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CASE REPORT

Electrophysiological study in a patient with Fabry disease and a short PQ interval

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A short PQ interval is a common finding in patients with Fabry disease. However, there have been few electrophysiological studies in Fabry disease, and it is not clear whether the short PQ interval that is present in this disease results from preexcitation or enhanced atrioventricular nodal conduction. We present a case of a 43-year-old man with syncope, sick sinus syndrome, a PQ interval of 80 ms, and palpitations. Electrophysiological study showed PA, AH, and HV intervals of 24, 32, and 34 ms, respectively, and features of enhanced atrioventricular nodal conduction. The presence of an atrioventricular accessory pathway was excluded. We conclude that the short PQ interval in Fabry disease can result from accelerated conduction in the atrioventricular node.

Introduction

Fabry disease is a hereditary metabolic disorder resulting from mutation in the alpha-galactosidase A gene in chromosome X that leads to progressive intracellular accumulation of globotriaosylceramide (Gb_3). Deposits of Gb_3 can be found in all cardiac tissues, with its presence having been confirmed in the conduction system of the heart.[1] Most patients with Fabry disease exhibit ECG abnormalities,[2] including high QRS amplitude, prolonged QRS duration, T-wave inversion, ST-segment depression, atrioventricular (AV) blocks, features of sinus node dysfunction, and short PQ interval. Although most of these abnormalities can be explained by hypertrophy of the left ventricle and degenerative changes in the sinus node, AV node, His bundle, and Purkinje fibers, the aetiology of a short PQ interval is still confounded by contradictory clinical interpretations.

Since degenerative damage to the conduction system in Fabry disease leads to impaired AV conduction, a short PQ interval is probably an early and transitional phenomenon. In four cross-sectional studies involving 20–72 patients, the frequency of short PQ interval (≤ 120 ms) ranged from 21 to 40%.[3–6] Some authors have used the term 'preexcitation' for ECG changes in Fabry disease and have considered supraventricular tachycardias to be AV reciprocating tachycardias.[1,6,7] However, we are not aware of any reports of electrophysiological studies, let alone RF ablations, that

would confirm such an interpretation of the short PQ interval and arrhythmias that are present in Fabry disease. We have found four reports of electrophysiological studies investigating short PQ interval in this disease: two showing a short atrio-His (AH) interval,[8,9] and two showing a short His-ventricle (HV) interval as the reason for accelerated AV conduction.[6,10] None of these studies confirms the presence of a bypass tract. An explanation of the mechanisms that lead to the short PQ interval in Fabry disease could improve our understanding of the complex physiology of the AV junction.

Case report

The patient was a 43-year-old male who, 12 years previously, had been diagnosed as having hypertrophic cardiomyopathy. His diagnosis had been recently revised when Fabry disease was suspected on the basis of skin changes (angiokeratomas), and then confirmed with low alpha-galactosidase A activity (0.9 μkat/kg protein, normal range: 22–36 μkat/kg protein). Fabry disease was also subsequently recognized in his sister (44 years old, with a pacemaker implanted due to sick sinus syndrome) and her son (20 years old, asymptomatic). The patient was referred to our cardiology department of a university teaching hospital due to presyncopal episodes and palpitations. Resting ECG showed a very short PQ interval (80 ms) and features of left ventricular (LV) hypertrophy (*Figure 1*). Holter monitoring revealed a very irregular rhythm, due to sinus bradycardia with over 2000 sinus pauses (maximum 5195 ms), and episodes of a 2:1 sinoatrial block. Echocardiography confirmed the presence of prominent LV

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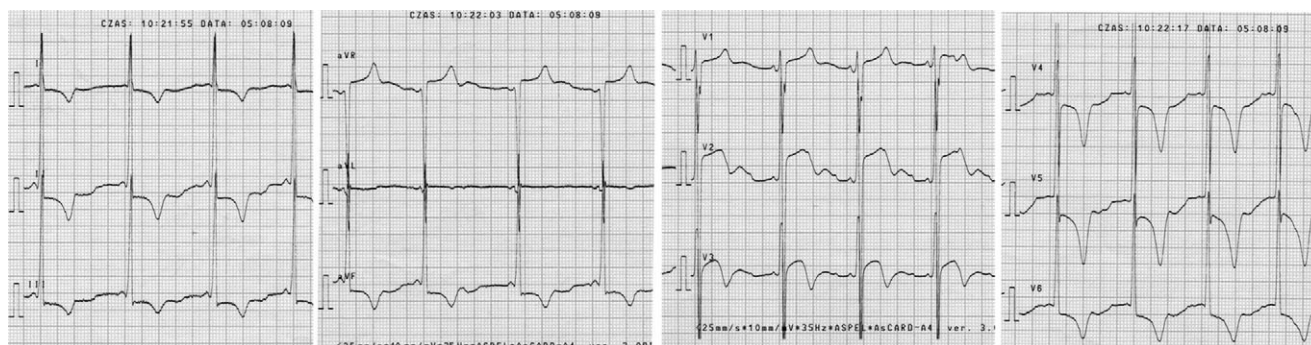*E-mail address*: mcjastrz@cyf-kr.edu.pl

