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(REVIEW ARTICLE)

A review on Alstrom Syndrome

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Abstract

Alström syndrome is a rare autosomal recessive genetic disorder characterized by cone-rod dystrophy, hearing loss, childhood truncal obesity, insulin resistance and hyperinsulinemia, type 2 diabetes, hypertriglyceridemia, short stature in adulthood, cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunction. There is no cure for Alström syndrome. Developmental delay is seen in almost half of people with Alström syndrome. Treatments target the individual symptoms and can include diet, corrective lenses, hearing aids, medications for diabetes and heart issues and dialysis and transplantation in the case of kidney or liver failure. Prognosis varies depending on the specific combination of symptoms, but individuals with Alström syndrome rarely live beyond 50.

Prevalence is fewer than 1 in 1,000,000 individuals in the general population. It was first described by Swedish psychiatrist Carl-Henry Alström and his three associates, B. Hallgren, I. B. Nilsson and H. Asander, in 1959.Ultimately research into the pathogenesis of Alström syndrome should lead to better management and treatment for individuals and have potentially important ramification for other rare ciliopathies, as well as more common cause of obesity, DM and other conditions common in general populations.

Keywords: Alström syndrome; Ciliopathy; Truncal obesity; ALMS1; Autosomal recessive genetic disorder

1. Introduction

Alström syndrome is a rare autosomal recessive genetic disorder, thought to have a prevalence of less than one per million in the general population. It is characterized by the progressive development of multi-organ pathology [1,2]. Symptoms first appear in infancy with great variability in age of onset and severity of clinical symptoms, even within families bearing identical mutations. The severity of the disease, often leading to organ failure, results in a reduced life expectancy, rarely exceeding 50 years

The clinical care of individuals is complex due to the combination of multiple endocrine disorders, sensorineural deficits, cardiac, renal, and hepatic abnormalities. There is no specific therapy and individuals are treated and monitored

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on the basis of individual symptoms. 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.

Alström Syndrome can affect people of all nationalities, ethnic groups and races. It is caused by a mutated gene called ALMS1. Both parents must be a carrier of one mutated ALMS1 gene in order to have a child with the syndrome. The affected child receives a copy of the mutated gene from both parents, giving them 2 mutated ALMS1 genes, which results in the child having Alström Syndrome [3].

