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Case Report

Alström syndrome: a rare genetic cardiomyopathy

Sheeba Thomas*, Carol Sara Cherian, Jacob Abraham, Jewel Maria George

Department of Paediatrics, Pushpagiri Institute of Medical Sciences and Research Centre, Thiruvalla, Kerala, India

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***Correspondence:**
Dr. Sheeba Thomas,
E-mail: sheebathomas33@gmail.com

ABSTRACT

With an incidence estimated at less than 1 100 000, Alstrom syndrome (AS) was first reported in 1959. AS is an autosomal recessive multi organ disorder, characterized by childhood obesity, adult short stature with initial accelerated childhood linear growth, progressive cone-rod dystrophy leading to blindness, and sensorineural hearing loss. Acanthosis nigricans, hyperinsulinemia, hypertriglyceridemia, hypothyroidism, infertility (hypergonadotrophic hypogonadism), and early-onset diabetes mellitus are the endocrinology consequences. In children dilated cardiomyopathy is the main cause of mortality, in older affected patients, renal failure is the main cause of death. We report a rare case of a 04-month-old girl with dilated cardiomyopathy, Global developmental delay, congenital nystagmus caused by ALMS1 mutation. This study demonstrates that genetic testing for cardiomyopathy without an obvious acquired cause help in determining the underlying cause, managing the condition appropriately, diagnosing syndromic forms early, and keeping an eye on and initiating pre-symptomatic treatment for related extracardiac complications.

Keywords: Alström syndrome, Dilated cardiomyopathy, Pediatric cardiomyopathy

INTRODUCTION

Alström syndrome (AS) is an uncommon genetic cause of cardiomyopathy. Pediatric cardiomyopathy itself is rare and often has an underlying genetic etiology. With advances in clinical genetic testing, knowledge of the genetic basis of cardiomyopathy is expanding, and novel causative genes continue to be identified. The availability of large population genetic datasets has further refined our understanding of the relevance of rare genetic variants. Independent studies by two research groups established that AS results from mutations in the ALMS1 gene.[1,2] The ALMS1 gene encodes a protein comprising 4,169 amino acids, featuring a large tandem-repeat domain of 47 amino acids. This protein is widely expressed and localizes to subcellular structures.[3] Evidence suggests that ALMS1 is involved in basal body or centrosome function.[3] While early studies showed normal ciliary morphology in fibroblasts from individuals with ALMS1 mutations, ALMS1 knockout mice exhibited abnormal ciliary structure, which could be restored using a prematurely truncated ALMS1 fragment containing the N-terminus.[3,4] These findings indicate that the N-terminal region of ALMS1 is critical for maintaining normal ciliary architecture.[4]

CASE REPORT

A 04-month-old female infant presented with h/o recurrent respiratory tract infection for 03 months of age, treated with nebulization and oral antibiotics She was brought at 04 months 27 days of age with c/o wet cough and breathing difficulty in the form fast breathing and chest indrawing. Mother also gives a history of abnormal to and fro movements of eyes noted since birth. H/o suck-rest-suck cycles and gross sweating during feeding was noted. She was born as second child of nonconsanguineous marriage via full term LSCS with a birth weight 2.56 kg. H/o breath holding noted on day 04 of life was observed in NICU. Echo, NSG, EEG done

then revealed normal study. Developmental delay in gross motor, fine motor, social and adaptive domains were noted in the child. MRI taken in view of congenital nystagmus revealed no definite morphological abnormality or focal lesion. VEP done was suggestive of left anterior optic pathway dysfunction. At the time of presentation, she was sick looking, dysmorphic facies with opsoclonus and nystagmus. She was tachypneic, in respiratory distress with oxygen saturation of 89% on RA. Her peripheries were cold with feeble peripheral pulsations. Chest examination revealed bilateral basal crepitations and wheeze. Heart sound showed soft S1with normal split S2 with no murmur. Liver just palpable just below the right costal margin. She had horizontal nystagmus with difficulty in fixation of eyes and following objects. In developmental assessment-head control was not achieved yet. She was able to transfer the objects and recognizes mother.

Her blood investigations revealed polymorpholeukocytosis and raised cardiac markers (NTproBNP, hsTropI). Echo done revealed global LV hypokinesia, severe LV systolic dysfunction, RV dysfunction, moderate to severe MR, mild TR, moderate PAH. Chest X-ray showed hyperinflated lung with cardiomegaly (CT ratio -0.64).

