Case Report

Journal Homepage: http://crcp.tums.ac.ir

A Rare Syndromic Report of a Young Patient with Type 2 Diabetes Mellitus: Alstrom Syndrome

Apoorva Suran*, **Jaideep Khare**

Department of Endocrinology, Peoples Medical College and Research Centre, Bhopal, M.P, India.

Use your device to scan and read the article online

Citation Suran A, Khare J. A Rare Syndromic Report of a Young Patient with Type 2 Diabetes Mellitus: Alstrom Syndrome. Case Reports in Clinical Practice. 2024; 9(6): 253-256. DOI:10.18502/crcp.v9i6.18944

Running Title A Rare Syndromic of Type 2 Diabetes Mellitus: Alstrom Syndrome

Article info:
Received: October 28, 2024
Revised: November 24, 2024
Accepted: December 26, 2024

Keywords:
Alström syndrome; Diabetes in adolescents; Alstrom syndrome; Normal BMI

ABSTRACT

Alström syndrome is a rare multi-system congenital disorder with varied phenotypic presentations, including obesity, early-onset blindness, hearing loss, and various cardiac and renal manifestations. We discuss a case of a young male who presented with Type 2 Diabetes Mellitus (T2DM) and dyslipidemia, with a history of blindness and hearing loss since childhood. His family history was significant, with three prior sibling deaths. Genetic evaluation confirmed the diagnosis of Alström syndrome. He did not have obesity or any cardiovascular complications. The rest of the systemic examination and blood work were normal. This case is noteworthy as it represents one of the few variants of Alström syndrome without obesity. Early diagnosis and management are crucial for these patients to prevent avoidable complications and improve their quality of life.

Introduction

Pathogenic mutations of the ALMS1 gene produce the rare multisystem genetic illness known as Alström Syndrome (ALMS). In 1959, Carl-Henry Alström was the first to identify this syndrome, which includes insulin resistance, neuronal hearing loss, obesity, and progressive retinal degeneration. Numerous endocrine abnormalities are typically linked to it. Clinical symptoms might vary greatly in intensity and age of onset, initially manifesting in infancy. The expected incidence of ALMS is one case per one million live births. Since early identification and intervention can reduce the progression of multi-organ dysfunctions and enhance patient quality of life, multidisciplinary and multiprofessional teams of experts are crucial for the management of patients with ALMS.

According to the age of manifestation, Marshall et al. initially provided major and minor criteria for the diagnosis of Alström Syndrome [1]. The two main criteria across all age groups were vision impairments and a family history of Alström Syndrome or an ALMS1 gene-verified mutation in one allele. All other multisystem features are considered minor criteria. The European Alström Syndrome Society (ASEU) has also released consensus guidelines for the management of Alström Syndrome in 2022 [2]. It is inherited in an autosomal recessive manner, caused by homozygous or compound heterozygous variants in the ALMS1 gene, which is located on chromosome 2p13. Of the 268 pathogenic variants identified so

* **Corresponding Author:**
Apoorva Suran
Address: *Flat 104, B9, Ruchi lifescapes, jatkhedi, Bhopal, 462026*
E-mail: *apoorvasuran170192@gmail.com*

far, 96% are nonsense or frameshift changes [2]. It is considered a ciliopathy. The first symptoms usually occur during the first year of life, either with visual disturbances and/or heart failure, and clinical findings evolve as affected individuals age.

Case Presentation

A 19-year-old male presented to our outpatient clinic with a history of type 2 diabetes mellitus (T2DM) and dyslipidemia for four years, for which he was already on oral antidiabetic medications (Acarbose 25 mg twice a day, Teneligliptin 20 mg once a day, and Metformin 500 mg twice a day). However, his blood glucose levels were not under control. He did not have any family history of T2DM.

His past history was significant as he developed near-complete blindness since the age of 1 year, with a current vision of 6/60 in both eyes, along with nystagmus and photophobia. He was detected to have bilateral (B/L) mild sensorineural hearing loss (SNHL) two years ago. His neonatal history was not significant, but there was a delay in gross motor milestone achievements (walking by 1.5 years and speech by 3–4 years). He had normal pubertal development with a slight delay at onset. Currently, he is well-virilized with normal development of male genitalia.

He is of short stature with normal weight and body mass index (BMI). He weighs 55 kg with a height of 157 cm (just below the 3rd centile) and a normal BMI (20 kg/m^2). He is studying in the 11th standard but has poor academic performance, averaging 40-45% marks. His social circle is limited, and outdoor activities are restricted.

