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Alström Syndrome

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ABSTRACT
Alström syndrome is a rare genetic disorder inherited in an autosomal recessive pattern, resulting from mutations in the ALMS1 gene. It presents with a wide range of progressive symptoms, including vision and hearing impairment, cardiomyopathy, obesity, type 2 diabetes, and dysfunction of multiple organs such as the liver, kidneys, and lungs. The condition is classified as a ciliopathy, where defective cilia contribute to systemic complications. Symptoms typically appear in early childhood and worsen over time, making diagnosis challenging due to similarities with other disorders. Genetic testing provides the most reliable confirmation of the condition. Currently, there is no cure, and treatment is focused on symptom management, including diabetes control, cardiac monitoring, and supportive care for sensory impairments. Research efforts continue to explore the underlying mechanisms of ALMS1 mutations, aiming to develop targeted therapies. Early diagnosis and a comprehensive, multidisciplinary approach are essential in improving patient outcomes. Greater awareness and increased research funding are vital for advancing treatment options and enhancing the quality of life for those affected by this complex disorder.

Keywords- Alström Syndrome, ALMS 1, recessive

I. INTRODUCTION

Alstrom syndrome is a genetic disorder of obesity that is autosomally recessive and affects less than one in per million people. It is an infrequent autosomal recessive genetic disorder secondary to pathogenic mutations involving the ALMS1 gene on the short arm of chromosome 2. The other clinical manifestations include cone-rod dystrophy, which leads to progressive vision and hearing loss, type 2 diabetes mellitus combined with hyperinsulinemia, dilated cardiomyopathy, and hepatic and renal failure. (1) Cone-rod dystrophy manifests as increasing visual impairment, photophobia, and nystagmus, typically beginning between birth and age 15 months. This disabling condition affects the eyes severely and retards their ability to perceive light. Reading large text becomes possible for only a small percentage of people with better ability to cope into their thirties. (2) Symptoms present themselves at an early age and the variation is massive in terms of age of onset, and level of severity of clinical symptoms, with even identical mutations within families. It is a significant cause of chronic disease burden and organ failure, with life expectancy being below 50 years. While this monogenic syndrome is rare, Alstrom syndrome has metabolic syndrome, obesity, insulin resistance, diabetes, hypertriglyceridemia, and hypertension to look into. There is a considerable amount of focus on the syndrome, especially at the molecular level and biochemical pathways to fully understand the syndrome. Retinal degeneration, sensorineural hearing loss, and cardiomyopathy as well as hepatic and renal failure are clinical features that are unexplored and are often seen in the general population. (3)

Alstrom syndrome is a rare autosomal recessive genetic disorder caused by mutations in the ALMS1 gene located on the short arm of chromosome 2. It affects fewer than one in a million individuals and is characterized by obesity, type 2 diabetes with hyperinsulinemia, dilated cardiomyopathy, and progressive liver and kidney failure. One of the hallmark features is cone-rod dystrophy, which results in progressive vision and

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hearing loss. Symptoms of cone-rod dystrophy, such as visual impairment, photophobia, and nystagmus, typically appear between birth and 15 months of age, severely impacting light perception. Only a small percentage of individuals retain the ability to read large text into their thirties. (1)

The syndrome presents early in life, but the age of onset and severity of symptoms vary widely, even among family members with identical genetic mutations. Alström syndrome significantly contributes to chronic disease burden and organ failure, with a life expectancy typically under 50 years. Although rare, the condition shares features with metabolic syndrome, including obesity, insulin resistance, diabetes, hypertriglyceridemia, and hypertension. Research efforts are heavily focused on understanding the molecular and biochemical pathways underlying the syndrome. (2)

Despite its rarity, Alstrom syndrome highlights critical clinical features such as retinal degeneration, sensorineural hearing loss, cardiomyopathy, and hepatic and renal failure, which are also observed in the general population. These aspects remain underexplored, emphasizing the need for further investigation into the syndrome's broader implications. (3)