She was put on HFNC support and dobutamine infusion. She was treated with Lasix infusion, IvIg, methylprednisolone and digoxin. She had opsoclonus for which USG abdomen was taken and ruled out neuroblastoma. Child improved symptomatically over the course of hospital stay, repeat echo done revealed improving LV function. Spironolactone along with Lasix and ACE inhibitors (Enalapril)was added.

In view of global developmental delay with congenital nystagmus and cardiac involvement genetic study was done which showed ALMS1 mutations in exon 8.

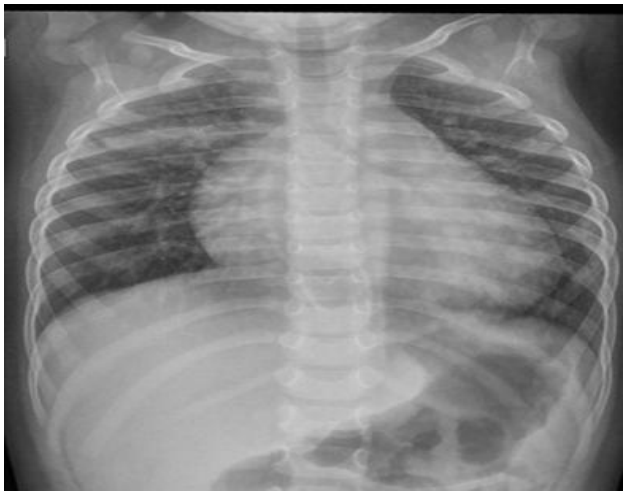

Figure 1: Chest X ray showing hyperinflated lung with cardiomegaly.

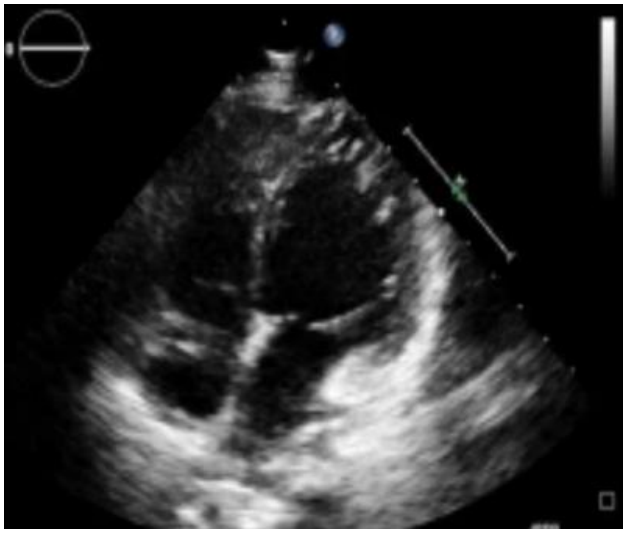

Figure 2: Echo showing LV systolic dysfunction.

Table 1: Gene and transcript.

Gene and transcript	Exon/ intron number	Variant nomenclature	Zygosity	Classification	Disease	Inheritance
ALMS1	Exon 8	c.2035C>T pArg679Ter	Homozygous	Pathogenic	AS	Autosomal recessive
MYBPC3	Exon 29	c.3064C>T pArg1022Cys	Heterozygous	Likely pathogenic	DCM, IMM	Autosomal dominant

Child is on regular follow up, during last follow up at 01 year 06 months of age she had fair LV function. Developmental assessment- she was able to sit with support and mother regards was present. Currently she is on ACE inhibitor (Enalapril) and diuretics (Lasix).

Genetic study of mother also showed same mutation, homozygous pathogenic variant in exon 8 of ALMS1 gene and a heterozygous likely pathogenic variant in exon 29 of the MYBPC3 gene. She is currently asymptomatic and on follow up.

DISCUSSION

So far, only about 500 cases of AS have been described in the literature, with an estimated frequency of less than one in a hundred thousand. Despite the complexity and possible mortality of AS, there is undoubtedly a lack of awareness about this condition. Affected people may also

develop insulin resistance, type 2 diabetes, and hypertriglyceridemia in addition to childhood obesity. As a result, AS might be understood as an uncommon hereditary illness that has many characteristics with the general metabolic syndrome. Before the recent identification of ALMS1 mutations responsible for AS, phenotype was the only factor used to diagnose AS. But even within families, AS demonstrates a high degree of phenotypic diversity, making it challenging to define AS universally.

