Severe Cardiac Involvement Is Rare in Patients with Late-Onset Pompe Disease and the Common c.-32-13T>G Variant: Implications for Newborn Screening

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Based on a review of a large patient cohort, published literature, and 3 newborn screening cohorts, we concluded that children diagnosed through newborn screening with late-onset Pompe disease and the common heterozygous c.-32-13T>G variant require frequent cardiac follow-up with electrocardiography for arrhythmias. However, there is limited evidence for performing repeated echocardiography for cardiomyopathy. *(J Pediatr 2018;198:308-12).*

Pompe disease is a progressive lysosomal storage disease caused by deficiency of the enzyme acid α–glucosidase (GAA), resulting in glycogen accumulation primarily in cardiac, skeletal, and smooth muscles. Classic infantile-onset Pompe disease is characterized by generalized muscle weakness, hypotonia, and rapidly progressive, severe hypertrophic cardiomyopathy (HCM), which ultimately progresses to dilated cardiomyopathy (DCM). Late-onset Pompe disease is predominantly characterized by weakness of the respiratory and lower extremity proximal skeletal muscles and may manifest as early as 1 year to as late as the sixth decade of life. Among white individuals with late-onset Pompe disease, the "leaky" splice site variant c.-32-13T>G is the most common pathogenic variant, with a frequency of 68%-90% in different patient cohorts.[1-4] This variant leads to aberrant splicing of exon 2 but allows for production of 10%-20% of normally spliced mRNA. The resulting low GAA activity manifests as a less severe clinical presentation when present in heterozygosity with a second pathogenic variant.[4,5]

In the US, 7 states are currently screening for Pompe disease as part of the recommended uniform screening panel for newborns, with several other states considering addition of Pompe disease to their newborn screening (NBS) panels. As additional states move to implement NBS for Pompe disease, the number of children identified with the c.-32-13T>G variant will increase, making it vital to determine whether this variant is associated with significant cardiac abnormalities and, if absent, cardiac monitoring frequency may be accordingly minimized. Current guidelines for patients identified with late-onset Pompe disease on NBS but without apparent clinical manifestations recommend cardiac evaluation every 3 months through the first year and then every 3-12 months as clinically warranted.[6]

DCM	Dilated cardiomyopathy
ECG	Electrocardiography
Echo	Echocardiography
GAA	Acid α–glucosidase
HCM	Hypertrophic cardiomyopathy
LVH	Left ventricular hypertrophy

Methods

Cardiac involvement in Pompe disease associated with the c.-32-13T>G variant was assessed by (1) medical record review of the Duke Pompe disease patient cohort, (2) literature review, and (3) review of NBS data from programs in the states of Missouri, Illinois, and New York.

Clinical history, *GAA* variants, physical examination at clinical evaluations, and cardiology evaluations including electrocardiogram (ECG) and echocardiography (Echo) were obtained via retrospective medical record review of the Duke Pompe disease patient cohort, including 144 patients with late-onset Pompe disease and 40 patients with classic infantile-onset Pompe disease followed at Duke University Medical Center. This study was conducted under Duke institutional review board–approved protocols, for which written informed consent was obtained from all patients and/or parent/guardians.

Literature was reviewed to document cardiac manifestations in patients with late-onset Pompe disease with the c.-32-13T>G variant, to determine whether patients with late-onset Pompe disease with severe cardiac manifestations harbor the c.-32-13T>G variant. Severe cardiac disease was defined as HCM, DCM, and arrhythmias or any other abnormalities that could result in death without intervention. The PubMed database was queried for studies published through December 2016 by using the National Library of Medicine Medical Subject Heading terms "glycogen storage disease type II," "glycogen storage disease type 2," "acid maltase deficiency," and "glycogenosis type ii," and the keywords "Pompe disease," "cardiac," "splice site," and "c.-32-13T>G." Studies in languages other than English and studies in nonwhite populations, in whom the c.-32-13T>G variant typically is absent, were excluded. Despite their small sample size, case reports and case

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series with relevant information were included. In addition, patients with late-onset Pompe disease who were reported to have severe cardiac disease were assessed for the c.-32-13T>G variant. Finally, studies in patients with infantile-onset Pompe disease were examined for reports of patients with HCM and the c.-32-13T>G variant. The distinction between atypical infantile-onset Pompe disease and late-onset Pompe disease is clinically subjective; therefore, patients with atypical infantile-onset Pompe disease were included in this review.

