Two Siblings with Alström Syndrome

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Introduction

Alström syndrome is a rare autosomal recessive genetic disorder characterized by retinal degeneration, bilateral sensorineural hearing loss, early-onset obesity, hypertriglyceridemia, insulin resistance, type 2 diabetes, cardiomyopathy, systemic fibrosis and progressive multi-organ organ failure. Patients have short stature as adults and their life expectancy is reduced due to progressive development of multi-organ pathology. Alström syndrome is caused by mutations in *ALMS1,* this protein is found in centrosomes, basal bodies and cytosol of all tissues affected by the disease. The identification of ALMS1 as a ciliary protein explains the range of observed phenotypes and their similarity to those of other ciliopathies such as Bardet- Biedl syndrome.

Currently there is no specific therapy for Alström syndrome. The treatment includes weight control and management of diabetes, hearing aid, treatment of cardiac disease and replacement of thyroid hormones.

Our aim is to present two siblings who were diagnosed in early childhood in order to emphasize the importance of early diagnosis and genetic counselling.

Case Presentation

Two sisters from Romania who admitted to paediatric neurology department due to lack of eye contact and speech delay were referred to paediatric endocrinology department for evaluation of obesity. There was no history of consanguinity. The older sister was three years five months old. She was born after an uncomplicated pregnancy, 2700 grams and the neonatal period was uneventful. She could sit at 6 months and walk at 18 months of age. She never talked, her constant anxiousness could only be ameliorated by eating

On admission her **height was 98.7 cm (-0.01 SDS), weight 24 kg (+3.5 SDS), BMI 24. 64 kg/m^2(+ 4.21 SDS), had craniofacial dysmorphism (round face, nystagmus, bitemporal flatting), photophobia, truncal obesity and hepatomegal**y (Figure 1). There was no evidence of cardiac involvement, hypertension and polydactyly.

Her two years one month old sister had learning difficulty, blindness and shortness of breath. Birth weight was 3000 grams, could sit at 6 months, walk at 16 months of age, she can currently talk 2-3 words. Her **height was 98 cm (+2.78 SDS), weight 28 kg (+6.91 SDS), BMI 29.15kg/m^2 (+5.45 SDS). She had round face, short neck, nystagmus, bitemporal flatting, and truncal obesity** (Figure 1). Denver developmental screening test demonstrated moderate retardation in older and mild retardation in younger sister (Table 1).

Laboratory findings revealed that both sisters had low HDL levels, hypertriglyceridemia, and vitamin D deficiency. The older sister had slightly elevated transaminases, the younger sister had insulin resistance and subclinical hypothyroidism. The ophthalmologic examination was notable for retinal degeneration in both, echocardiography and abdominal ultrasounds were normal. Hearing test could not be applied due to incompatibility. The older sibling had bilateral serous otitis media, the younger sister had acute suppurative otitis media; auditory brainstem response testing under general anaesthesia was planned after treatment of otitis. Appropriate nutrition was arranged. **The genetic analysis revealed homozygous mutation in *ALMS1* gene (c.10563_10564del p.(His3521Glnfs*17).**

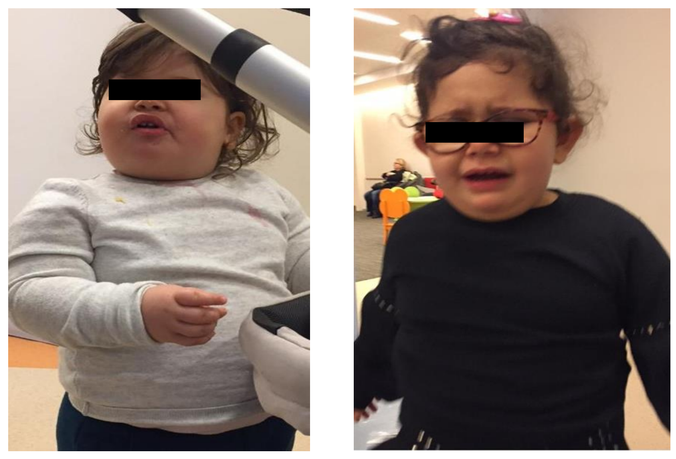

Figure 1: General apperance of our patients older sister (left), younger sister(right)

	Sibling 1	Sibling 2
Age	3 years 5/12	2 years 1/12
Birth weight	2700 grams	3000 grams
Height (SDS)	98,7 cm (-0,01)	98 cm (+2,78)
Weight (SDS)	24 kg (+3,5)	28 kg (+6,91)
Head circumference(SDS)	49 cm (-0,36)	49 cm (+0,62)
Body mass index (SDS)	24, 64 kg/m^2 (+ 4,21)	29,15 kg/m^2 (+5,45)
Glucose (mg/dL)	81	76
Insulin (µU/mL)	9,0	20,6
AST (U/L)	46	28
ALT (U/L)	36	19
Total Cholesterol (mg/dL)	99	145
LDL-Cholesterol (mg/dL)	54	94
HDL- Cholesterol (mg/dL)	24	33
Triglyceride (mg/dL)	129	115
TSH (µIU/mL)	4,50	5,99
FT4 (pmol/L)	17,65	16,55
25OH Vitamin D (ng/mL)	7,99	6,11
Denver Test results	Personal- social development: 11 months Fine motor skills: 7 months Language skills: 7.5months Gross motor skills: 16 monts	Personal- social development: 13 months Finemotor skills: 11 months Language skills: 16 months Gross motor skills: 16 months
Echochardiography	Cardiac anatomy and function within normal limits, left ventricle is mild spherical but volume and contraction are normal	Cardiac anatomy and function within normal limits, left ventricle is mild spherical but volume and contraction are normal
Abdominal Ultrasonography	Normal	Normal
ENT examination	Adenoid hypertrophy and bilateral serous otitis media	Acute suppurative otitis media
Opthalmologic examination	Retinal dystrophy, salt and pepper apperance	Retinal dystrophy, salt and pepper apperance

Table 1: Clinical and laboratory features of two siblings with Alström syndrome

Discussion

Although Alström syndrome and Bardet-Biedel syndrome share some features such as retinitis pigmentosa, hearing loss, obesity and mental retardation, polydactyly and hypogonadism are uncommon in Alström syndrome. Patients with testicular atrophy and high gonadotrophin levels have been reported however secondary sexual charachteristics develop normally in most patients. Vision loss due to retinal degeneration develop in early ages, whereas diabetes ocur mostly in second decade. Our patients had nystagmus and photophobia since infancy. The age of onset and severity of clinical symptoms may differ even within families. The diagnosis of patients might be delayed beyond infancy due to these phenotypical variability. Early diagnosis may allow genetic counselling; identification of the first sibling prior the birth of the second child could provide the use of pre-implantation genetics.The endocrinological-metabolical disorders in Alström syndrome are insulin resistance, hyperlipidemia, hyperuricemia, secondary or subclinical hypothyroidism and short stature. Our patients had mild elevation of triglyceride levels and subclinical hypothyroidism but no severe insulin resistance nor hepatosteatosis.

In conclusion, the diagnosis may be delayed due to great varibility in pheotypic features of Alström syndrome which is recently identifed as a ciliopathy. Early diagnosis may allow genetic consultation. Although Alström syndrome is a rare genetic disease, it should be kept in mind in patients with early onset obesity and speech delay.