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Differences in the clinical spectrum of two adolescent male patients with Alström syndrome

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Abstract

Alström syndrome is a rare disorder typified by early childhood obesity, neurosensory deficits, cardiomyopathy, progressive renal and hepatic dysfunction, and endocrinological features such as severe insulin resistance, type 2 diabetes, hyperlipidemia, and hypogonadism. Widespread fibrosis leads to multiple organ failure. Mutations in *ALMS1* cause Alström's syndrome. Two age-matched, unrelated adolescent males of Serbian descent with Alström syndrome underwent an extensive workup of blood chemistries, and ophthalmological, audiological, and genetic evaluations. Although both showed typical features of Alström syndrome in childhood, several differences were observed that have not been reported previously. Patient 1 was first studied at the age of 13 years for multisystemic disease and re-evaluated at the age of 15.5 years. Patient 2 is a 15-year-old boy who presented at birth with epilepsy and psychomotor developmental delay and generalized tonic–clonic seizures with severe cognitive impairment, features not documented previously in this syndrome. Sequencing analysis indicated two novel *ALMS1* mutations in exon 8: p.E1055GfsX4 and p.T1386NfsX15. Metabolic and physiological similarities were observed in both patients, including severe insulin resistance, and truncal obesity with fat loss suggestive of partial lipodystrophy, supporting evidence for a role for *ALMS1* in adipose tissue function. The unusual phenotypes of clonic–tonic seizures and severe cognitive abnormalities and lipodystrophy-like adiposity pattern have not been documented previously in Alström syndrome and may be an under-reported abnormality.

Keywords

ALMS1; Alström syndrome; hypogonadotropic hypogonadism; partial lipodystrophy; tonic–clonic epilepsy

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Conflicts of interest

There are no conflicts of interest.

Introduction

Alström syndrome (ALMS) (MIM 203800) is a rare, recessively inherited, monogenic disorder associated with a complex constellation of traits that affect multiple organ systems (Marshall *et al.*, 2005, 2007a). There is considerable variability in phenotypic expression in ALMS and not all symptoms are congenital, but develop later during childhood or within the second decade of life, which can complicate early diagnosis. For this reason, the patient's age must be considered for a differential diagnosis of ALMS (Marshall *et al.*, 2005).

Most frequently, the first presentation occurs in infancy as photodysphoria and nystagmus. Progressive cone-rod retinal dystrophy subsequently results in childhood blindness. Bilateral sensorineural hearing loss is usually present by early to late childhood. Children develop endocrinological features such as severe insulin resistance (IR) and hyperinsulinemia, truncal obesity, mixed hyperlipidemia (predominantly hypertriglyceridemia), hypothyroidism, hypogonadotropic hypogonadism, alopecia, growth hormone deficiency, and type 2 diabetes mellitus (Marshall *et al.*, 2005, 2007a). There is usually normal height in childhood, but an early cessation of growth in adolescence results in short adult stature and scoliosis (Marshall *et al.*, 2005).

Other common clinical features include dilated cardiomyopathy with congestive heart failure (CHF), which can occur in infancy (60%). In older children, the cardiomyopathy can be of the restrictive form with fibrosis, causing impairment of both ventricles. Prognosis is poor and CHF is one of the major causes of death in these patients. Progressive and widespread hepatic, cardiac, pulmonary, and renal fibrosis eventually leads to multiple organ failure, which is the major cause of morbidity and mortality in adult patients (Marshall *et al.*, 2005).

Although sometimes early developmental milestones are delayed, normal cognitive ability distinguishes ALMS from the more common ciliopathy, Bardet Biedl syndrome (BBS), which often involves developmental abnormalities and various degrees of mental retardation and learning challenges (Waters and Beales, 2011). Morphological brain abnormalities have been detected in patients with BBS and in two reports of patients with ALMS, which may play a role in cognitive and neuroendocrine deficits (Yilmaz *et al.*, 2006; Baker *et al.*, 2011; Ta demir *et al.*, 2012). Mild 'absence' seizure activity has been described in a subset of patients with ALMS, but to date, extensive neurological evaluations have not been carried out (Marshall *et al.*, 2005).

ALMS is caused by mutations in *ALMS1*, a large gene with ubiquitous expression (Collin *et al.*, 2002; Hearn *et al.*, 2002). More than 100 disease-causing mutations in *ALMS1* have been reported (Marshall *et al.*, 2007b; Marshall *et al.*, 2011; Pereiro *et al.*, 2011). The recognition and interpretation of alterations in *ALMS1* can be challenging; therefore, diagnosis is often based on clinical studies (Marshall *et al.*, 2007a).

