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Case Report

Semaglutide in Alström Syndrome: An Improvement in the Natural Course of Cardiomyopathy

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Abstract

Alström syndrome (ALMS) is a rare autosomal recessive genetic disorder with multisystem involvement (obesity, type 2 diabetes, cone-rod dystrophy, hearing loss, dilated cardiomyopathy…). Heart failure presents in infancy (1 - 4 months), apparent recovery of cardiac function within 3 years, but it recurs in adolescence or adulthood. Gradual and irreversible fibrosis leads to a progressive pulmonary, hepatic and cardiac dysfunction with poor prognosis. We report a Spanish 21-year-old male with ALMS and a body-mass index (BMI) of 31.0. The first clinical manifestation was a sudden abrupt onset of heart failure due to dilated cardiomyopathy by 4 months of age, with an apparently full recovery by age 2 years. However, despite treatment (diet, exercise, metformin, statin, fenofibrate, and topiramate), weight and analytical parameters did not improve. By age 20 years, treatment was considered with once-weekly subcutaneous semaglutide and after 12 months, BMI decreased and cardiovascular risk factors improved, with normal cardiac study (ECG, echocardiogram and magnetic resonance imaging). Obesity is associated with chronic low-grade inflammation, and may play an important role in development and progression of myocardial fibrosis, the pathogenesis of later onset cardiomyopathy in ALMS. Semaglutide could be considered, not only to promote weight loss and inhibit appetite, but also to improve cardiovascular risk factors, and therefore, it could delay or even prevent recurrence of heart disease in adulthood in patients with ALMS.

Keywords: *Alström Syndrome; Cardiomyopathy; Obesity; Semaglutide; Weight Loss*

Abbreviations

ALMS: Alström Syndrome; DCM: Dilated Cardiomyopathy; GLP-1: Glucagon-Like Peptide-1; OSA: Obstructive Sleep Apnea

Introduction

Alström syndrome (ALMS, OMIM 203800) is a rare autosomal recessive genetic disorder that was first reported in 1959 by Carl Henry Alström., *et al.* from Sweden [1]. ALMS is caused by mutations in ALMS1 gene, which is located on the short arm of Chromosome 2 (2p13) and consists of 23 exons, encoding a large protein of 4169 amino acids. The ALMS1 protein localizes to centrosomes and basal bodies of ciliated cells and is ubiquitously expressed in all tissues that are pathologically affected in patients with ALMS [2].

The actual incidence is unknown due to undiagnosed cases, but is estimated to be in the range from 1 in 500.000 to 1 in 1.000.000. Worldwide, approximately 1.200 cases of ALMS have been identified, and affects both sexes equally [3].

Alström syndrome is characterized by the progressive development of severe multiorgan pathology that stars in infancy (dilated cardiomyopathy, nystagmus with impaired vision due to cone-rod dystrophy), further during childhood (obesity, sensorineural hearing loss, type 2 diabetes mellitus, insulin resistance, hyperlipidemia), and later in life (nonalcoholic fatty liver disease, chronic kidney disease, urologic disorders, pulmonary involvement, hypertension, restrictive cardiomyopathy). The clinical diagnosis of ALMS is based on major and minor criteria depends on the age of onset features [4]. Given de complexity of the phenotype of this syndrome, the ALMS1 protein appears to have multiple functions in different tissues and fibrosis of multiple organs is a common finding [5].

Cardiomyopathy occurs in the majority of ALMS patients at some time in their lives. Dilated cardiomyopathy (DCM) may arise in infancy (between 3 weeks and 4 months of age), then often resolve within apparent recovery of cardiac function within 3 years, but it may recur in adolescence or adulthood (progressive restrictive cardiomyopathy). Cardiomyopathy is caused by diffuse interstitial fibrosis in the heart [6].

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that induces weight loss by decreasing appetite and reducing energy intake. Semaglutide is approved, at doses up to 1 mg administered subcutaneously one weekly for the treatment of type 2 diabetes mellitus in adults [7].

