A CLINICAL REVIEW ON ALSTROM SYNDROME

K.N.S.R.Jyothi1, Y.Navya2, Venkata Rohit Kumar.Chandolu3, J.N.Suresh Kumar3

1 V PHARM.D Students, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopeta, Guntur (Dist.), Andhra Pradesh, India, 522601.
2Assistant Professor, Department of Pharmacy Practice, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopeta, Guntur (Dist.), Andhra Pradesh, India, 522601.
3Principal, Department of Pharmaceutics, Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopeta, Guntur (Dist.), Andhra Pradesh, India, 522601.

ABSTRACT

Alstrom Syndrome, a recessively inherited autosomal rare genetic disorder usually caused by the mutations in ALSM1 gene located on chromosome 2p13 characterised by the progressively developing multi organ pathology from the infancy stage but the exact function of ALSM1 gene was still unknown. Alstrom Syndrome encompasses Cone Rod Retinal Dystrophy, Loss of Hearing, Truncal Obesity, Hypertriglyceridemia, Hyperinsulinemia, Insulin Resistance, Dilated Cardiomyopathy, Progressive Hepatic, Renal and Pulmonary Dysfunction Short Stature Infertility and normal intelligence but delayed psychomotor and intellectual development. Acquiring Clinical features, Age of Onset and severity of disease vary greatly among and even within family bearing identical mutations due to interactions of genetic modifiers. Progressive development of multigain damage leads to reduced lifespan not exceeding 50 years. Diagnosis is usually based on the clinical features observed but due to delay of onset of symptoms molecular genetic tests at any age confirms the diagnosis of disease. Due to gradual evolvement and variability of expression leads to delay in onset of symptoms which often leads to misdiagnosis. So far, there is no specific treatment that can cure, prevent or reverse the medical complications associated with Alstrom Syndrome. Early assessment of the disease, intensive medical management and multidisciplinary approach can detect and anticipate the complications that can be prevented and treated. Close monitoring. Prompt interventions and social support improve the overall outcomes generally and improve the life expectancy and quality of life of all patients.

Key Words: Electroretinography (ERG), Dual Energy X-ray Absorptiometry (DEXA), Dilated Cardiomyopathy (DCM), Gamma-Glutamyl Transpeptidase (GGT), Thyroid Stimulating Hormone (TSH), transjugular intrahepatic portosystemic shunt (TIPS).

INTRODUCTION

Alstrom Syndrome a rare monogenic autosomal recessive inherited disorder first described in 1959 by Alstrom Syndrome caused by mutations in ALSM1 gene genetic factor that causes the syndrome was a reciprocal translocation in an ALSM1 gene. The ALMS1 gene present on chromosome 2p13 encodes a protein lacking previously described domains. The protein is found primarily in centrosomes and basal bodies of ciliated cells with implicated roles in ciliary function, cellular quiescence, and intracellular transport. Affected fibroblasts show cytoskeleton abnormalities and migration impairment, expression and production of collagens are up-regulated hence multiple-organ fibrosis occurs. The major phenotypes usually observed in children with Alstrom Syndrome include cone-rod retinal dystrophy beginning in infancy and leading to eventual juvenile blindness, sensorineural hearing impairment, insulin resistance, and obesity. In some cases, infants present with congestive heart failure (CHF) due to dilated cardiomyopathy (DCM). As patients reach adolescence, more of the major phenotypes develop, including type 2 diabetes mellitus (T2DM), hypertriglyceridemia, and adolescent-onset DCM. Short stature, scoliosis, alopecia and male hypogonadism and hyperandrogenism in female patients may be present when patients reach adulthood. Pulmonary, hepatic, and renal phenotypes are progressive. Fibrosis in multiple organs has been described. Even though Alström syndrome has been described as a homogeneous alteration resulting from a mutation in a single gene; families have been described with variable clinical presentations. A diagnosis is usually established on the basis of clinical features observed but may be delayed as a result of gradual evolvement and variable expression. Since Alström syndrome is caused by mutations in the ALMS1 gene, molecular genetic analysis can be used to confirm the clinical diagnosis. The identification of two mutated alleles or a single mutated ALMS1 allele in the presence of four age-dependent primary features or three primary

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features plus two age-dependent secondary features are criteria for diagnosis. Heterozygous carriers are asymptomatic, and testing for at-risk relatives, prenatal diagnosis, and pre-implantation genetics usually requires prior identification of disease-causing mutations in the family.

There is, thus far, no treatment that can cure Alström Syndrome or prevent or reverse the medical complications. Children with Alström Syndrome require a detailed history and thorough initial assessment along with intensive medical management and multidisciplinary follow-up to anticipate and detect the complications that can be treated. Careful monitoring of the systemic manifestations and prompt intervention can generally improve the overall outcome. Social support might be needed Weight reduction and physical exercises, classic advice for patients with metabolic disorders, are also important for individuals with Alström Syndrome.