Aggregate NBS data were obtained from the states of New York, Missouri, and Illinois, which include Pompe disease as part of recommended uniform screening panel. Data collected included the total number of patients with Pompe disease with the c.-32-13T>G identified by NBS variant and results of cardiac evaluations including chest radiograph, ECG, and Echo. These data were obtained from personal communications with the NBS state laboratory/clinical team in each state.

Results

GAA variant data were available for 130 (40 infantile-onset Pompe disease, 90 late-onset Pompe disease) of 184 patients with Pompe disease followed at Duke (40 infantile-onset Pompe disease, 144 late-onset Pompe disease). Among the 90 genotyped patients with late-onset Pompe disease, 83, all of them white, had the c.-32-13T>G variant present on at least 1 allele (92.22%). None of the Duke patients with classic infantile-onset Pompe disease had the variant. The median age of the Duke c.-32-13T>G cohort was 48 years (range 0.5-78 years) with median age at diagnosis of 36 years. A total of 60.2% were female (50/83). Five patients were homozygous for the c.-32-13T>G variant.

In patients of age ≤18 years, median age at initial cardiac screening was 0.82 years (range 0-16.71 years) and length of cardiac follow-up available ranged from 0.17 to 12.17 years (median 2.31 years). In those >18 years, median age at initial cardiac screening was 46.86 years (range 21.6-67.41 years); cardiac follow-up data were available for a time period of 1.76-35.64 years (median 6.87 years).

Twenty-nine patients (29/83, 34.9%) had some manifestation of a cardiac abnormality, 6 who were of age ≤18 years and 23 patients who were ≥19 years (**Table I**). Abnormalities reported in the age <18 years group included arrhythmia and minor valvular abnormalities but no left ventricular hypertrophy (LVH). Patients who were ≥19 years reported myocardial involvement in the form of LVH in addition to arrhythmias and valvular involvement. The most common abnormality identified in the cohort was valvular dysfunction affecting the mitral, tricuspid, and pulmonary valves (21.7%, 18/83, **Table I**). Valvular dysfunction that was judged as "trace," "trivial," or "mild" was considered as a normal variant as long as there was normal valve morphology by imaging (eg, no valvular prolapse or abnormal leaflets). None of these abnormalities required medical or surgical intervention. One patient had mild aortic root dilation at age 49 years in addition to LVH and a history of hypertension.

Arrhythmias were reported in 12 of 83 (14.5%) of the cohort. Among patients ≤18 years, arrhythmia was reported in 1 patient who had a history of premature ventricular contractions in childhood; this patient had nonspecific ST elevation and left-axis deviation in the most recent ECG. Patients ≥19 years were found to have atrioventricular block of differing degrees (n = 2), supraventricular tachycardia (n = 2), and right bundle branch block (n = 1) in addition to minor findings such as RSR′ pattern and nonspecific ST elevation. Four adult patients required treatment for their arrhythmia; 1 patient developed complete heart block at age 63 years for which a pacemaker was implanted; a second patient developed atrial fibrillation at age 74 years and is on treatment with antiarrhythmic medication; a third patient reported an episode of cardiac arrest with pulseless electrical activity for which cardioversion was performed at age 45 years; and the fourth patient had supraventricular tachycardia treated by radiofrequency ablation at age 43 years.

Myocardial abnormalities (20.4%), including LVH and left atrial enlargement, were present exclusively in adult patients in our cohort. LVH was seen in 16.87% (14/83, not shown). Echo showed that LVH was mild in all patients. Moreover, all patients with LVH were adults with additional cardiovascular risk factors such as hypertension, restrictive lung disease, chronic respiratory failure, type 2 diabetes mellitus, or hyperlipidemia. Left atrial enlargement was seen in 4 patients (4.8%, 4/83).

