Received: 20 September 2022 | Revised: 24 November 2022 | Accepted: 28 November 2022

DOI: 10.1002/ccr3.6720

CASE REPORT

Clinical Case Reports Open Access WILEY

A child resides within a young adult: The first reported case of Alström syndrome in Bangladesh

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Abstract

A 32-year-old male case with short stature presented to us with audio-visual impairment, obesity, impaired glucose tolerance, dyslipidemia, and hypogonadism. The single-gene genetic analysis revealed an ALMS1 gene mutation. A diagnosis of ALMS was reached for meeting one major and four minor criteria.

KEYWORDS

ALMS1, alström syndrome, alström–hallgren syndrome, ciliopathy, hereditary sensory and motor neuropathy

1 | BACKGROUND

Alström syndrome (ALMS), also called Alström–Hallgren syndrome is a rare, autosomal recessive disorder with a prevalence of 1/1000,000 in Europe and North America. A much higher frequency was noted in populations with a high level of consanguinity. More than 950 cases have been identified worldwide to date.[1] This syndrome involves multiple organs and commonly manifests as cone-rod retinopathy, sensorineural hearing loss, cardiomyopathy, cardiac failure, and hepatic, renal, and pulmonary dysfunction.[2,3] Metabolic abnormalities of ALMS include severe insulin resistance and hyperinsulinemia, type 2 diabetes mellitus, hypogonadism in males, dyslipidemia, hypothyroidism, truncal obesity, short stature, scoliosis or kyphosis, and growth retardation.[4] Other features include organ fibrosis, chronic otitis media in childhood, gastrointestinal disturbances, and neurological disturbances such as absence seizures.[5] Clinical manifestation, age of onset, disease progression, and severity of the features are variable, even within a family. Disease manifestations develop in childhood with the gradual involvement of multiple organs in adulthood. The main cause of ALMS is mutations in the ALMS1 gene, which contains 23 exons on chromosome 2p13.[6] and codes for a protein of 4169 amino acids found in centrosomes, basal bodies, and the cytosol

of all tissues affected by the disease. Common mutations include insertions, deletions, frameshift, and nonsense mutations, vastly in exons 8, 10, and 16 and multiple alternate splice forms exist. To this date over 300 variants of mutations have been identified worldwide. There is limited evidence demonstrating the correlation between genotype and a specific phenotype. As a result, it is assumed that environmental factors may play a significant role in phenotypic variation.[7] There is no cure for ALMS and life expectancy depends on the degree of organ dysfunction. Treatments target the individual symptoms and can include diet, corrective lenses, hearing aids, medications for diabetes and heart issues, and dialysis and transplantation in the case of kidney or liver failure. Prognosis varies depending on the specific combination of symptoms.

2 | CASE PRESENTATION

This 32-year-old Bangladeshi male came to us with difficulty seeing objects in darkness and mild hearing impairment for a variable period of time. His height was 144 cm (predicted adult height = mid paternal height ± 5 cm =168 cm −178 cm) and his BMI was 38 kg/m^2. Anthropometry reveals the upper-to-lower segment ratio to be proportionate (0.96). He had microcephaly (OFC: 51 cm, normal >57 cm), a short neck, low-set ears, a unibrow, brachydactyly, and acanthosis nigricans in the neck and axilla with normal hair distribution (Figure 1). His testes were small and soft (the left one smaller than the right one) and had micropenis (stretched penile length (SPL): 6 cm; micropenis if SPL <9 cm). His right lower limb is shorter than his left lower limb by approx. 3.8 cm (LLD). He had no organomegaly, lymphadenopathy, thyromegaly, or gynecomastia. All vital signs were found within normal range.

His birth history was not uneventful. He had a H/O premature birth by normal vaginal delivery in the seventh month of gestation, followed by a few days of hospital stay in the neonatal intensive care unit. He had had dysmorphic features and disproportionately small hands and feet since birth. He had delayed developmental milestones with poor intellectual development and first talked a full sentence and walked independently successively at the ages of 8 and 9 years. He had dysarthria and a formal IQ assessment revealed an IQ of 60. He began school at the age of 12 and struggled for 4 years to be promoted to the next class. Also, he had poor emotional and cognitive development. He gained excessive weight over the last 10 years, with his usual

FIGURE 1 Physical profile of the patient. (A) Short stature. (B) Microcephaly, short neck, low-set ears, a unibrow, and acanthosis nigricans in the neck. (C) Brachydactyly

dietary habits. His family history revealed that his siblings are in good health, but one of the paternal cousins has had a hearing impairment since childhood and two of them have learning difficulties.

