Early-Onset Alström Syndrome: Clinical Clues from a Pediatric Case Series

Evelina Maines[1,#], Fiorenza Soli[2], Francesca Rivieri[2], Vittoria Cauvin[1], Maria Bellizzi[1], Massimo Soffiati[1] and Roberto Franceschi[1,3,*]

[1]*Division of Pediatrics, S. Chiara General Hospital, APSS, 38122 Trento, Italy*

[2]*Division of Medical Genetics, S. Chiara General Hospital, APSS, 38122 Trento, Italy*

[3]*Centre for Medical Sciences (Cismed), University of Trento, 38122 Trento, Italy*

Abstract: *Background;* Alström syndrome (AS) is characterized by core clinical features, including cone-rod dystrophy, early-onset obesity, progressive bilateral sensorineural hearing loss, type 2 diabetes mellitus, and cardiomyopathy. Age-specific diagnostic criteria have been proposed. Early diagnosis is critical due to the variable and progressive nature of clinical manifestations. The limited number of reported cases hinders a comprehensive understanding of the natural history of the disease.

Methods; We present three pediatric cases of AS, highlighting the syndrome's clinical variability and discussing the challenges of early diagnosis in the pediatric age.

Results; Case 1 involves a 4-year-old girl who presented with nystagmus, poor vision, photophobia, and sensorineural hearing loss starting at 3 months of age, later developing type 2 diabetes and early-stage dilated cardiomyopathy. Cases 2 and 3 illustrate marked intrafamilial phenotypic variability, with one sibling experiencing fatal neonatal cardiomyopathy and the other presenting a milder clinical course.

Conclusions; Our cases show that the clinical features of AS evolve over time, with ocular manifestations appearing in early infancy and others emerging later. Significant intrafamilial phenotypic variability underscores the need for individualized clinical management, even within the same family. Given the potential for rapid and fatal progression of cardiomyopathy in infancy, early cardiac screening is strongly recommended in patients with early-onset nystagmus and in all individuals diagnosed with AS.

Keywords: Alström syndrome, Case series, Pediatric, Phenotypic variability, Natural history.

INTRODUCTION

Alström syndrome (AS) (OMIM #203800) is an ultrarare autosomal recessive monogenic disorder caused by pathogenic variants in the *ALMS1* gene, located on chromosome 2p13 [1]. The *ALMS1* gene encodes a centrosome-associated protein involved in the regulation of several ciliary and extraciliary processes, including apoptosis, cell cycle regulation, and receptor trafficking [2].

The exact prevalence of AS is difficult to determine, partly due to underdiagnosis and the presence of atypical or attenuated phenotypes. Estimates range from 1 in 100,000 [3] to 1 in 1,000,000 individuals [4], with approximately 950 cases reported worldwide [1].

AS is a multisystemic disorder characterized primarily by progressive pigmentary retinal dystrophy, early-onset obesity, progressive bilateral sensorineural hearing loss (SNHL), and insulin resistance or type 2 diabetes mellitus (T2DM). Other common features include non-alcoholic fatty liver disease (NAFLD), progressive chronic kidney disease (CKD), hyperlipidemia, infantile-onset dilated cardiomyopathy (DCM) or late-onset restrictive cardiomyopathy, and additional systemic manifestations [1, 5].

Clinical diagnosis is based on the presence of cardinal clinical features that emerge progressively throughout infancy, childhood, and early adulthood [1, 6]. Diagnostic criteria have been proposed for three age groups: infants (birth-2 years), children (3-14 years), and adolescents/adults (> 15 years) [1]. Molecular genetic testing of *ALMS1* gene can confirm the diagnosis [1].

The earliest signs typically appear within the first few months of life, with cone-rod dystrophy presenting as progressive visual impairment, photophobia, and nystagmus between birth and 15 months of age [1]. Truncal obesity, hearing impairment, and cardiomyopathy are also hallmarks in pediatric patients. On the contrary, renal failure and hepatic dysfunction occur later, usually in the second and third decade of life [1, 6, 7]. Heart failure is the leading

*Address correspondence to this author at the Division of Pediatrics, S. Chiara General Hospital, Largo Medaglie d'oro, 9, 38122 Trento, Italy; Tel: + 39 0461/903538; Fax: + 39 0461/903824; E-mail: roberto.franceschi@apss.tn.it

#Maines E and Franceschi R contributed equally to the work.

cause of death in children and adolescents, while end-stage renal disease is a major cause of mortality in adulthood [3, 8].

Although early diagnosis is critical for management, it is often challenging due to the progressive and variable onset of signs and symptoms. The limited number of reported cases also hampers a comprehensive understanding of the natural history of the disease, especially during the pediatric age.

Here, we report three pediatric cases of AS to illustrate the clinical variability of the syndrome in early childhood and to highlight the challenges of achieving a timely diagnosis.

CASE 1

A 4-year-old Albanian girl was referred to our Pediatric Unit at the General Hospital of Trento due to poor vision, photophobia, nystagmus, and bilateral SNHL. She was born at term following an uncomplicated pregnancy and delivery. There was no parental consanguinity. Family history revealed T2DM in the maternal grandfather.

Nystagmus was noted at 3 months of age, but a severe visual deficit had not been previously suspected before the admission to our hospital. No history of familial blindness or significant visual impairment was recorded by the parents or relatives.

Ophthalmic examination revealed severe nystagmus, photophobia and poor visual acuity (estimated <1/10). Retinoscopy showed patchy retinal pigment epithelium atrophy with increased pigmentation in midperiphery. The optic disc and retinal vasculature were unremarkable. Electroretinography (ERG) demonstrated markedly reduced cone responses with relative sparing of rod function.

