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CASE REPORT / OLGU SUNUMU

A novel *ABCD1* gene mutation in a patient with X-linked adrenoleukodystrophy with atypically normal plasma levels of very long chain fatty acids

Plazmada çok uzun zincirli yağ asidi düzeyleri normal olan bir X'e bağlı adrenolökodistrofi hastasında daha önce tanımlanmamış bir *ABCD1* gen mutasyonu

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is a rapidly progressive neurodegenerative disorder characterized by progressive demyelination of central nervous system, adrenocortical insufficiency and elevated levels of very long chain fatty acids (VLCFAs) in plasma and tissues. Here, a seven-year-old patient who had atypically normal plasma levels of VLCFAs and whose diagnosis of X-ALD is confirmed by a novel mutation of *ABCD1* gene is described.

Keywords: X-ALD, *ABCD1* gene, VLCFA

ÖZ

X'e bağlı adrenolökodistrofi (X-ALD) hızlı ilerleyici nörodejeneratif bir hastalık olup, santral sinir sisteminin ilerleyici demiyelinizasyonu, adrenokortikal yetersizlik ve plazma çok uzun zincirli yağ asidi (VLCFAs) düzeylerinin yükselmesiyle karakterizedir. Bu yazıda, plazma VLCFA düzeyleri beklenenin aksine normal sınırlarda olan ve X-ALD tanısı *ABCD1* geninin daha önce tanımlanmamış bir mutasyonunun gösterilmesiyle konulan 7 yaşındaki erkek hasta sunulmuştur.

Anahtar kelimeler: X-ALD, *ABCD1* geni, VLCFA

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Introduction

X-linked adrenoleukodystrophy (X-ALD) is a rapidly progressive neurodegenerative disorder resulting from dysfunction of a peroxisomal adenosine triphosphate (ATP)-binding fatty-acid transporter due to mutations in the *ABCD1* gene (NM_000033.3) localized to Xq28 [1]. It is characterized by progressive demyelination of central nervous system, adrenocortical insufficiency and elevated levels of very long chain fatty acids (VLCFAs) in plasma and tissues. Diagnosis is usually based on clinical, radiological and serological examinations and it should be confirmed with molecular analysis of *ABCD1* gene [2, 3]. To date, more than 1300 mutations have been reported and listed in X-ALD database [4]. In this report, a seven-year-old Turkish patient who had atypically normal plasma levels of VLCFAs and whose diagnosis of X-ALD is confirmed by a novel mutation of *ABCD1* gene is described.

Case Report

A seven-year-old male patient was admitted to our outpatient clinic with complaints of weakness of lower extremities, difficulty in spatial orientation, aggressive behavior and inarticulate speech. He appeared to be healthy in his first six years and he achieved developmental milestones appropriate with his age. During the last year before his admission to our department, diminished school performance and inattention were noted by his teachers.

His physical examination revealed reduced muscle strength as 3/5 in lower extremities, hyperreflexia of both superior and inferior extremities, pathological Babinski sign and inarticulate speech. Results of extensive examinations

including hematological and biochemical investigations, quantitative amino acid analysis, acylcarnitine analysis performed by tandem mass spectrometry (MS), urinary organic acids, plasma lactate and ammonia levels were found normal.

His brain T2 weighted magnetic resonance imaging (MRI) findings showed high signal intensity lesions in the parieto-occipito-fronto-temporal periventricular white matter, especially around the atrium of the lateral ventricle, the posterior half of the corpus callosum, posterior limb of the internal capsule and along the pyramidal tract of the brainstem. As the radiological findings were highly predictive of X-ALD, fasting plasma levels of VLCFAs were measured. Plasma VLCFAs levels were normal as C22:0=42 µmol/L (normal: 0-105µmol/L), C24:0=50,2 µmol/L (normal:0-80 µmol/L) and C26:0=0,89µmol/L(normal:0-0,92 µmol/L). His C24:0/C22:0 and C26:0/C22:0 ratios were slightly elevated at 1,2 (normal:0,51-1,19) and 0,02 (normal:0,006-0,014) respectively.