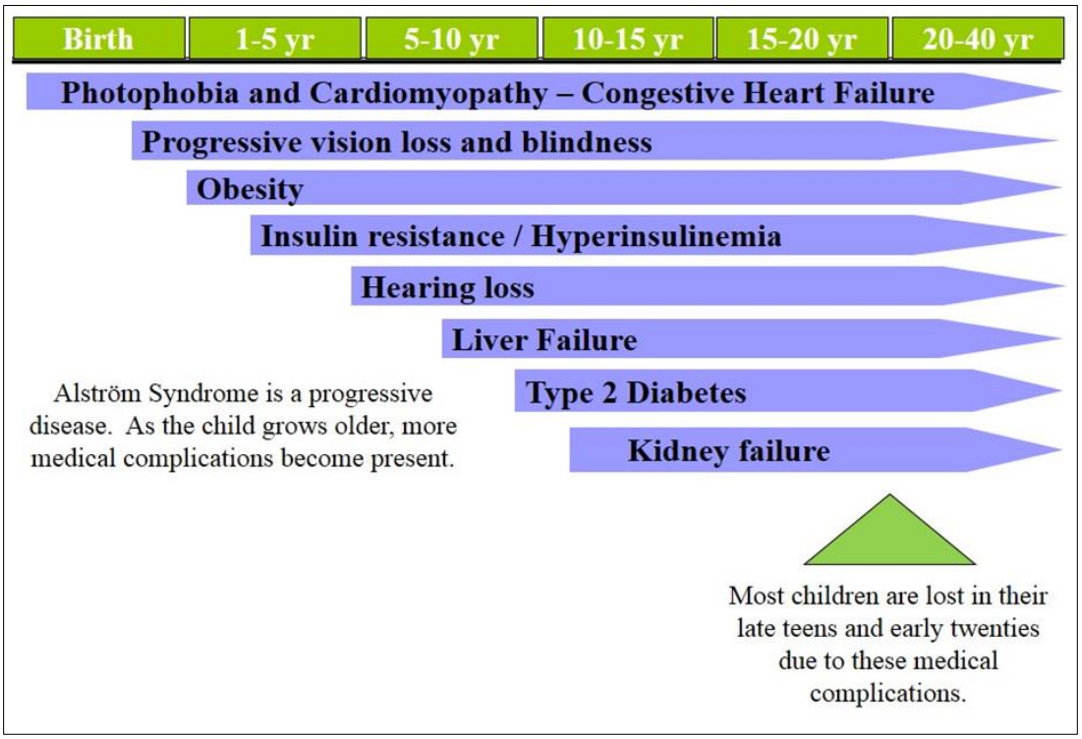

Figure 1 Alstrom Syndrome Typical Disease Progression

2. Clinical Manifestations

Alström Syndrome is one of the most brutal diseases there is, as it touches every organ in the body. Most children are lost in their late teens and early twenties due to these medical complications.

Children with Alström Syndrome will battle:

- Nystagmus (wobbly eyes) and photophobia (light sensitivity) in early infancy
- Progressive vision loss, leading to blindness in childhood
- Childhood obesity
- Mild to moderate hearing loss
- Normal intelligence—delayed developmental milestones in some
- Insulin resistance
- Type 2 diabetes
- Progressive, chronic kidney failure
- Congestive heart failure secondary to dilated cardiomyopathy
- Liver dysfunction and failure
- High cholesterol / high triglycerides
- Hypothyroidism
- Small genitalia in males; female hormonal irregularities
- Urological problems
- Frequent pulmonary infections, asthma and chronic obstructive pulmonary disease (COPD)
- Learning difficulties, possibly due to vision and hearing loss

- Scoliosis or kyphosis (curvature of the spine)
- Premature frontal balding in both girls and boys
- Seizures[4,5].

3. Hepatic pathology

There is extensive phenotypic variation in the slowly progressive hepatic dysfunction in Alström syndrome, which begins with clinically silent elevation of transaminases, and steatosis. The initial presentation is usually steatosis and hepato-splenomegaly followed by fibrotic and inflammatory processes with lymphocytic infiltration in the portal and parenchyma areas. Hepatocellular adenoma with pericellular fibrosis has been described. In the final course of hepatic disease, there is significant fibrosis, cirrhosis, portal hypertension, esophageal varicies, encephalopathy, with upper GI hemorrhage leading to death. Inflammatory changes resulting in fibrosis do not appear to be autoimmune related because antinuclear antibodies and other typical markers of autoimmune hepatitis are negative. End stage liver disease is the cause of death in about 10% of individuals [6].

4. Causes

Alström syndrome is inherited in an autosomal recessive manner. Alström syndrome is caused by a mutation in the ALMS1 gene, located on the short arm of chromosome 2. The gene mutation is inherited as an autosomal recessive trait. This means both parents have to pass a defective copy of the ALMS1 gene in order for their child to have the syndrome, even though the parents may not show signs or symptoms of the condition.

