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SYNDROMAL DISLIPIDEMIA - CASE REPORT OF A FAMILY WITH ALSTROM SYNDROME

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РЕЗЮМЕ

СИНДРОМАЛЬНОЕ ДИСЛИПИДЕМИЯ - КЛИНИЧЕСКИЙ СЛУЧАЙ СЕМЬИ С СИНДРОМОМ АЛЬСТРЁМА.

Синдром Альстрёма. (ALMS) является аутосомно-рецессивным заболеванием, вызванным мутациями в гене ALMS1. Представляется случай семьи (мальчик - 9 мес. и девочка 17 - лет), в которой первоначально диагностирован нистагм, фотофобия и дистрофия сетчатки. Физическое обследование и анализ истории болезни предполагали синдром Альстрёма. Анализ секвенирования эгзома выявила в гене ALMS1 две гетерозиготные мутации: (c.8164C> T (p.Arg2722 *) в экзоне 10 и c.8656 C>Tp.(Arg2886) chr2) гена *ALMS1*, что подтвердило диагноз. Пациенты с синдромом Альстрёма достигают взрослого возраста со значительным бременем заболевания, которое постоянно снижает качество их жизни. Дистрофия сетчатки, ожирение, инсулинорезитентность сахарный диабет 2 типа, двусторонняя нейросенсорная тугоухость и низкий рост – вот лишь некоторые из многих проблем, возникающих при ведении этих пациентов. Дислипидемию при тщательном наблюдении и раннем выявлением можно лечить, следуя изменением образа жизни, а фармакологические вмешательства необходимы для эффективного лечения с целью предотвращения сердечно-сосудистых заболеваний. Дислипидемия является как правило результатом несбалансированной диеты, но в данном случае, нарушение представлено как симптом проявления генетического расстройства (Alström syndrome).

Ключевые- слова: синдром Альстрёма; АЛМС; ожирение; инсулинорезистентность; диабет

REZUMAT

DISLIPIDEMIA SINDROMALĂ – RAPORTARE DE CAZ CLINIC A UNEI FAMILII CU SINDROM ALSTRÖM

Sindromul Alström (ALMS) este o patologie recesivă autozomală cauzată de mutații ale genei ALMS1. Raportăm cazul unei familii cu 2 copii (băiat 9 luni și o fetiță de 17 ani), diagnosticați inițial cu nistagmus, fotofobie și distrofia retinei. Datele anamnestice, obiective și clinice au determinat suspecția sindromului Alström. Analiza prin secvențiere a întregului exon a relevat 2 variante heterozigote ale genei *ALMS1*: (c.5926deIGp Glu19765erfs.8chr2.73679577 și c.8656 C>Tp. (Arg2886) chr2.737177739). ceea ce a confirmat diagnosticul. Pacienții cu sindromul Alström ating vârsta adultă cu o povară semnificativă a bolii care le reduce continuu calitatea vieții. Distrofia retinei, obezitatea, diabetul zaharat de tip 2, insulinorezistența, surditatea neuro-senzorială bilaterală și hipostatura sunt doar câteva dintre numeroasele provocări ale managementului acestor pacienți. Aceste tulburări pot fi controlate prin detectarea lor precoce și monitorizarea adecvată. Dislipidemia ușoară până la moderată poate fi gestionată prin respectarea modificărilor stilului de viață, iar intervențiile farmacologice sunt esențiale pentru un tratament eficient în vederea prevenirii bolilor cardiovasculare. Dislipidemia este generată de o alimentație dezechilibrată, dar în cazul prezentat, aceasta a servit ca unicul semn biochimic din cadrul unui sindrom genetic (Alström syndrome).

Cuvinte-cheie: Sindrom Alström: ALMS; obezitate, insulinorezistență; diabet

Introduction

Alström syndrome is a rare genetic autosomal recessive disease characterized by multi-systemic involvement, produced by a mutation in the *ALMS1* gene, located on chromosome 2p13 [3]. It has a prevalence of < 1/100 000. Alström syndrome (AS) was first described in 1959 by Alström et al.[1,2]. The *ALMS1* gene contains instructions for creating (encoding) a specific protein known as ALMS1. The role and function of this protein in the body is involved in ciliary function, cell cycle control and intracellular transport. The ALMS1 protein is expressed in all organ tissues of the body (ubiquitously expressed). Regarding the fact that symptoms of Alström syndrome vary greatly among family members, researchers suspect that additional genetic or environmental factors may play a role in the development and progression of Alström syndrome. This gene encodes a protein whose mutation leads to progressive fibrosis of various organs characterized by cone-rod dystrophy, hearing loss, childhood truncal obesity, insulin resistance and hyperinsulinemia, type 2 diabetes, hypertriglyceridemia, short stature in adulthood, cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunction. Symptoms first appear during childhood and the progressive development of multiorgan pathology reduces life expectancy. [2,4].

