CASE REPORT Albanian Journal of Biomedical Science 2017, Volume I
ISSN 2521-7321

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THE FIRST REPORT OF AN ABCD1 GENE MUTATION IN AN ALBANIAN FAMILY

Mirela DRAGONI[1], Armand SHEHU[2], Arben RROJI[3], Maksim CIKULI[1]

[1]Service of Medical Genetics, UHC "Mother Teresa", Tirana, Albania
[2]Service of Neuropediatrics, UHC "Mother Teresa", Tirana, Albania
[3]Service of Neuroradiology, UHC "Mother Teresa", Tirana, Albania
(Corresponding author: mirelatabaku@yahoo.com)

X-linked adrenoleukodystrophy (X-ALD), a progressive neurodegenerative disease, is characterized by an abnormal function of the peroxisomes, which leads to an accumulation of the Very Long Chain Fatty Acids (VLCFA) in plasma and tissues, especially in the white matter of the central nervous system and the cortex of the adrenal glands (Kallabi 2016, Wiesinger 2015). X-linked adrenoleukodystrophy is a monogenic disease caused by mutations in the ABCD1 gene located on Xq28 (Wiesinger 2015). Mutations in the ABCD1 gene affect the function of the encoded protein ALDP, an ATP-binding cassette transporter located in the peroxisomal membrane protein (Kallabi 2016, Wiesinger 2015). Being an X-linked disease it affects mostly males, although some women who are carriers can have milder forms of the disease (Santosh 2013). The phenotypic expression and prognosis of an affected male is unpredicta variable (Kallabi 2016). Clinically, X-ALD can present with a wide range of phenotypic manifestations (Wiesinger 2015, Engelen 2012, Kemp 2016). Three main phenotypes are seen in affected males: 1) Childhood cerebral form – appearing in mid-childhood, 2) Adrenomyelopathy – occurring in men in their 20s or later and 3) Impaired adrenal gland function (called Addison disease or Addison-like phenotype) – adrenal gland does not produce enough steroid hormones. (Santosh 2013, Kemp 2016)

The present paper reports the clinical, biochemical, MRI imaging and molecular investigation in an Albanian family with an affected male with childhood cerebral adrenoleukodystrophy. His mother and sister carry the same mutation too. We believe that this is the first publication of ABCD1 gene mutation in an Albanian family.

Case Report

The patient was 8 years old when he was hospitalized due to severe headache, vomiting, confusion and intermittent *loss of consciousness (syncope)*. For months before the hospitalization, the patient had shown inattention, deterioration in handwriting skills and diminishing school performance, but his parents did not pay too much attention on them. The boy had febrile seizures when he was 7 and 22 months old. On admission to hospital, Magnetic Resonance Imaging (MRI) suggested adrenoleukodistrophy. MRI revealed the following findings: bilateral high signal lesion on T2 and FLAIR

in bilateral peri-atrial regions, which show peripheral enhancement after administration of i/v contrast and extention to splenium of corpus callosum and bilateral lemniscal tract. Biochemical reports also showed elevated levels of very long chain fatty acids in plasma.

After 3 weeks of treatment in the hospital the clinical status and neurological examination of the patient was almost normal. Later the patient showed difficulty in understanding speech, difficulty in reading, spatial orientation, and comprehension of written material; hearing difficulties, a decline in visual acuity and a hyperactivity.

Discussion

Leukodystrophies comprise a broad group of progressive, inherited disorders affecting mainly myelin (Santosh 2013, Kemp 2016). X-linked adrenoleukodystrophy is a neurodegenerative recessive disorder caused by mutations in the ABCD1 gene located on Xq28 (Kallabi 2016, Wiesinger 2015, Kemp 2016). The ABCD1 gene codes for the peroxisomal transporter ATP-binding cassette subfamily D member 1 (ABCD1, formerly ALDP) contain ten exons and spans 20 kb of genomic DNA. The 3616-bp transcript has 2,235 bp of coding sequence (Wiesinger 2015, Kemp 2016). ABCD1 gene mediates the import of very long-chain fatty acid (VLCFA) CoA esters across the peroxisomal membrane and its dysfunction results in impaired degradation of VLCFAs in peroxisomes and consequently leads to their accumulation in various lipid species in tissues and body fluids. (Kallabi 2016, Wiesinger 2015, Klouwer 2016, Wiesinger 2013,8). X-ALD manifests clinically as dysfunctions of the central nervous system (CNS), adrenal glands, and testicles (Kallabi F 2016, Wiesinger Ch 2015, Kemp S 2016).

The diagnosis of ALD is primarily based on clinical, MRI imaging, biochemical and genetic studies. (Santosh 2013, Wiesinger 2015, Kemp 2016)

The childhood cerebral form of three main phenotypes which are observed in affected males manifest themselves most commonly between ages four and eight years. Boys with symptoms of attention deficit disorder (ADD) show signs of progressive behavioral disturbance, vision loss, difficulty in understanding spoken language, worsening handwriting, incoordination or other neurologic disturbances and motor function ones, dementia follows the initial symptoms and often leads to total disability within two years. Other variants observed in approximately 5%-10% of affected males incclude headache, increased intracranial pressure, hemiparesis or visual field defect, aphasia or other signs of localized brain disease with the onset usually between age four and ten years (Kemp 2016, Wiesinger 2015).