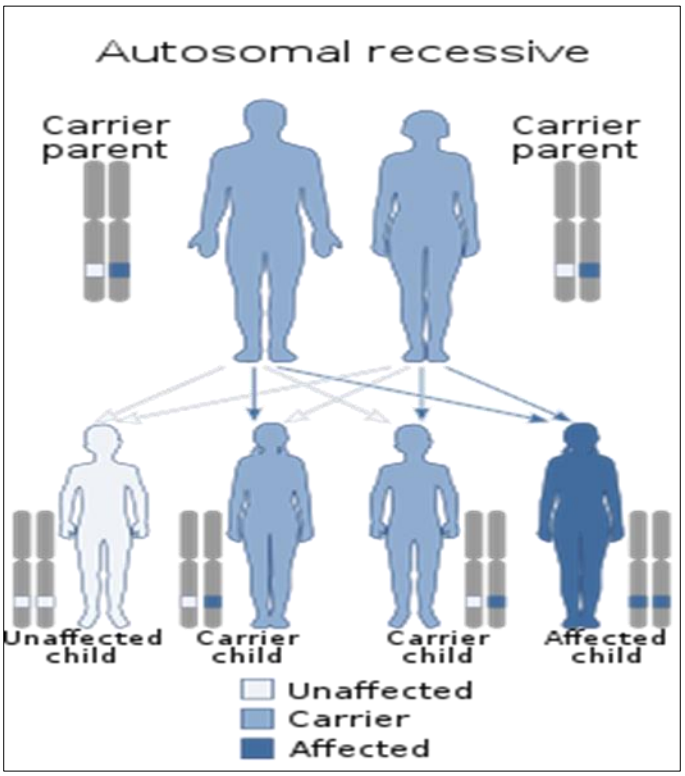

Figure 2 Genetic pattern of disease

The ALMS1 gene contains instructions to encode a specific protein known as ALMS1. The protein then is involved in ciliary function, cell cycle control and intracellular transport. In addition, the protein is expressed in all organ tissues of the body. It has a role in the proper function, maintenance and formation of cilia, which are found in all types of cells in the body. At least 239 disease-causing mutations in ALMS1 have been described as of 2015. Most of these mutations have led to the production of a dysfunctional version of the ALSM1 protein which are present in tissues, but at low levels.

5. Diagnosis

It is possible to clinically detect Alström syndrome in infancy, but more frequently, it is detected much later, as doctors tend to detect symptoms as separate problems. Currently, Alström syndrome is often diagnosed clinically, since genetic testing is costly and only available on a limited basis.

A physical examination would be needed to properly diagnose the patient. Certain physical characteristics can determine if the patient has some type of genetic disorder. Usually, a geneticist would perform the physical examination by measuring the distance around the head, distance between the eyes and the length of arms and legs. In addition, examinations for the nervous system or the eyes may be performed. Various imaging studies like computerized tomography scans (CT), Magnetic Resonance Imaging (MRI) or X-rays are used to see the structures within the body.

Family and personal medical history are required. Information about the health of an individual is crucial because it provides traces to a genetic diagnosis.

Laboratory tests, particularly genetic testing, are performed to diagnose genetic disorders. Some of the types of genetic testing are molecular, biochemical and chromosomal. Other laboratory tests performed may measure levels of certain substances in urine and blood that can also help suggest a diagnosis.

6. Prevention

Prevention for Alström syndrome is considered to be harder compared to other diseases/syndromes because it is an inherited condition. However, there are other options that are available for parents with a family history of Alström syndrome. Genetic testing and counseling are available where individuals are able to meet with a genetic counselor to discuss risks of having the children with the disease. The genetic counselor may also help determine whether individuals carry the defective ALSM1 gene before the individuals conceive a child. Some of the tests the genetic counselors perform include chorionic villus sampling (CVS), pre-implantation genetic diagnosis (PGD) and amniocentesis. With PGD, the embryos are tested for the ALSM1 gene and only the embryos that are not affected may be chosen for implantation via in vitro fertilization.

7. Treatment

There is no cure for Alström syndrome; however, there are treatment aims to reduce the symptoms and prevent further complications. Some of these treatment aims include:

- Corrective lenses: Tinted lenses that help with the sensitivity from bright lights. The patients may have to adapt to reading in Braille, use adaptive equipment, mobility aids and adaptive computing skills.
- Education: Patients with Alström syndrome who have intellectual disabilities must have access to education. They must be able to receive free and appropriate education. Some Alström syndrome patients are educated in normal classrooms. Other patients have to take special education classes or attend to specialized schools that are prepared to teach children with disabilities. Staff members from schools have to consult with patient's parents or caregivers in order to design an education plan based on the child's needs. In addition, the school may document the progress of the child in order to confirm that the child's needs are being met.
- Hearing aids: The battery-operated devices are available in three styles: behind the ear, in the ear and inside the ear canal. Behind the ear aims for mild-to-profound hearing loss. In the ear aims for mild to severe hearing loss. Lastly, the canal device is aimed for mild to moderately severe hearing loss. Patients that have severe hearing loss may benefit from a cochlear implant.
- Diet: An appropriate and healthy diet is necessary for individuals with Alström syndrome because it could potentially decreases chances of obesity or diabetes.
- Occupational therapy: The therapist helps the child learn skills to help him or her perform basic daily tasks like eating, getting dressed and communicating with others.
- Physical Activity: Exercising reduces chances of being obese and helping control blood sugar levels.
- Dialysis: helps restore filtering function. With hemodialysis, a patient's blood circulates into an external filter and clean. The filtered blood is then returned into the body. With peritoneal dialysis, fluid containing dextrose is introduced into the abdomen by a tube. The solution then absorbs the wastes into the body and is then removed.
- Transplantation: Patients that endure a kidney failure may undergo kidney transplantation.
- Surgery: If the patient endures severe scoliosis or kyphosis, surgery may be required.

- Antibiotics: Patients with lung problems will be prescribed antibiotics because they are more prone to infections like bronchitis.
- Oral diabetes medications: These are taken by mouth to treat diabetes. Can be taken combined into a single pill, which may be more effective and convenient for people with diabetes. It is usually taken once or twice daily before meals. Some of these medications includes:
    - Meglitinides (Repaglinide and Nateglinide): taken to stimulate the cells found in the pancreas to release insulin. These drugs are taken by mouth daily before each meal and could cause a drop in blood sugar.
    - Biguanide (Metformin): decreases the amount blood sugar being released by the liver and by stimulating the cells within muscles to take up blood sugar. Taken twice daily.
    - Thiazolidinediones (Rosiglitazone and Pioglitazone): taken to help insulin work more efficiently in muscle and fat cells causing the liver to release less glucose. Is associated with heart failure.
    - Dipeptidyl peptidase IV (DPP-4) inhibitors (Sitagliptin): helps with improving blood sugar levels by decreasing the action of an enzyme breaking down GLP-1 (lowers the blood sugar level).
    - Injectable diabetes medicine: taken by an injection into the fat below the skin. Sometimes referred as subcutaneous injections. Some of these medications include the following:
        - ✓ Amylin agonist(Pramlintide):It acts centrally (via the brain) to reduce food intake and blood sugar. It is most commonly used at mealtimes by people with type 1 and type 2 diabetes.
        - ✓ GLP-1 receptor agonist (Exenatide): It increases secretion of insulin, decreases the secretion of glucagon from the pancreas and reduces food intake.
- Cholesterol-lowering medications: It is necessary when cholesterol levels are high. HMG-CoA reductase inhibitors, also called "statins," effectively lower levels of low-density lipoprotein, cholesterol and triglycerides. High-dose nicotinic acid (niacin) may also reduce cholesterol levels.
- Heart medications: Angiotensin-converting enzyme (ACE) inhibitors, diuretics, digoxin and beta-blockers may help with the management of cardiomyopathy and heart failure[7].

8. Conclusion

Alström syndrome is a complex pleiotropic disorder caused by mutations in ALMS1. Systemic characteristics of this disorder include truncal obesity, hyperinsulinemia, and T2DM, acanthosis nigricans, short adult stature, and vision and hearing loss, dilated or restrictive cardiomyopathy (infancy or adolescence/adulthood) with CHF, hypothyroidism and hypogonadism. Death usually occurs due to progressive cardiac, hepatic and renal failure, often associated with pulmonary disease. The cellular and molecular mechanisms underlying the disorder remain to be understood although widespread severe fibrosis may significantly contribute to the disease pathology [8-9]. The ALMS1 is a ciliary protein and plays a role in normal centrosome/basal body function and their associated intracellular trafficking events allows new hypotheses to be formulated and to make further progress in understanding and treating Alström syndrome [10].

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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