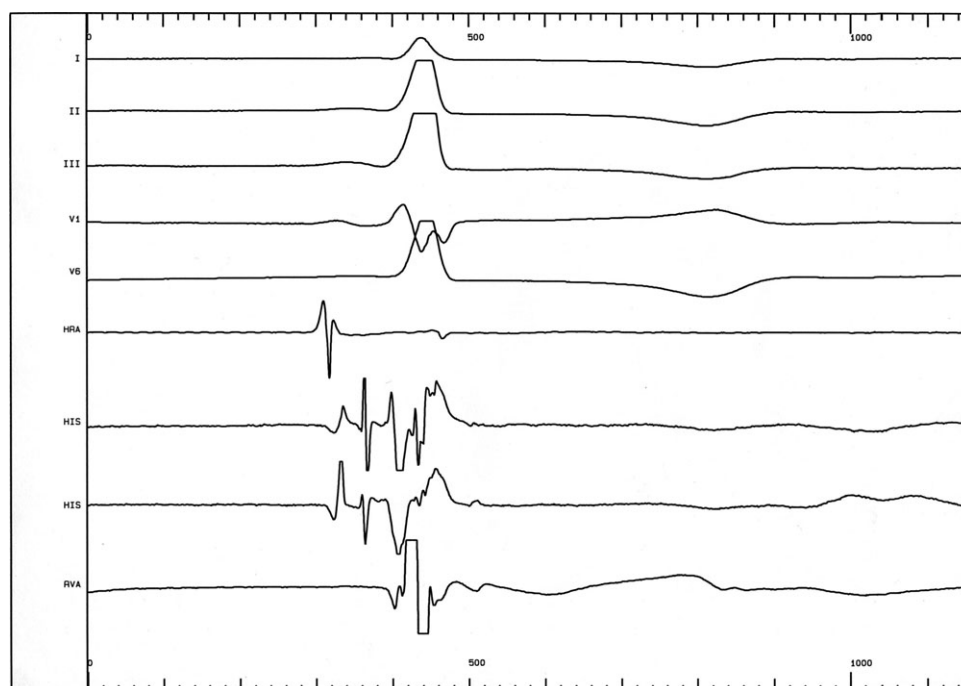**Figure 1** Resting 12-lead ECG. Paper speed: 25 mm/s.

Figure 2 Intracardiac recordings at baseline. Paper speed: 200 mm/s.

hypertrophy with good contractility (a diastolic interventricular septal thickness of 18 mm, a diastolic posterior wall thickness of 23 mm, and an LV ejection fraction of 80%). Apart from skin, heart, and eye (cornea verticillata) involvement, there were no other disease manifestations. Because of the history of palpitations and short PQ interval in the ECG, a formal electrophysiological study was requested before planned pacemaker implantation for sick sinus syndrome.

The electrophysiological study was performed with a BARD LabSystem Duo EP Laboratory (Bard, Lowell, MA, USA), Universal Heart Stimulator 20 (Biotronik, Berlin, Germany), and Cordis diagnostic catheters (Cordis-Webster, Diamond Bar, CA, USA). Quadripolar catheters were positioned in the high right atrium, His bundle area, and right ventricular apex, and a decapolar catheter was placed in the coronary sinus. Atrioventricular conduction times at a sinus rate of 60 bpm were 24, 32, and 34 ms for the PA, AH, and HV, respectively (*Figure 2*), with concentric ventricular activation. The incremental atrial pacing results were a Wenckebach point at 200 bpm with gradual AH interval prolongation (a maximal AH interval of 221 ms) and no

changes in the HV interval, QRS morphology, or ventricular activation pattern. The ventriculoatrial (VA) conduction was concentric and decremental (the VA interval increased from 142 ms to 178 ms). The retrograde Wenckebach point was not reached; at a rate of 240 bpm one-to-one VA conduction was still present. The parahisian pacing showed VA intervals of 90 and 150 ms with and without His capture, respectively. Programmed atrial and ventricular stimulation (up to three extrastimuli with several drive train cycle lengths, repeated during isoprenaline infusion) yielded no evidence of preexcitation or dual AV node physiology, and apart from non-sustained atrial flutter no arrhythmias were induced. The administration of adenosine (24 mg, bolus injection into the femoral vein) resulted in no AV block, no QRS morphology change, no HV change, and only a slight transient AH interval prolongation to 44 ms. Ajmaline administration (1 mg/kg body weight) resulted in a slight transient AH interval prolongation to 45 ms and HV prolongation to 42 ms. Neither sinus node recovery time nor sinoatrial conduction time were assessed due to many symptomatic sinus pauses of 6 to >10 s being observed

during the study. On the following day the patient received a DDDR pacemaker and bisoprolol (5 mg/day), and he remained asymptomatic at the 6-month follow-up.