His family history was significant, as all three of his previous siblings had expired due to unknown causes, with no history of consanguinity. The eldest brother expired as a neonate, but no records are available. Another male, second in order, lived up to 22 years of age but had similar issues to the current case—early-onset vision loss, hearing loss—and later succumbed to liver failure and congestive heart failure. He was obese since childhood, unlike our primary case. The third-born sibling, a girl, expired as a neonate, probably due to respiratory infections (records not available).

A picture of our patient is shown in Figure 1. The family pedigree is attached in Figure 2.

Fig. 1. Depicts facial features of Alstrom Syndrome patient, without any Acanthosis nigricans

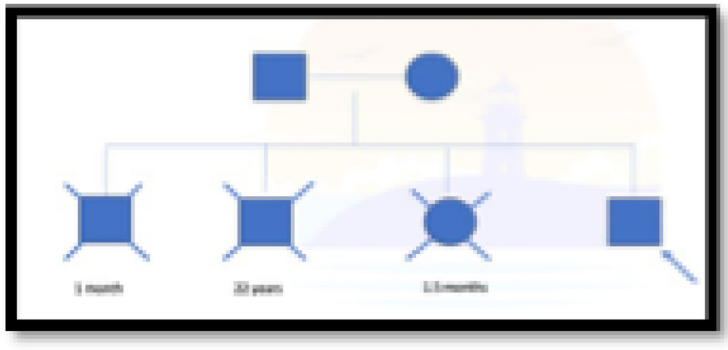

Fig. 2. Pedigree chart showing the index case and his affected siblings with their respective age of demise.

Table 1. Routine baseline investigations

Hb (g/dl)	12.3
Serum Creatinine(mg/dl)	0.86
SGOT/PT (U/L)	25/30
HbA1c (%)	8.2
Total Cholestrol / Triglycerides (mg/dl)	250/355
HDL/ d-LDL(mg/dl)	40/138
TSH (miU/ml)	3.2

In view of the multisystem involvement with diabetes and significant family history, a whole exome sequencing was advised which showed a pathogenic mutation- homozygous 4 base pair deletion in exon 8 of ALMS1 gene, suggestive of Alstrom syndrome of AR inheritance.

The routine blood work was normal for our case, with normal liver function test, as listed in Table 1.

Ultrasonography of the whole abdomen showed grade 1 fatty liver with mildly raised left renal parenchymal echogenicity; otherwise, the genitourinary tract was normal. ECG and 2D-color Doppler echocardiography did not show any abnormalities. He was advised to follow up regularly with a multidisciplinary approach in the future. His parents were also advised to undergo WES, but they declined.

Currently, his glucose levels are well maintained on twice-daily Acarbose 25 mg and Pioglitazone 15 mg OD, and at his last visit, his HbA1c was 7.1%. We also started him on Rosuvastatin 10 mg and Fenofibrate 160 mg. After two months, his lipid profile showed significant improvement. We have planned to continue the same medications for diabetes and dyslipidemia along with lifestyle modifications.

Discussion

Any young age of onset of hyperglycemia should raise suspicion for Type 1 DM, Latent Autoimmune Diabetes of Adults (LADA), or Maturity-Onset Diabetes of the Young (MODY), but Type 2 DM should not be completely ruled out based solely on age at presentation. Our patient had an onset of diabetes at 12 years of age, with a normal BMI, no clinical signs of insulin resistance, and no known diabetic family history. He had not yet experienced any episodes of diabetic ketoacidosis. Blood glucose levels were maintained on oral antidiabetic medications for the past four years, making a diagnosis of Type 1 DM less likely. MODY was also improbable, as his family history was not positive for DM.

Although he had a normal BMI, LADA could not be ruled out completely as no autoimmune diabetes panel was performed, and he had not required insulin to date. Given his multisystemic involvement and significant family history, we considered this to be Type 2 DM associated with a genetic syndrome. Later, genetic testing confirmed a diagnosis of Alström Syndrome.

Alström Syndrome is a rare disorder, with only 950 cases reported worldwide and approximately 20–30 cases from India [3]. The most common finding, observed in nearly all instances, is retinal dystrophy, which often appears in the first year of life and progresses to near blindness before the second decade. Seventy percent of patients with hearing impairment are diagnosed before the age of ten, making it the second most prevalent clinical finding. It presents as progressive SNHL, as seen in our patient (confirmed by audiometry).

