

Scientific letters

Alström Syndrome: A Rare Cause of Cardiomyopathy**Síndrome de Alström: una rara causa de miocardiopatía****To the Editor,**

We present the case of a 27-year-old woman admitted to our hospital for heart failure. When she was 5 months old, she was admitted for acute heart failure. Echocardiographic studies showed a dilated cardiomyopathy with severely depressed left ventricular ejection fraction with subsequent recovery in the follow-up and the patient was diagnosed with myocarditis. She had nystagmus, cone-rod dystrophy, and atrophy of the optic pathway from the first months of life with bilateral blindness and perceptive hearing loss since adolescence. She had had a history of obesity since childhood and was diagnosed with type 2 diabetes and hypertriglyceridemia at 14 years of age. All these findings raised the alarm for a mitochondrial encephalopathy but muscle biopsy and Sanger genetic study were negative for the A8344G mutation point involved in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged-red fibers (MERRF).

At the current admission, the patient complained of dyspnea for the past few months that progressed to New York Heart Association functional class III/IV.

Transthoracic echocardiography revealed mild left ventricle dilatation with severe systolic dysfunction without areas of hypertrabeculation, hypertrophy, or thinned myocardial areas after administration of echocardiographic contrast. The patient progressed favourably with standard medical therapy with resolution of congestive symptoms and was discharged with a scheduled magnetic resonance imaging to complete the assessment of her dilated cardiomyopathy.

The presence of a dilated left ventricle with severe systolic dysfunction was confirmed at magnetic resonance imaging, with pathological contrast enhancement in the subepicardial region at the insertion point of both ventricles and with intramyocardial enhancement at the septal middle segment, compatible with myocardial fibrosis (Figure A, Figure B, Figure C, Figure D, Figure E and Figure F).

On the basis of these findings, and after previous exclusion of a mitochondrial disease with a high degree of certainty, Alström syndrome was diagnosed as the patient met the clinical diagnostic criteria (Table). Genetic study by next-generation sequencing was requested for the *ALMS1* gene, which is involved in this disease. This study was positive for 2 mutations on exons 8 and 11 of the gene with pathogenic significance establishing the definitive diagnosis.

Our patient was the first case of this disease to be described in her family. Genetic study for these mutations were negative in her parents and, for this reason, she seems to have a spontaneous mutation on this gene.

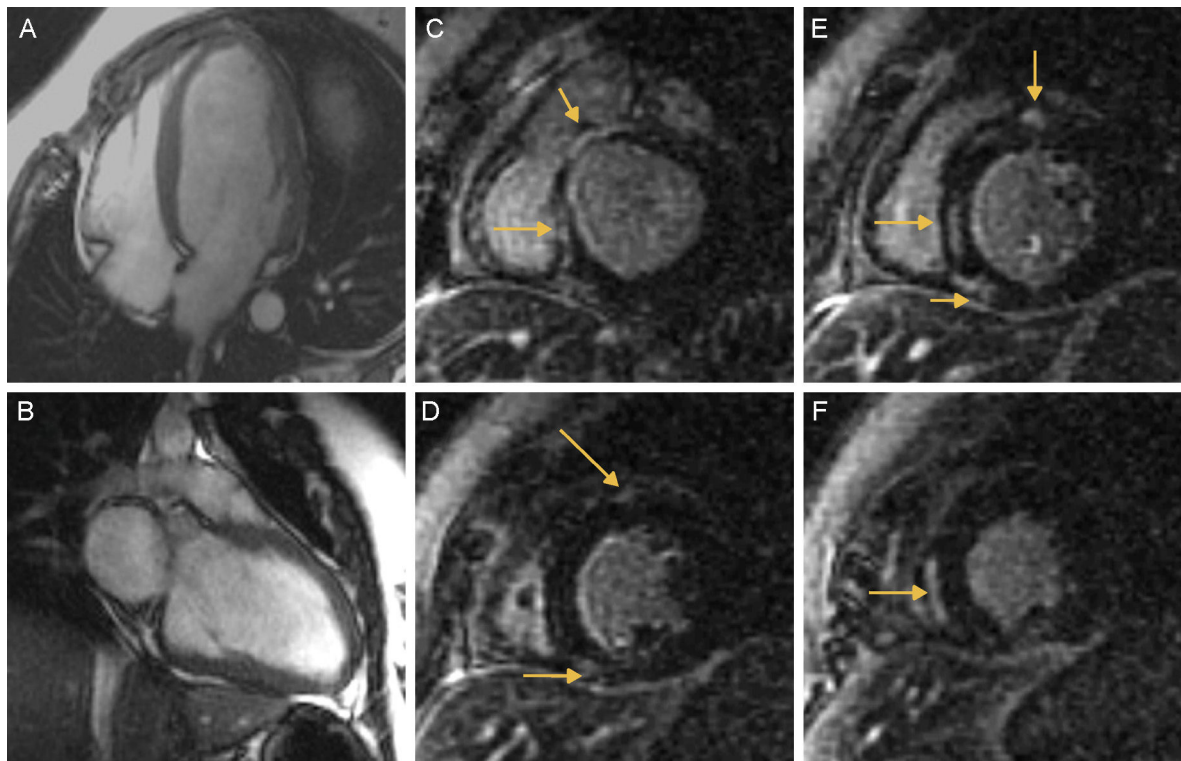


Figure. A, B: echo-gradient images long-axis 4 and 2 chamber view exhibited a dilated left ventricle. C-F: late gadolinium enhancement in the subepicardial region at the insertion point of both ventricles and intramyocardial enhancement at the septal middle segment (arrows).

