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Screening of Fabry disease in patients with an implanted permanent pacemaker

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ABSTRACT

Background: Anderson-Fabry disease (AFD) is an X-linked inherited lysosomal disease caused by a defect in the gene encoding lysosomal enzyme α-galactosidase A (*GLA*). Atrio-ventricular (AV) nodal conduction defects and sinus node dysfunction are common complications of the disease. It is not fully elucidated how frequently AFD is responsible for acquired AV block or sinus node dysfunction and if some AFD patients could manifest primarily with spontaneous bradycardia in general population. The purpose of study was to evaluate the prevalence of AFD in male patients with implanted permanent pacemaker (PM).

Methods: The prospective multicentric screening in consecutive male patients between 35 and 65 years with implanted PM for acquired third- or second- degree type 2 AV block or symptomatic second- degree type 1 AV block or sinus node dysfunction was performed.

Results: A total of 484 patients (mean age 54 ± 12 years at time of PM implantation) were enrolled to the screening in 12 local sites in Czech Republic. Out of all patients, negative result was found in 481 (99%) subjects. In 3 cases, a *GLA* variant was found, classified as benign: p.Asp313Tyr, p.D313Y). Pathogenic *GLA* variants (classical or non-classical form) or variants of unclear significance were not detected.

Conclusion: The prevalence of pathogenic variants causing AFD in a general population sample with implanted permanent PM for AV conduction defects or sinus node dysfunction seems to be low. Our findings do not advocate a routine screening for AFD in all adult males with clinically significant bradycardia.

1. Introduction

Anderson-Fabry disease (AFD) (OMIM Number 301500) is an X-linked inherited lysosomal disease caused by pathogenic variants in the gene (*GLA*) encoding lysosomal enzyme α-galactosidase A (α-GAL A) [1]. The resulting absence or severe deficiency of enzymatic activity

Abbreviations: AFD, Anderson-Fabry disease; α-galA, α-galactosidase A; Gb_3, Globotriaosylceramide; lyso-Gb_3, Globotriaosylsphingosine; LVH, Left ventricular hypertrophy; HCM, Hypertrophic cardiomyopathy; AV, Atrio-ventricular; ERT, Enzyme replacement therapy; PM, Pacemaker; *GLA*, Gene encoding α-galactosidase A.

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leads to intracellular storage of glycosphingolipids, in particular globotriaosylceramide (Gb_3) and elevated levels of its deacylated form – globotriaosylsphingosine (lyso-Gb_3). Lysosomal sphingolipids accumulation can be detected in different organs and tissues.

The storage within the heart affects all types of cells including cardiomyocytes, conduction system tissue, vascular endothelial and smooth muscle cells, and valvular fibroblasts [2,3]. Cardiac involvement represents a major cause of premature morbidity and mortality in adult patients with AFD [4]. Left ventricular hypertrophy (LVH) is the most frequent and well-recognized cardiac manifestation in adults [2,3,5]. In some patients with AFD, isolated cardiac involvement may exist as exclusive LVH mimicking sarcomeric hypertrophic cardiomyopathy (HCM) [6]. Other frequent complications and changes in adult patients with AFD include atrial fibrillation, non-sustained ventricular tachycardia, QRS broadening, shortening of PR interval or conversely development of atrio-ventricular (AV) blocks, and sinus node dysfunction [7–13]. In addition, patients may develop mild to moderate valve insufficiencies, dilatation of the proximal aorta, arterial hypertension, and coronary artery disease [3,14–17].

Early identification of affected patients is of utmost importance as available specific treatment with enzyme replacement therapy (ERT) and pharmacological chaperone (migalastat) may slow down the disease progression and induce functional and structural improvements [4,18].

Several studies have reported pacemaker (PM) implantation for spontaneously occurring bradycardia, including sinus node disease or AV conduction defects, in 1–12% of AFD patients [10,11,13,19,20] with the annual implant rate 2.1% [11]. Recently, Vijapurapu et al. have shown that 42% of AFD patients with implantable cardiac electronic devices had pacemakers [21].

