Various presentations of X-linked adrenoleukodystrophy: case reports

Alina Daniela Fădur¹, Aurora Constantinescu², Cristina Rusu², Adina Manolache³, Ioana Bodescu³, Dumitru D Brânișteanu³, Cristina Preda³, Voichita Mogoș³, Carmen Vulpoi³

¹Department of Endocrinology, University of Medicine and Pharmacy "Gr.T.Popă Iași", Romania; ²Department of Neurology, Romania; ³Department of Genetics, University of Medicine and Pharmacy "Gr.T.Popă Iași", Romania

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)

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.
- The clinical findings of AD can delay the diagnosis of CCALD (3).

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.
- The role of ELOVL1 in very long chain fatty acid homeostasis and X-linked ALD (2).

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) symptoms at the age of 18
- The clinical findings of AD (hypopigmentation 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.

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

<table>
<thead>
<tr>
<th>Frequency (%)</th>
<th>CCALD</th>
<th>AdolCALD</th>
<th>ACALD</th>
<th>ANN no cerebral disease</th>
<th>ANN cerebral disease</th>
<th>Addition only</th>
<th>Women with X-ALD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCALD</td>
<td>31-35</td>
<td>11-10</td>
<td>2-5</td>
<td>40-46</td>
<td>20</td>
<td>Decreasing</td>
<td>Unknown</td>
</tr>
<tr>
<td>Age at onset</td>
<td>2.5-10</td>
<td>10-40</td>
<td>&gt;21</td>
<td>18&lt;18</td>
<td>&gt;18 18&lt;2</td>
<td>variable</td>
<td>40</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>-</td>
<td>Possible</td>
<td>-</td>
<td>or</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>-</td>
<td>Possible</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Endocrine</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disorder</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Slow</td>
<td>Slow</td>
<td>Slow</td>
<td>Slow</td>
</tr>
</tbody>
</table>

Prognostic and evolution

- As the disease progresses, neuroligic 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 alogliptin 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: