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Characteristics of cardiomyopathy in Alström syndrome: Prospective single-center data on 38 patients[☆]

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Abstract

Background—Alström syndrome (AS) is a rare monogenetic disorder with multi-organ involvement. Complex metabolic disturbances are common and cardiomyopathy is a well-recognized feature in infants as well as in older children and adults. Although the mechanism of cardiomyopathy is not known, previous reports suggest that individuals with infantile-onset cardiac disease recover completely.

Methods—In this single center prospective series of 38 children and adults (age range 1.7 to 37.9 years; 20 females) with AS, we evaluated cardiac manifestations in detail, in the context of specific *ALMS1* mutations and multisystem involvement. All patients underwent *ALMS1* sequencing, biochemical testing, electrocardiogram, and echocardiographic imaging with speckle

[☆]Dedication: This paper is dedicated to the memory of our colleague, Jan Davis Marshall, who worked passionately on Alström syndrome for 23 years making a huge difference in the lives of Alström patients and families around the world.

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tracking to evaluate systolic strain; 21 patients underwent cardiac magnetic resonance imaging with T1 mapping.

Results—Approximately half of patients (17/38) had a previous diagnosis of cardiomyopathy. Global longitudinal strain, a measure of systolic contractile function, was abnormal in 94% of patients and correlated with body mass index ($r = 0.602$, $p = 0.002$) and C-reactive protein level ($r = 0.56$, $p = 0.004$), but only in children. Electrocardiographic abnormalities were seen in two-thirds of patients, and left ventricular dilatation and/or dysfunction was present in 4 adults and 4 children.

Conclusion—AS patients with a history of resolved infantile cardiomyopathy continue to have residual impairment in cardiac function. For patients with a normal ejection fraction and no prior cardiac history, strain can be abnormal, suggesting subclinical cardiac involvement. Close cardiac screening and aggressive modification of other manifestations of AS that are risk factors for cardiac disease, including obesity, inflammation, diabetes and dyslipidemia, are essential in caring for patients with AS.

Keywords

Alström; Cardiomyopathy; Echocardiography; Strain imaging; MRI

1. Introduction

Alström syndrome (AS) (OMIM #203800) is a rare monogenetic disorder characterized by progressive multi-organ involvement, including early retinal dystrophy and blindness, hearing loss, type 2 diabetes mellitus (T2DM), hypertriglyceridemia, obesity, and cardiomyopathy [1]. The prevalence of AS is estimated to be 1–10 per million, and life expectancy rarely exceeds 50 years. AS is caused by biallelic mutations in *ALMS1* (chr 2q13), which is ubiquitously expressed in fetal and postnatal tissues and encodes multiple isoforms of ALMS1 protein, ranging from 3858 to 4169 amino acids in size [2,3]. At the subcellular level, ALMS1 localizes to the cytoplasm, cytoskeleton, microtubule organizing center, centrosomes and ciliary basal bodies, but its function has not been fully elucidated [2,3]; nevertheless, ALMS1 is known to play roles in the formation and maintenance of cilia, cell cycle regulation, endosomal trafficking, cell migration and extracellular matrix production [4–9].

Cardiomyopathy occurs in the majority of AS patients at some time in their lives. A review of 182 patients with AS [10] identified two separate groups of patients with cardiomyopathy: infantile onset (43%) and later onset (18%). The remaining patients (39%, ages 2–33 years) did not manifest cardiomyopathy. Most of those with infantile onset of cardiomyopathy (before age 1) had apparent recovery of cardiac function within 3 years. Histopathology showed diffuse interstitial fibrosis affecting the myocardium, a finding later confirmed by cardiac MRI [11,12]. The mechanism and timing of intra-myocardial fibrosis is not known; in addition to loss of ALMS1 function, the complex metabolic disturbances (severe insulin resistance, activation of the renin angiotensin aldosterone system and increased triglycerides) may all be contributing factors [13,14]. Due to the rarity of AS, most

series report a small number of patients [15]; prospective cardiac evaluation with strain echocardiographic imaging has not been described in a large cohort of patients with AS.

Here we report comprehensive data on cardiac involvement in 38 children and adults with AS who were prospectively evaluated at the National Institutes of Health (NIH) Clinical Center. We present detailed cardiac manifestations of AS in the context of *ALMS1* mutations and other organ system disease.