It is not elucidated if some AFD patients could manifest primarily with spontaneous, clinically significant bradycardia in absence of other signs of AFD-related cardiac involvement characterized mainly as HCM. The real prevalence of AFD as a primary cause of AV nodal conduction defects or sinus node dysfunction requiring PM implantation is also not clear. Therefore, we sought to examine the prevalence of AFD in a large cohort of patients with implanted permanent PM.

2. Methods

We performed a prospective nationwide multicentric screening of AFD in 493 consecutive male patients who had implanted PM for AV conduction defect or sinus node dysfunction up to age of 65 years. The screening protocol was conducted between May 2018 and December 2020. The study was performed according to good clinical practice and in compliance with the Helsinki declaration. An individual written consent was obtained from each patient. The study was approved by the local Ethics committee (Ethics Committee in General University Hospital in Prague) - No. 2072/17-S-IV.

2.1. Patient population

Men with implanted PM for sinus node dysfunction or acquired AV block aged between 35 and 65 years were eligible for inclusion. For purpose of the screening AV block means acquired third- or second-degree type 2 AV block with or without symptoms or symptomatic second-degree type 1 AV block. Patients with evidence of reversible cause of bradycardia or condition which is likely to be a complication of other disorder (i.e., acute coronary syndrome, sarcoidosis, borreliosis, cardiac surgery, congenital heart defect, etc.) were excluded from the study. Evidence of hypertrophic cardiomyopathy or known AFD were also set up as exclusion criteria. Both inclusion and exclusion criteria are listed in Table 1.

2.2. Screening of AFD

Cardiologist who had agreed to participate were asked to collect and report data on the patient's age, the exact indication for permanent pacemaker implantation, evidence of LVH on echocardiography (> 15 mm in any segment), family history of hypertrophic cardiomyopathy, family history of pacemaker implantation, any symptoms of AFD including angiokeratoma, acroparaesthesia, cornea verticillata, proteinuria or chronic kidney disease, history of stroke or transient ischemic attack.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Male gender
Implanted pacemaker for 3rd or second type 2 AV block or sinus node dysfunction
Age 35–65 years at pacemaker implantation
Exclusion criteria
Reversible cause of bradycardia
Known other aetiology of bradycardia
Hypertrophic cardiomyopathy
Diagnosed Anderson-Fabry disease

AFD was screened using dried blood spots in a stepwise manner combining enzyme testing, lysoGb$_3$ assessment and, if positive, sequencing of the *GLA* gene. Peripheral blood was drawn and transferred to commercially available filtration paper (CentoCard, CentoGene AG). Samples were allowed to dry at room temperature, stored in a plastic sleeve at room temperature for no more than one week until sent for analysis. All samples of patients were analyzed in the designated study laboratory CentoGene AG (Rostock, Germany). The distribution of CentoCard, their collection and shipment to CentoGene AG was supported by Shire/Takeda (Takeda Pharmaceutical Company Limited). The enzymatic activity of α-Gal-A and the concentration of the biomarker lyso-Gb_3 were determined using fluorimetry and liquid chromatography-mass spectrometry, respectively [22]. If the activity of α-Gal-A was decreased <15.3 μmol/l/h and/or the concentration of lysoGb$_3$ was increased >1.8 ng/ml, the *GLA* gene was sequenced. The *GLA* gene was analyzed next generation sequencing of the entire coding region, and the highly conserved exon-intron junctions (using reference sequence of the *GLA* gene was NM_000169.2). The result of AFD screening was reported to the referring physician. Patients with detected low α-GAL A enzyme activity or disclosed GLA variant (whatever pathogenic, of unknown significance or benign) were evaluated in the national referral centre for Fabry disease at General University Hospital in Prague.

2.3. Statistics

Data are expressed as the mean value ± SD for normally distributed variables or by median with interquartile range or as a number and percentage of subjects. All analyses were performed using the STATISTICA vers.12 software (Statsoft, Inc., Tulsa, USA).