Case Report

We report a Spanish 21-year-old male with ALMS and a body-mass index (BMI) of 31.0. The first clinical manifestation was a sudden abrupt onset of heart failure due to dilated cardiomyopathy by 4 months of age. He was admitted to the Pediatric Intensive Care Unit with the initial diagnosis of acute myocarditis without congenital heart disease. Furosemide, inotropic and ventilatory support therapy were required to ensure adequate tissue oxygenation and to achieve cardiovascular stability. The cardiomyopathy resolved with an apparently full recovery by age 2 years, only non-specific ventricular repolarization abnormalities (ST-T changes) on the surface electrocardiogram (ECG), no cardiac treatment since then. Clinical features emerge throughout infancy and childhood: nystagmus, photophobia and decreased vision (12 months); asthma, frequent upper respiratory infections, recurrent otitis media, bilateral sensorineural hearing impairment (3 years), truncal obesity (normal birth weight) with insulin resistance and hyperlipidemia (4 years), progressive decreased in renal-hepatic function, and urologic dysfunction (10 years); normal intelligence but with obsessive-compulsive behaviour, hyperphagia (12 years), obstructive sleep apnea requiring nasal continuous positive airways pressure, scoliosis and short stature (16 years). Genetic testing (ALMS1 gene): mutation 1 (m1) c.5142T>G, p.(Tyr 1714Ter), and mutation 2 (m2) c.1615-1616delCT, p.(Ser3872TyrfsTer19).

The mutation 1 (m1) is detected in the father, in heterozygosis (one mutated allele and one normal allele). It is a deletion of two base pairs at the DNA level, which results in a shift of the reading pattern in the mRNA and finally generates a stop codon 19 amino acids later. The mutation 2 (m2) is the maternal mutation, in heterozygosis, and is a change of a thymine to a guanine at position 5142 of the DNA, which causes a change of the amino acid tyrosine to a stop codon at position 1714 of the mRNA at the same point. Both mutations are expected to produce truncated proteins (smaller than the original) that could be non-functional and, being recognised by the cellular system, would be degraded. Our case report is a double heterozygote, as he has both mutations (Figure 1).

In addition to diet and exercise, drug treatment was recommended, metformin for type 2 diabetes mellitus, statin plus fenofibrate for hyperlipidemia, and topiramate for weight management. However, despite treatment, weight and analytical parameters did not improve.

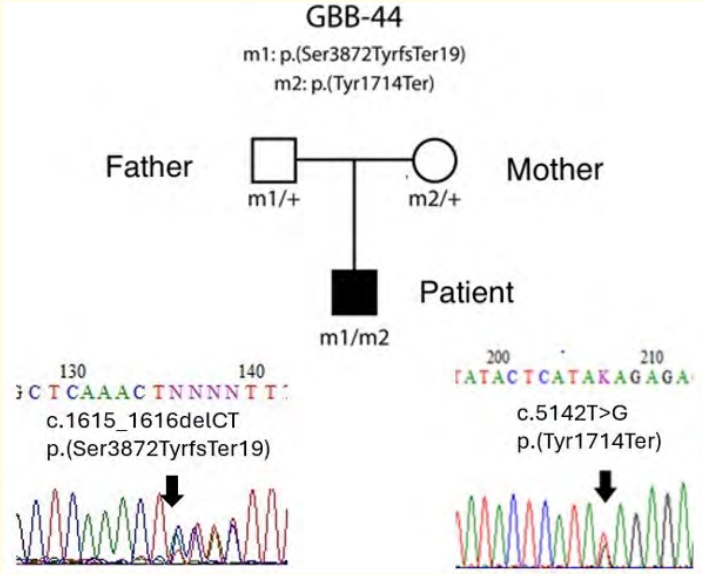

Figure 1: *Family tree, father with mutation 1 (m1), mother with mutation 2 (m2), and affected son with both mutations (double heterozygote).*

In June 2022 (20 years), treatment was considered with glucagon like peptide-1 receptor agonist (GLP-1RA), once-weekly subcutaneous semaglutide with dose-escalation schedule (0,5 mg to 1 mg). Treatment was well tolerated, without hypoglycemia or gastrointestinal adverse effects. After semaglutide, at low doses, for 12 months, body mass index decreased and cardiovascular risk factors improved (Table 1). We incorporate polysomnography into clinical practise according to guidelines of the international consensus document on obstructive sleep apnea 2021 [8].

Evolution with semaglutide	June 2022	June 2023
Weight (kg)	74.8	59.0
Height (m)	155	155
BMI (kg/m^2)	31.0	24.6
Blood Pressure (mmHg)	130/90	110/60
Glucose (mg/dl)	101	86
HOMA-IR	8,23	5,97
HbA1C (%)	5.4	4.6
Triglycerides (mg/dl	508	139
Total Cholesterol (mg/dl)	268	121
HDL-Col (mg/dl)	28	35
Creatinine (mg/dl)	0.96	0.88
ALT (U/L)	180	49
AST (U/L)	89	29
GGT (U/L)	108	23

Creatinine (mg/dl)	0.88	0.88
Apnea-Hypoapnea-Index (AHI)	33	10.6
BMI: Body Mass Index; BP: Blood Pressure; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TG: Triglycerides; Col: cholesterol; HDL-Col: High-Density Lipoprotein Cholesterol.		