Bilateral acoustic prostheses were implanted due to hearing impairment.

At age 10, the patient's BMI z-score was +1.68 z-score. She developed T2DM (glucose 503 mg/dL, HbA1c 15.3%, negative autoantibodies, C-peptide 0.64 ng/mL), hyperlipidaemia (1770 mg/dL, total cholesterol 259 mg/dL) and mild hypertransaminasemia (ALT 100 U/L, AST 48 U/L). She was placed on a diet and metformin. Thyroid function was normal, and antithyroid and celiac antibodies were negative.

Cardiac ultrasound (US) revealed mild left ventricular and atrial dilation suggestive for early stage dilated cardiomyopathy (DCM). Abdominal US showed hepatomegaly and hepatic steatosis.

A clinical diagnosis of AS was made (1 major criteria: nystagmus/photophobia/impaired vision; 3 minor criteria: SNHL, T2DM/liver steatosis/hypertriglyceridemia, DCM).

Genetic sequencing of *ALMS1* gene did not reveal any mutation.

CASE 2

A 3-year-old boy was admitted to our Pediatric Clinic with nystagmus and visual impairment.

He was born at term following a normal pregnancy and delivery.

At evaluation, he exhibited obesity (BMI = 2.43 z-score) but had normal glucose metabolism (HbA1c 5.3%) and negative pancreatic autoantibodies. Lipid profile, hepatic, and renal function were within normal limits.

Cardiac US revealed mild left ventricular dilation.

ALMS1 gene analysis revealed a known pathogenic variant.

A diagnosis of AS was made (2 major criteria: ALMS1 mutation, nystagmus/impaired vision; 2 minor criteria: obesity, DCM).

CASE 3

The patient was the sister of Case 2.

She was diagnosed with severe DCM, absent foveal reflex, and retinal dystrophy at 1 month of age.

She died at 4 months due to a severe acute respiratory failure. A post-mortem diagnosis of AS was made (3 major criteria: family history of AS, nystagmus/impaired vision; infantile DCM).

DISCUSSION

Alström syndrome is likely underdiagnosed due to its rarity and wide phenotypic variability. Core clinical features may appear at different stages of life, from infancy through adulthood [1].

Our cases confirm that AS manifestations evolve over time, with some features appearing in early infancy (as ocular findings) and others emerging later

in development. As a result, diagnosis is often delayed. Case 1 illustrates a classic progression of AS manifestations: nystagmus, photophobia, and visual impairment beginning at 3 months of age, followed by the onset of sensorineural hearing loss, type 2 diabetes, and early-stage dilated cardiomyopathy.

Furthermore, our experience highlights how clinical manifestations may differ significantly even among individuals from the same family. Cases 2 and 3 demonstrate marked intrafamilial phenotypic variability, with one sibling experiencing fatal neonatal cardiomyopathy and the other presenting a milder clinical course. This finding is consistent with previous reports of phenotypic heterogeneity within families [9, 10], and it further complicates early recognition of the syndrome.

Case 1 also highlights the value of clinical diagnosis in AS, particularly when genetic confirmation is unavailable or inconclusive. In this instance, negative *ALMS1* sequencing may be due to limitations in standard methodologies, including failure to detect variants in regulatory or deep intronic regions. Additionally, routine sequencing may not identify intragenic deletions or duplications, which require complementary analyses such as MLPA [1].

The fatal outcome in Case 3 underscores the potential severity of infantile-onset cardiomyopathy in AS and reinforces the need for early cardiologic assessment. As cardiomyopathy may be rapidly progressive and even fatal in infancy, in the case of early nystagmus onset, an open-mind approach could include heart US screening to exclude severe DCM that could be fatal.

Although no disease-specific therapy exists for AS, some nutritional and pharmacologic interventions could be evaluated. The potential benefit of vitamin A or docosahexaenoic acid (DHA) supplementation in slowing retinal degeneration remains uncertain [11]. Inositols have shown promise beyond their role in managing insulin resistance [12]. Furthermore, early psychological support may improve parent-child bonding and reduce parental distress [13].

CONCLUSIONS

Early diagnosis of AS remains critical due to the variable and progressive onset of clinical manifestations. While genetic testing can aid in confirming the diagnosis, clinical evaluation remains central, especially when genetic findings are inconclusive. Increasing awareness among clinicians is crucial for early diagnosis, and we suggest heart US screening in case of early nystagmus onset. Diagnosis of AS and optimal management requires a multidisciplinary approach.

PATIENT CONSENT STATEMENT AND ETHICAL APPROVALS

The latest revision of the Helsinki declaration as well as the Oviedo declaration were the basis for the ethical conduct of the study. The study protocol was designed and conducted to ensure adherence to the principles and procedures of good clinical practice and to comply with the Italian laws. Written informed consents for publication of the clinical details and clinical images was obtained from the parents of patients.

COMPETING INTEREST STATEMENT

All authors state that they have no competing interests to declare. None of the authors accepted any reimbursements, fees or funds from any organization that may in any way gain or lose financially from the results of this study.

FUNDING

This research was no supported by funding.

AUTHORS' CONTRIBUTION

Conceptualization, EM, RF; methodology, RF; investigation, FR, FS, CV, MB; data curation, FR, FS, CV, MB; writing-original draft preparation, EM; writing-review and editing, RF, MS. All authors have read and agreed to the published version of the manuscript.

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Received on 05-04-2025 Accepted on 10-05-2025 Published on 16-05-2025

https://doi.org/10.12974/2311-8687.2025.13.02