3. Results

Altogether we have enrolled 493 patients fulfilling inclusion criteria in 12 local sites. Out of all screened patients, 9 (1.8%) males with missing data were excluded from the final survey. All excluded patients had negative screening of AFD. Final dataset included 484 patients. The proportion of patients enrolled in local sites is shown in supplementary material (S1 Table).

The baseline demographical and clinical characteristics are summarised in Table 2. According to the clinical questionnaire 32 (6.6%) of the patients had a potentially non-cardiac AFD manifestation such as renal insufficiency, proteinuria, stroke, or transitory ischemic attack history, acroparaesthesia or angiokeratomas. More details are given in Table 2. Sixty patients (12%) were screened at the time of PM implantation. The median time since PM implantation was 5.7 years (IQR 12 months to 11 years).

Table 2
Baseline clinical and demographical data.

Parameter	$N = 484$
Age at implantation (years)	54 ± 12
Indication for permanent pacing	
- 3rd degree AV block	191 (39%)
- 2nd degree type 2 AV block	101 (21%)
- Sinus node dysfunction	192 (40%)
LV hypertrophy	20 (4.1%)
Suspected HCM in family history / unclear evidence of HCM in family history	8 / 4 (1.7% / 0.8%)
Bradycardia in family history	73 (15%)
Angiokeratoma	1 (0.2%)
Acro-paraesthesia	9 (1.9%)
Neuropathic pain	3 (0.5%)
Anhidrosis / hypohidrosis	0 (0%) / 0 (0%)
Gastrointestinal problems (nausea, vomiting, abdominal pain, diarrhoea, constipation)	8 (1.6%)
Stroke / TIA	21 (4.3%) / 1 (0.2%)
Renal insufficiency (CKD stage 4 or 5) (total)	6 (1.2%)
Renal insufficiency (CKD stage 4 or 5) with proteinuria	2 (0.4%)
Coronary artery disease	10 (2.1%)

Data are expressed as mean ± SD or n (%).
AV – atrio-ventricular; LV – left ventricle; HCM – hypertrophic cardiomyopathy; TIA – transitory ischaemic attack; CKD – chronic kidney disease.

Out of these 484 patients, we identified 8 patients in whom AFD diagnosis was suspected based on α-Gal-A activity. Furthermore, one patient had normal α-Gal-A activity but elevated lyso-Gb_3 level. In these 9 patients, the *GLA* gene was sequenced. However, neither a pathogenic variant nor a variant of unknown significance was detected by the subsequent *GLA* gene sequencing. In 3 cases we identified a *GLA* variant classified as pseudodeficiency and considered as a benign variant (p. Asp313Tyr, p.D313Y) [23], Table 3.

The clinical profiles of patients with variant p.Asp313Tyr are listed in Table 4. Patients were implanted at 64, 47 and 59 years of age. Two of them reported family history of permanent PM implantation in relatives and two had LVH on echocardiography. Both patients with LVH also had a history of arterial hypertension and one had a severe aortic stenosis. One subject had documented non-sustained ventricular tachycardia on Holter ECG and one presented with episodes of atrial fibrillation.

4. Discussion

The prospective multicentric screening in almost 500 consecutive males with implanted permanent PM did not identify any pathogenic or of unknown significance variants in the *GLA* gene. Within the screened cohort we identified three patients carrying the p.Asp313Tyr variant.

The classical cardiac manifestation of AFD is usually characterized by progressive diffuse LVH with low frequency of LV outflow tract obstruction. Later stages are associated with inflammation, accelerated apoptosis and development of progressive myocardial replacement fibrosis affecting typically mid-wall layer of posterolateral basal LV segments and interstitial fibrosis, potentially also within the conduction system [2,11].

Table 3
Main results of screening.

Performed tests	493
Negative results (total)	490
Patients with complete data and results	484
Negative results in patients with complete data based on α-Gal-A and lyso-Gb3	481
Reduced α-Gal-A activity	8
Increased lyso-Gb3	1
Pathogenic variant within *GLA*	0
Variant of nuclear significance within *GLA*	0
Benign polymorphism (p.Asp313Ty)	3

Data are expressed as n.
α-Gal-A – α-galactosidase A; lyso-Gb3 – plasma globotriaosylsphingosine; *GLA* – gene encoding α-galactosidase A.

