of adrenomyeloneuropathy of varying severity but without brain or adrenal involvement [2].

Cerebral adrenoleukodystrophy in children consists of central involvement with impaired cognitive, sensory and motor functions. Several clinical forms have been described based on the first cerebral regions affected.

The parieto-occipital form (2 cases/3) presents clinically at an average age of 7 years, but the cerebral lesions appear approximately two years earlier at the level of the splenium of the corpus callosum [6]. The first symptoms are cognitive, behavioral and psychiatric [7]. In a second phase, visual, auditory and motor functions deteriorate, leading to a bedridden state that can last 2 to 3 years. In the case of the frontal form (1/5 cases), which appears later and progresses more slowly

attention and executive function attention and executive functions precede the unilateral motor impairment. The last two forms consist of unilateral or bilateral pyramidal damage, which is asymptomatic for a long time, and of initial damage to the auditory pathways. The latter is only symptomatic when occipital or frontal lesions appear [2]. Adrenal insufficiency is part of the clinical picture in most cases (90% minimum) [2-4, 6].

Diagnosis is based primarily on plasma VLCFA assays and brain magnetic resonance imaging (brain CT is less sensitive in the early stages of the disease). The sensitivity of the VLCFA assay in male patients with an ABCD1 mutation is 100% [2-7]. Brain magnetic resonance imaging (MRI) shows hyperintense areas of Flair and T2 signal in the white matter only. MRI is also useful in the follow-up of asymptomatic patients. Therapeutic choices are based in part on a 34-item radiological evaluation (Loes score) [4]. The extent of impairment is also assessed by neurophysiological and neuropsychological tests. EPI is an additional tool in the therapeutic decision. A prolongation of the p100 latency (positive wave at 100 msec) is present in the early stage of the disease. In the literature, other alterations of the tracing, specific to the asymptomatic period, have been reported [9]. Neuropsychologically, the performance IQ decreases while the verbal IQ is preserved in the asymptomatic stage. Regular psycho-cognitive evaluation is part of the basic follow-up of patients [10].

This clinical picture is very suggestive by the clinical and imaging findings and does not have a true differential diagnosis. Before the onset of purely neurological symptoms, the picture may point to a diagnosis of hyperactivity syndrome. This diagnosis will be ruled out as soon as cerebral lesions are detected on imaging. Involvement of the white matter could suggest ADEM (acute disseminated encephalomyelitis), but not the clinic. Indeed, ADEM is characterized by an acute or subacute onset of symptoms and the immediate presence of signs of neurological involvement.

Most other leukodystrophies occur in the early years of life (e.g. Aicardi-Gouttières syndrome, Krabbe disease, Pelizeaus Mezbacher like disease, Canavan disease, Alexander disease, megalencephaly-cyst leukodystrophy). Refsum's disease has a later onset (adolescence) but signs of peripheral neuropathy predominate the inaugural clinical picture. In Alexander disease, cognitive functions are preserved. The juvenile form of metachromatic leukodystrophy, due to an enzymatic deficiency of arylsulfatase A (an enzyme involved in the metabolism of cerebroside sulfates), has clinical similarities with X-ALD. The first symptoms are cognitive and precede the motor impairment, beginning at about 5 years of age. The analysis of the activity of the deficient enzyme (arylsulfatase A) allows the differential diagnosis. In Zellweger's disease, due to a disorder of fatty acid beta-oxidation, plasma VLCFAs are also increased. Nevertheless, this pathology is not included in the differential diagnosis because of its clinical features (dysmorphism, ocular disorder, hepatic and renal impairment, polymicrogyria on MRI).

Treatment

The only curative treatment for X-ALD is allogenic bone marrow transplantation. Lorenzo's oil (rich in erucic and oleic acids), combined with a total avoidance of VLCFAs in the diet, allows a reduction in plasma VLCFA levels without stopping the evolution of brain lesions [2]. Some authors propose its use as a preventive measure in asymptomatic patients, although no consensus has been reached [11].

Bone marrow transplantation cannot be offered to all patients. Indeed, X-ALD once symptomatic is rapidly progressive and the effects of the transplant are not immediate. This latency period is accompanied by excessive clinical deterioration in the advanced stages of the disease [6]. The risk-benefit balance is only favorable in the early stages of the disease. Patients are selected on the basis of clinical and radiological criteria [4]. A scale based on the degree of symptoms and the extent of their impact on the patient's autonomy (X-linked adrenoleukodystrophy- disability rating scale or ALD-DRS), developed in the USA, is also used to guide the therapeutic decision [6]. A minimum cell replacement rate of 80% is necessary to obtain stabilization or even regression of the demyelinating lesions. The mortality rate associated with treatment is 15-20%.

Gene therapy trials have been performed to treat X-ALD. Autologous transplantation of hematopoietic stem cells transduced with a lentiviral vector expressing the ABCD1 gene has shown similar results to allogeneic bone marrow transplantation. With these techniques, patients without an HLA-matched donor or cord blood could be treated.

In addition, the risks of an autologous transplant are lower than those of an allogeneic transplant. Further clinical trials are needed to refine the techniques and determine their long-term effectiveness.

Genetic Counseling

Genetic counseling is offered to families of newly diagnosed patients. The goal is to identify carriers for whom an antenatal diagnosis can be proposed during a possible pregnancy possible pregnancy. From these hemizygous women, the male subjects to be screened are selected. Asymptomatic carriers can then be identified and followed up.

Screening

Family screening consists of measuring the plasma VLCFAs of family members who are likely to be carriers. However, VLCFAs are normal in 5 to 20% of hemizygous women. Screening in these cases

consists of genetic analysis. Prenatal screening is performed, if the fetal karyotype is male, by trophoblast puncture. Depending on whether or not the maternal mutation is known, genetic analysis or assay of VLCFAs and/or ALD protein is performed. This technique is more time consuming as it requires the culture of trophoblastic cells [2]. Nevertheless, the lack of genotype-phenotype correlation makes the decision to terminate a pregnancy complex and delicate.

The integration of VLCFA assay in routine newborn screening seems judicious and even justified. Indeed, a greater number of carriers would be identified and would benefit from the appropriate treatment for their phenotype [13, 14].

It should be noted that approximately 40% of the patients screened will not have the brain form of the disease. This underlines the importance of a complete follow-up (neurological, neuropsychological, radiological and adrenal) on a regular basis (biannual in the first decade and annual thereafter) in order to make the best therapeutic decision [6].

CONCLUSION

Cerebral adrenoleukodystrophy in children is an X-linked disease with a fatal outcome. Diagnosis is based on brain MRI and blood levels of very long chain fatty acids. At present, allogeneic bone marrow transplantation is the only curative therapeutic outcome. It can only be offered to patients who are at an early stage or asymptomatic. The latter are the result of screening (antenatal, neonatal or family) following which a clinical and radiological follow-up is regularly carried out in order to propose the appropriate treatment at the appropriate time.

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