Patients with ALMS typically present with heart failure, occult myocardial infarction, and cardiomyopathy as cardiovascular manifestations. Although our case had no history of cardiac symptoms and his 2D echocardiography was normal, we will continue to monitor him regularly.

Endocrine manifestations include partial or complete empty sella, hypothyroidism, male hypogonadism, female hyperandrogenism, and short stature. Despite having a delayed puberty onset, our case involved a well-virilized male with typical secondary sexual characteristics. His height was slightly below the third centile on the IAP 2015 growth charts.

Renal complications such as chronic kidney disease, dyslipidemia, and hypertension are common. However, our case had not yet developed any of these issues.

Individuals with ALMS may also experience delayed developmental milestones, most commonly in the areas of fine and gross motor skills, with frequent learning difficulties. Although our patient did not undergo a formal IQ test, he exhibited learning difficulty.

The majority of ALMS patients experience childhood obesity. Even when birth weight falls within the standard range, there is a noticeable increase in weight between two and thirty-six months of age. Increased leptin levels, which correlate with body weight, and fat accumulation in subcutaneous rather than visceral areas are hallmarks of this illness. Obesity in ALMS is most likely caused by higher intake rather than a reduced metabolic rate. By adolescence, the majority of affected individuals acquire type 2 diabetes and insulin resistance.

Our patient had normal weight for his height with a normal BMI. We did not analyze his body composition, so we are uncertain about his visceral versus subcutaneous fat distribution. He has been advised to exercise regularly and maintain his weight. Other metabolic complications include a deranged lipid profile with hypertriglyceridemia, normal total cholesterol, and low HDL levels. Patients with ALMS are also prone to developing non-alcoholic fatty liver disease that is disproportionate to age, BMI, and duration of T2DM, which can progress to liver cirrhosis at an early age.

Our patient was already on a statin for dyslipidemia and had grade 1 fatty liver with normal liver enzymes.

More than 200 mutations have been described as causative for ALMS. The presenting case had a pathogenic mutation homozygous 4-base-pair deletion in exon 8 of the ALMS1 gene suggestive of Alström Syndrome with autosomal recessive inheritance.

Management of ALMS requires a multidisciplinary approach. An individualized treatment protocol is essential, as disease phenotypes can vary significantly among patients. Regarding diabetes management, insulin-sensitizing medications such as metformin and thiazolidinediones are helpful. Newer pharmacotherapies, including sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 inhibitors, may play a crucial role. However, lifestyle modifications, including diet and weight management, remain the cornerstone for managing hyperglycemia and other metabolic complications.

Our case was somewhat different from the rest of the reported cases of Alström Syndrome in the literature, as our patient had a normal BMI with no other systemic complications [4].

Conclusion

In summary, not all young diabetes patients present with type 1 DM or LADA. Type 2 DM can occur at a young age, with or without clinical signs of insulin resistance (IR). A syndromic cause of diabetes should be suspected in any young individual presenting with diabetes and multisystem involvement.

ALMS is one of the rare causes of young-onset DM, mainly due to IR. These individuals can be managed with lifestyle modifications and oral insulin sensitizers. Long-term follow-up is essential, with the goal of early detection of complications and their timely management.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

Funding

No funding was received to assist with the preparation of this manuscript.

Conflict of Interests

The authors have no conflict of interest to declare.

References

[1] Marshall JD, Beck S, Maffei P, Naggert JK. Alström syndrome. Eur J Hum Genet. 2007 Dec;15(12):1193–202. https://doi.org/10.1038/sj.ejhg.5201933

[2] Tahani N, Maffei P, Dollfus H, Paisey R, Valverde D, Milan G, et al. Consensus clinical management guidelines for Alström syndrome. Orphanet J Rare Dis 15, 253 (2020). https://doi.org/10.1186/s13023-020-01468-8

[3] MS R, Rajan MG, Puneeth A, Soundarya M. Alstrom syndrome—a diagnostic dilemma. Int J Diabetes Dev Ctries. 2017 Mar;37:88-91. https://doi.org/10.1007/s13410-016-0520-7

[4] Koç E, Bayrak G, Suher M, Ensari C, Aktas D, Ensari A. Rare case of Alstrom syndrome without obesity and with short stature, diagnosed in adulthood. Nephrology (Carlton). 2006 Apr;11(2):81-4. https://doi.org/10.1111/j.1440-1797.2006.00443.x