Table 1: *Laboratory analysis and cardiovascular risk factors before and after one year of semaglutide treatment.*

Last laboratory test reveals: serum N-Terminal probrain natriuretic peptide (NT-proBNP) 7.77 pg/mL (<400), serum Troponin T 7.3 pg/mL (3-14), serum Creatinine Phosphokinase (CPK) 53 U/L (34-171), serum amylase 51 U/L (34-171). At the moment, the patient remains cardiologically asymptomatic, and the cardiac study is normal so far. The electrocardiogram and echocardiogram are normal, with left ventricular (LV) internal diameter end diastole 49,5 mm (LVIDd, Z-score + 0.33), LV ejection fraction 71% (LVEF), LV global longitudinal strain -16% (LVGLS). CMR confirms normal measurements of left ventricular and right ventricular volumes and ejection fractions, without late gadolinium enhancement (Figure 2).

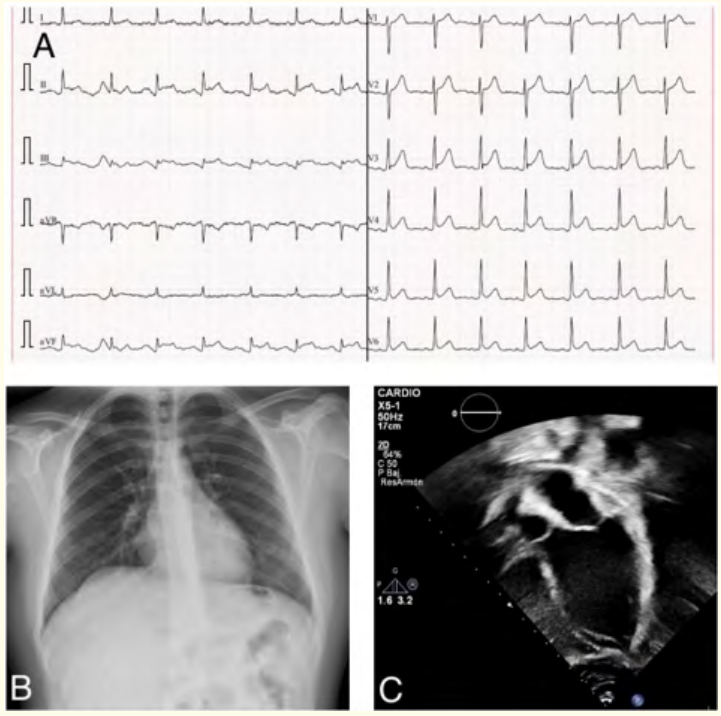

Figure 2: *A: Normal electrocardiogram with non-specific ventricular repolarization abnormalities known since infancy. B: Thoracic radiography. C: Echocardiogram with apical long axis and (left atrium, left ventricle and its outflow tract).*

Discussion

In ALMS, we identify two separate groups of patients with cardiomyopathy: infantile onset (first months of life) and later onset (adolescence or adulthood). The clinical course of the infantile onset cardiomyopathy is variable, even in twin neonates [9].

Many infants have apparent recovery of cardiac function within 3 years and remain stable for many years, but all ALMS patients are at risk for developing cardiomyopathy at any time, with rapid progression and a poor clinical prognosis [10].

Obesity cannot be simply considered the result of an energy imbalance between calorie intake and expenditure. We know that obesity is associated with chronic low-grade inflammation, and may play an important role in development and progression of myocardial fibrosis, the pathogenesis of later onset cardiomyopathy in ALMS [11].

Obesity is a strong independent predictor of cardiovascular diseases, but also increases other cardiovascular risks: type 2 diabetes mellitus, insulin resistance, hypertension, dyslipidemia, endothelial dysfunction, obstructive sleep apnea (OSA) [12].

No therapy exists to prevent the progressive organ involvement of Alström syndrome. For obesity, a healthful, reduced-calorie diet with restrictive carbohydrate intake and regular aerobic exercise (with adaptations for the blind) were recommended to control weight gain, but in our patient, it was not successful. Clinical guidelines suggest adjunctive pharmacotherapy for adults with a BMI o 30 or greater, or 27 or greater in persons with coexisting conditions, as if the case of our patient with ALMS [13].