**CLINICAL CHARACTERISTICS**

A wide range of clinical variability is observed among individuals with Alström syndrome, including among siblings. The first clinical syndrome is usually nystagmus caused by cone rod dystrophy resulting in childhood blindness.

**CONE ROD DYSTROPHY**

The retinal dystrophy in Alström Syndrome usually develops within a few weeks after birth and virtually all children exhibit low vision within the first year of life. The first symptoms are nystagmus and extreme photodymsphoria or light sensitivity. Cataract is a common finding and some patients might transiently benefit from its treatment/removal. Exudative retinopathy was also observed. Electroretinography (ERG), required to establish the diagnosis of cone-rod dystrophy, is abnormal from birth, eventually with impairment of both cone and rod function. By 9 years of age, approximately one-third of patients are totally blind; 50% by age 12, and 90% by age 16. The severity and age of onset of the retinal degeneration vary among AlS patients. Vision may be aided in the first few years if the child is given prescription dark, red-tinted glasses.

**Progressive Sensorineural Hearing Loss**

Alström Syndrome patients who have hearing impairment have sensorineural hearing loss rather than conductive loss. The hearing impairment is bilateral and slowly progressive and cannot be treated or prevented. Vestibular function is abnormal in some patients. There is a high incidence of otitis media and fluid retention along with a high susceptibility to glue ear, which compounds the existing sensorineural impairment. Myringotomy can be of benefit in some individuals with chronic otitis media. Cochlear implantation also has been successful, but surgery complications are known to occur in this rare syndrome. Eighty-nine percent of individuals develop slowly progressive bilateral sensorineural hearing loss in the first decade that usually progresses to the moderate-to-severe range.

**Obesity**

Obesity is an early and consistent feature observed in most children with Alström syndrome. The obesity observed is probably a primary consequence of the alteration of the Alström gene, ALMS1, as it is an early and consistent feature observed in nearly all affected children. Since ALMS1 is expressed in almost every cell type in the body, peripheral tissues such as liver and skeletal muscle may contribute to the pathogenesis of obesity. Excess weight gain does not usually begin until approximately 6 months to 1 year of age and may moderate after puberty. Wide shoulders, a barrel chest, a ‘stocky’ build, and truncal obesity are typical. Dual energy x-ray absorptiometry (DEXA) scans have estimated total body fat. BMI for males and females range between 21 and 53. In some individuals body weight tends to normalize, decreasing into the high-normal to normal range after adolescence. The moderation of weight does not seem to be correlated with the onset of other serious complications such as CHF, T2DM, or renal failure.

**AGE OF ONSET AND INCIDENCE OF COMMON FEATURES OF ALSTROM SYNDROME**

<table>
<thead>
<tr>
<th>Features</th>
<th>Age of Onset Range (Mean)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone-rod dystrophy</td>
<td>Birth - 15 months (5 months)</td>
<td>100%</td>
</tr>
<tr>
<td>Obesity</td>
<td>Birth - 5 years (2.5 years)</td>
<td>98%</td>
</tr>
<tr>
<td>Progressive sensorineural hearing loss</td>
<td>2-25 years (9 years)</td>
<td>88%</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>2 weeks - 4 months</td>
<td>42%</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>Juvenile - late 30s</td>
<td>18%</td>
</tr>
<tr>
<td>Insulin resistance type diabetes mellitus</td>
<td>4-30 years / 8-40 years (16 years)</td>
<td>92% / 60%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Birth-adolescence</td>
<td>25%-30%</td>
</tr>
<tr>
<td>Short stature</td>
<td>Puberty - adult</td>
<td>98%</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>10+ years</td>
<td>78% of males</td>
</tr>
<tr>
<td>Urologic disease</td>
<td>Adolescence - adult</td>
<td>48%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Adolescence - adult</td>
<td>Variably progressive with age in all individuals</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>8-30 years</td>
<td>23%-92%</td>
</tr>
</tbody>
</table>

**Dilated Cardiomyopathy**

Dilated cardiomyopathy occurs in approximately two thirds of patients with Alström Syndrome at some stage during their lives and are major causes of morbidity and mortality. Individuals are
at risk of sudden abrupt onset of CHF at any age, but often during infancy with onset in the first weeks of life prior to the appearance of other clinical features of Alström syndrome. Most of these children survive and make an apparently full recovery in infancy. A subset of 10-15% of patients does not experience infantile DCM, but develop cardiomyopathy for the first time as adolescents or adults. Studies showed that while one-third of adult-onset DCM patients died, ~74% of infantile-onset DCM patients survived. Therefore, all Alström Syndrome patients are at risk for developing DCM at any age.