Although the specific function of the ALMS1 protein is unclear, the localization to centrosomes and basal bodies of ciliated cells suggests roles in centriolar and/or ciliary function as a cause of the pathogenesis of ALMS, allowing its classification of ALMS as a ciliopathy (Collin *et al.*, 2005; Hearn *et al.*, 2005; Li *et al.*, 2007).

To date, the frequency of ALMS has been estimated to be 1 in 7 00 000–10 00 000 individuals (Marshall *et al.*, 2011; http://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN#REPORT_RARE_DISEASES). ALMS is found in all ethnicities and races. Here, we describe the first detailed phenotypic account of Serbian cases of ALMS identified in two unrelated, age-matched males: one with a classic presentation of ALMS and the other with some unusual presentations.

Materials and methods

Patients

The patients were diagnosed with ALMS at the Mother and Child Healthcare Institute of Serbia, Belgrade, on the basis of their clinical presentation. Informed consent was obtained from all participants in the study. The study was carried out according to a protocol approved by the Institutional Review Board of The Jackson Laboratory.

Molecular analysis

Genomic DNA was extracted from whole anticoagulated blood according to standard procedures. DNA samples were placed on a dedicated primer extension genotyping array established for screening 311 mutations, single nucleotide polymorphisms, and rare variants from 12 genes: *ALMS1*, *BBS1*, *BBS2*, *BBS3*, *BBS4*, *BBS5*, *BBS6*, *BBS7*, *BBS8*, *BBS10*, *PHF6*, and *GNAS1* (Pereiro *et al.*, 2011; <http://www.asperbio.com/asper-ophthalmics>). In patient 2, the coding sequences of exons 8, 10, and 16 of *ALMS1* were PCR-amplified, purified, and products were directly sequenced according to standard methods (<http://www.preventiongenetics.com>). Sequences were compared with *ALMS1* coding sequences (GenBank NM_015120.4) using MacVector 7.2.3 (MacVector Inc., Cary, North Carolina, USA).

Clinical and developmental assessments

Both patients underwent complete physical examinations including ophthalmological, audiometric, and psychosocial evaluations. Laboratory tests and neurological assessments were carried out according to traditional laboratory and hospital procedures.

The evaluation of early psychomotor development was carried out on the basis of motor and social milestones. Mental status and cognitive function was assessed by the level of school and social performance. Intelligence quotient (IQ_{TOTAL}) was determined using the Wechsler Intelligence Scale for Children-Revised.

Results

Here, we report the clinical spectrum of two adolescent boys of the same age and ethnicity who share a history of photophobia and nystagmus beginning at birth, and progressive cone-rod retinal dystrophy throughout childhood. They both had bilateral, moderate sensorineural hearing loss, normal digital extremities, dyslipidemia, IR, and obesity in childhood, type 2 diabetes mellitus, renal insufficiency, and hepatic dysfunction, fulfilling the diagnostic criteria established for their age (Marshall *et al.*, 2007a). However, several important differences were observed between them.

Case 1

Patient 1 was initially assessed at 13 years and again at 15.5 years. He had centripetal obesity, and selective loss of adipose tissue in his legs and gluteal region (Fig. 1 b). He had acanthosis nigricans, gynecomastia, and scoliosis (Fig. 1). There was no evidence of hypogonadism at the age of 13 years (Tanner stage 3), with normal testicular volume (12.15 ml) and normal penis length, with well-developed cavernous bodies.

Blood urea nitrogen and creatinine and blood pressure were normal and uric acid was only slightly elevated. However, additional renal function tests, including 24 h urine protein, night-time albumin excretion rate, and estimated glomerular filtration rate, confirmed glomerulopathy. The tubular reabsorption of phosphate index was normal (Table 1). Echocardiography did not indicate any abnormalities at this time.

At the age of 15.5 years, he had a height gain of only 0.1 cm in 2 years and his weight was above the 97th centile. He had a 3-year advanced bone age. He remained hyperinsulinemic, with hyperlipidemia, disproportional to his level of obesity.

Between the ages of 13 and 15.5 years, his clinical picture progressed, indicating the importance of metabolic and cardiac follow-up care. His ECG and 24 h Holter ECG were normal, but echocardiography showed restrictive filling of the left ventricle and significant early atrial contraction. In addition, subclinical primary hypogonadism with impairment in endocrine and germinative testicular function was identified.

