

**ALSTROM SYNDROME: A CASE REPORT**B. R. Shivakumar <sup>1</sup>, Hareesh R<sup>2</sup>, Rekha G<sup>3</sup><sup>1</sup>Professor and HOD, Department of General Medicine, Dr. B. R. Ambedkar Medical College and Hospital, K. G. Halli, Bengaluru.<sup>2</sup>Assistant Professor, Department of General Medicine, Dr. B. R. Ambedkar Medical College and Hospital, K. G. Halli, Bengaluru.<sup>3</sup>Post Graduate, Department of General Medicine, Dr. B. R. Ambedkar Medical College and Hospital, K. G. Halli, Bengaluru.

**ABSTRACT:** Alstrom Syndrome was first described by Carl Henry Alstrom in 1959. The key features include childhood onset obesity, congenital retinal dystrophy leading to blindness, sensori-neural deafness. The associated endocrinologic aspects are early onset type 2 Diabetes Mellitus, hyperinsulinemia, hypertriglyceridemia. Mutations in the ALMS1 gene have been found to be causative for AS. The normal protein is present at very low levels in most tissues. The mutation results in a non-functional protein, explaining the various signs and symptoms of Alstrom's. Here we report on a case with Alstrom Syndrome at the age of 28 years. She came with the complaints of generalised swelling of the body, breathlessness, decreased urine output with a significant past history of visual and hearing impairment, diabetes, hypertension, and recurrent urinary tract infections. Awareness of Alstrom Syndrome is lacking despite the complexity and lethality of this disorder. Thus Alstrom Syndrome can be thought of as a rare genetic disorder with several features similar to metabolic syndrome. It is a rare disease and difficult to make differential diagnosis with other similar syndromes, therefore this case will be a good example of Alstrom Syndrome for the literature.

**KEYWORDS:** Rare Genetic Syndrome, Multi-Organ Dysfunction.

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**INTRODUCTION:** Alstrom Syndrome is a rare genetic disorder, inherited as autosomal recessive. Progressive multi-organ pathology is characteristic of this syndrome.<sup>1</sup> Symptoms vary greatly with respect to age of onset and severity. Organ failure being the most common cause of death; leads to a lowered life expectancy, approximately 50 years. The syndrome involves cone-rod dystrophy which has its onset in infancy, loss of hearing, truncal obesity, type 2 diabetes mellitus, hyperinsulinemia, hypertriglyceridemia, dilated cardiomyopathy, renal, pulmonary and hepatic dysfunction.<sup>2</sup> The clinical care is complex due to multi-organ dysfunction and therapy is directed to individual symptoms.

**CASE REPORT:** A 28 year old visually impaired unmarried female, resident of Bangalore, Karnataka was brought to the Out-patient Department with complaints of generalised swelling of the body, breathlessness, decreased urine output, fever, vomiting and difficulty swallowing. Her prior history included Type-2 Diabetes Mellitus since 3 years on oral hypoglycaemic agents; Hypertension since 2 years on anti-hypertensives, hearing impairment since 3 years and history suggestive of recurrent urinary tract infections. Menarche at 13 years and amenorrhoeic since 4 months. She was born to a non-consanguinously married couple and no similar complaints were found in other family members; apparently attained all developmental milestones appropriate for age.

On physical examination, significant findings included rotatory nystagmus, overcrowding of teeth, acanthosis nigricans, hirsutism, pallor, facial puffiness and pitting pedal edema, raised JVP, sensorineural hearing loss. Height of 165 cms, weight of 74 kg, BMI of 27.2 kg/m<sup>2</sup>.

On fundus examination, found to have retinitis pigmentosa and bilateral optic atrophy.

**Biochemical Attributes and Investigations:** 2D-echo showed pericardial effusion with preserved ejection fraction; CXR showed bilateral pleural effusion; ERG showed delayed implicit time of b wave; ECG showed low voltage complexes; PTA showed bilateral sensorineural hearing loss; USG abdomen showed moderate ascites, with grade-2 renal parenchymal changes and non-obstructive renal calculi; deranged lipid and thyroid profiles, high Fasting and Post prandial blood glucose and HbA1C, absent GAD 65 and ICA antibodies and normal fasting insulin levels.

**Treatment:** When the patient presented to the out-patient department; our major concern was to treat the symptoms of heart failure aggressively and glycemic control. Patient was treated with diuretics and Insulin for controlling of blood glucose levels. Patient was put on low carbohydrate and renal diet. Fibrates are used for lowering triglycerides along with low fat diet.

**DISCUSSION:** Our aim of presenting the case report is to highlight the very rare genetic syndrome. It has a prevalence of less than one per million in the general population.<sup>2</sup> All over the world only 266 cases have been reported and over 501 known cases in 47 countries.

**Genetics:** Mutations in the ALMS1 gene is located on the 2p13 chromosome. These children are born to heterozygous carriers who are asymptomatic. ALMS1 in Alstrom Syndrome is expressed in most tissues like retinal photoreceptors, organ of Corti, pancreatic islets, renal tubules, liver, widely in brain including hypothalamus.<sup>(3,4,5,6,7)</sup>

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Normal ALMS protein is involved in ciliary function, adipocyte differentiation and intracellular trafficking.<sup>(6-10)</sup> 109 mutations have been recognised in ALMS1 gene and most of them are frame-shift and nonsense which lead to premature termination codons.<sup>(2,3,11-16)</sup>

Diagnosis depends on the clinical features that appear through various stages of infancy, childhood and adulthood.