Table I. Prevalence of cardiac abnormalities detected in this late-onset Pompe disease cohort compared with the literature

Cardiac findings	Herbert et al, n = 83 (%, N)					Literature review of late-onset Pompe disease cohorts with the c.32.13.T>G variant; n = 254 (%, N)	General population (%)
	Overall	≤18 y (n)		≥19 y (n)			
		Minor	Major	Minor	Major		
Structural*	21.7% (18)	4	0	13	1	14% (5.5)	13%-19%[25,26]
Myocardial†	20.4% (17)	0	0	17‡	0	24% (9.45)	0.6%-40%[27,28]
Arrhythmia§	14.5% (12)	1	0	7	4	15% (5.91)	Minor ECG abnormalities: 3.6%-39%[29-33] Major ECG abnormalities: 6.2%-29%[29,30,33]

N, number of affected individuals.
*Structural abnormalities include mitral/tricuspid/atrioventricular valve dysfunction. Minor includes those reported as "mild/ trace/trivial," and major refers to those reported as "moderate/severe."
†Includes LVH and left atrial enlargement.
‡Severity of LVH unknown in 2 patients.
§Mild denotes ectopy, RSR′ pattern, nonspecific ST elevation, interventricular conduction delay, and first-degree atrioventricular block; major includes complete heart block, supraventricular tachycardia, and right bundle branch block.

Table II. Literature reports of cardiac manifestations in patients with late-onset Pompe disease and the c.-32-13T>G variant

Authors (N = 10)	Year	Total patients	Patients with IVS1 variant	Cardiac manifestations in patients with the c.32-13T>G variant	Other risk factors present in affected patients
van Capelle et al[7]	2016	31	21	WPW syndrome, minor valvular defects thought to be incidental findings and unrelated to Pompe.	—
Montagnese et al[8]	2015	30	29	Mild interventricular septum hypertrophy, reduced ejection fraction, mild valvular impairment.	—
Remiche et al[9]	2014	36	35	None of the patients exhibited major heart function, rhythm or conduction defect.	—
van der Beek et al[10]	2012	94	92	Mild HCM, minor cardiac abnormalities.	Age, HTN, pre-existing cardiac pathology
Angelini et al[11]	2012	74	62	Variable degree of left ventricular and/or septal hypertrophy.	HTN
Byrne et al[12]	2011	742	178/345 (51.6%,)	A subset of patients (14.7%) <12 mo of age did not have CM; these patients had later age at first symptoms and diagnosis compared with those with infantile Pompe disease. Among those with symptom onset <12 mo of age, IVS1 variant was mostly reported in those without CM.	—
Crescimanno et al[13]	2015	8	8	Mild septal hypertrophy.	—
van der Beek et al[14]	2008	68	68	WPW pattern, mild hypertrophic CM, minor cardiac abnormalities.	HTN, DM, smoking
Soliman et al[15]	2008	46	46	Conduction abnormalities, RVH and LVH, mild diastolic dysfunction grade I, isolated low systolic mitral annular velocities, mild LV diastolic dysfunction.	HTN, DM, smoking
Sacconi et al[16]	2014	131	Reported in 4	Severe atrioventricular block requiring pacemaker implantation.	—

CM, cardiomyopathy; *DM*, diabetes mellitus; *HTN*, hypertension; *IVS1*, intervening sequence 1; *RVH*, right ventricular hypertrophy; *WPW*, Wolff–Parkinson–White.

The initial PubMed search returned 1367 articles. Narrowing the search results with the keywords "c.-32-13T>G," "splice site," or "cardiac" returned 22, 15, and 326 articles, respectively. After careful review, manuscripts not relevant to the aims of this study were excluded. The following were included in the final analysis; 10 studies reporting cardiac findings in patients with late-onset Pompe disease and the c.-32-13T>G variant (**Table II**). The total number of patients in these 10 studies was adjusted to 492 to take into account 51 patients who were re-reported in multiple publications.[10,14,15] The most common cardiac finding was cardiac hypertrophy, including LVH and septal hypertrophy reported in 24 patients in 6 studies.[8,10,11,13-15] However, several of these studies suggested that cardiac phenotypes in these patients likely resulted from other cardiovascular risk factors and not Pompe disease.[14,15] Mild valvular abnormalities were reported in 14 patients in 3 studies.[7,8,14] Conduction abnormalities including Wolff–Parkinson–White syndrome, short PR interval, right bundle branch block, left bundle branch block, and atrial rhythms were reported in 15 patients in 4 studies.[7,14-16] The majority of cardiac manifestations were reported in adults, apart from arrhythmias, which were reported in children <18 years. Arrhythmia requiring surgical ablation and pacemaker implantation was reported in 1 patient with the c.-32-13T>G variant.[14]

