X-Linked adrenoleukodystrophy (X-ALD) presenting as Addison's disease in childhood: a case report.

Antonella Meloni[1], Mauro Congia[1], Maria Rosaria Casini[1], Silvia Ibba[1], Marco Bonomi[2], Maria Cristina Rosatelli[3]

1. Ospedale Pediatrico "Microcitemico" Antonio Cao, Università degli Studi di Cagliari, Azienda Ospedaliera Brotzu, Cagliari (Italy)
2. Laboratorio di Ricerche Endocrino Metaboliche, Istituto Auxologico Italiano IRCCS, Milano (Italy)
3. Medicina Clinica e Molecolare, Dipartimento di Sanità Pubblica, Università degli Studi di Cagliari, Cagliari (Italy)

BACKGROUND: X-Linked adrenoleukodystrophy (X-ALD; OMIM#300100) is an inherited peroxisomal disease (estimated incidence, 1:20,000 white males) caused by mutation in the ABCD1 gene (chromosome Xq28), which encodes a peroxisomal ATP-binding cassette transporter protein (ALDP). ALDP deficiency leads to impaired very long chain fatty-acids (VLCFA) beta-oxidation and the accumulation of saturated VLCFA (particularly, exacosanoic (C26:0) and tetracosanoic fatty acids (C24:0)) in plasma and tissues. Diagnosis is made on the basis of raised concentrations of VLCFA in plasma and/or cultured skin fibroblasts; the next step is to confirm diagnosis by performing ABCD1 mutation analysis. Gene defects result in an extremely variable phenotype (see Table 1) in male X-ALD patient, ranging from isolated adrenocortical insufficiency and slowly progressive myelopathy to devastating childhood cerebral ALD.

CASE PRESENTATION: An 4,8 years old boy was referred to our clinic because of oral melanosis with the suspicion of Peutz-Jeghers syndrome. He was the first child of non consanguineous parents and was born from uncomplicated pregnancy (weight 3,180g, length 52cm and head circumference 35cm). Family history was unremarkable. Past medical history was positive for febrile seizures at age 2 and 3 years. Except for cutaneous-mucosal hyperpigmentation, physical examination and growth were normal (height 112 cm, 75th percentile; weight 18 Kg, 25-50th percentile; head circumference 50 cm, 50th percentile). Neurological examination was negative. Serum adrenocorticotropic hormone (ACTH) and cortisol (F) concentrations were compatible with primary adrenal failure (ACTH < 1250 pg/ml, F <10 µg/l) (see Table 2); promptly, glucocorticoid replacement therapy was started (hydrocortisone 15 mg per day). Adrenocortical autoantibodies were negative.

Molecular analysis of AIRE, DAX1, AAAS, MC2R and MRAP genes was normal.

The biochemical analysis of VLCFA showed elevated plasma concentrations of exacosanoic fatty acids (C26:0), suggesting the diagnosis of X-ALD (see Table 3). Genotype analysis with ABCD1 gene sequencing confirmed diagnosis of X-ALD (see Table 4). The identification of the mutation (C.310C>T (p.R104C)) in the hemizygous patient was inherited from the mother (heterozygote).

At diagnosis, Brain MRI revealed a very faint hypersignal of the parietal-occipital white matter on T2/FLAIR sequences, without gadolinium enhancement; extensive electrophysiological studies and neurophysiological testing were normal. The patient is carefully monitored with clinical examination every 2 months, brain MRI, electrophysiological test and psychometric test every 6 months, or earlier if new symptoms occur.

In addition to the glucocorticoid therapy for the adrenal insufficiency, he reduced the VLCFA oral intake with a diet poor in fatty foods.

Tab 1: Phenotypes seen in male X-ALD patients

Phenotype	Age of onset	Estimated relative frequency
Childhood cerebral	3-10 years	31-35%
Adolescent	11-21 years	4-7%
Adrenomyeloneuropathy	19-37 years	40-46%
Adult cerebral	Adulthood	2-5%
Olivopontocerebellar	Adolescence or adulthood	1-2%
Addison's only	Common before 7.5 years	Varies with age; up to 50% in childhood
Asymptomatic	Biochemical abnormality only	Diminishes with age
		Common <4years
		Very rare >40 years

Adapted from Maser et al., 2000

Tab 2

Laboratory	
Na 136 mEq/L; K 4,7 mEq/L; Cl 104 mEq/L	
Cortisol <10 µg/L	(normal value: 50-250 µg/L)
ACTH >1250 pg/ml	(normal value: 5-46 pg/ml)
17-OH-P 400 pg/ml	(normal value: 30-900 pg/ml)
D4 <0,20 ng/ml	(normal value: <0,2 ng/ml)
Renin 4,9 pg/ml	(normal value: 2,71-16,51 pg/ml)
Aldosterone 14,7 pg/ml	(normal value: 10-160 pg/ml)

Tab 3:Plasma Very-Long-Chain Fatty Acids (VLCFA)

Plasma VLCFA		Range
C22:0	45,0 umol/L	26,5-75,3
C24:0	75,1umol/L	24,9-73,0
C26:0	**4,260 umol/L**	0,460-0,980
C24:0/C22:0	**1,66**	0,62-1,01
C26:0/C22:0	**0,094**	0,008-0,026

VLCFA concentrations are measured by GC/MS

Tab 4

Molecular Genetic testing
Method: ABCD1 gene sequencing, including point mutations and small rearrangements (deletions/insertions) of codificant regions and splice site variants (Ref. Seq.NCBI:NG_009022.1).
Results: ***C.310C>T (p.R104C) ABCD1 mutation***

CONCLUSION: Addison's disease can be the presenting symptom of X-ALD in boys and men, years or even decades before the onset of neurological symptoms. The severity and progression of X-ALD cannot be predicted for individual patients. Therefore, it is important to consider X-ALD in any boy presenting with Addison's disease, in particular if circulating adrenal autoantibodies are negative.

Because of the prognostic implications, the need for genetic counselling and the potential benefit of therapeutic intervention (bone marrow transplantation), such patients need to be identified promptly. Close monitoring is necessary to find first radiological signs of cerebral ALD, before appearance of the clinical symptoms.

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Antonella Meloni
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