2. Methods

2.1. Patient population

Between the dates of February 2013 and June 2014, 38 patients with AS were evaluated at the NIH Clinical Center under the protocol “Clinical and Molecular Investigations into Ciliopathies” (www.clinicaltrials.gov, trial NCT00068224), approved by the Institutional Review Board of the National Human Genome Research Institute (NHGRI). Patients were recruited through Alström Syndrome International, a support group for families and health care providers of patients with AS. All 38 patients fulfilled the clinical diagnostic criteria for AS and had mutations in the *ALMS1* gene. Patients or their parents gave written informed consent.

2.2. Molecular genetics and biochemical laboratory testing

All 38 patients had molecular genetic testing using Sanger sequencing, microarray-based arrayed primer extension (APEX), or targeted gene sequencing and custom analysis (TaGSCAN) testing as previously described [16]. Kidney and liver function tests, hemoglobin A_{1c} (HbA_{1c}), lipid panel, high-sensitivity C-reactive protein (hs-CRP), and pro-brain natriuretic peptide (pro-BNP) concentrations were measured.

2.3. Cardiac evaluations

Standard 12-lead electrocardiograms (ECGs) were recorded using commercially available systems with measurement of PR interval, QRS duration and QT. The rate-corrected QT intervals were calculated using both the Bazett and the Fridericia formulas. Prolonged QTc was defined as > 460 ms for women, >450 ms for men, >440 ms for children, as measured by both formulas.

Transthoracic echocardiograms were performed using commercially available systems; standard views were obtained with patients in the left lateral recumbent position. Cardiac measurements were performed according to American Society of Echocardiography guidelines [17]. Mitral inflow recordings were obtained with the pulsed Doppler sample volume at the level of the mitral leaflet tips during maximal opening in diastole. Tissue Doppler recordings were measured with sample volumes at both the septal mitral annulus and lateral mitral annulus. The ratio of early diastolic LV inflow velocity to septal or lateral mitral annular velocity (LV E/e') was calculated as an estimate of LV filling pressure. Speckle tracking echocardiography was used to evaluate myocardial strain in order to further quantify global myocardial function. Myocardial strain parameters were measured off-line using a specialized strain software (EchoInsight; Epsilon Imaging Inc., Ann Arbor, MI).

Global longitudinal strain (GLS) was averaged from the three standard apical views for the left ventricle and was obtained from the apical four chamber view for the right ventricle (RV free wall strain).

Cardiac magnetic resonance (CMR) imaging studies were electrocardiogram gated and performed at 3 T (Siemens Medical Solutions, Erlangen, Germany). CMR was performed to assess cardiac anatomy and systolic function as well as to quantify myocardial T1. A single mid-ventricular short axis slice was selected for T1 quantification with a motion-corrected Modified Look-Locker Inversion (MOLLI) recovery sequence during a breath-hold. The MOLLI acquisition followed a 5s(3s)3s protocol with a steady-state free precession (SSFP) read-out. Typical parameters included a field of view of $270 \times 360 \text{ mm}^2$, a slice thickness of 8 mm, a 164×256 matrix size, and a parallel imaging factor of 2, but these were modified by the technologist as appropriate for body size. Gadolinium contrast was administered to only one patient, using 0.15 mmol/kg gadobutrol (Gadavist®, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA). Late gadolinium enhancement imaging parameters were field of view $270 \times 360 \text{ mm}^2$, slice thickness of 8 mm, 163×256 matrix size, and inversion time set to null normal myocardium. Imaging parameters were adjusted to body size. Cardiac volumes, dimensions, ejection fraction, and myocardial T1 were measured on a clinical workstation (Siemens Medical Solutions, Erlangen, Germany).

2.4. Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation. Minimum and maximum values are shown in parenthesis. Statistical analyses were performed using SPSS version 23 (Chicago Inc.). Pearson correlation was performed between strain measurements and other markers of interest (including age, BMI-z-score, blood pressure, log-transformed lipid levels, hs-CRP, and log-BNP). Partial correlation was used to evaluate the relationship between strain abnormality and bio-markers with adjustment for BMI z-score, age, gender, and history of cardiomyopathy.

3. Results

3.1. Clinical characteristics, molecular genetics and biochemical laboratory testing

The patients included 18 males and 20 females, ranging in age from 1.7 to 37.9 years (mean 16.0, SD 10.5). There were 12 young children (< 10 year), 13 older children and adolescents (11–17 year) and 13 adults (≥ 18 year). Races included 35 Caucasians and three African-Americans. One family contributed three siblings (Family #1, Table 1), and four families (Families # 7,15,16 and 30) contributed two siblings each including two sets of dizygotic twins, leaving 32 independent families. In addition, in two other families (Families # 27 and 29), there was history of affected siblings who passed away due to cardiomyopathy in their early 20s; patient 32 lost a younger sister and patient 34 lost two younger brothers. We identified bi-allelic mutations in *ALMS1* in 31 families; in one family only one mutation was identified (Table 1). Consanguinity was present in three families (Families # 2, 8 and 32).

Most AS patients had severe metabolic abnormalities that began in childhood. Among the 25 children in this study, only five (20%) were normal weight, while two (8%) were overweight (BMI 85th percentile) and 18 (72%) were obese (BMI 95th percentile) (Tables 1, 2). None of the 13 adult patients were normal weight; two (15%) were overweight (BMI 25 kg/m²) and 11 (85%) were obese (BMI 30 kg/m²). There was a high prevalence of T2DM (20% and 69%, respectively, for children and adults) with HbA1C of the cohort ranging from 4.7 to 12.0% ($6.1\% \pm 1.8\%$). Blood pressure in the prehypertension range (systolic or diastolic 90th percentile for age/sex/height or $> 120/80$ mm Hg) was observed in five children (20%) and 6 adults (46%), and in the stage 1 hypertension range (> 95 th percentile or $> 140/90$ mm Hg) in 6 children (24%) and 1 adult (8%). Nine children (36%) and 2 adults (15%) had hypercholesterolemia (> 200 mg/dL), and 10 children (40%) and 10 adults (77%) had hypertriglyceridemia (> 150 mg/dL). The pro-BNP was elevated in four children (16%) and five adults (38%). In 22 patients (58%), the hs-CRP was in the high-risk range (> 3 mg/L).

3.2. Cardiac evaluations

Almost half of patients (17/38, 47%) had been diagnosed with cardiomyopathy prior to their NIH visit (Table 1). In 13 patients, the onset was in infancy, while four patients had been diagnosed during adolescence or early adulthood. The 13 patients with infantile onset cardiomyopathy reportedly responded to heart failure treatment and their ejection fractions improved to the lower end of normal with no recurrence of their cardiomyopathy. Twelve of these thirteen patients presented with acute heart failure symptoms prior to diagnosis and one was asymptomatic but was detected by cardiac imaging because his twin brother presented with heart failure. Among the four patients with later-onset cardiomyopathy, two had reportedly normalized their ventricular function. In all but one of the seven families with multiple affected children (Families # 1, 7, 15, 16, 27, 29 and 30), the sibling sets were concordant for cardiomyopathy; in Family #1 the oldest patient had severe infantile cardiomyopathy while his two younger brothers, who were monitored by echocardiograms every 6 months starting from birth, did not display any impairment in myocardial function.

At the time of the evaluation at the NIH Clinical Center, all 38 patients were clinically stable, without symptoms or signs of heart failure. Blood pressure was well controlled in most patients (Table 2), and we found no significant resting tachycardia. Four patients were receiving beta blockers, 12 were on angiotensin converting enzyme inhibitors, two were taking angiotensin receptor blockers, and three were on other medications for blood pressure. Nine patients were taking a statin or fibrate medication for dyslipidemia.

The ECG was normal in 25 patients and abnormal in 12 patients (Table 3). Abnormalities included left ventricular hypertrophy ($n = 4$), left axis deviation ($n = 3$), non-specific T wave changes ($n = 3$), poor R wave progression ($n = 4$), right axis deviation ($n = 1$), first degree atrioventricular block ($n = 1$), non-specific intraventricular conduction delay ($n = 1$), prolonged QT ($n = 1$), and atrial premature complexes ($n = 1$). The child with prolonged QT had both QTcB (481 ms) and QTcF (447 ms) prolongation with a heart rate of 92 bpm and associated LVH and poor R wave progression. In nine other patients (7 children, 2 adults),

there was isolated prolongation of QTcB that was not associated with QTcF, and the ECG was otherwise normal.

Echocardiographic imaging was suboptimal in one adult patient. Among all other patients, we found left ventricular dilatation or systolic dysfunction in eight patients (8/38 or 21%, 4 adults, 4 children) (Tables 3 and 4). Valvular involvement was also noted in three patients (2 children, 1 adult) with thickened mitral valve leaflets and moderate mitral regurgitation. Congenital abnormalities were identified in two children (1 bicuspid aortic valve, 1 patent ductus arteriosus). Two patients (1 adult, 1 child) experienced arrhythmias during echocardiography.