Table 4
Clinical profile of patients with (Asp313Ty).

	Patient # 1	Patient # 2	Patient # 3
Age at implantation (years)	64	47	59
Indication for permanent pacing	AV block 2nd degree	AV block 3rd degree	Sick sinus syndrome
Bradycardia in family history	YES	NO	YES
HCM in family history	NO	NO	NO
Arterial hypertension	YES	NO	YES
Diabetes mellitus	NO	NO	YES
Coronary artery disease	NO	NO	NO
Stroke / transient ischemic attack	NO	NO	NO
Atrial fibrillation	NO	NO	YES
Non-sustained ventricular tachycardia	NO	YES	NO
LV hypertrophy	YES	NO	YES
Interventricular septum in A4C (mm)	15	11	14
LV posterior wall in A4C (mm)	14	9	13
EF LV (%)	63	60	60
Other cardiac disease	NO	NO	Aortic stenosis
Renal insufficiency	NO	NO	NO
Proteinuria	NO	NO	NO
Plasmatic Alfa-galactosidase A (μmol/l/h)	14.8	14.2	14.6
Plasmatic globotriaosylsphingosine (ng/ml)	1.1	0.7	0.8

LV – left ventricle; HCM – hypertrophic cardiomyopathy; AV – atrio-ventricular; EF LV – ejection fraction of left ventricle; A4C – apical four chamber view.

Arrhythmias in AFD develop due to multiple reasons. A benign finding in patients with AFD is represented by a short PR interval caused both by AV conduction acceleration and P wave shortening (the finding usually does not represent a real pre-excitation). Subsequently, AV conduction worsens leading to AV blocks of different degrees [24]. AFD may also lead to bradycardia due to autonomic dysfunction associated with the disease itself and chronotropic incompetence potentiated by LV diastolic dysfunction compromising the ability of adequate heart rate increase during exertion. A proportion of patients may present with atrial fibrillation with slow heart rate.

A recent study showed that symptomatic sinus node dysfunction and/or atrial fibrillation-related bradycardia is an important reason for pacing occurring in 37% of those receiving pacemakers [21]. This observation is in agreement with another retrospective study of 204 patients with AFD from UK. In this dataset, the 5-year cumulative incidence of pacemaker implantation for spontaneously occurring bradycardia reached 12%, and 58% patients were implanted for sinus node disease while AV conduction defects lead to pacemaker implantation in a smaller remaining proportion of patients [11]. Recently, Vijapurapu et al. have shown that permanent pacemaker was used in 42% of all patients with AFD and implantable cardiac electronic devices. Indication for device implantation was sinus node dysfunction in 24% and third- or second- degree type 2 AV block in 24% or 26% of cases, respectively [10]. Some trials reporting pacemaker need in AFD show that pacing is more frequently needed in male patients and the rates are increasing with age. Other predictors include increased LV mass, borderline PR interval, and prolongation of QRS duration [11,13,21].

The current study was designed to assess whether screening for AFD in patients with unexplained bradycardia requiring implantation of permanent PM is relevant. The negative result of our screening is the most likely given by low prevalence of AFD in general population compared to common cardiovascular diseases leading to pacemaker need, including coronary artery disease, myocarditis, or electrolyte disorders [25]. The prevalence of AFD, based on large screening of male

new-borns, does not usually exceed 1:8000. However, many of the identified variants are not clearly pathogenic or cause a late-onset disease [26]. Moreover, acquired spontaneous bradycardia is not specific to AFD. Another reason that explains the negative result is the fact that bradycardia is usually a relatively late complication of AFD. Many of the implanted cases have an AFD diagnosis established before the implantation due to the presence of heart failure, significant LVH and other signs of AFD. In a recently published series of 82 AFD patients, bradycardia was never presenting symptom and always occurred in patients with full AFD phenotype [13]. We speculate that the age range of 35–65 years could have also limited the efficacy of the screening, enrolling many young patients with a low pre-test probability of having AFD. On the other hand, the rate of PM implantation in AFD patients is ~25 times higher than that observed in the general population [11] and 2,5% of AFD patients received anti-bradycardic pacing, mostly for AV block, prior to the diagnosis of AFD [11].