Discussion

Progressive PQ interval shortening observed during a 3- to 12-year follow-up,[1,3,10] and its prompt reversibility, seen with substitution treatment with alpha-galactosidase A,[11,12] suggests that Gb$_3$ deposits, rather than a bypass tract, are responsible for fast atrioventricular conduction in Fabry disease.

In our patient, the short PQ interval of 80 ms was caused mainly by fast conduction at the level of AV node, resulting in a very short AH interval. Both atrial and ventricular activation was concentric with the earliest antegrade and retrograde activation at the His bundle catheter, and gradual AH interval prolongation during incremental atrial pacing without change in the HV or QRS morphology supports the presence of enhanced AV nodal conduction rather than an atrioventricular or atrio-His bypass. Moreover, very rapid VA conduction is considered to be more compatible with enhanced AV nodal conduction, rather than with an atrio-His bypass.[13] The negative results of paraHisian pacing also make the presence of a concealed septal AV bypass unlikely. The response to Ajmaline was also typical for fast conduction through the AV node rather than the presence of an atrio-His bypass. The absence of an AH bypass was also supported by the lack of changes in the HV interval and QRS morphology after Adenosine administration. However, it is notable that there was no AV block in response to the large bolus dose of Adenosine into a central vein. It may be that alteration of the electrophysiological properties of AV node tissue by intracellular deposits also influences the sensitivity to Adenosine. The lack of AV block in response to Adenosine has been reported in another storage disease presenting with LV hypertrophy and short PQ interval— the mutation in the gene for the γ_2 subunit of Adenosine monophosphate activated protein kinase (PRKAG2). This response was observed in patients with an AV bypass, as expected, and also in those without an AV bypass.[14]

There were many similarities between the results of our study and those of Pochis *et al.*[8] In both patients the presence of a bypass tract was not confirmed and features of enhanced AV nodal conduction were evident, and yet the AH interval prolongation during incremental atrial pacing was too large (i.e. >100 ms) to fulfill all the criteria for enhanced AV nodal conduction proposed by Gallagher. Another intriguing finding is the borderline short HV interval in both cases. Moreover, the sister of our patient who was also diagnosed as having Fabry disease and sick sinus syndrome showed a fixed HV interval of 30 ms without an AV bypass and with normal PQ and AH intervals. There are two other reports of a short HV interval in Fabry disease: one describes a patient with a fixed HV interval of 10 ms in the absence of a bypass tract, and the other describes a patient with an HV interval of 28 ms.[6,10] This suggests that acceleration of conduction in this disease also affects the distal conduction system. We consider that intracellular deposits and an increase in cell volume may lead to fast conduction due to the rearrangement of fibres and their connections in the area of the AV junction. This may also result in electrocardiographic and electrophysiological patterns that resemble those seen in enhanced AV nodal conduction or in an atrio-His or even a fasciculoventricular bypass.

There are a few other storage diseases that result from metabolic abnormalities in the glycogen pathway such as Pompe disease, Danon disease, and PRKAG2 mutation that show a similar clinical picture: LV hypertrophy with short a PQ interval and AV blocks. These diseases could share a common mechanism that leads to PQ interval shortening. An electrophysiological study in one case of Pompe disease showed a short AH interval with a normal HV interval as the reason for the short PQ interval.[15] In contrast, there are reports that idiosyncratic bypass tracts can be responsible for the preexcitation in Danon disease and in some cases of the PRKAG2 mutation.[14,16] However, the detailed electrophysiological findings in these patients were not reported.

Conclusion

Here we present the most detailed electrophysiological study in a case of Fabry disease with a short PQ interval reported so far. The results demonstrate that the short PQ interval in this disease can result from accelerated AV nodal conduction. This is consistent with published clinical data, and we believe that this is the dominant (if not the only) reason for the short PQ interval observed in Fabry disease. However, the scarcity of electrophysiological studies makes it impossible to rule out that other mechanisms leading to PQ interval shortening could be present in other patients with this disease.

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