One child and one adult had mild diastolic dysfunction. Strain parameters of the left ventricle, including GLS, were calculated in all but three patients, for whom good quality high frame-rate images were not available. GLS of the left ventricle was abnormal in 92% of children (22/24) and in all adults (11/11) (Fig. 1). The GLS was normal only in two twin brothers (Table 1, Family 16, Patients 20 and 21) who were not overweight and did not have T2DM. They both had HTN, one of them had hypercholesterolemia, and their pro-BNP and hs-CRP were normal. Due to limited views of the right ventricular free wall, right ventricular strain could be calculated in only 10/25 children and 4/13 adults. All right ventricular strain measurements were normal except in one child with limited image quality. Since GLS is known to be abnormal in hypertension [18], diabetes [19,20], dyslipidemia and obesity [21], we tested for correlations between GLS and cardiac risk factors (HTN, DM, hyperlipidemia) and other biomarkers (total cholesterol, HDL, LDL, triglycerides, CRP, and pro-BNP). In children, hemoglobin A_{1c} level ($r = 0.465$, $p = 0.025$) and hs-CRP levels ($r = 0.512$, $p = 0.01$) were moderately correlated with GLS. Even after adjusting for BMI z-score, these markers of insulin resistance and inflammation remained independently correlated with GLS (Hgb A_{1c} $r = 0.471$, $p = 0.027$; hs-CRP $r = 0.536$, $p = 0.01$). With adjustment for age, both Hgb A_{1c} and hs-CRP remained significant. Adjustment for gender or for a history of cardiomyopathy showed that only hs-CRP remained a significant correlate of GLS. In adults, there were no significant correlations between GLS and cardiac risk factors or other biomarkers.

CMR was performed in 11 adults and 10 children. Three patients (3/21, 14%) had a dilated left ventricle and six (29%) had evidence of decreased left ventricular function (Table 4). One adult who received gadolinium contrast (Fig. 2) had mild enlargement of both ventricles and atypical, mid-wall late gadolinium enhancement of the basal and mid-interventricular septum. This was considered consistent with a dilated, non-ischemic cardiomyopathy despite his low normal global left ventricular function with an ejection fraction of 57%. The patient did have mildly reduced mitral annular excursion consistent with impaired longitudinal left ventricular systolic function. T1 measurements, performed in 15 patients with 6 mid-ventricular segments per patient, were normal in all segments except for one segment in a patient with a known cardiomyopathy and one segment in an otherwise normal patient.

In our cohort, four patients had undergone endomyocardial biopsy, and three of these results were available to us. Two children with a history of infantile-onset cardiomyopathy had

reportedly normal biopsy results; one patient with late onset cardiomyopathy at age 13 had hypertrophy of myocytes and fibrosis.

4. Discussion

AS is a complex disorder that affects multiple organ systems and has significant cardiac involvement. Its extreme rarity represents a challenge for single center studies. This study describes the first large cohort of AS patients who prospectively underwent thorough multisystem evaluations at one institution. Hence, we are able to present comprehensive cardiac data in the context of the extra-cardiac manifestations as well as molecular genetic findings.

We identified evidence of overt ventricular dysfunction in approximately one-third of our cohort of 38 children and adults with AS. Although prior studies have suggested that AS patients with infantile onset of cardiomyopathy recover completely [22], we did not confirm this finding. Of the 13 patients (age 3 to 33) with a history of infantile cardiomyopathy, nine had abnormalities on ECG, echocardiography or CMR, and the remaining four patients had evidence of subclinical myocardial dysfunction by strain imaging at the time of NIH evaluation. The EF of these 13 patients ranged from 40 to 66% with one child having moderate systolic dysfunction and the remaining children having only mild systolic dysfunction. Strain imaging showed abnormalities in almost all subjects, suggesting that cardiac involvement in AS is more common than previously reported. Whether this mild cardiomyopathy progresses into more significant disease in all AS patients remains to be determined through longitudinal follow-up studies. In addition, we do not know why only a subset of AS patients develop infantile cardiomyopathy, or why some AS patients develop overt late onset cardiomyopathy while other patients of similar ages display only subclinical abnormalities such as abnormal strain. All *ALMS1* mutations in our cohort are null mutations that are expected to result in complete absence of ALMS1 function; however, varied impairment of function of each ALMS1 isoform may be playing a role. Interestingly, among the three affected brothers in family #1 with the same *ALMS1* mutations, only 1 developed infantile cardiomyopathy, possibly due to modifier genes or environmental factors.

