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ALSTRÖM SYNDROME WITH EARLY VISION AND HEARING IMPAIREMENT

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ABSTRACT

Alström syndrome (ALMS) is an autosomal recessive disorder characterized by multiple organ involvement, including progressive cone-rod dystrophy, sensorineural hearing loss, childhood obesity, and type 2 diabetes mellitus. Pathogenic variants in the ALMS1 gene are the known cause for the occurrence of this devastating condition.

Here we report on a 12 year old boy referred to the University Clinic with early signs of impaired hearing and vision, obesity, and scoliosis. Central vision was first affected, followed by peripheral vision. In addition, his weight began increasing after the age of two years, reaching 78 kg at a height of 157 cm (BMI 31.64). No polydactyly was present. His mental development was normal in spite of his hearing and vision impairments. There was acanthosis nigricans on the neck. ECG and the cardiac ultrasound were normal. At the age of 12 years, his testicles are 12 ml and his pubertal status is P2 A2. OGTT revealed impaired glucose tolerance with elevated insulin concentrations 121ulU/mL (reference range 2,00-29,1 ulU/mL). Renal function was unaffected, liver functions were normal. Uric acid and lipids were within normal plasma concentrations. A Whole Exome Sequencing was performed and a homozygous ALMS1 pathogenic, frameshift gene variant (LRG_741t1(ALMS1):c.4156dup; p.Thr1386AsnfsTer15) was determined as the cause of the disease. Both parents were carriers for the variant. The absence of mental retardation and polydactyly differentiates Alström and Bardet-Biedle syndrome.

Keywords: Alström Syndrome, cone-rod retinal dystrophy, sensorineural deafness, ALMS1 gene

INTRODUCTION

Alström Syndrome (ALMS) is a multisystem disorder characterized by progressive cone-rod dystrophy, sensorineural hearing loss, cardiomyopathy, renal dysfunction, extreme insulin resistance (IR), childhood obesity, and type 2 diabetes mellitus [1]. The diagnosis of ALMS can be challenging as some features begin at birth and others emerge later in childhood. There is considerable variation in the clinical presentation within and among families. The disease is relentlessly progressive in nature [1, 2].

ALMS is a monogenic disorder caused by homozygous or compound heterozygous variants in the ALMS1 gene. Of the 268 pathogenic

variants identified so far, 96% are nonsense or frameshift changes (insertions and deletions) [3].

We report a severe phenotype in a 12 year old boy with a homozygous ALMS1 gene pathogenic variant c.4156dup (p.Thr1386AsnfsTer15).

PATIENT AND METHODS

A 12 year old child was admitted to the endocrinology department of the University Clinic for Paediatrics in Skopje with a high fasting glycaemia of 10 mmol/L (4.10-5.90 mmol/L), obesity and acanthosis nigricans on the neck. The child had early signs of impaired hearing and vision. There are no similar manifestations in the family.

Central vision was first affected, followed by peripheral vision. In addition, his weight started to increase after the age of two years, reaching 78 kg at a height of 157 cm (BMI 31.64). No polydactyly was present. His mental development was normal, in spite of his hearing and vision impairments.

ECG and the cardiac ultrasound were normal. At the age of 12 years, his testicles are 12 ml and pubertal status is at P2 A2. OGTT revealed impaired glucose tolerance, with elevated insulin concentrations 121ulU/mL (reference range 2,00-29,1 ulU/mL). Renal function was unaffected, liver functions were normal. Uric acid and lipids were within normal plasma concentrations.

Whole-exome sequencing was performed in the proband using an Illumina NovaSeq 6000 sequencer and Twist Human Core Exome Panel (Twist Bioscience). ACMG guidelines were followed for the pathogenicity assessment of identified variants. The analysis revealed a homozygous pathogenic variant LRG_741t1(ALMS1):c.4156dup; p.Thr1386AsnfsTer15 in exon 8 of the ALMS1 gene (fig.1). The variant is an insertion of one nucleotide-adenine, changing the amino acid threonine with asparagine at position 1386 and the reading frame leading to termination of protein synthesis after 15 amino acids. The variant was classified as pathogenic in the ClinVar database (ID:210127) and it has already been reported in the literature as a cause of Alström disease [7]. Sanger sequencing of exon 8 in ALMS1 gene was performed with BigDye v.1 (Thermo Fisher) on an ABI 3500 genetic analyser (Applied Biosystems). This was performed for confirmation of the result. Both parents were found as a carriers for the ALMS1 c.4156dup; p.Thr1386AsnfsTer15 gene variant.

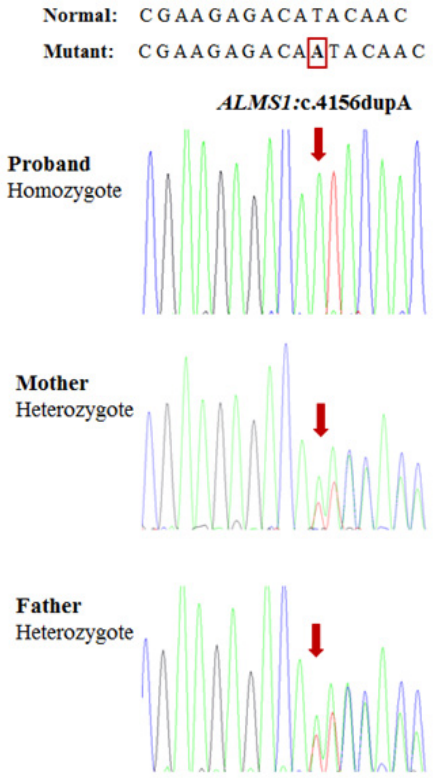

Figure 1. *Sanger sequencing confirmed the homozygous insertion of adenine at codon 4156 in exon 8 of the ALMS1 gene in the proband. Both parents were heterozygous for the insertion.*