**Type II Diabetes Mellitus**
Severe insulin resistance, hyperinsulinemia, and impaired glucose tolerance often present in very early childhood. T2DM develops in childhood, adolescence, or adulthood, with a mean age of onset at 16 years. Reduced carbohydrate intake may prove more effective than fat restriction for control of hyperglycaemia and hyperinsulinemia. Acanthosis nigricans, a skin condition sometimes associated with obesity, hyperinsulinemia, and insulin resistance, is described in about one-third of patients, whether or not they have diabetes. Interestingly, ALMS patients with T2DM do not appear to develop typical peripheral sensory neuropathy symptoms and maintain good protective sensation despite comparable hyperglycaemia and dyslipidaemia seen in other types of diabetes.

**Growth and Development**
Growth hormone deficits and disturbances in the growth hormone/insulin-like growth factor I have been reported in a number of cases. Children grow rapidly and are initially tall for their age with a height >50th centile, with 2–3 years advanced bone age prior to puberty but early closure of the growth plates results in height below the 50th centile by age 14–16 years.

**Hypogonadotropic Hypogonadism**
Male hypogonadotrophic hypogonadism results in low plasma testosterone secondary to low plasma gonadotropin concentration. Male adolescents have small testes and penises, impaired or delayed puberty, gynecomastia, and low sperm count. Normal-to-high follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels and low testosterone levels indicate primary hypogonadism. Males are unlikely to be fertile, but have normal secondary sexual characteristics such as facial and abdominal hair. In female adolescents, sexual development usually progresses normally and menstrual cycle is not delayed. Secondary sexual characteristics such as axillary and pubic hair is normal. The external genitalia, uterus, and fallopian tubes are normal, but menstruation is often scant, sporadic, or irregular. Increased androgen production and hirsutism are common.

**Hepatic Dysfunction**
Nearly all patients with Alström Syndrome are at risk for some degree of liver involvement with a highly variable age of onset, clinical course, and prognosis. Initially, transaminases and gamma-glutamyl transpeptidase (GGT) are elevated but overt clinical manifestations are absent. Progression to hepatic failure can occur in childhood but usually worsens in the second to third decades. Portal hypertension, hepatosplenomegaly, cirrhosis, oesophageal varices, ascites, and liver failure are among the late clinical signs and the upper gastrointestinal haemorrhage due to portal hypertension is a cause of death in some patients.

**Renal Dysfunction**
Slowly progressive nephropathy, progressive glomerulofibrosis, and a gradual destruction of the kidneys are a major feature in adult patients with Alström Syndrome. Age of onset, progression rate, and severity are variable. Histopathologic changes include hyalinization of tubules and interstitial fibrosis. Lower urinary tract dysfunction, recurrent infections, vesicoureteral reflux, urethral stenosis, and detrusor instability have been reported.

**Pulmonary Function**
Chronic respiratory illness is one of the most frequent complaints. Symptoms range from frequent colds and flu, to chronic bronchitis, sinusitis, and recurrent bouts of pneumonia. Pulmonary problems range in severity from frequent bronchial infections to chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). Pulmonary hypertension is common in some patients, as inflammation continues, the lungs are infiltrated by fibrotic lesions and moderate to severe interstitial fibrosis has been reported.

**Urological Dysfunction**
Males and females with ALMS can experience varying degrees of urinary problems. Minor symptoms include urinary urgency, difficulty initiating or poor flow, long intervals between voiding, incomplete voiding (urinary retention) or abdominal pain before or during urination. Anatomical abnormalities can also occur in ALMS, including calyceal deformities, narrow ureteropelvic angles, dilated ureters, and misalignment of the kidneys.

**Anthropometrics**
There is no facial dysmorphism, but patients have distinctive facial characteristics including deep-set eyes with a rounded face, thick ears, premature frontal balding, and thin hair. Dental anomalies include discoloured teeth, gingivitis, a large space between the front teeth, and extra or missing teeth.

**Developmental Delay**
Delay of cognitive impairment is not a common feature of ALMS; delay in early developmental milestones is seen in ~45% of affected children. Particularly sitting, standing, and walking, is typically delayed by 1–2 years and there may be deficits in coordination, balance, and fine motor skills. Hearing and vision deficits probably contribute to the early developmental.
expressive and receptive language, and learning delays seen in many young children with ALMS. Other neurologic manifestations may include absence seizures and general sleep disturbances.

**Hypothyroidism**

A hypothyroid condition, mostly primary (low free thyroxine (FT4), High thyroid stimulating hormone (TSH)), is observed in approximately 20% of patients.