Electrocardiographic abnormalities were few and nonspecific. The previously reported QT prolongation was not observed in our study. This difference may be explained by the fact that we corrected the QT interval using both the Bazett and Fredericia formulas. The Fredericia formula has been proven to be superior to the Bazett formula, especially in terms of risk assessment for mortality [23]. In addition, in our cohort, we did not identify an increased incidence of arrhythmias or symptoms related to abnormal heart rhythms.

As expected, our AS cohort had significant metabolic disturbances including T2DM and elevated triglyceride and cholesterol levels. However, cardiomyopathy appeared to be a primary manifestation of AS not caused by these metabolic disturbances. For example, Patient # 16 was obese, yet had no hypertension or T2DM and developed late-onset cardiomyopathy at 8 years of age. Although some patients had a history of significant cardiac risk factors for many years, we were unable to find a relationship between metabolic

derangements and cardiac abnormalities. Our finding of subclinical strain abnormalities in nearly all patients in our cohort suggests the presence of myocardial disease in patients without overt cardiomyopathy, including but not limited to those who have recovered from infantile cardiomyopathy. Toulany et al. reported subclinical systolic dysfunction in all five children and adolescents whom they studied with tissue Doppler and strain echocardiography [24]. Our finding of abnormal GLS of the left ventricle in 22 of 24 children and in 11 of 11 adults confirms their results in our larger cohort of patients. This finding is of particular importance because it may reflect a persistent subclinical cardiomyopathy that could become overt after an insult and manifest with clinical heart failure. Recognition of this subclinical entity is important in order to aggressively control cardiac risk factors.

Diffuse interstitial fibrosis is the most common pathologic finding in AS; it affects the kidneys, pancreas, liver, lungs, and the heart as well as other organs [10,25]. Moderate to severe interstitial fibrosis was found in the cardiac tissues of AS patients with history of dilated cardiomyopathy (DCM) while mild interstitial myocardial fibrosis was present in patients without a prior history of DCM [10]. The mechanism for the fibrosis is unknown, although inflammation and insulin resistance are suspected mediators; it is possible that fibrosis in AS may be a primary pathology caused directly by the loss of function of the *ALMS1* protein. While fibrosis may be an important player in late onset cardiomyopathy in AS, the acute infantile cardiomyopathy in this disorder appears to have a different pathophysiology. A mitogenic cardiomyopathy associated with an increased number of cardiomyocytes in mitosis was part of the histopathology of two siblings with AS [26]. Consistent with this observation, Shenje et al. showed increased cardiomyocyte proliferation in two-week old homozygous *Alms1*-mutant mice and concluded that deficiency of *ALMS1* protein impairs postnatal cardiomyocyte cell cycle arrest [7]. They also sequenced *ALMS1* in six infants with mitogenic cardiomyopathy leading to death or transplantation, and found *ALMS1* mutations in all four of them. As expected, none of these infants had other clinical features to suggest a diagnosis of Alström because other features of the syndrome are not present in newborns. These data suggest that there may be a larger, number of unrecognized Alström patients among those infants who do not recover from infantile cardiomyopathy. Hence, sequencing of *ALMS1* is warranted in idiopathic neonatal cardiomyopathy. In our cohort, two children with history of infantile-onset cardiomyopathy had reportedly normal biopsy results; differences in timing of the biopsy may explain the absence of increased mitosis in cardiomyocytes of these patients.

Intramyocardial fibrosis in AS has also been demonstrated as patchy late gadolinium enhancement (LGE) using CMR [11] and as diffuse fibrosis using low pre-contrast T1 relaxation time or higher signal intensity on T1 weighted images [25]. Edwards et al. [12] found that one-third of 28 AS patients had LGE in a diffuse, non-coronary distribution. Moreover, they used newer T1 mapping techniques to quantify the size of the extracellular volume (ECV) as a more sensitive marker of diffuse fibrosis; half of the patients had an ECV level greater than matched controls. They also noted that expansion of the ECV was present in patients with a normal ejection fraction and was associated with impairment in peak systolic strain. Although increased ECV was associated with a prolonged QT interval and elevated serum triglyceride levels, pro-BNP, a marker of cardiac stretch, remained

normal. The authors noted significant variation in ECV levels and suggested the possibility of myocardial fat deposition or a combination of fat and fibrosis due to insulin resistance and/or inflammation. In our study, we used gadolinium contrast with CMR in only one adult patient; other subjects were too young, had renal dysfunction, or were unable to tolerate longer imaging times. In contrast with an earlier study [25], the majority of our T1 measurements were normal and did not appear to distinguish the presence or absence of interstitial fibrosis.