Two hallmark features of AS are sensorineural hearing loss and congenital retinal degeneration. In most cases, photodysphoria and pendular or searching nystagmus appear within the first year of life. Visual impairment typically begins with loss of cone function, followed by progressive rod degeneration, ultimately leading to early-onset blindness. By the age of 16 years, approximately 90% of affected individuals are blind. Vision loss may be further aggravated by the development of subcapsular cataracts. There have also been reports of exudative retinopathy in AS. Approximately 80% of those affected will experience bilateral sensorineural hearing loss. Hearing impairment happens gradually and can occasionally be accompanied by conductive hearing loss as a result of glue ear or chronic otitis media. Early alterations in neurosensory capacities have a profound effect on a child's social development as well as ability to adapt to their surroundings. While delayed cognitive development is not a frequent characteristic of AS, approximately 45% of children with AS experience delayed developmental milestones. Generalized sleep problems and absence seizures are possible additional neurologic symptoms.[5]

A round face, deep-set eyes, thick ears, dental deformities, hyperostosis frontalis interna, and premature frontal baldness are among the characteristic facial traits frequently associated with AS. Their feet are usually described as being big and wide, whereas their fingers and toes are usually small and stubby with neither polydactyly nor syndactyly. More than 95% of those with AS had childhood obesity. Nevertheless, regardless of BMI, waist circumference and body fat percentage (as determined by dual-energy X-ray absorptiometry) both showed a negative correlation with age, suggesting the potential recruitment of more metabolically active fat stores.

Patients with AS also exhibit hypertriglyceridemia and type 2 diabetes, which are characteristics of the metabolic syndrome. Over 80% of those older than 16 have been diagnosed with type 2 diabetes, and insulin resistance and hyperinsulinemia have been shown in people as early as 1 year old, even before obesity manifests itself. Acute pancreatitis due to hypertriglyceridemia occurs in around 5% of affected persons, while hypertriglyceridemia is observed in approximately 50% of cases. Additional endocrinologic symptoms of AS include ovarian cysts and hirsutism in females, short stature with abnormalities in the IGF-growth hormone system, hypothyroidism, hypogonadism (especially in men), and alterations in the onset of puberty.[5]

About 60% of people have dilated cardiomyopathy (DCM), which can happen at any age but usually does so in infancy. Even though DCM is the most frequent underlying cause of mortality during the infancy, survival rates for DCM with an infantile onset are often higher than those for DCM with an adult onset. According to Marshall et al around 74% of patients with infantile-onset DCM survived, compared to one-third of those with adult-onset DCM. Those who have survived infantile-onset DCM, both adults and children, are nonetheless vulnerable to unexpected recurrences. Patients with AS may also experience recurrent pneumonia, sinusitis/bronchitis, alveolar hypoventilation, persistent asthma, and other respiratory issues in addition to heart issues. Hepatic involvement may occur in about 80% of AS patients; symptoms can range from a slight increase in liver transaminases to hepatic steatosis to overt cirrhosis with portal hypertension. Constipation, persistent diarrhea, gastroesophageal reflux, and upper gastrointestinal pain are some other gastrointestinal side effects. About 50% of people with AS experience renal insufficiency. Uncertainty surrounds whether hypertension causes or results from renal insufficiency, yet it is present in approximately 30% of people. Urge incontinence, poor flow, urine retention, and trouble starting to void are common signs of urologic dysfunction in both men and women.[5] Narrowed ureteropelvic angles, dilated ureters, kidney misalignment, and calyceal deformities are examples of urologic anatomical anomalies that can also arise in AS.[6]

CONCLUSION

Multiorgan dysfunction is the hallmark of AS, an uncommon autosomal recessive illness. Childhood obesity, sensorineural hearing loss, and blindness from congenital retinal dystrophy are the main characteristics. Hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia are associated endocrinologic characteristics. Dilated cardiomyopathy is the main cause of death in young affected patients. In this case child had cardiac involvement (dilated cardiomyopathy) with nystagmus and global development delay. Child is on anti-cardiac failure measures, regular follow up with improving cardiac function with no other systemic involvement.

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