Various presentations of X-linked adrenoleukodystrophy: case reports

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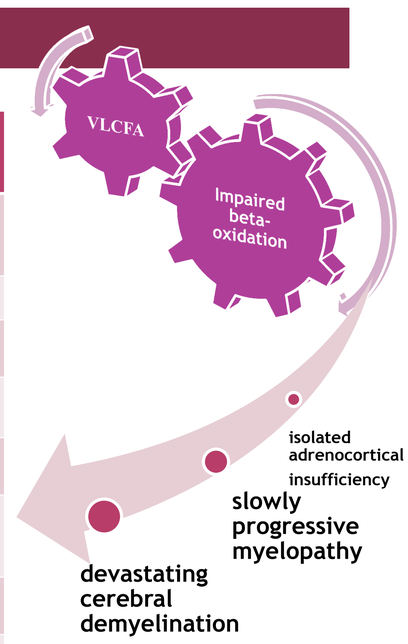
Introduction

Adrenoleukodystrophy (ALD)
❖X-linked disease characterized by
✓impaired beta-oxidation of very long-chain fatty acids (VLCFA)
✓and, in the most severe cases,
✧inflammatory demyelination in the brain,
✧adrenocortical insufficiency (AI) (1)
❖caused by mutations in the **ABCD1 gene** located on the X-chromosome (2)
❖**Seven phenotypes** were described, with a higher prevalence of the cerebral forms (Table 1).(1)
❖With an estimated birth incidence of 1 in 17.000 newborns (male and female), X-ALD is the most common peroxisomal disorder. (3)

Table 1. The X-ALD Phenotypes (after Engelen M, Kemp S, Visser M)

	CCALD	AdolCALD	ACALD	AMN no cerebral disease	AMN cerebral disease	Addison only	Women with X-ALD
Frequency (%)	31 - 35	4 - 7	2 - 5	40 - 46	20	Decreasing with age	Unknown
Age at onset	2.5 - 10	10 - 21	➢21	➢18	> 18	>2	variable > 40
Myelopathy	-	Possible preclinical	+ or -	+	+	-	+
White matter lesions on brain MRI	Extensive	Extensive	Extensive	Wallerian degeneration	Parieto-occipital, frontal	-	Very rare
Behavioral/cognitive Disorder	+	+	+	-	+	-	Very rare
Peripheral Neuropathy	-	Rare	Possible	Sensory-motor, mostly axonal, demyelinating	Sensory-motor, mostly axonal	-	+/−
Endocrine Disorder	often AD	often AD	often AD	often AD + testicular insuf	often AD + testicular insuf	AD	AD rare (< 1%)
Progression	Rapid	Rapid	rapid	Slow	rapid	-	slow

- = absent; + = present; CCALD = childhood cerebral ALD; AdolCALD = adolescent cerebral ALD; ACALD = adult cerebral ALD; AMN = adrenomyeloneuropathy; AD= Addison-disease.



Case reports

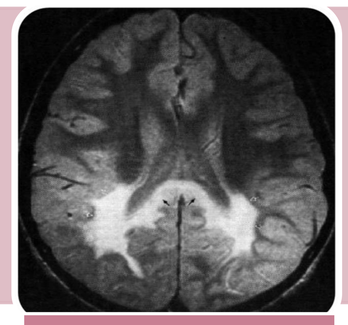
First case: Childhood cerebral ALD (CCALD)

❖11 years old boy with normal early development
❖ history of head trauma at the age of 8
❖ presented at the age of 10 progressive cognitive perturbations:
- ❖declining school performance
- ❖behavioural changes

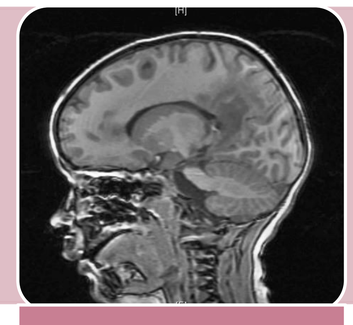
❖ neurological disturbances:
- ❖decreased visual acuity
- ❖seizures
- ❖slowly progressive tetraparesis

❖ after ruling out other neurological disorders and infections, the supposition of ALD was confirmed by brain MRI (specific white matter lesions) and increased VLCFA in the blood.
❖no family history could be found.
❖In the absence of clinical signs, the laboratory testing (normal cortisol and high ACTH > 1250 pg/ml) diagnosed subclinical AI.
❖Treatment: Lorenzo's oil, ASEA with slight amelioration
❖Genetic test: in progress.

Neurological perturbations of the first case:
-progressive tetraparesis
-seizures
-visual disturbancies
-severe psychomotor retardation, profound hypotonia with depressed deep tendon reflexes (DTRs)
-impaired hearing



MRI of the first case showing the typical pattern of posterior white-matter involvement.



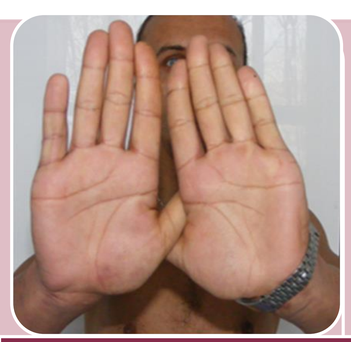
Brain MRI of the first case:
bilateral symmetric demyelination of various parts of the brain.