Ocular examination revealed he had impairment in distant vision with normal near vision, increased cup disc ratio bilaterally in fundoscopy, and keratoconus corneal topography. Pure-tone audiometry (PTA) with impedance audiometry revealed mild to moderate bilateral conductive hearing loss. He had a low serum testosterone level. All other hormone analyses were within the normal reference range. Ultrasonography (USG) of the whole abdomen revealed grade II fatty change in the liver and USG of the scrotum revealed bilateral smaller testes (volume of right testes: 5.4 cc and left testes: 2.2 cc). Laboratory investigations also revealed dyslipidemia, hyperuricemia, and impaired glucose tolerance (IGT) (Table 1). However, his MRI of the brain, liver function tests, renal function tests, and echocardiography revealed no abnormality. A single gene study revealed a mutation in the ALMS1 gene, which is diagnostic.

A multidisciplinary was formed and his parents were counseled about the condition, treatment options, and prognosis. Spectacles were given for refractive error and he was put on the oral hypoglycemic agent liraglutide. He was advised to seek psychosocial support from a proper support group. Regular cardiac, renal, auditory, and ophthalmic evaluation with retinal imaging and functional testing was advised as a patient of ALMS develop gradual multiorgan impairment. He was followed up 6 months later with no deterioration of hearing or visual impairment, Echocardiography revealed normal ventricular architecture with preserved function and Renal function was unremarkable.

3 | DISCUSSION

In this study, we report a case of ALMS with the following characteristics. First, he was found to have low visual acuity. Variable ocular manifestations like low vision, nystagmus, photodysphoria, and retinal dystrophy are major manifestations that affect almost 100% of patients with Alström Syndrome. Visual symptoms tend to progress slowly but usually occur shortly after birth.[8] Secondly, he was found to have a sensorineural hearing impairment, which is found in 88% of reported cases to date.[9] Third, he presented with many metabolic abnormalities like obesity (BMI of 38 kg/m^2) with impaired glucose tolerance, dyslipidemia, and hypogonadism. Obesity is a characteristic feature of ALMS with more subcutaneous fat accumulation than in the visceral regions.[10] Unlike insulin resistance caused by simple obesity, *ALMS1* mutations affect islet ciliary body function.[11] Our patient had hypogonadism with small testes and a penis with a low basal testosterone level, which is found in 77% of males with ALMS. In these cases, puberty is often delayed.[9,12] In a previous study of 182 cases, some neurobehavioral manifestations such as delayed developmental milestones (46%), fine and gross motor skills (21%), mixed receptive-expressive language delays (11%), absence seizures, autistic-spectrum behavioral abnormalities (8%), muscle dystonia, and hyporeflexia (20%) were observed. Though all features must not be present in a case, we significantly found delayed developmental milestones, language delay, difficulty in fluency and articulation, learning difficulty, judgment error, intellectual retardation (IQ 60), and emotional lability in our indexed case.[9,13] A significant percentage of patients with ALMS manifest cardiac, renal, hepatic, urologic, and gastrointestinal abnormalities. But in our case, we did not have any such abnormalities. The symptoms and organ impairment of ALMS show variability in terms of age of onset, severity, and prognosis, and this variability derives from variable genotypes and mutations as well as subsequent environmental and family factors.[14] Yet regular monitoring for organ impairment should be done. Family history bears a very significant role in diagnosing ALMS. Though our case had a family history of hearing impairment and learning difficulty, their detailed evaluation could not be done due to the reluctance of the patient's attendance. Given the symptoms of short stature, facial dysmorphism, microcephaly, obesity, and mild intellectual disability (ID) the other differential diagnosis for this can be Prader-Willi Syndrome and MEHMO (Mental retardation, Epileptic seizures, Hypogenitalism, Microcephaly, and Obesity) syndrome. But microcephaly, absence of characteristic facies, absence of h/o feeding difficulty, and hypotonia in childhood hyperphagia lie against Prader–Willi syndrome. Again, the patient's age, absence of h/o epilepsy, absence of severe ID, visual and hearing impairment, and IGT all these lies against MEHMO syndrome. The patient's clinical presentation also resembles a few other syndromes, for example, Laurence–Moon–Bardet–Biedl syndrome, Leber congenital amaurosis, Usher syndrome, Kearns–Sayre syndrome, etc., although not meeting the diagnostic criteria for them. For confirmation of diagnosis, we availed a single gene study which revealed an *ALMS1* mutation, which is diagnostic for Alström syndrome. Marshall et al. set the diagnostic criteria for clinicians to use in reaching the diagnosis for patients of ALMS of different ages, as manifestations widely vary between infancy and adulthood.[15] For patients above 15 years of age to adulthood, the following two major and two minor criteria or one major and four minor criteria need to be fulfilled (Table 2).