Table
Marshall's Age-specific Diagnostic Criteria

Age, y	Major criteria	Minor criteria	Other supportive evidence	Diagnosis
≤ 2*	<ul style="list-style-type: none"> ALMS 1 mutation in 1 allele and/or family history of AS Vision (nystagmus, photophobia) 	<ul style="list-style-type: none"> Obesity Dilated cardiomyopathy/congestive heart failure 	<ul style="list-style-type: none"> Recurrent pulmonary infections Normal digits Delayed developmental milestones 	2 major criteria or 1 major + 2 minor criteria
3-14	<ul style="list-style-type: none"> ALMS 1 mutation in 1 allele and/or family history of AS Vision (nystagmus, photophobia, decreased acuity, cone dystrophy by ERG) 	<ul style="list-style-type: none"> Obesity and/or insulin resistance History of dilated cardiomyopathy/congestive heart failure Hearing loss Hepatic dysfunction Renal failure 	<ul style="list-style-type: none"> Recurrent pulmonary infections Normal digits Delayed development milestones Hyperlipidemia Scoliosis Flat wide feet Hypothyroidism Hypertension GH deficiency Recurrent UTI 	2 major criteria or 1 major + 3 minor criteria
> 15	<ul style="list-style-type: none"> ALMS 1 mutation in 1 allele and/or family history of AS Vision (legal blindness, history of nystagmus in infancy/childhood, cone and rod dystrophy by ERG) 	<ul style="list-style-type: none"> Obesity and/or insulin resistance and/or diabetes mellitus type 2 History of dilated cardiomyopathy/congestive heart failure Hearing loss Hepatic dysfunction Renal failure Short stature Males – hypogonadism Females – irregular menses and/or hyperandrogenism 	<ul style="list-style-type: none"> Recurrent pulmonary infections Normal digits History of developmental delay Hyperlipidemia Scoliosis Flat wide feet Hypothyroidism Hypertension GH deficiency Alopecia Recurrent UTI or urinary dysfunction 	2 major + 2 minor criteria or 1 major + 4 minor criteria

AS, Alström syndrome; ERG, electroretinogram; GH, growth hormone; UTI, urinary tract infections.

* These diagnostic criteria should be reevaluated when the patient becomes older.

Currently the patient is 29 years old and is in New York Heart Association grade I/IV without new episodes of decompensation, despite persistent severe left ventricular systolic dysfunction in follow-up visits.

Alström syndrome (AS) was first described in 1959 by Alström et al.¹ It has a prevalence of < 1/100 000.^{1,2} Alström syndrome is a rare genetic autosomal recessive disease characterized by multi-systemic involvement and produced by a mutation in the *ALMS1* gene located on chromosome 2p13.³ This gene encodes a protein whose mutation leads to progressive fibrosis of various organs 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. Symptoms first appear during childhood and the progressive development of multiorgan pathology reduces life expectancy.²⁻⁴ Prior to the discovery of *ALMS1* mutations, the diagnosis was made solely based on phenotype. However, the high degree of variability, even within families, creates difficulties for a universal definition.⁵ Marshall defined AS using age-specific criteria (Table).⁶

Ocular involvement is a cardinal sign of AS^{1,5,6} that leads to progressive visual dysfunction and blindness, usually during the second decade of life. In addition, around 80% will develop neurosensory hearing loss that will progress throughout life.⁴⁻⁶

Childhood obesity is a common and early manifestation. It is usually accompanied by a characteristic phenotypic expression and affected individuals often develop type 2 diabetes with insulin resistance and hyperinsulinemia, as well as hypertriglyceridemia. For these reasons, the metabolic profile leads to an increase in cardiovascular risk.^{1,5}

Cardiac involvement is characterized by the development of dilated cardiomyopathy with systolic dysfunction, myocardial fibrosis, and decreased myocardial mass.^{2,3} Cardiac involvement is

a common manifestation, the leading cause of morbidity and mortality in these patients and the first cause of death in childhood. It can manifest as acute heart failure at any time of life, although the onset is often in the first weeks or months of life as the first manifestation, as in our case.²⁻⁶ Subsequent recovery of cardiac function is common as well as recurrence during adolescence or adulthood.^{2,5}

The prognosis is variable and will depend on the progression of the involvement of the different organs and systems. Life expectancy is usually less than 50 years.⁵ Although there is no specific treatment, and measures should be targeted to treat damage to each of the different systems, early diagnosis, a multidisciplinary approach and appropriate prevention strategies will slow progression and thereby improve patient survival.^{2,3,5}

Genetic syndromes are often difficult to diagnose and in most cases lack a specific treatment. A high degree of suspicion is crucial to establish the diagnosis, which will not only allow us to improve the care of our patient, but will also be necessary to provide genetic counselling and screening of family members, if indicated.