DISCUSSION

As ALMS has a variable sequence of occurrence of symptoms, oftentimes over a long time frame, the diagnosis can be challenging [4]. Additional problems are often related to limited access to genetic testing in countries with limited resources as well as the rarity of the syndrome. Taken together with the rarity of ALMS, with an incidence estimated at 1/1,000,000 children [5], children often face a long road to proper diagnosis. Therefore, diagnostic criteria which rationally consider major and minor criteria in different age groups is of utmost importance [6]. Our patient, a boy aged 12 years, fulfilled the criteria for his age group, having two major criteria: both alleles with ALMS1 mutation and vision loss, due to cone dystrophy. The boy had obesity, in-

sulin resistance, and hearing loss, all are taken as minor criteria [6]. A somewhat similar history of symptom occurrence, as found in our patient, have been reported [7]. An adult male lost his vision when he was two years old and lost his hearing at seven years old. This was followed with diabetes at 12 years, and sequentially with autism, severe hepatic dysfunction, and pulmonary dysfunction, hyperlipidaemia, hypogonadism, GERD, and scoliosis [7]. The authors also reported an earlier onset of ALMS in a 12 year old girl who lost vision at the age of six years and then developed dilated cardiomyopathy, hypertension, diabetes, hepatic dysfunction, and obesity.

Kuburović et al. (2013) [8] reported on a patient with an unusual clinical presentation and a heterozygous ALMS1 pathogenic variant in exon 16, c.10568_10569delAT; p.His3523Terfs17. The clinical features included centripetal obesity with selective loss of adipose tissue in his legs and gluteal region, acanthosis nigricans, gynecomastia, scoliosis, glomerulopathy, subclinical primary hypogonadism, restrictive filling of the left ventricle, and significant early atrial contraction. Their second patient had epilepsy at the age of two years, followed by vision and hearing impairments, hypertension, hepatic dysfunction, mental retardation (IQ 40), hypogonadotropic hypogonadism, renal dysfunction, acanthosis nigricans, and truncal obesity with reduced femoral-gluteal fat. The authors propose that variable neurological involvement, including seizure activity, should be included as a rare occurrence, and as a part of the phenotypic spectrum of ALMS [8].

Dilated cardiomyopathy [9] was noted as a leading symptom, while ALMS was also understood as a model for diabetes mellitus type 2 [10]. Non-classical phenotypes are also reported [11] in a patient with exon five compound variants of (c.777delT:p.D260fs*26) and exon 20 (c.12145_12146insC:p.S4049fs*36). The authors concluded that the current diagnostic criteria might not properly diagnose some ALMS patients [11].

The challenge in diagnosing ALMS is significant. In our patient, identification of a pathogenic variant c.4156dup (p.Thr1386AsnfsTer15) in the ALMS1 gene in homozygous state made the diagnosis and shortened the diagnostic voyage. Unfortunately, two disease-causing mutations are not always easily discovered as the gene is huge (23 exons). Therefore the set of diagnostic criteria devised for different age groups (infants under the age of two, children aged three to fourteen, and adolescents/adults above the age of fifteen) (Marshall JD et al 2007) [6]. The period between the occurrences of first symptoms to final diagnosis can be significantly shortened via careful clinical examination of all signs and symptoms mentioned in the table of diagnostic criteria.

Early attention to the set of clinical signs and symptoms in our patient could have also shortened the long diagnostic voyage of our patient. Namely, blindness, obesity, hearing loss, no polydactyly, and mental retardation (Bardet-Biedle syndrome) are sufficient enough to choose a direct genetic analysis.

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Резиме

АЛСТРОМ-СИНДРОМ СО РАНО ОШТЕТУВАЊЕ НА ВИДОТ И НА СЛУХОТ

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Алстром-синдромот (АЛМС) е автосомно рецесивно нарушување, кое се карактеризира со афекција на повеќе органи, вклучувајќи прогресивна дистрофија на стапчиња и чунчиња во окото, сензо-неврален губиток на слух, појава на обезност кај децата и дијабет тип 2. Патогените варијанти на генот ALMS1 се познати причини за појава на ова заболување.

Ова е случај на 12-годишно момче што беше упатено на Универзитетската клиника за педијатрија поради рани знаци на оштетен слух и вид, обезност и сколиоза. Најпрво бил засегнат централниот вид, по што следувала афекција и на периферниот. Покрај тоа, започнувајќи од 2-годишна возраст, неговата телесна тежина почнала да се зголемува, за да достигне 78 kg на висина од 157 cm (BMI 31,64). Не беше присутна полидактилија. Неговиот ментален развој беше нормален и покрај оштетувањата на слухот и на видот. На вратот имаше acanthosis nigricans. ЕКГ-то и ехосонографијата на срцето беа уредни. На 12-годишна возраст неговите тестиси се 12 ml, а пубертетскиот статус е P2 A2. ОГТТ откри нарушување на толеранцијата на глукоза, со покачено ниво на инсулин 121 uIU/ml (референтни вредности 2–29,1 uIU/ml). Реналната и хепаталната функција не беа засегната. Мочната клиселина и липидите во серум беа во границите на референтните вредности. Беше направено WES, и хомозиготна ALMS1 патогена мутацијата што води до промена на рамката (LRG_741t1(ALMS1):c.4156dup; p.Thr1386AsnfsTer15) беше најдена како причина за болеста. Двајцата родители се носители на оваа варијанта. Отсуството на ментална ретардација и полидактилија го диференцираа синдромот Алстром од синдромот Бардет Бидл..

Клучни зборови: Алстром-синдром, дистрофија на ретинални стапчиња и чунчиња, сензо-неврална глувост, ген ALMS1