This study is not fully novel. Previous data, however, were not fully consistent and studies included slightly different patient populations. In a cohort of 188 individuals (66% males) with conduction abnormalities requiring PM implantation at <70 years of age, none were found to have AFD with genetic screening [27]. In different study, out of 531 male patients with implanted PM or cardioverter defibrillator at age between 30 and 76 years, *GLA* mutation (p.Ala143Thr) was identified in three cases [28]. The pathogenicity of the p.Ala143Thr missense variant has been questioned, although some studies reported a higher prevalence of p.Ala143Thr in AFD patients compared to frequency in general population and could be associated with a broad phenotype, oligosymptomatic cardiac or neurological presentations, and asymptomatic patients [29].

Our screening identified three patients with p.Asp313Tyr (p.D313Y) variant. Although this variant is considered as a pseudodeficiency and benign polymorphism [32] with a similar frequency of this variant in screened cohorts as in the general population [30], some investigations in the past suggested its potential association with cerebrovascular complications [30–32]. Such a result is not exceptional since the variant was frequently diagnosed in other high-risk populations for AFD (i.e., subjects with LVH, renal impairment, and neurological disorder) with an overall prevalence of up to 0.8% without a final confirmed diagnosis of AFD. Hence, such observations are not sufficient to prove the p. Asp313Tyr pathogenicity.

Our study further emphasize that careful consideration should be given to confirm or establish or in contrast rule out the pathogenicity of any identified *GLA* variant (37). All three patients with p.Asp313Tyr variant identified by our screening had an extensive cardiac involvement including LVH, atrial fibrillation, non-sustained ventricular tachycardia. However, we believe that p.Asp313Tyr did not play a causal role in the development of the bradycardia since all detected abnormalities are frequently observed in paced patients and could be explained by other conditions, such as arterial hypertension or aortic stenosis in particular. We cannot rule out other less common aetiology of bradycardia. It has been published, that among 32 patients with implanted PM for AV block or sick sinus syndrome of unknown aetiology in age < 55 years, 4 patients had pathogenic mutation in genes associated with channelopathies or cardiomyopathies and 6 had variants of uncertain significance [33]. In all three patients, an initial evaluation did not uncover other inherited conditions at the time of implantation.

Interestingly, 5 more patients manifested low level of α-GAL A activity without detection of *GLA* variant. That finding is in concordance with previously published data showing some low level of false positive results of DBS in detection of lysosomal storage disease [34].

Limitations

Our study has several limitations including absence of independent data monitoring. The screening was performed in male population with strict age limit at time of implantation. The reason for choosing only male patients was based on the fact that hemizygous males are usually more affected that heterozygous females, thus the chances for finding a positive case among paced patients is higher. The age limit was selected mainly because of a reduced life-expectancy of untreated FD males and the higher rates of degenerative AV node disease in older patients in the general population [35,36]. Even though patients with hypertrophic cardiomyopathy were not included to the study, 12 patients with suspected family history of hypertrophic cardiomyopathy were enrolled. The number of those patient was, however, low to make significant bias. The results cannot be expanded to a general population of patients with implanted PM.

5. Conclusion

Our data suggest that the prevalence of AFD in male patients requiring permanent pacing is very low and does not justify a systematic screening for AFD among those patients. AV conduction disorder or sinus node dysfunction are usually not among the first manifestations of AFD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.062.

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Declaration of Competing Interest

ZF and SH received the travel grants and speaker's honoraria from Takeda. GD received honoraria and travel funding from Sanofi Genzyme, Takeda, Protalix, and Greenovation Biotech GmbH. DG is a consultant for Amicus Therapeutics, Sanofi Genzyme, and Shire; has received research support from Sanofi Genzyme and Shire; and has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire. AL received consultancy honoraria from Amicus Therapeutics, Sanofi Genzyme, Takeda, and speaker's honoraria from Sanofi Genzyme and Takeda.

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