Letter to the Editor

Atypical presentation and a novel mutation in ALMS1: implications for clinical and molecular diagnostic strategies for Alström syndrome

To the Editor:

Alström syndrome (ALMS; MIM 203800) characterized by progressive phenotypes affects nearly all organs. Approximately 100 different ALMS1 mutations cluster primarily in exons 8, 10 or 16 (1, 2). ALMS1 localizes to centrosomes and basal bodies of ciliated cells and is ubiquitously expressed, suggesting roles in ciliary function and/or intraflagellar transport (2).

Clinical presentation begins with vision loss in the first year leading to childhood blindness. Dilated cardiomyopathy (DCM) can occur in infancy or adulthood. Obesity begins early and persists into adulthood. In childhood, sensorineural hearing loss and insulin-resistant type 2 diabetes mellitus (T2DM) develop. Multiple organ failure progresses gradually in the second to third decade. Males have small genitalia and infertility, typified by disordered basal testosterone and baseline luteinizing hormone/follicle stimulating hormone (LH/FSH) levels. Fibrotic seminiferous tubules and an absence of Leydig cells have been documented (1). Normal intelligence serves as a differential diagnosis to Bardet Biedl syndrome (BBS), a phenotypically similar ciliopathy (3).

We report an 18-year-old male, born to first-cousin consanguineous parents from a small, remote village in central Turkey, who presented febrile convulsions at 1 week of age. Deteriorating retinal and optic disc pathology led to blindness by the age of 8 years and initial hearing deficits progressed. Hepatomegaly was discovered by ultrasonography, but transaminases were only mildly elevated. There was no portal hypertension.

At 16 years, he manifested DCM with dilated atria and ventricles, grade 3 tricuspid insufficiency and grade 2 mitral insufficiency, grade 2 mitral and tricuspid regurgitation, and mitral valve prolapse (Fig. 1a). At 18.75 years, he was again hospitalized with congestive heart failure (CHF). Echocardiography showed restrictive and DCM, pericardial effusion, grade 3/4 tricuspid insufficiency and grade 2/3 mitral insufficiency. Ascites, probably due to CHF, was documented. Atrial fibrillation developed and the patient died due to cardiac arrest.

The patient’s haplotype was homozygous within a < 2-Mb region surrounding ALMS1 (Fig. 1d). Sequencing of all ALMS1 exons and splice sites revealed a novel homozygous mutation, 9749C > A (Ser3250X) in exon 11 (Fig. 1e). We identified a heterozygous intronic polymorphism, IVS19-8 del T, present only in the maternal lineage, suggesting that the variation was a recent event arising after the common ancestor from either the mother or maternal grandparent.

There were several deviations from the classical presentation. Although body mass index (BMI) was not documented in childhood, his parents state that he was always underdeveloped and was never obese. At 18 years, his BMI (kg/m²) was 22 [146.5 cm/47.5 kg (both < 3rd centile)]. Oral glucose tolerance testing (OGGT) showed that he lacked insulin resistance (IR), or T2DM. Growth hormone insulin-like growth factor-1 (IGF-1), bone age, glycated hemoglobin (HbA1C), lipids, thyroid and renal function were normal. Further, he did not show genital anomalies, but his testosterone was 52 ng/dl (134–625), LH [13.9 ng/dl (0.8–7.6)] and FSH [32.4 ng/dl (0.7–11.1)].

The patient had additional features not been previously described in ALMS. Ultrasound showed an abnormal thickening of the gallbladder wall, a condition common in individuals with BBS (3). It is unclear whether this thickening could be attributed to the massive fibrosis of multiple organs of patients with ALMS (2) or to dysfunction in the motile cilia in the gallbladder.

Neuroanatomical brain abnormalities and profound cognitive impairments are reported in BBS, but not ALMS (3). Structural magnetic resonance imaging (MRI) revealed prominent cerebellar hemisphere folium due to atrophy, and a mildly thin brain stalk in conventional sagittal T1-weighted and axial T2-weighted flair brain images. Prominent peripheral and central cerebrospinal fluid distance secondary to cortical atrophy and thin corpus callosum infundibulum were noted. Fourth ventricle at infratentorial sections, basal ganglia and thalamus were normal in examination of the supratentorial sections (Fig. 1c). These changes are unlikely to be due to vision loss, which is frequent in...
ALMS patients without MRI abnormalities. Electroencephalography was normal. He had significant cognitive impairment with social developmental delays, and was unable to perform aspects of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) intelligence test at age 18 years, resulting in a score of <40 (normal range 80–120).

Several hypotheses could explain the presence of such unusual characteristics in this patient. It is plausible to consider that the location of the mutation in ALMS1 exon 11 may affect splice variants producing different isoforms.

The variability seen in this patient may also be due to genetic modifiers that could impact neurodevelopment, obesity, and hypogonadism. The full range of clinical heterogeneity in individuals harboring ALMS1 mutations is still unknown. Genetic confirmation of ALMS in this patient expands the phenotypic spectrum and suggests that, in patients with milder features or unusual phenotypes, one should not rule out seeking a genetic diagnosis of ALMS.

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