A heterozygous *ALMS1* mutation was detected in exon 16, c.10568_10569delAT; p.H3523Xfs×17, which, along with his clinical presentation, confirmed the diagnosis of ALMS (Fig. 1e).

Case 2

This patient was first evaluated at the age of 15 years (Fig. 1c). His neonatal and postnatal periods were complicated by frequent vomiting and failure to thrive.

At 7 months, he experienced the first of several generalized tonic–clonic seizures occurring during sleep, with convulsions of the whole body and extremities, lasting for 3–4 s, without foam at the mouth, urination, or defecation. Such seizures were repeated at the age of 10 months, and again during the second year. Epilepsy was diagnosed and phenobarbital was introduced.

After normal early developmental milestones, psychomotor development, social skills, and speech development became delayed, considered to be because of vision and hearing impairments. At 8 years, episodes of epilepsy recurred with similar characteristics but with variable frequencies and durations under 2 min, sometimes twice a week, sometimes once in several months. Carbamazepine was introduced as an additional therapy. EEG during sleep showed very frequent bilateral spike wave complex in short series in parietal, occipital, and temporal areas (Fig. 2).

At 15 years, he was hypertensive (140/90 mmHg) and had symptoms of severe CHF. Echocardiography showed pericardial effusion and dilated cardiomyopathy with an ejection fraction of 29% and fractional shortening of 16%, requiring standard anticongestive therapy and venous inotropic support. Ectopic atrial tachycardia with a first-degree AV block and STsegment depression in precordial leads (V2–V5) was documented by 24 h Holter ECG monitoring.

Abdominal ultrasound showed diffuse ascites as well as cholelithiasis. His C-reactive protein, serum transaminases, γ -glutamyl transferase, and triglycerides were elevated. He was taken off carbamazepine at the age of 15 years, after 4 years without seizure activity, and because of his hepatic dysfunction. A developmental assessment indicated an IQ_{TOTAL} of 40.

Masculinization and secondary sexual characteristics were normal, but hormonal evaluation confirmed hypogonadotropic hypogonadism, and testicular volume was less than 1 ml. He had significant gynecomastia.

Abnormal creatinine and blood urea nitrogen as well as proteinuria prompted additional renal function tests including 24 h urine albumin, creatinine clearance, and glomerular filtration rate. The tubular reabsorption of phosphate index was normal. He had hyperglycemia, with an HbA1C of 7.2%.

He had severe IR, acanthosis nigricans, and truncal obesity with reduced femoral-gluteal fat (Fig. 1d). Direct sequencing of ALMS1 identified two novel mutations, c. 3163dupG; p.E1055Gfs×4 and c.4156dupA; p.T1386Nfs×15 in exon 8, confirming his diagnosis of ALMS.

Table 1 summarizes the clinical and molecular findings in the two patients at the age of 15 years.

Discussion

Most ALMS patients have normal intelligence (Marshall *et al.*, 2005). However, a broad spectrum of minor neurologic and behavioral abnormalities has been described, including delay of early fine and gross motor skills, receptive-expressive language delays, autistic-spectrum behavior, clonic tics, mild absence seizures, unexplained peripheral pain, dystonia, and hyporeflexia (Marshall *et al.*, 2005, 2007a). It is noteworthy that many ciliopathies share serious neurological disturbances such as significant mental retardation and certain nervous system abnormalities, but the degree to which these relate to the neurocognitive disease in these patients is not understood (Lee and Gleeson, 2010).

The delayed diagnosis in patient 2 was partially because of the history of generalized tonic-clonic seizures and severe cognitive deficits, which are not typical components and have never been reported before in ALMS. We propose that variable neurological involvement, including seizure activity, should be included as a rare occurrence, but part of the phenotypic spectrum of ALMS. The impact of the childhood epilepsy on cognition in this case is not known (Meinardi *et al.*, 1992).

Interestingly, both patients had severe IR, dyslipidemia, hepatic steatosis, and truncal obesity disproportional to their adiposity, but lacked extremity and gluteal adipose tissue mass, a distribution pattern similar to what is observed in partial lipodystrophy. Partial lipodystrophy is characterized by partial loss of subcutaneous fat, muscular hypertrophy, hypertension, severe IR, and elevated triglycerides. The consequences of ciliary protein dysfunction with respect to the molecular pathogenesis of the severe IR in ALMS are not clear. Deficits during adipogenesis have been observed in ALMS, suggesting a potential role for the centrosome and/or the basal body in maintaining metabolic homeostasis (Zulato *et al.*, 2011).