In our patient, treatment with semaglutide at low doses, 1 mg once a week for up to 12 months reduced weight, BMI, HbA1c level, and insulin resistance (HOMA-IR), but also, improved other cardiovascular risks, such as, blood pressure, hyperlipidemia and OSA. All this was obtained without side effects.

OSA is associated with adverse cardiovascular consequences: intermittent hypoxia-reoxygenation, excessive arousals, increased sympathetic and decreased parasympathetic activity. The large negative intrathoracic pressure swings in OSA increases left ventricular afterload and myocardial oxygen consumption [14].

In our patient, weight loss provided major improvement of OSA and hyperlipidemia. The apnea-hypopnea index (AHI) fell from 33 to 10.6 and made it possible to stop the use of nasal continuous positive airways pressure (CPAP), that was poorly tolerated. Weight loss, also was associated with a deceased triglyceride levels and allowed discontinuation of fibrates which was poorly tolerated by the patient (gastrointestinal effects and elevated liver enzymes). Deterioration in renal function is a very known adverse effect of fibrate treatment, and our patient had a progressive decreased in renal-hepatic function due to ALMS. All of this, in the end, has led to an improvement in the quality of life in a patient with ALMS.

Myocardial fibrosis and diffuse interstitial fibrosis are an important player in late onset cardiomyopathy in ALMS, and progresses over time. The mechanism is unknown, but metabolic disturbances in ALMS, insulin resistance, activation of the renin-angiotensin-aldosterone system and raised serum triglycerides, have a potential role in the development of myocardial fibrosis. Inflammation (obesity is a chronic low-grade inflammation) is suspected to be mediator.

Cardiac evaluations should be assessed at regular intervals: standard 12-lead ECG yearly, transthoracic echocardiograms yearly or as per clinical need, and cardiac magnetic resonance (CMR) imaging for older children and adult at baseline and 3 to 5 yearly intervals [15].

CMR is the gold standard for non-invasive measurement of left ventricular and right ventricular volumes and ejection fraction, and late gadolinium enhancement (LGE) has become the cornerstone of myocardial tissue characterization (identification and efficient quantification of fibrosis). CMR imaging can demonstrate silent progression of diffuse interstitial fibrosis by elevation in T1 relaxation and increased extracellular volume [16]. Echocardiographic analysis with left ventricular ejection fraction (LVEF) is the most widely used parameter for assessing cardiac function and is a predictor of outcomes. However, it has several intrinsic limitations. Recent studies have reported that left ventricular global longitudinal strain (GLS) is a more sensitive measure of myocardial dysfunction and is more reproducible than LVEF. Myocardial strain imaging reflects changes in tissue (fibrosis) and detect sub-clinical myocardial dysfunction [17].

For left ventricle GLS analysis, a digital loop was acquired from three apical views (four-, two- and three-chamber views). After the manual cardiac cycle selection, the LV endocardial border was manually traced at the end-systolic frame (aortic valve closure was used for the end-systole timing). As, in our patient, CMR is normal without late gadolinium enhancement, echocardiography with LVGLS will be useful to assess short-term evolution of cardiac function, while maintaining treatment with once-weekly low-dose subcutaneous semaglutide.

Once-weekly semaglutide results in substantial reduction in BMI in adolescents with obesity [18]. Furthermore, this treatment leads to larger reductions in heart failure related symptoms and physical limitations in patients with obesity-related heart failure [19]. Semaglutide has an overall beneficial risk/benefit-profile for treatment, and it reinforces the safety aspects of this drug [20].

Obesity is associated with adverse cardiac remodeling and is a key driver for the development and progression of heart failure. Once-weekly semaglutide has been shown to improve adverse cardiac remodeling compared [21].

Conclusion

Patients with ALMS may develop sudden onset dilated cardiomyopathy during their first months of life. Although, many infants have apparent recovery of cardiac function within 3 years and remain stable for many years, all of them are at risk for developing cardiomyopathy at any time, especially in adolescence and adulthood, due to gradual and irreversible myocardial fibrosis. Obesity (chronic low-grade inflammation) plays an important role in development and progression of myocardial fibrosis, the pathogenesis of later onset cardiomyopathy in ALMS. Once-weekly low-dose subcutaneous semaglutide could be considered, not only to promote weight loss and inhibit appetite, but also to improve cardiovascular risk factors, and therefore, it could delay or even prevent recurrence of heart disease in adulthood in patients with ALMS.

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Conflict of Interest

The authors declare no conflicts of interest.

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