ETIOLOGY

Alstrom syndrome is caused by mutations in the ALMS1 gene. This gene provides instructions for producing a protein whose exact function is not fully understood but is thought to be involved in ciliary function, cell cycle regulation, and intracellular transport. Mutations in the ALMS1 gene, likely result in an abnormally shortened, nonfunctional version of the ALMS1 protein. This protein is expressed at low levels in most tissues, so the loss of its normal function may explain the signs and symptoms of Alstrom syndrome, which affects many parts of the body. Some research suggests the protein product of the ALMS1 gene plays a role in the proper functioning, formation, and/or maintenance of cilia-the hair-like structures found in almost all types of cells in the body as well as some related structures such as the basal body (which "anchors" the cilia to a cell. A related condition, Bardet-Biedl syndrome, has also been linked to ciliary malfunction. Several diseases, known as ciliopathies, have been associated with cilia dysfunction. Further studies are required to determine whether related cilia and structures play a role in the pathogenesis of Alstrom syndrome. (4)

The ALMS1 gene is located on chromosome 2 in the short arm, p 13. Chromosomes are considered a component carrying an individual's genetic information housed within the human cell nucleus. In general, the human cell has 46 chromosomes. Human Chromosomal pairs: numbers 1 – 22 are sex chromosomes assigned with the letter case, X or Y. Both a short "p" arm and a long "q" arm are characteristics of each chromosome. Chromosomes are split into several numbered bands. Therefore, "2q13" refers to chromosome 2, long arm, band 13; the numbered bands indicate the localization of thousands of genes on every chromosome. (5)

EPIDEMIOLOGY

Alstrom syndrome is considered a rare condition, with an estimated prevalence ranging from 1 in 100,000 to 1 in 1 million individuals. (6) However, many cases may go undiagnosed due to their rarity and the wide spectrum of clinical symptoms, which can vary from mild to severe. To date, around 1,200 cases of Alstrom syndrome have been reported globally. (7,8) Based on data from a combined national Alstrom service in Europe, at least 263 cases have been recorded, including 89 from the United Kingdom, 64 from France, 60 from Turkey, 39 from Italy, and 15 from Spain. (9)

MOLECULAR GENETICS

Alstrom syndrome is an inherited disorder caused by mutations in the ALMS1 gene, located on chromosome 2p13. Unlike some other genetic conditions, there is no evidence of heterozygous carriers or tri-allelic inheritance, which contrasts with conditions like Bardet-Biedl syndrome (BBS) (10, 3). This multisystem disorder presents with a wide range of symptoms, including congenital nystagmus, cone-rod dystrophy, bilateral sensorineural hearing loss, cardiovascular disease, insulin resistance and type 2 diabetes, chronic kidney disease, non-alcoholic fatty liver disease, short stature, male hypogonadism, bladder dysfunction, and obesity. The ALMS1 gene encodes a protein localized to the base of cilia and centrosomes (11, 3). Spanning 23 exons, ALMS1 is known to produce multiple alternatively spliced transcripts, though the specific exon composition of each variant remains to be fully determined (12). While the precise function of the ALMS1 protein is not fully understood, it is believed to play a role in metabolic regulation, homeostasis, cytoplasmic transport, cell signaling, cell differentiation, and cell cycle control (13, 14).

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CLINICAL OVERVIEW

NEUROSENSORY

By the age of 15, nearly all patients experience progressive vision loss, photo-dysphoria (light sensitivity), and early-onset nystagmus, leading to legal blindness. Retinal abnormalities such as macular degeneration and optic disc pallor are common, and electroretinograms reveal cone dysfunction with progressive rod degeneration. Among patients aged 10 to 44, 32% develop subcapsular cataracts (15). While surgical removal of bilateral subcapsular cataracts, which are frequently observed, may temporarily improve vision, it does not halt the progression of retinal deterioration. Childhood retinal changes include increasing retinal pigment epithelium (RPE) atrophy, optic disc pallor, and vascular narrowing. Histological findings show features such as bone spicules, optic disc drusen, and asteroid hyalosis (16, 17-19). Optical coherence tomography (OCT) imaging in young children reveals macular thinning, delayed development, and an immature retinal structure. Although there is no cure for progressive vision loss, early intervention with Braille, mobility training, and visual aids is recommended to prepare patients for inevitable blindness. Early diagnosis and support can significantly improve the quality of life (20).