Four studies reported patients with late-onset Pompe disease and severe cardiac involvement.[7,16-18] Of these, only 1 study reported the presence of a severe cardiac phenotype, atrioventricular block, in 4 patients with late-onset Pompe disease and the c.-32-13T>G variant; these patients were between ages 37 and 57 years at pacemaker implantation. Echo did not show cardiac hypertrophy in these patients.[16] Patients in the other 3 studies had HCM but did not have the c.-32-13T>G variant.[17,18]

A total of 59 patients were diagnosed with late-onset Pompe disease following NBS in the states of Illinois, New York, and Missouri, 53 (89%) of whom had the c.-32-13T>G variant on at least 1 allele. Of these, 15 of 53 (28.3%) were homozygous for this variant. Patient age at the time of data collection ranged from 9 weeks to 5 years. All patients had normal cardiac function at baseline evaluation by chest radiograph, ECG, and Echo. Cardiac follow-up data were available for 29 of 53 (54.7%) patients. Length of follow-up ranged from 2 months to 4.5 years, with a median of 2.21 years. At the time of reporting, none of these children reported HCM, DCM, or rhythm disturbances at baseline or on follow-up by ECG and Echo.

Discussion

Severe cardiomyopathy (HCM or DCM) is rare in patients with late-onset Pompe disease with the c.-32-13T>G variant. However, arrhythmias are not uncommon in this subset of patients with late-onset Pompe disease. Although isolated reports of patients with late-onset Pompe disease and HCM exist in the literature, none of these patients had the c.-32-13T>G variant.[16-18] In rare instances when HCM is seen in patients with late-onset Pompe disease with the c.-32-13T>G variant, it is important to investigate alternative etiologies such as connective tissue disorder or PRKAG2 syndrome.[19] Ganesh et al reported a patient with late-onset Pompe disease with severe DCM.[20] He was found to have a variant of uncertain significance in the *MYH6* gene, which is reportedly associated with familial HCM, DCM, and arrhythmias. In addition, a connective tissue etiology was considered in this patient, as he had pectus excavatum, thoracic aortic ectasia, scoliosis, and hypermobility of joints.

LVH is likely not a concern for children with late-onset Pompe disease and the c.-32-13T>G variant with no other cardiovascular risk factors. However, the primary cardiac concern for these individuals is arrhythmia, which has been reported across all age groups in literature.[14,21,22] A number of patients, including those ≤18 years of age, in the Duke cohort had arrhythmias, 4 of whom required medical management or surgical ablation. Follow-up with ECG in children is appropriate because arrhythmias have been reported in patients with late-onset Pompe disease with the c.-32-13T>G variant who are as young as 8 years old.[14]

Although frequent Echo monitoring for HCM in patients with late-onset Pompe disease and the c.-32-13T>G variant is likely unnecessary, Echo cannot be forgone completely due to the risk of aortic root dilation in late-onset Pompe disease.[23,24] However, there are no reports of aortic involvement before age 18 years; the earliest report of aortic dilatation appears to be age 28 years.[23]

The prevalence of cardiac findings such as arrhythmias, valvular disease, and LVH in the Duke late-onset Pompe disease cohort varies from that in other late-onset Pompe disease cohorts reported in literature (**Table II**). This can be attributed to the methodologic differences among studies; some did not report cardiac findings, although others reported ECG and/or Echo findings. However, the prevalence reported here are in general comparable with that documented in the general population.[25-33]

We recommend that infants who harbor the common c.-32-13T>G variant in heterozygous or homozygous form have an initial cardiac screening with ECG and Echo. Patients with no cardiac abnormalities at initial screening can subsequently receive ECG every 6 months to 1 year. Follow-up Echo can be done less frequently, every 2-3 years or as clinically indicated, unless significant LVH is noted on ECG.

Reducing the frequency of cardiac clinical follow-up has implications for multiple stakeholders. For patients, it will ensure that newly diagnosed children, especially those who are at lower risk, do not undergo unnecessary repeated testing. For family members, this will allay anxiety associated with pediatric testing. Family members also can be reassured that risk of cardiac disease in their child is low. It will also lower indirect healthcare costs associated with the long-term follow-up such as out-of-pocket copayments, and loss of wages from missing work for clinical appointments. For physicians, this will help not only for appropriate monitoring of potential cardiac involvement but also to realize that the focus should be on musculoskeletal involvement which is more likely in patients with late-onset Pompe disease. ■

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