Prior to the discovery of ALMS1 mutations, the diagnosis was made solely based on phenotype. However, the high degree of variability, even within families, creates difficulties for a universal definition. [5]. Ocular involvement is a cardinal sign of AS [5], that leads to progressive visual dysfunction and blindness, usually during the second decade of life. In addition, around 80% will develop neurosensorial hearing loss that will progress throughout life [1,5,6] . Birth weight is normal in infants with Alström syndrome, but excessive eating beyond the normal need to satisfy hunger (hyperphagia) and rapid weight gain may occur during the first year of life. Some affected children develop childhood truncal obesity, a condition in which fat is disproportionately distributed on the abdomen and chest rather than the arms and legs. As affected individual's age rises, some may see their body weight fall, often regaining normal or slightly above-average weight for their size. Childhood obesity is a common and early manifestation that is usually accompanied by a characteristic phenotypic expression. The affected individuals often develop type 2 diabetes with insulin resistance and hyperinsulinemia, as well as hypertriglyceridemia. Affected individuals may also have elevated levels of certain fats (lipids) in the blood (hyperlipidemia). Hyperlipidemia is usually characterized by elevated triglycerides in the blood (hypertryglyceridemia), which can cause inflammation of the pancreas (pancreatitis). Pancreatitis can be associated with abdominal pain, chills, jaundice, weakness, sweating, vomiting, and weight loss. The prognosis is variable and will depend on the progression of the involvement of the different organs and systems. Life expectancy is usually less than 50 years. [5]. Although there is no specific treatment, and measures should be targeted to treat damage to each of the different systems, early diagnosis, a multidisciplinary approach and appropriate prevention strategies will slow progression and thereby improve patient survival.

Case report. We are reporting on a case of a non-consanguineous healthy couple that required the first medico-genetic consultation in relation to their 3 children. They observed that their youngest child started to develop the same symptoms from the age of 5 months similar to those as their oldest girl, that gradually developed a severe mental retardation after 2 years old, uninvestigated before. Their oldest girl from the first pregnancy of mother was born at term without any peculiarities in pregnancy or at birth. Her neuropsychic and motor development during the first two years was practically certified in acceptable limits, with some particularities of excessive weight gain (more than 1 kg/month), somewhat short of energy, speech development deficiency (until 2 years old she tried to repeat only some syllables), overall suggestive of Prader-Willi Syndrome, but not investigated later. At the age of 6 months, during routine neurological follow-up nystagmus and photophobia have been attested, for which no specific investigations were conducted. After the age of 2 years old, a progressive neuropsychomotor delay was observed with the occurrence of stereotypical movements, signs of atypical autism, gradual loss of vision (at the age of 14-15) and cognitive acquisition, including verbal activity. There were suspected some pathological conditions during her pediatric control, but no specific investigations to confirm the diagnosis were recommended at that time. From the age of 13 years old there were seizures attested, partially responsive to anti-epileptic treatment. Presently, the older girl is 17 years old, with severe neuropsychomotor delay, complete loss of vision, she can hear, move with support, often in a flexed position, has some elementary autonomy (can go to the bathroom alone, led by someone because she cannot see), eats unaided, does not talk, sometimes experiences seizures. No metabolic and/or genetic investigations were performed before to elucidate the diagnosis. From the secondary pregnancy, the couple has a healthy girl of 9 years old. From the third pregnancy, the family has a boy born at term by caesarean section with normal body weight (2890g). During pregnancy, mother mentioned anxiety, a non-invasive prenatal (extended) test has been performed without any major suspicion, including Prader-Willi Syndrome, for which the first girl was suspected in her first year of life. In the first months of life, parents had no concerns regarding developmental milestones of child. In contrast, from the age of 5 months old, a horizontal left nystagmus occurred and after ophthalmologic examination partial optic atrophy was determined. Then, at the 9 months of age, the child developed pronounced distressing photophobia

and photosensitivity when outside in daylight. All other developmental categories were appreciated within normal limits. He has been reviewed by pediatricians, neurologists and geneticists. Due to the similarity between the boy`s clinical manifestations (horizontal nystagmus, photophobia) and the onset manifestations of the affected girl (table 1) there was a genetic disorder not raise the suspicion of a dysfunction in an extended panel.