In addition to vision issues, sensorineural hearing loss is often worsened by recurrent acute and chronic otitis media, sometimes accompanied by conductive hearing loss. Myringotomy can be beneficial in chronic cases, and cochlear implants have shown effectiveness. However, due to the rarity of the condition, surgical risks may be higher. Early intervention is crucial to minimize the impact of hearing impairment (15, 21).

ENDOCRINE FUNCTION

Over 80% of individuals with Alstrom syndrome (AS) are diagnosed with type 2 diabetes and hypertriglyceridemia by the age of 16, with signs of insulin resistance often appearing as early as infancy. Approximately 50% of affected individuals experience hypertriglyceridemia, and 5% may develop acute pancreatitis. The syndrome is also associated with various endocrine issues, such as ovarian cysts, hirsutism, hypothyroidism, hypogonadism, disrupted puberty, and short stature linked to abnormalities in the IGF-growth hormone axis. Early screening and management are crucial (15, 22).

For managing hyperglycemia and hyperinsulinemia in AS, reducing carbohydrate intake may be more effective than restricting fat. In some cases, strict calorie restriction has shown benefits. Insulin therapy may be required for glycemic control, while medications like metformin and DPP-4 inhibitors can also be useful. Unlike in the general population, type 2 diabetes in AS is not primarily driven by weight. Interestingly, those affected may have a reduced risk of developing peripheral sensory neuropathy (23, 24).

CARDIOLOGY FUNCTION

Cardiac complications are common in Alstrom syndrome, with significant variability in severity and presentation among affected individuals. A frequent and serious manifestation is heart failure, often due to dilated cardiomyopathy, which is a central feature of the disease. This condition accounts for about 60% of cases and is a leading cause of mortality. The exact cause of cardiomyopathy in Alstrom syndrome remains unclear (25, 26, 27).

In approximately half of the cases, dilated cardiomyopathy develops during infancy. With appropriate treatment, many infants show significant improvement in cardiac function within three years, often achieving near-normal heart function that can persist into adulthood. However, it is crucial to note that congestive heart failure that first appears in infancy may recur during adolescence or adulthood, often with a poor prognosis (26, 27, 28).

Research suggests that increased stiffness of major arteries may contribute to maladaptive heart contractions, ultimately leading to left ventricular dysfunction in individuals with Alström syndrome. However, a 2007 study found no clear connection between left ventricular anatomy and function and major artery function, indicating that primary cardiac disease likely plays a key role in the development of cardiomyopathy. A 2017 study further suggested that, despite the presence of severe cardiac risk factors in some individuals, there was no definitive link between metabolic abnormalities and cardiac dysfunction. Additionally, a 1996 study identified a clinical and histological association between cardiomyopathy and Alstrom syndrome in five patients (26, 27, 29).

Histopathological studies of the heart in these cases have shown no distinctive features other than varying degrees of cardiac enlargement and scarring (26, 27). Myocardial fibrosis is typically a slow, irreversible process, making the early onset and rapid resolution of dilated cardiomyopathy in infants difficult to fully explain.

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For instance, a 2012 study proposed that cardiac fibrosis and infantile dilated cardiomyopathy might have separate pathogenic mechanisms. Importantly, comorbidities associated with Alstrom syndrome may contribute to early coronary artery disease. A 2012 study recommended that individuals with Alstrom syndrome be screened for traditional coronary risk factors and undergo targeted diagnostics to rule out coronary artery disease (30, 31).