TABLE 1 Laboratory parameter of the patient

Investigations	Patient values[a]	Reference values
Hemoglobin	12.6 g/dL	12.4 to 16.4 g/dL
Red blood cell count	4.9 million/cmm	4.0 to 5.5 million/cmm
White blood cell count	11,000/cmm	4000 to11,000/cmm
Platelet count	3,60,000/cmm	1,50,000 to 4,00,000/cmm
S. creatinine	0.95 mg/dL	0.70 to 1.30 mg/dL
S. uric acid	**9 mg/dL**	3 to 7 mg/dL
S. ALT	29 U/L	10 to 40 U/L
S. calcium	9.6 mg/dL	8.6 to 10.2 mg/dL
S. albumin	39 g/L	35 to 55 g/L
Fasting lipid profile	Total cholesterol: 156 mg/dL	Total Cholesterol: <200 mg/dL
	HDL cholesterol: 30 mg/dL	HDL cholesterol: >40 mg/dL
	LDL cholesterol: 81 mg/dL	LDL cholesterol: <100 mg/dL
	Triglyceride: 190 mg/dL	Triglyceride: <100 mg/dL
Fasting plasma glucose	4.7 mmol/L	<5.6 mmol/L
Two-hour plasma glucose value during a 75 g OGTT	**8.6 mmol/L**	<7.8 mmol/L
S. TSH	1.83 mIU/L	0.55–4.78 mIU/L
S. testosterone	**4.2 nmol/L**	4.94–32 nmol/L
S. FSH	8.79 IU/L	1–12 IU/L
S. LH	5.4 IU/L	<9 IU/L
P. ACTH	21.6 pg/mL	10–60 pg/mL
P. cortisol	285.2 nmol/L	138–690 nmol/L
S. prolactin	12.5 mg/mL	2.5–17 mg/mL

Abbreviations: ALT, alanine aminotransferase; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OGTT, oral glucose tolerance test; P., plasma; S., serum; TSH, thyroid-stimulating hormone;

[a]Abnormal patient values are in bold.

TABLE 2 Diagnostic criteria of Alström syndrome for those above 15 years of age to adulthood

Major Criteria	• ALMS1 mutation in 1 allele and/or family history of Alström syndrome* • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)
Minor Criteria	• Obesity and/or insulin resistance and/or T2DM* • (history of) DCM/CHF • Hearing loss* • Hepatic dysfunction • Renal failure • Short stature* • Males: hypogonadism*, Females: irregular menses and/or hyperandrogenism

Abbreviations: DCM/CHF, dilated cardiomyopathy with congestive heart failure; ERG, electroretinogram; T2DM, type 2 diabetes mellitus.

*Criteria met in this case.

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In our case, we have established one major and four minor criteria for establishing the case as Alström syndrome.

4 | CONCLUSION

Alström syndrome is a rare autosomal recessive disorder involving multiple organs. It is mainly caused by the ALMS1 gene mutation. We have reported a case of a 32-year-old male with delayed growth, mental retardation, audio-visual impairment, obesity, insulin resistance, dyslipidemia, and hypogonadism with a diagnostic ALMS1 gene mutation. The clinical expression shows wide variation in onset, severity, and progression that may be due to genetic variation, environmental factors, or family factors.

AUTHOR CONTRIBUTIONS

Mushfiq Newaz Ahmed: Conceptualization; project administration; resources; supervision; writing – review and editing. **Nowshin Jabin:** Data curation; validation; writing – original draft. **Mohammad Azmain Iktidar:** Data curation; validation; visualization; writing – review and editing. **Shohael Mahmud Arafat:** Project administration; resources. **Abed Hussain Khan:** Project administration; resources. **Avrow Mitra:** Project administration; resources. **Romana Chowdhury:** Project administration; resources.

ACKNOWLEDGMENTS

We thank all the clinical staff who participated in the treatment of the patient.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

ETHICAL APPROVAL

The study is exempt from ethical approval in our institution.

CONSENT

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and the accompanying images.

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How to cite this article: Ahmed MN, Jabin N, Iktidar MA, et al. A child resides within a young adult: The first reported case of Alström syndrome in Bangladesh. *Clin Case Rep*. 2022;10:e06720. doi:10.1002/ccr3.6720