Organic acids in the urine were also negative. At the same time the karyotype was recommended to be analyzed, which revealed normal result (46, XY). Considering the insignificant results of the biochemical and metabolic investigations for the establishment of a final diagnosis,

Table 1. Clinical manifestations in affected children.

Clinical presentation	Patient I	Patient II
Sex	Boy	Girl
Age	9 months old	17 years old
Birth weight (g)	2890	3150
Diminished visual acuity	-	+ (observed at 2 years old)
Photophobia	+	+
Nystagmus	+ (from 5 months old)	+
Reduced ERG	+	+
Sensorineural hearing loss	-	Conductive hypoacusis (5 years)
Obesity	+ (2 years)	+ (4 years)
Insulin resistance	-	+(14 years old)
Diabetes	-	+(15 years old)
Endocrine involvement	Subclinical hypothyroidism (2 years)	Subclinical hypothyroidism (4 years)
Hpertriglyceridemia	+ (2 years old)	+ (3 years old)
Renal involvement	-	Episodes of pyelonephritis
Orthopedic involvement	-	Scoliosis (5 years)
Liver involvement	-	Elevated transaminase levels (5 years)

suspected and probably an inborn error of metabolism. There were considered many disorders as Neuronal Ceroid Lipofuscinosis or a multisystem affecting disease as mitochondrial disease or even Congenital Disorder of Glycosylation as well. Considering the difficulty of investigation of the the girl, a decision was made to begin the investigation of the boy through biochemical and metabolic work-up analysis has been performed.

The biochemical analysis of blood revealed low Fe-2,86 mmol/L(*ref. val.*: 4,8-19,5 mmol/L), high level of Cholesterol-8,05 mmol/L(*ref. val.*: 0-5,2 mmol/L), LDL-Cholesterol-5,64 mmol/L(*ref. val.*: <2,59 mmol/L), Triglycerides-2.06 mmol/L(*ref. val.*: <1,7 mmol/L, upper limit-1,7-2,25 mmol/l) and LDH-586

U/L (*ref. val.*:207-414 mg/L). The metabolic investigation showed slightly elevated value of Ammonia-79,8 µmol/L (*ref. val.*:16-60 µmol/L) and Lactic Acid-2,4 mmol/L(*ref. val.*: 0-2,2 mmol/L) that were currently insignificant. There were determined extremely minor deviations in the plasma and urinary amino acid content that were not suggestive of any primary disorders of amino acid metabolism or their reabsorption. Testing for metabolic diseases (aminoacidopathies, organic acidurias, fatty acid oxidation defects) by LC-MS/MS from DBS method did the sequencing of the whole exome (WES) of two affected children (the youngest boy and the oldest girl) and the parents has been recommended. The WES identified two heterozygous variants in the *ALMS1* gene (table 2).

Interpretation:

- c.5926deIGp (Glu19765erfs.8) which leads to a frameshift effect, results in a premature stop codon, and subsequent mRNA degradation (nonsense-mediated) or truncation of the protein. Parallel analysis of parents and the affected sister WES data revealed that the sister and mother are heterozygous carriers of this variant. The variant has already been described in the literature as pathogenetic for mitogenic cardiomyopathy, which might be considered as early presentation of the Alström syndrome (PMID: 24595103). Considering the available information the variant is classified as pathogenic.
- C.8656 C>Tp.(Arg2886) which creates a premature stop codon, and subsequent mRNA degradation (nonsense-mediated decay) or truncation of the protein. Parallel analysis of parents and the affected sister WES data revealed that the sister and father are heterozygous carriers of the detected variant. The variant has already been described in the literature in

Table 2. The results of WES of affected children and the parents.