Echocardiography is essential for diagnosing, managing treatment, and predicting outcomes in Alstrom syndrome (32). Magnetic resonance imaging (MRI) provides valuable pathological insights, enabling early detection of functional abnormalities. It also helps monitor disease progression, evaluate treatment effectiveness, and determine the need for heart transplantation (33). Early diagnosis is critical for managing cardiac issues, particularly cardiomyopathy, which can be severe in childhood, affecting about 45% of patients. If not promptly identified, this condition can be life-threatening and often recurs (34).

Alstrom syndrome is also characterized by a wide range of hepatic dysfunction, typically beginning with asymptomatic elevations in liver enzymes and the development of steatosis (35, 36). Common early signs include steatosis and hepatosplenomegaly, which can progress to fibrotic and inflammatory changes with lymphocytic infiltration in both portal and parenchymal areas. Hepatocellular adenomas with pericellular fibrosis have also been observed. Advanced liver disease in these patients often involves severe fibrosis, cirrhosis, portal hypertension, esophageal varices, hepatic encephalopathy, and upper gastrointestinal bleeding, which can be fatal. Notably, markers of autoimmune hepatitis, such as antinuclear antibodies, are absent, suggesting that the inflammatory processes driving fibrosis are not autoimmune. End-stage liver disease accounts for approximately 10% of deaths in individuals with Alstrom syndrome (15).

OBESITY

Obesity is a common and early feature in most children with Alstrom syndrome, although birth weight and body mass index (BMI, kg/m²) are typically normal during the first few months of life. A significant and rapid increase in weight begins within the first or second year, becoming a major medical concern, particularly during childhood. Adipose tissue is distributed throughout the body but is primarily found subcutaneously and viscerally. Dual-energy x-ray absorptiometry (DEXA) scans indicate that total body fat often falls within the top 25th percentile (37). BMI in affected individuals ranges from 21 to 53 for both males and females. While BMI tends to normalize in older individuals, insulin resistance continues to worsen. This normalization of BMI with age does not appear to correlate with the onset of conditions such as renal failure, heart failure, or type 2 diabetes mellitus (T2DM). Reduced physical activity, often compounded by dual neurosensory impairments, has been observed in Alstrom syndrome, though no formal metabolic studies have been conducted. Although childhood hyperphagia has been suggested as a potential contributor to obesity, evidence supporting this remains anecdotal (38). A combination of disrupted appetite regulation and reduced physical activity may therefore play a role in the development of obesity in this disorder. Leptin levels are elevated in Alstrom syndrome and correlate with body weight (39). However, mild increases in leptin levels, when adjusted for BMI, suggest the presence of leptin resistance (40). To date, no formal trials have been conducted to manage obesity in Alstrom syndrome using appetite suppressants or lipase inhibitors.

TYPE 2 DIABETES MELLITUS

Severe insulin resistance, hyperinsulinemia, and impaired glucose tolerance often appear in early childhood and are frequently accompanied by acanthosis nigricans. Even when compared to controls with similar pubertal stages and body composition, individuals with Alstrom syndrome exhibit significantly greater insulin resistance. T2DM typically develops during childhood, adolescence, or adulthood, with an average age of onset at 16 years.

For some individuals with Alstrom syndrome, reducing carbohydrate intake may be more effective than restricting fat to manage hyperglycemia and hyperinsulinemia (41). Lee and colleagues (38) reported that strict caloric restriction helped moderate hyperinsulinemia in a young child with Alstrom syndrome (42). Medications such as metformin and dipeptidyl peptidase 4 (DPP4) inhibitors have been effective in some cases, though hyperglycemia can sometimes be difficult to control, necessitating insulin therapy (43). Unlike in the general population, the onset of T2DM in Alstrom syndrome does not appear to be linked to the

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degree of obesity, and there is some evidence suggesting a reduced risk of clinical peripheral sensory neuropathy (44).