**DIAGNOSIS**

Alström Syndrome is characterized by a constellation of progressive and highly variable disease symptoms. Diagnosis is made on the basis of clinical features observed, usually without genetic confirmation. A major problem in arriving at a diagnosis of ALMS is the high phenotypic heterogeneity that can occur even within the same affected family. Delay of onset of some of the characteristic features (T2DM, DCM/CHF, hepatic dysfunction, pulmonary, and renal disease) makes early differential diagnosis very difficult in young children. As many of the cardinal features do not become apparent until the teenage years, a diagnosis of Alström Syndrome is proven at any age when two ALMS1 mutations, each coming from one parent, have been identified in the patient. Genetic testing should be undertaken when the combination of major (vision) and minor criteria does not permit a clinical diagnosis. The identification of a single mutated ALMS1 allele would confirm the diagnosis. There is an established set of diagnostic criteria suggested for infants through 2 years, children aged 3–14 years, and adolescents/adults over 15 years. To aid the clinician in making an early diagnosis, we have designated ‘major’ criteria for a diagnosis, along with ‘minor’ criteria that can be used as evidence of Alström Syndrome, according to age.

**DIFFERENTIAL DIAGNOSIS**

I. **Bardet-Biedl syndrome (BBS)**

shares some features of Alström syndrome. The major clinical features of BBS are rod-cone dystrophy, postaxial polydactyly, central obesity, cognitive impairment, hypogonadism, and renal dysfunction. A major difference between Alström syndrome and BBS is the timing of the onset of visual problems: in Alström syndrome, visual problems are usually apparent in the first two years of life; in BBS, the average age of onset of visual problems is 8.5 years. Polydactyly, which is common in BBS, has not been described in Alström syndrome. Cognitive impairment is well described in BBS, while in most persons with Alström syndrome intelligence is normal. Pathogenic variants in at least 14 different genes are causative. Inheritance is autosomal recessive.

II. **Early-onset Dilated Cardiomyopathy**

Dilated cardiomyopathy, characterized by cardiac dilation and reduced systolic function, is the end stage of a number of inherited and acquired disorders. Familial dilated cardiomyopathy may be inherited in an autosomal dominant manner and less frequently in an autosomal recessive manner with ventricular dilation and systolic dysfunction becoming apparent in the third and fourth decades.

**III. Inherited mitochondrial disorders**

Represent a heterogeneous group of complex disorders that may be caused by pathogenic variants in mitochondrial DNA or nuclear DNA. Clinical features common to mitochondrial disorders and Alström syndrome include cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus; however, central nervous system involvement and muscle weakness occur in individuals with mitochondrial disorders, while they are not reported in Alström syndrome. Generally, mitochondrial disorders present in late childhood or in adulthood, unlike Alström syndrome, which usually presents during the first year of life.

**MANAGEMENT**

There is no treatment at this time that can cure ALMS or prevent or reverse the medical complications. The main causes of death in ALMS are from cardiomyopathy, pulmonary, kidney or liver failure. Early diagnosis is important to allow counselling of parents and institution of appropriate supportive medical treatment. In the absence of specific therapy to correct the underlying genetic defect, ALMS remain a progressive disease and regular intensive medical management is essential to track progression and to anticipate the emergence of new symptoms and disease manifestations.

**Rod-Cone Dystrophy**

Early on when photodysphoria is significant, the use of red-orange tinted prescription lenses may reduce symptoms. Regular ophthalmologic evaluations should be sought as soon as possible. Educational planning should anticipate future blindness, therefore, early mobility training and Braille or other non-visual language skills is critically important for the learning environment of the child. Computing skills (including voice recognition and transcription software), and the use of large print reading materials early on while vision is still present are crucial.

**Obesity/Insulin resistance/Type 2 diabetes**

The major clinical treatment focus is on control of obesity and T2DM. Therapeutic intervention to treat severe insulin resistance and possibly prevent the transition from insulin resistance to overt diabetes include insulin-sensitizing drugs (metformin and thiazolidinediones) and beta cell-preservation drugs (incretins, thiazolidinediones). Exenatide, an injectable analogue of glucagon-like peptide 1(GLP-1) could be promising in adults with ALMS. Weight loss exercises should play a pivotal role in weight reduction plan for ALMS patients, as in other patients diagnosed with diabetes and obesity. Caloric restriction helps control obesity, glucose tolerance and hyperinsulinemia.
CONCLUSION
Alström syndrome is a complex pleiotropic disorder caused by mutations in ALMS1. Death usually occurs due to progressive cardiac, hepatic and renal failure, often associated with pulmonary disease. Full understanding of the phenotypic characteristics and sharing of information about Alström Syndrome continues to improve our ability to make valid diagnoses and to find the best combination of therapeutic approaches for each child by developing targeted therapies, certain debilitating aspects of ALMS could be prevented or treated earlier, improving the overall outcome in this complex disorder. Careful clinical and genetic studies can contribute to a better understanding of the disease evolution. This article is very useful for the future aspects of Paediatrics, Adults, and Geriatrics.

REFERENCES

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