4.1. Limitations

This study involved outpatients who were healthy enough to travel to NIH so we may have missed inclusion of sicker AS patients with cardiac involvement. Although all patients underwent comprehensive echocardiograms, we were only able to image a subset of patients with CMR. The majority of patients did not receive gadolinium contrast during CMR as discussed above, so we were unable to confirm echo strain abnormalities using ECV measurements.

5. Conclusion

Our comprehensive cardiac evaluation of 38 children and adults with AS suggests that cardiac function in AS patients with a history of infantile cardiomyopathy improves within the first 2–3 years of life but does not return to normal; in fact, the majority of AS children and adults have residual impairment in cardiac function. Cardiomyopathy in AS is a primary manifestation caused by absence of ALMS1 function, while other primary manifestations of AS including T2DM and hyperlipidemias may contribute to the progression of cardiac disease.

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Fig. 1.

Example of strain imaging in the apical four-chamber echo view (left panel) of a 19 year old AS patient with a normal LV ejection fraction of 61%. Time vs longitudinal strain curves (right panel) show strain (top), strain rate (middle), and the ECG for one cardiac cycle. The LV global longitudinal strain was abnormal at -14% and was an average of the six colored segments shown as well as the segments in the apical two-chamber and apical three-chamber views.

Fig. 2.

19 Year-old male with AS. Late gadolinium enhancement (LGE) images in the 4 chamber (left) and short axis (right) views show midwall enhancement of the interventricular septum (arrows), a finding consistent with myocardial fibrosis from a nonischemic etiology.

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Hearing loss	BMI category	Type 2 diabetes	Blood pressure category	Elevated triglycerides	Elevated total cholesterol	GFR	Portal hypertension	Infantile-onset cardiomyopathy	Late-onset cardiomyopathy
Undetermined	Obesity	No	HTN	No	No	85	No	No	No
Slight	Obesity	No	Normal	No	Yes	115	No	No	No
Moderate	Obesity	No	Pre-HTN	Yes	Yes	109	Yes	Yes	No
Undetermined	Obesity	No	Normal	No	No	166	No	No	No
Undetermined	Obesity	No	Normal	No	Yes	120	No	Yes	No
Undetermined	Obesity	No	Normal	No	No	103	No	No	No
Normal	Obesity	No	Normal	Yes	No	166	NA	Yes	No
Undetermined	Obesity	No	Normal	No	Yes	121	No	Yes	No
Moderate	Obesity	No	Pre-HTN	No	No	127	NA	No	No
Mild	Obesity	No	Normal	Yes	No	120	No	No	No
Moderate	Obesity	No	HTN	No	No	61	Yes	Yes	No
Mild	Obesity	No	Normal	No	No	110	No	No	No
Normal	Obesity	No	Normal	No	Yes	143	No	Yes	No
Moderate	Obesity	No	Normal	No	No	171	No	No	No
Moderate	Obesity	Yes	HTN	Yes	Yes	102	Yes	No	No
Moderate	Obesity	No	Normal	Yes	No	98	No	No	Yes(8y)
Moderate	Normal	Yes	Pre-HTN	Yes	No	99	No	No	No
Mild	Overweight	No	Pre-HTN	No	No	114	No	Yes	No
NA	Normal	No	HTN	No	No	98	No	Yes	No
Normal	Normal	No	Normal	Yes	No	109	No	Yes	No
Slight	Normal	No	Pre-HTN	No	No	128	No	Yes	No
Moderate	Obesity	Yes	HTN	Yes	Yes	96	No	No	No
Moderate	Obesity	Yes	HTN	Yes	Yes	80	Yes	No	No
Moderate	Overweight	Yes	Normal	Yes	Yes	75	Yes	No	Yes(14y)
Mild	Normal	No	Normal	No	No	92	No	Yes	No
Moderate	Obesity	Yes	Normal	Yes	Yes	57	Yes	No	Yes(17y)