DYSLIPIDEMIA

Children with Alstrom syndrome often exhibit elevated lipid levels from an early age. Hypertriglyceridemia is common but variable and is not always associated with hypercholesterolemia. There is no clear connection between high triglyceride levels and insulin resistance, hyperinsulinemia, or obesity (45). In severe cases, hypertriglyceridemia can lead to pancreatitis (46, 47). The combination of obesity, severe insulin resistance, T2DM, and early-onset renal impairment may increase the risk of cardiovascular disease (48). However, MRI studies have shown that the cardiac and renal failures seen in Alstrom syndrome are not linked to coronary artery vascular disease (32).

HEPATIC PATHOLOGY

Alstrom syndrome is associated with a slowly progressing liver dysfunction that shows significant phenotypic variability. The condition typically starts with asymptomatic increases in liver enzymes (transaminases) and steatosis (fatty liver) (33, 35). Early signs often include steatosis and hepatosplenomegaly (enlarged liver and spleen), followed by fibrotic and inflammatory changes with lymphocytic infiltration in the portal and liver tissue areas. In some cases, hepatocellular adenoma with pericellular fibrosis has been observed (36). As the liver disease advances, severe fibrosis, cirrhosis, portal hypertension, esophageal varices, and encephalopathy develop, with upper gastrointestinal bleeding often leading to death. The inflammatory changes causing fibrosis do not appear to be linked to autoimmune processes, as tests for antinuclear antibodies and other markers of autoimmune hepatitis are negative. Approximately 10% of individuals with Alstrom syndrome die from end-stage liver disease (15).

RENAL DISEASE

Progressive kidney impairment in Alstrom syndrome includes glomerular disease, reduced glomerular filtration rate, and albuminuria. Over time, patients may develop decreased urine-concentrating ability, hypertension, renal tubular acidosis, polyuria and polydipsia. Nephrocalcinosis has been reported (49), along with focal glomerulosclerosis and interstitial renal fibrosis (15, 50). Additionally, lower urinary tract dysfunction, recurrent infections, vesicoureteral reflux, urethral stenosis, and detrusor instability are common (15, 45). In severe cases, indwelling catheterization may be necessary. End-stage renal disease (ESRD) can occur as early as the late teens and is a major cause of illness. While kidney and kidney-pancreas transplants have been successful in some patients, obesity and other organ complications may make individuals ineligible for the procedure (51).

RESPIRATORY ILLNESS

Chronic respiratory tract infections often begin in early childhood, leading to conditions like chronic bronchitis, asthma, and chronic rhinosinusitis, particularly in children. The severity of pulmonary issues varies, ranging from frequent bronchial infections to chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). Pulmonary hypertension is common, and early inflammatory changes in the small airways have been observed. Severe interstitial fibrosis and obliterating fibrosis can occur, with some patients unable to maintain adequate oxygen levels, requiring continuous positive airway pressure (CPAP). Blood oxygen levels can drop rapidly, especially during or after surgical procedures (21, 52).

HYPOGONADISM

Both males and females with Alstrom syndrome may experience hyper- or hypogonadotropic hypogonadism, though it is more common in males. Low-normal testosterone levels and elevated gonadotropins suggest primary gonadal failure (53, 54). Males often have small external genitalia, testicular atrophy, and fibrosis of the seminiferous tubules, though some spermatozoa may still be present in seminal fluid (15). Secondary sex characteristics are typically normal. In females, hypogonadism may not be noticeable until puberty, when delays in secondary sex characteristics and menarche become apparent. Females may also experience hyperandrogenism, hirsutism (excessive hair growth), and alopecia (hair loss), likely due to insulin resistance (55). Pathological findings include cystic ovaries with dense fibrosis, few or no follicles, and absent corpora lutea (15). Abnormal breast development, precocious puberty, endometriosis, irregular menstrual cycles, or amenorrhea have also been reported. Monitoring gonadotropin and sex hormone levels as children approach puberty is essential to determine if hormone replacement

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therapy is needed. Treatments like metformin,progesterone's, or estrogen-progesterone medications have helped regulate menstrual cycles in females. No individuals with Alstrom syndrome are known to have reproduced.