In addition, the multisystem fibrosis in ALMS raises the possibility that alterations in the extracellular matrix may introduce further constraints to adipose tissue expansion *in vivo*, known to compromise metabolic function (Semple *et al.*, 2011). The precise molecular basis of the underlying fibrosis in ALMS and whether fibrotic changes are a primary or a secondary event has yet to be determined.

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Fig. 1.

Clinical photos and genotypes of patients 1 and 2, each at the age of 15 years. Note the common feature of abdominal and truncal obesity, and loss of fat mass in the gluteal region. Both have gynecomastia, kyphosis, and acanthosis nigricans in abdominal skin flexures. (a, b) patient 1, (c, d) patient 2. (e) A heterozygous two base pair deletion in exon 16, c. 10568_10569delAT; p.H3523Xfs17, was identified in patient 1. (f) Heterozygous single base pair duplications in exon 8, (c.3163dupG; p.E1055GfsX4 and c.4156dupA; p.T1386NfsX15), were identified in patient 2. All mutations result in a premature termination signal in *ALMS1*. Black arrows demarcate the site of the frameshift mutations. ALMS, Alström syndrome.

Fig. 2.
 Epileptic spike and wave discharges monitored with EEG of patient 2 at the age of 8 years.
 (a)(b)(c) represent three separate EEG measurements.

Table 1

Medical history and clinical features in age-matched male

Clinical phenotype	Case 1		Case 2
Birth weight (g)	3250		2900
Cone-rod dystrophy	+		+
Bilateral SNHL	+		+
Childhood truncal obesity	+		+
Abnormality in fat tissue distribution	+		+
Gynecomastia	+		+
IR	+		+
Acanthosis nigricans	+		+
T2DM	+		+
Renal insufficiency	+		+
Hepatic dysfunction	+		+
Cardiomyopathy	Early restrictive		Advanced
Hypertension	–		+
Hypogonadism	Subclinical		+
Hypothyroidism	+		+
Scoliosis/kyphosis	+		+
Clonic-tonic seizures	–		+
Laboratory data	Case 1 at 13 years	Case 1 at 15.5 years	Case 2 at 15 years
Height (cm)	151.7	151.8	153.5
Weight (kg)	67.7	65.0	63.7
BMI (kg/m ²)	29.4	28.2	27.0
Waist circumference (cm)	97.5	94	82
Glucose (< 5.85 mmol/l)	19.2	4.5	7.9–32.0
Insulin (2.6–25.0 mIU/l)	101.4	34.0	41.8
HbA1C	13.4	4.6	7.2
GGT (< 48 IU/l)	151	101	211
AST/ALT	Normal	Normal	80/100
Triglycerides (< 1.7 mmol/l)	5.5	3.8	2.7
Cholesterol (mmol/l)	5.8	5.8	5.7
BUN (mg/dl)	Normal	5.5–7.0	12.3
Creatinine (μmmol/l)	Normal	82	144
Protein urine (g/l)	0.936	0.229	10
Uric acid (μmol/l)	422	522	573
Amylase (< 100 U/l)	83	155	84
TSH (mIU/l)	2.69	3.99	5.46
fT4 (mcg/dl)	–	14.9	13.4
Testosterone (10–30 μmol/l)	Normal	15.5	0.3
LH (1.7–8.6 IU/l)	Normal	15.8	0.3/0.3
FSH (1.5–12.4 IU/l)	Normal	26.5	0.4

Clinical phenotype	Case 1		Case 2
Tanner stage	3	4	3
Creatinine clearance (ml/min/1.73)	94	81	86
C-reactive protein (mg/dl)	–	–	38
24-h urine albumin (g)	–	–	2.24
Night-time albumin excretion rate (ug/min)	–	396.5	–
24-hour urine protein (g)	–	1.42	–
GFR (ml/min)	–	93.6	85
TRP (%)	–	94.7	92

+, present; –, absent; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; FSH, follicle stimulation hormone; FT4, free thyroxine; GFR, glomerular filtration rate; GGT, γ -glutamyl transferase; IR, insulin resistance; LH, luteinizing hormone; SNHL, sensorineural hearing loss; T2DM, type 2 diabetes mellitus; TRP, tubular reabsorption of phosphate index; TSH, thyroid-stimulating hormone.