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Hearing loss	BMI category	Type 2 diabetes	Blood pressure category	Elevated triglycerides	Elevated total cholesterol	GFR	Portal hypertension	Infantile-onset cardiomyopathy	Late-onset cardiomyopathy
Moderate	Obesity	No	Normal	Yes	No	120	No	No	No
Moderate	Obesity	Yes	Normal	Yes	No	37	No	Yes	No
Moderate	Overweight	Yes	HTN	Yes	Yes	112	Yes	No	Yes(24y)
Moderate	Obesity	Yes	Normal	Yes	No	32	Yes	No	Yes(13y)
Moderate	Obesity	No	Pre-HTN	Yes	No	94	Yes	No	No
Moderate	Obesity	Yes	Normal	No	No	44	Yes	No	No
Severe	Obesity	No	Pre-HTN	Yes	No	49	No	Yes	No
Severe	Overweight	Yes	Pre-HTN	Yes	No	69	Yes	No	No
Moderate	Obesity	Yes	Pre-HTN	Yes	No	117	No	No	No
Moderate	Obesity	Yes	Pre-HTN	Yes	No	44	Yes	No	No
Moderate	Obesity	Yes	Normal	No	No	50	No	No	No
Severe	Obesity	No	Pre-HTN	No	No	21	No	No	No

Table 2

Demographics, hemodynamics, and laboratory features in adults and children with Alström syndrome.

	Children ^a (n = 25)	Adults ^a (n = 13)
Age (years)	10 ± 4 (1–17)	28 ± 7 (18–37)
Male	12 (48%)	6 (46%)
BMI (kg/m ²)	25.6 ± 4.6 (19–37)	38.2 ± 14.1 (27–69)
HbA1C(%)	5.7 ± 1.5 (4.7–12)	7.0 ± 2.1 (5.1–11.8)
Systolic BP (mm Hg)	115 ± 8 (99–132)	120 ± 10 (104–140)
Diastolic BP (mm Hg)	63 ± 6 (53–73)	67 ± 8 (56–82)
Heart rate (beats/min)	92 ± 20 (53–133)	73 ± 14 (54–101)
Triglycerides (mg/dL)	284 ± 637 (42–3291)	319 ± 185 (80–592)
Cholesterol (mg/dL)	161 ± 48 (105–286)	164 ± 38 (89–251)
Pro-BNP (pg/mL)	89 ± 52 (31–239)	201 ± 243 (11–729)
hs-CRP (mg/L)	4.6 ± 7.1 (0.2–33.5)	11.6 ± 10.7 (2.1–32)

BMI= body mass index; HbA1C= hemoglobinA1c; BP= blood pressure; Pro-BNP= pro-brain natriuretic peptide; hs-CRP = high-sensitivity C-reactive protein

^aMean + Standard Deviation (range).

Table 3

ECG and echocardiographic parameters in children and adults with Alström syndrome.

	Children (<i>n</i> = 25)	Adults (<i>n</i> = 13)
ECG normal	20 ^a	5
ECG abnormalities:		
Left ventricular hypertrophy	2	2
Left axis deviation	1	2
Non-specific T wave changes	1	2
Poor R wave progression	1	3
Right axis deviation	0	1
First degree AVB	0	1
Non-specific IVCD	0	1
Prolonged QTc	1	0
Atrial premature complex	0	1
Echo parameters:		
Ejection fraction (%)	60 ± 7 (45–71)	60 ± 9 (43–68)
LV mass (g/m ²)	65 ± 14 (48–93)	74 ± 20 (47–109)
LVEDD (mm)	43 ± 6 (30–52)	47 ± 7 (36–56)
LVESD (mm)	29 ± 5 (20–40)	33 ± 7 (23–43)
E/A ratio	2.3 ± 0.9 (0.7–5.1)	2.2 ± 0.8 (1.1–3.8)
Septal S wave (cm/s)	6.4 ± 1.1 (4.6–8.7)	7.3 ± 2.0 (5.5–12.7)
Lateral S wave (cm/s)	7.6 ± 1.9 (5.4–12.8)	7.5 ± 1.6 (5.4–10.1)
Septal e' wave (cm/s)	10.5 ± 2.3 (6–15)	9.0 ± 1.7 (6.4–12.4)
Septal E/e' ratio	10 ± 2.1 (4.9–14.5)	10.3 ± 2.1 (8.2–13.9)
Lateral e' wave (cm/s)	16.9 ± 3.7 (7–24)	15.1 ± 4.5 (6.8–23)
Lateral E/e' ratio	6.3 ± 1.6 (3.2–10)	6.6 ± 2.4 (3.7–12.8)
Left atrial volume index (mL/m ²)	22 ± 7 (9–39)	21 ± 7 (14–37)
LV global longitudinal strain (%)	−15.5 ± 2.9 [−21]–[−8.3]	−12.8 ± 1.9 [−10.6]–[−16]
RV free wall strain (%)	−24.3 ± 5.6 [−30]–[−11]	−26.2 ± 4.3 [−31]–[−21]

AVB = atrioventricular block; IVCD = interventricular conduction delay; LV = left ventricular; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; RV = right ventricular.