OTHER ABNORMALITIES

Individuals with Alstrom syndrome often display distinctive facial features, including deep-set eyes, a rounded face, thick ears, premature frontal balding, and thin hair. Hyperostosis frontalis interna is also observed. Many children exhibit wide, thick, and flat feet, along with short, stubby fingers and toes (brachydactyly), but without polydactyly or syndactyly. Scoliosis and kyphosis are common, varying in severity, and can exacerbate cardiac issues by restricting lung function. Chronic abdominal pain, bloating, or constipation may occur, sometimes resolving on their own, though rare cases of cecal volvulus have been reported (15, 52).

Dental abnormalities are also common, including missing, misplaced, or extra teeth, gingivitis, and light yellow-brown enamel discoloration on the front teeth. Histological studies of the gingiva have shown irregularities in the thickness of the basal lamina and delamination of the myelin sheath (56).

DIAGNOSIS

A comprehensive physical examination is essential for diagnosing Alstrom syndrome. A geneticist typically conducts the examination, measuring head circumference, eye spacing, and limb length. Neurological and eye exams may also be performed. Imaging techniques such as CT scans, MRIs, or X-rays are used to assess internal structures (57).

Diagnosis is based on clinical findings, including cone-rod dystrophy, sensorineural hearing loss, cardiomyopathy, obesity, kidney dysfunction, and diabetes, alongside medical and family history. The variability in symptom onset complicates diagnosis. Unlike similar conditions such as Bardet-Biedl or Laurence-Moon syndromes, Alstrom syndrome does not typically involve polydactyly or intellectual disability.

Molecular genetic testing, while not mandatory, can confirm the diagnosis by identifying mutations in the ALMS1 gene. Testing detects mutations in approximately 70-80% of individuals of Northern European descent and 40% globally. However, the absence of ALMS1 mutations does not exclude the diagnosis (2).

Diagnostic criteria include major and minor indicators. Major criteria involve a pathogenic ALMS1 allele or family history of the syndrome, along with visual impairments such as nystagmus or cone-rod dystrophy. Minor criteria include obesity, diabetes, cardiomyopathy, hearing loss, liver or kidney dysfunction, short stature, and hypogonadism. Diagnosis requires either two major criteria or one major criterion plus 2-4 minor criteria, depending on age (22, 1).

TREATMENT

There is no cure for Alstrom syndrome, so treatment focuses on managing symptoms. Due to the progressive nature of kidney dysfunction, regular monitoring of renal function is critical. ACE inhibitors are commonly used for kidney protection, and kidney transplantation may be necessary in severe cases (15).

For cardiomyopathy, a combination of diuretics, spironolactone, digitalis, beta-blockers, and ACE inhibitors is often prescribed (22). Diabetes management may involve carbohydrate restriction, high-dose insulin, biguanides, thiazolidines, or GLP-1 agonists. Thiazolidines have shown effectiveness in addressing insulin resistance in Alstrom syndrome (58, 59, 60).

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ABBREVIATION

1. AS - Alstrom syndrome
2. ALMS1- Alström syndrome 1
3. BBS - Bardet-Biedl syndrome
4. RPE- Retinal Pigment Epithelium
5. OCT - Optical Coherence Tomography
6. MRI- Magnetic Resonance Imaging
7. CT- Computed Tomography
8. T2DM- . Type 2 diabetes mellitus
9. DPP4- Dipeptidyl Peptidase 4
10. BMI- Body Mass Index
11. DEXA - . Dual-Energy X-ray Absorptiometry
12. ESRD- End-Stage Renal Disease
13. CPAP- Continuous Positive Airway Pressure
14. ARDS- acute respiratory distress syndrome
15. COPD- Chronic Obstructive Pulmonary Disease
16. ACE- Angiotensin Converting Enzyme
17. GLP-1- Glucagon Like Peptide 1