Gene (isoform)	OMIM-P (Mode of inheritance)	Variant	Index	Sister	Mother	Father	MA gnomAD	Literature	Classification
ALMS1(NM_015120.4)	203800(AR)	c.5926delGp (Glu19765erfs.8) chr2.73679577	het.	het.	het.	-	0	24595103	Pathogenic
		c.8656 C>Tp. (Arg2886) chr2.737177739	het.	het.	-	het.	het.	17594715	Pathogenic

patients with Alström syndrome (PMID: 17594715, 24463507). It is found in 0.00041% of the overall population (1 heterozygous, no homozygous). Considering the available information, this variant is also classified as pathogenic.

- Given the obtained results, the index and the affected sister are compound heterozygous for two pathogenic variants in the *ALMS1* gene. Considering the supportive phenotype of the patient and his affected sister and compound heterozygosity of two pathogenic variants in the *ALMS1* gene, a genetic diagnosis of Alström syndrome is confirmed for both of them.

Discussion

Alström Syndrome is an autosomal recessive, single gene disorder (ALMS1-2p13) characterized by childhood obesity associated with hyperinsulinemia, and type 2 diabetes mellitus, progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss and function loss of multiple organs [1,6,7]. In our case, the initial manifestations were visual problems - nystagmus, photophobia and occasionally controlled dyslipidemia, presented in the first year of life. As Marshall et al. (2007) categorized the features of Alström syndrome, our patient (the oldest girl) had similar findings like a progressive neuropsychomotor delay with the occurrence of stereotypical movements, signs of atypical autism, gradual loss of vision (at the age of 14-15) and cognitive acquisition, including verbal activity [1]. It was reported in an investigation paper with 182 cases of Alström Syndrome that 38% of patients had no cardiac failure (age range, 2-33 years), although there is a risk for developing dilated cardiomyopathy (DCM) in the future. Dilated cardiomyopathy occurred in 62% of patients. They notified that patients could be divided into two groups: infant and adult onset. Infant onset patients consisted 43% of patients, most of them survived and had no cardiac dysfunctions during three years. In contrary, between the age of 5 and 36 years, 24 of these patients had DCM recurrence and 10 had died. The second group consisted 18% of patients who had no cardiac failure in infancy but developed DCM as adolescents or adults (age range, 7-32 years) [4]. According to our patient's echocardiography, there were no congenital or other cardiac problems observed. Otherwise, with this information, we took him to cardiac controls with a period of six months. We know that DCM can develop in any time in the rest of his life. Marshall et al. reported 35 patients of 182 had gastroesophageal reflux. They also reported 92% of patients had elevation of liver transaminase levels [8]. But our patient had normal rate of liver transaminase levels and no gastro-esophageal reflux at this stage. The hypertension prevalence in Alström Syndrome is 30% [8], our patient was not hypertensive and kidney function tests were normal. We planned controls of these tests because of renal failure risk in the future.

Referring to the biochemistry results of suspected boy and his phenotype, there were no specific symptoms that could be considered suggestive for a genetic disease. But regarding the fact that there is another similar case in family history, dyslipidemia may be considered as a symptom of a genetic syndrome. Dyslipidemia in childhood usually appears due to genetic or secondary causes as familial hypercholesterolemia or hereditary hypertriglyceridemia, sometimes as a consequence of a high fat diet. The biochemistry analyses of parents' fat profile excluded familial dyslipidemia. To conclude, the hyperlipidemia (high cholesterol and triglycerides) attested in this child, may suggest a family disorder, but being accompanied by visual problems and especially related with nystagmus and photophobia, it must be taken into consideration and suppose Alström Syndrome, with very poor outcome.

Conclusion: Patients with Alström syndrome reach the adult age with a significant burden of the disease that continuously reduces their quality of life. The cone-rod retinal dystrophy, obesity, insulin resistance type 2 diabetes mellitus, bilateral neurosensory deafness and short stature are just few of the many challenges in the management of these patients. These disorders can be controlled with close observation and early detection.

Most patients with mild to moderate dyslipidemia can be managed by adherence to lifestyle modifications and pharmacologic interventions that are essential for effective treatment in order to prevent cardiovascular diseases. Dyslipidemia should be considered not only as a manifestation of unhealthy diet or obesity complication, but this case demonstrated that should be taken into consideration as a sign of a genetic disorder like Alström syndrome.

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