Atypical pattern of normal plasma levels of VLCFAs despite the existence of neurological and clinical manifestations and MRI findings compatible with X-ALD led the necessity of molecular analysis of *ABCD1* gene. Genomic DNA was extracted from peripheral blood obtained from the patient after taking the inform consent of the parents. The coding region of *ABCD1* including the intron-exon boundaries of all exon 1-10 were amplified using the polymerase chain reaction (PCR). Molecular analysis of *ABCD1* gene which was applied by next-generation sequencing (NGS) showed the c.713_730del18 mutation in homozygous state. As this mutation of the *ABCD1* gene has not been reported before, molecular analysis of *ABCD1* gene of the mother was also performed. The analysis result of the mother showed c.713_730del18 mutation in heterozygote state. Both of the mutations were confirmed by Sanger sequencing. Two single-nucleotide polymorphisms were detected (c.2019C>T (p.F673=); c.2190G>A (p.P730=)) that were previously reported in X-ALD database [4]. His initial diagnosis was based on neurological and clinical manifestations and MRI findings. His diagnosis was confirmed by genetic evidence of an *ABCD1* mutation.

Discussion

Adrenoleukodytsrophy (ALD) is mainly classified as cerebral ALD (childhood, adolescent and adult forms), adrenomyeloneuropathy, Addison-only, olivopontocerebellar ALD and asymptomatic ALD [3]. Clinical manifestations depend on demyelination of central nervous system and adrenocortical insufficiency. The childhood cerebral ALD form is the most severe phenotype of the disease with onset of neurological symptoms between 5 and 12 years of age. Initial symptoms may be subtle and nonspecific as diminished school performance, attention deficit and behavioral changes. Our patient was seven years old when he was admitted to our department but his initial symptoms, like diminished school performance and inattention started a year ago. Devastating neurological symptoms such as severe visual and hearing impairment, quadriplegia and cerebellar ataxia and seizures can develop following the initial symptoms as the disease progresses. Brain MRI reveals characteristically symmetrical cerebral lesions involving the white matter in the parietal and occipital lobes [5]. Brain MRI findings of our patient showed high signal intensity lesions in the parieto-occipito-fronto-temporal periventricular white matter.

In the X-ALD database, more than 1,300 mutations have been reported to date in *ABCD1* gene. These mutations were described as 51% missense mutations, 11% nonsense mutations, 28% frameshift mutations, 6% amino acid insertions/deletions, and 3% deletion of one or more exons. There is no clear correlation between the phenotype and genotype of ALD patients [6].

Elevated levels of VLCFAs represent the standard biomarker for diagnosis of X-ALD. Elevation of VLCFAs due to accumulation is observed in most of male X-ALD patients regardless of age, metabolic status, or clinical symptoms. The most frequently used diagnostic parameter is the concentration of total C26:0. In addition, ratio of C26:0/C22:0 or C24:0/C22:0 can be used, because C22:0 remains unchanged or is even slightly reduced in plasma samples of X-ALD patients. As the increased measurement of VLCFAs can only be detected in 85% of female carriers, additional mutation analysis of the *ABCD1* gene is necessary for definite diagnosis of heterozygous X-ALD females [7].

In our patient, although the imaging findings and neurological symptoms were compatible with X-ALD, levels of plasma VLCFAs were in normal ranges. His diagnosis was confirmed by genetic evidence of an *ABCD1* mutation. c.713_730del18 mutation in homozygous state in the *ABCD1* gene has not been reported before.

In conclusion, normal plasma levels of VLCFAs do not exclude the diagnosis of X-ALD in the existence of clinical and radiological suspicion. Mutational analysis of the *ABCD1* gene can lead to proper diagnosis.

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