### 1. Birth to 2 years:

- **Major Criteria:**
  - a) ALMS1 mutation in 1 allele AND/OR
  - b) Family history of Alstrom syndrome.
  - c) Vision (nystagmus, photophobia).
- **Minor Criteria:**
  - a) Obesity.
  - b) Dilated cardiomyopathy/ congestive heart failure.
- **Other variable supportive Evidence:**
  - a) Recurrent respiratory tract infections.
  - b) Normal digits.
  - c) History of delayed developmental milestones.

2major criteria or 1 major+2minor criteria is the minimum required for diagnosis.

### 2. 3years to 14 years:

- **Major criteria:**
  - a) ALMS1 mutation in 1 allele AND/OR.
  - b) Family history of Alstrom syndrome.
  - c) Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG).
- **Minor criteria:**
  - a) Obesity and/or insulin resistance and/or T2 Diabetes Mellitus.
  - b) (History of) Dilated cardiomyopathy/Congestive heart failure.
  - c) Hearing loss.
  - d) Hepatic dysfunction.
  - e) renal failure.
  - e) Advanced bone age.
- **Other variable supportive Evidence:**
  - a) Recurrent respiratory tract infections
  - b)Normal digits
  - c) History of delayed developmental milestones.
  - d) Hyperlipidemia
  - e) Scoliosis
  - f) Flat wide feet
  - g) Hypothyroidism
  - h) Hypertension
  - i) Growth hormone deficiency
  - j) Recurrent UTI.

2 major criteria OR 1 major + 3 minor criteria is required for diagnosis.

### 3. 15years-adults:

- **Major criteria:**
  - a) ALMS1 mutation in 1 allele AND/OR.
  - b) Family history of Alstrom syndrome.
- **Minor criteria:**
  - a)Obesity and/or insulin resistance and/or T2DM
  - b) History of Dilated cardiomyopathy/Congestive heart failure.
  - c) Hearing loss
  - d) Hepatic dysfunction
  - e) Renal failure
  - f) Short stature
  - g) Males: hypogonadism
  - h) Females: irregular menses and/or hyperandrogenism.
- **Other variable supportive Evidence:**
  - a)Recurrent respiratory tract infections
  - b) Normal digits
  - c) History of delayed developmental milestones
  - d) Hyperlipidemia
  - e) Scoliosis
  - f) Flat wide feet
  - g) Hypothyroidism
  - h) Hypertension
  - i) Growth hormone deficiency
  - j) Recurrent UTI / urinary dysfunction
  - k) Alopecia.

2 major + 2 minor criteria OR 1 major + 4 minor criteria is required for diagnosis.<sup>7</sup>

**Treatment:** Primary management is limiting end-organ damage with good glycemic control. Early monitoring and management of disease by multi-speciality approach is required. J. A. L. Minton et al., conducted a cross-sectional cohort study of 12 unrelated subjects with AS. They identified mutations in ALMS1 in more than 80% of patients with no genotype-phenotype correlation. In AS, severe childhood obesity, waist circumference, and body fat decrease with age, whereas insulin resistance increases.

The abdominal obesity, insulin resistance, diabetes, hypertriglyceridemia, and hypertension suggest that AS could represent a monogenic model for the metabolic syndrome.<sup>17</sup> Jan.D.Marshall et al., studied 182 cases and described cardiac, pulmonary, neuro-behavioural manifestations included clonic and absence seizures, hepatic, urologic, gastrointestinal manifestations of the disease. Dilated cardiomyopathy occurred in 60% of patients in study population.<sup>18</sup>

**RESEARCHES:** The Jackson Laboratories in Maine, USA, carry out research on Alström syndrome. Internet: [www.alstrom.org](http://www.alstrom.org). In Sweden, research about Alström syndrome is carried out at the Audiology Clinic/Swedish Institute for Disability Research, Örebro University Hospital, 701 85 Örebro. For more information contact Professor ClaesMöller, tel +46 19 602 37 94 (Secretary Ann-Marie Helgstedt), email:[claes.moller@orebroll.se](mailto:claes.moller@orebroll.se).

Research is also carried out by the Swedish expert team for the diagnosis of deaf-blindness. Address: Svärdsvägen 21, Box 570, SE-182 15 Danderyd, Sweden. Email: expertteamet@mogard.se.

**CONCLUSION:** Ahlstrom Syndrome, a complex multi-organ disorder caused by ALMS1 mutations. Characteristics include Type-2 Diabetes Mellitus, obesity, hyperinsulinemia, vision and hearing impairment, acanthosis nigricans, short stature, cardiomyopathy, hypothyroidism and hypogonadism. Death occurs due to progressive multi-organ dysfunction.

Studies suggest that defects in structure, functioning or maintenance of cilia form the basis for the pathogenesis of Alstrom Syndrome. Ahlstrom Syndrome, being one of the rarest of the syndromes can be easily identified based on the cardinal clinical features. Early diagnosis and management can delay the progression of the disease and prolong the life expectancy.

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