Our patient had almost a normal development until he reached 8 years old when he was hospitalized due to severe headache, vomiting, confusion and intermittent loss of consciousness. His clinical data before hospitalization (inattention, deterioration in handwriting skills, diminishing school performance) and after hospitalization (difficulties in reading, in understanding speech, in spatial orientation, in hearing etc), are typically found in the childhood cerebral form of X-linked adrenoleukodystrophy. Our patient has reached a total disability within one year and benefits from the general supportive care of parents, as well as of the hospital.

Besides, MRI images of the patient were compatible and consistent with active demyelination as usually observed in childhood cerebral X-ALD (Santosh 2013). MRI is always abnormal in boys with cerebral disease and often provides the first diagnostic lead. In approximately 85% of affected individuals, MRI shows a characteristic pattern of symmetric enhanced T2 signal in the parieto-occipital region with contrast enhancement at the advancing margin (Santosh 2013, Kemp 2016).

Typically, when a diagnosis of X-ALD is suspected based on clinical presentation or magnetic resonance imaging abnormalities, biochemical testing for elevated plasma VLCFA levels is performed. Biochemical reports show elevated levels of very long chain fatty acids in plasma (Wiesinger 2015, Santosh 2013, Klouwer 2016, Wiesinger 2013). Plasma concentration of very long chain fatty acids (VLCFA) is abnormal in 99% of males with X-ADL regardless of age, disease duration, metabolic status, or clinical symptoms (Wiesinger 2015, Kemp 2016). Three parameters usually are analyzed: Concentration of C26:0 Ratio of C24:0 to C22:0 Ratio of C26:0 to C22:0. All three parameters are elevated in the majority of males, though some variation is observed (Kemp 2016). Thus, an elevated level of VLCFAs, as in our case, represents the standard biomarker for diagnosis of X-ALD, but does not predict the phenotype or progression of disease (Wiesinger 2015).

In our case report, magnetic resonance imaging (MRI) as well as the high levels of VLCFAs prompted the diagnosis the X-ALD. Molecular analysis of ABCD1 gene has shown a pathogenic mutation. Sequence analysis of all ABCD1 gene was performed and identified the following hemizygous mutation: c1553G>A (pArg518 Gln). No additional pathogenic mutations were identified in the ABCD1 gene. The found mutation is a missense one. A tremendous number of different disease-causing mutations have been described in X-ALD (Wiesinger 2015, Schackmann 2016, Karkar A 2015). Missense variants have been found in all parts of the gene but are most common in the membrane domain or the ATP-binding domain, emphasizing the importance of these two domains for the function of ALDP (Kemp 2016). A comprehensive overview of all described mutations can be found in the X-ALD database (http://www.x-ald.nl) (Wiesinger 2015). This mutation has been previously reported (http://www.x-ald.nl).

The phenotype cannot be predicted by VLCFA plasma concentration or by the nature of the ABCD1 pathogenic variant as the same pathogenic variant can be associated with each of the known phenotypes (Kemp 2016, Wiesinger 2015). No relevant genotype–phenotype correlation exists in X-ALD. Some current, ongoing SNP association studies suggest that multiple loci, rather than a single modifier gene, likely contribute to the phenotype (Kemp 2016, Brose 2012, Semmler 2009).

While the majority of patients typically inherit the defective ABCD1 allele from one parent, between 4.1% and 19% of X-ALD cases have been reported to carry mutations acquired de novo (Kemp 2016). The ABCD1 gene sequencing indicated the same missense mutation c1553G>A (pArg518 Gln) in the exon 6 of the ABCD1 gene in the patient, his mother and his sister too.

Approximately 20% of females who are carriers develop neurologic manifestations like mild to moderate spastic paraparesis that resemble AMN but have later onset (age ≥35 years) and milder disease than do affected males (Kemp 2016). His mother clinically has a mild form of the disease. Finding the same mutation at his sister is helpful to clarify the carrier status and for the discussion of the availability of prenatal testing before her future pregnancy (Kemp 2016).

As the conclusion, familiarity by the pediatricians, neuropediatricians with the clinical-pathologic manifestations and progressive MR imaging features of childhood cerebral X-linked ALD is helpful in evaluating affected patients (Santosh 2013, Wiesinger 2015, Klouwer 2016).

To establish the extent of disease and requirements in an individual diagnosed with X-linked adrenoleukodystrophy (X-ALD), the following evaluations are recommended: neurologic examination, brain MRI, adrenal function tests and medical genetics consultation. Evaluation of at-risk family members, often implemented insufficiently, is important for the management and genetic counseling (Kemp 2016, Wiesinger 2013).

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