^aECG was not performed in one patient.

Table 4

Summary of cardiac findings in Alström syndrome.

Patient no.	Family no.	Age CM diagnosed (years)	Age at NIH visit (years)	ECG	Echo findings	Echo EF (%)	Echo strain (%)	MRI findings	MRI EF (%)
5	3	1	3	Not done	Mildly decreased EF, thickened MV, mod MR	46	-13.3	Not done	
7	5	1	5	Normal	Thickened MV, moderate MR	63	-17.3	Not done	
8	6	1	6	Normal	Mildly decreased EF, brief run of SVT	53	-16	Not done	
11	8	1	8	Normal	Normal	55	-12.3	Not done	
3	1	1	9	Normal	Normal	49	-16	Not done	
13	10	1	10	Normal	Normal	57	-13.3	Not done	
16	13	8	12	Normal	Normal	53	-14.3	Normal	62
18	15	1	12	Nonspecific T abnormality	Normal	58	-14	Mild LVE, low normal LV function	-
19	15	1	12	Normal	LVE, moderately decreased EF	40	-11.6	Not done	
20	16	1	12	Normal	Bicuspid AV, normal aorta	57	-20	Bicuspid AV, normal aorta	66
21	16	1	12	Normal	Normal	66	-21	Not done	
23	18	-	16	LVH, poor RWP	Patent ductus arteriosus	58	-15	Not done	
24	19	14	17	Normal	Limited study, mildly decreased LV function	42	-8.3	Mildly decreased LV function	54
25	20	1	18	Normal	Mild LVE	60	-16.6	Mild LVE, mod LAE	60
26	21	17	19	Normal	Normal	61	-14	Mild LVE, mild RVE, gad + basal and mid septum, small PE	57
27	22	-	19	Normal	Normal	60	-12.3	Mildly decreased function, mild LAE	54
28	23	1	21	Normal	Mild-mod MR, mildly decreased LV function	45	-11.3	Mildly decreased LV function	46
29	24	24	21	Borderline LAD	Mild LVE, mildly decreased EF	49		Mildly decreased LV function, mild AR	52
30	25	13	24	LVH, poor RWP, LAFB	Mildly decreased EF	43	-10.6	Mod LVE, mildly decreased LV function, abnormal T1, T2 mid-septum	47

Patient no.	Family no.	Age CM diagnosed (years)	Age at NIH visit (years)	ECG	Echo findings	Echo EF (%)	Echo strain (%)	MRI findings	MRI EF (%)
33	28	I	33	RAD/LPFB	Normal	59	-10.6	Mildly decreased LV function, mild LVH, mild LAE, mild RAE	53
34	29	-	34	Nonspecific T abnormality	Normal	61	-14	Mild LAE	55
35	30	-	35	APCs, IAVB, NSIVCD	Ectopy noted during study	68	-16	Frequent ectopy, Mild LVE, mod LAE, normal LV function	-
37	39	-	37	LVH, nonspecific T abnormality, poor RWP	Normal	65	-15.6	Normal	55
38	32	-	38	Low voltage, poor RWP	Normal	65	-12.6	Not done	

I = infant; EF = ejection fraction; MV = mitral valve; MR = mitral regurgitation; SVT = supraventricular tachycardia; LVE = left ventricular enlargement; LV = left ventricular; AV = aortic valve; LVH = left ventricular hypertrophy; RWP = R-wave progression; LAE = left atrial enlargement; RVE = right ventricular enlargement; RAE = right atrial enlargement; PE = pulmonary embolism; AR = aortic regurgitation; LAFB = left anterior fascicular block; RAD = right axis deviation; LAD = left axis deviation; LPFB = left posterior fascicular block; APC = atrial premature complexes; AVB = atrioventricular block; NSIVCD = non-specific interventricular conduction delay.