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;■■:■■-■■).*

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.

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