Second case: Adolescent cerebral ALD (AdolCALD)

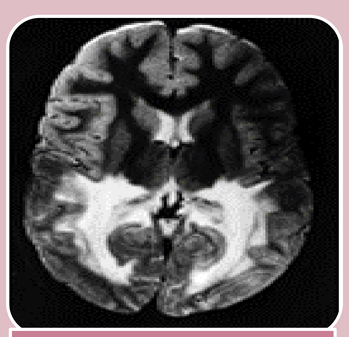
❖ 27 years old man
❖ family history of ALD :
- ❖ 1 sister with genetic confirmation
- ❖ 2 deceased male nephews at the age of 8

❖ onset of progressive neurological (spastic paraparesis) and cognitive (behavioural changes) perturbances at the age of 18.
❖ the clinical findings of AD (hyperpigmentation of the skin, low blood pressure, astenia) were biologically confirmed (ACTH>1250 pg/ml, cortisol=7.36 ng/dl) and treated with substitutive doses of glucocorticoids.

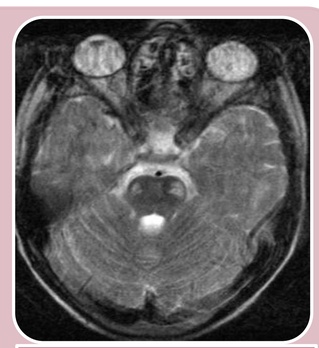
ALD Phenotype	ACTH (pg/ml)	Cortisol (ng/dl)	VLCFA
First case: Childhood cerebral ALD	ACTH>1250	6.5	C26=2.72 umol/l, N:0.51-1.05, C26:0/C22:0=0.079, N: 0.008-0.026, C24:0/C22:0=1.846, N:0.72-1.02
Second case: Adolescent cerebral ALD	ACTH>1250	7.36	-



Clinical signs of the second case:
-skin hyperpigmentation (palmar creases)
-asthenia
-low blood pressure.



Second case:The predominant pattern of demyelination seen by brain MRI is posterior (parieto-occipital lobes) in 80-85% of cases.



Brain MRI of the second case: confluent and symmetric bilateral hyperintensities in white matter of the parieto-occipital regions.

* All pictures are reproduced with informed consent.

Discussions

Cerebral ALD (childhood, adolescent)
➢most frequently present in childhood (childhood cerebral ALD; CCALD), however never before the age of 2.5 years (1)
➢most rapidly progressive and devastating phenotypes of X-ALD (2)
➢the onset of CCALD is insidious, with deficits in cognitive abilities that involve the spatial and motor visual functions or attention and reasoning. (1)
➢in boys and adolescents it initially results in a decline of school performance
➢these early clinical symptoms are often misdiagnosed as attention deficit hyperactivity disorder and can delay the diagnosis of CCALD.(3)

Prognostic and evolution
➢As the disease progresses, neurologic deficits become apparent: decreased visual acuity, hemiparesis or spastic tetraparesis, cerebellar ataxia and seizure like in our **first case**: progression is extremely rapid and devastating.
➢The evolution in **the second case** is slower, with psychiatric, neurological disturbances (motor functions) and cognitive decline.
➢Eventually, patients are bedridden, blind, unable to speak or respond, requiring full-time nursing care (first case) and feeding by nasogastric tube or gastrostomy.
➢Usually death occurs two to four years after onset of symptoms, or – if well-cared for - patients may remain in this apparent vegetative state for several years.(1)

Conclusion

❖The clinical presentation of ALD is highly variable and, without accurate diagnosis, X-ALD will continue to spread and mystify the medical professionals (early clinical symptoms are often misdiagnosed and there is no genotype-phenotype correlation, in spite of identical ABCD1 gene mutations) (1).
❖Early diagnosis has important implications for genetic counselling and management. The eventual phenotype in an individual will be determined by the combination of several epigenetic and environmental modifiers.
❖For the majority of patients with X-ALD there is currently no curative or preventive treatment. However, several promising new approaches will hopefully succeed in the future. For example, it has been demonstrated in X-ALD cells that small interfering RNA (siRNA)-mediated inhibition of ELOVL1 reduces VLCFA synthesis and levels (3). Recognition of X-ALD is highly important, since in some cases treatment is available, such as allogeneic hematopoietic stem cell transplantation in the early stage of CCALD and endocrine replacement therapy for adrenocortical insufficiency. (1)
❖More research and new treatments strategies are desperately needed and prenatal testing, biochemical diagnosis to prevent unnecessary new cases of this devastating disease should become available in more countries.

References: (1). Engelen M *et al* X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet Journal of Rare Diseases 2012;7:51; (2). Kemp S *et al*. Method for measurement of peroxisomal very-long-chain fatty acid beta-oxidation in human skin fibroblasts using stable-isotope-labeled tetracosanoic acid. Clin Chem 2004;50:1824–1826.(3). Ofman R *et al*. The role of ELOVL1 in very long-chain fatty acid homeostasis and X-linked adrenoleukodystrophy. EMBO Mol Med 2010;2:90–97.