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REFERENCES

1. Alström CH, Hallgren B, Nilsson LB, Asander H. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from Laurence-Moon-Biedl syndrome; a clinic endocrinological and genetic examination based on a large pedigree. *Acta Psychiatr Neurol Scand.* 1959;34:1–35.
2. Makaryus AN, Zubrow ME, Marshall JD, Gillam LD, Mangion JR. Cardiac Manifestations of Alström Syndrome: Echocardiographic Findings. *J Am Soc Echocardiogr.* 2007;20:1359–1363.
3. Corbetti F, Razzolini R, Bettini V, et al. Alström syndrome: cardiac magnetic resonance findings. *Int J Cardiol.* 2013;167:1257–1263.
4. Hearn T, Renforth GL, Spalluto C, et al. Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alström Syndrome. *Nat Genet.* 2002;31:79–83.
5. Joy T, Cao H, Black G, et al. Alström syndrome (OMIM 203800): a case report and literature review. *Orphanet J Rare Dis.* 2007;2:49.
6. Marshall JD, Beck S, Maffei P, Naggert JK. Alström syndrome. *Eur J Hum Genet.* 2007;15:1193–1202.

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Selection of the Best of 2017 in Acute and Chronic Heart Failure



Selección de lo mejor del año 2017 en insuficiencia cardiaca aguda y crónica

To the Editor,

Heart failure is a leading health care problem in Spain and other countries due to its rising incidence (population aging) and prevalence (higher survival rates among patients with heart disease). While improvements have been made in both diagnosis and treatment, prognosis is still poor and the high rehospitalization rates associated with this condition place an enormous burden on the health care system.

Conceptually speaking, the latest European guidelines for the diagnosis and treatment of acute and chronic heart failure distinguish between 3 groups of heart failure based on left ventricular ejection fraction (LVEF). This distinction has therapeutic implications, as most of the current evidence is based on the treatment of heart failure with reduced LVEF (< 40%). No treatments to date have been shown to be effective or to improve prognosis in patients with preserved LVEF (> 50%). The most novel concept in the European guidelines is the inclusion of heart failure with mid-range LVEF,¹ a move aimed at promoting research and building scientific evidence to improve the management of patients with LVEF between 40% and 49%.

Natriuretic peptides are now recognized as key biochemical markers for early heart failure screening. They are mostly used in primary care and emergency departments as an adjunct to history and physical examination. They have also proven useful as a prognostic stratification tool, although approaches based on serial measurements are not perhaps the most valid option for guided therapy (GUIDE-IT study²).

None of the treatments applied to patients with acute heart failure to date have succeeded in improving prognosis. We have witnessed the failure of promising new treatments, such as recombinant serelaxin and ularitide (TRUE-AHF trial³). We are also learning that early treatment of acute heart failure, with shorter door-to-diuretic times, improves prognosis and is becoming a quality metric that should be implemented across hospitals (REALITY study⁴).

The most notable aspect of chronic heart failure treatment is the now widespread use of angiotensin receptor neprilysin inhibitors (ARNIs) to treat symptomatic disease in patients with systolic dysfunction. ARNIs have emerged as an alternative to traditional angiotensin-converting enzyme inhibitors II(ARA-II), and the latest US guidelines⁵ recommend their use at an earlier stage than that proposed by the European guidelines (where they are ranked at the same level as mineralocorticoid receptor antagonists).

Another interesting development is the increasing importance attached to the adequate management of comorbidities in a bid to improve quality of life, prevent disease progression, improve prognosis, and reduce heart failure hospitalizations. Intravenous iron therapy, for example, has been shown to improve functional capacity in patients with systolic dysfunction, although its effectiveness in reducing hospitalizations due to heart failure remains to be confirmed in clinical trials. Promising reductions in hospitalization rates have been reported in trials of sodium-glucose cotransporter 2 inhibitors (SLGT-2), where particularly good results have been observed for empagliflozin, although specific evidence is lacking for diabetic patients with heart failure. Finally, although sleep disorders are known to play a role in the pathophysiology and perpetuation of heart failure, no benefits have been observed for the use of specific systems to treat central sleep apnea in this setting.

Heart failure is the paradigmatic example of a chronic disease that requires new treatment approaches if there is to be a true impact on prognosis. Apart from specific therapeutic interventions, we need integrated care systems that bring together the different actors involved to form multidisciplinary teams, with carers and patients taking a leading role. Improved adherence to treatment guidelines has been found to have a favorable impact on prognosis and on heart failure hospitalizations in particular (QUALIFY study⁶). Health care managers, professionals, and society at large must all engage in fostering a coordinated multidisciplinary strategy aimed at improving outcomes in patients with heart failure and reducing associated health care costs.

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