High-degree atrioventricular block revealing hypertrophic cardiomyopathy related to a mutation in MYBPC3 gene

Bloc auriculo-ventriculaire de haut degré révélant une cardiomyopathie hypertrophique liée à une mutation du gène MYBPC3

Hypertrophic cardiomyopathy (HCM) is both the most common genetic cardiac disorder [1] and most common cause of sudden cardiac death in healthy young individuals. HCM is characterized by left ventricular (LV) hypertrophy in the absence of another cause for the increased cardiac mass [2]. The identification of patients who are at risk for sudden death remains an important challenge and emerging role of cardiovascular magnetic resonance imaging (MRI) for risk stratification is increasingly highlighted [2,3]. In most patients, sudden death is thought to be caused by ventricular arrhythmias, and implantable defibrillator has become the cornerstone in the management of high risk patient [2]. Although tachyarrhythmias are common in HCM, complete atrioventricular (AV) block is very rare [4-9]. In this observation, we describe unique features associated with an HCM related to a mutation in the myosin-binding protein C (MYBPC3) gene, revealed by minimally symptomatic high-degree AV block.

A 37-year-old male patient was referred to our arrhythmia department with a recent history of decrease in performance during exercise. Indeed, the patient had intensive sports activity practice of 50 miles running per week. The initial assessment by the referring cardiologist highlighted asymmetrical hypertrophy (interventricular septum 18 mm, posterior wall 11 mm); and 24-h Holter ECG documented asymptomatic diurnal episodes of 2nd degree Mobitz 1 and 2 AV block. The patient was then referred for further investigations. On further questioning, he only mentioned decrease in exercise performance since a few months, and also a decrease in exercise heart rate of ~20 beat/min recorded on a heart rate monitor while jogging. Neither personal history of presyncope and/or syncope nor family history of syncope or sudden death were noted. He was the latest in a family of 5 children. Physical examination was normal; blood pressure 130/70 mmHg and BMI 23 kg/m². There was a grade 1-2/6 systolic ejection murmur at the left sternal border. 12-lead ECG revealed a bi-fascicular block with complete right bundle branch block + left anterior fascicular block (QRS 170 msec), associated to 1st degree AV block with PR interval 250 msec (figure 1).

In 2-D echocardiographic examination, end-diastolic thickness of septum was 18 mm, posterior and lateral walls 10 mm, and apex 11 mm (e-component figure 1). There was no systolic anterior motion of the mitral valve and no LV outflow tract gradient was detected either at rest or during exercise. The Valsalva maneuver did not induce LV outflow tract obstruction. Mild mitral regurgitation was observed. The asymmetric LV hypertrophy was confirmed by cardiac MRI with a maximum end-diastolic septal, antero-basal and infero-basal wall thickness of 19 mm (figure 2a), with a marked nodular late gadolinium enhancement (LGE) in the same hypertrophied LV walls, as well as in the medio-ventricular side wall and bottom wall of the right ventricle (figure 2b).

Both telemetric monitoring and 24-h Holter ECG documented several episodes of 2nd degree Mobitz 1 and 2 AV blocks, along with few episodes of diurnal and nocturnal high-degree AV block, responsible for ventricular pauses of 3 to 5 second’s duration, all of them being asymptomatic. No episode of non-sustained ventricular tachycardia was recorded, and the systolic blood pressure response to exercise was normal. Electrophysiological study, indicated to localize the site of the block, showed a prolonged HV interval at 68 msec. Several episodes of both 2nd degree AV block of supra-His and infra-His levels were spontaneously recorded, sometimes successively (e-component figure 2).

A dual-chamber defibrillator was subsequently implanted, despite the absence of major risks factors for sudden death. Screening of others family members was negative. Further comprehensive assessment (biopsy of salivary glands, muscle biopsy and fundus) was normal. Exhaustive research of mitochondrial cytopathic, viral myocarditis, amyloidosis or laminopathy was negative. Genetic molecular analysis identified a causal heterozygous missense mutation (c.3358C>T, p. Arg1120Cys) in myosin-binding protein C gene (MYBPC3), while screening in β-myosin heavy chain (MYH7) and troponin T (TNNT2) genes was negative.

During follow-up, several episodes of non-sustained ventricular tachycardia were found in defibrillator monitors. Remote device monitoring was therefore activated. Due to the worsening of conduction disturbances leading to complete 3rd degree AV block with slow ventricular escape rate at 33 beat/min, the...
FIGURE 1
12-D ECG at admission showing bi-fascicular block pattern (complete right bundle branch + left anterior bundle branch block) with QRS duration of 170 msec associated to 1st degree AV block with PR duration of 250 msec

FIGURE 2
a: cardiovascular MRI in the axial and short-axis oblique projections showing asymmetric thickening of the left ventricular myocardium with market septal, antero-basal and infero-basal hypertrophy of 19 mm maximum; b: late gadolinium enhancement sequences in short-axis views showed extensive nodular enhancement in the same left ventricle segments suggestive of extensive fibrosis. Late gadolinium enhancement of medio-ventricular sidewall and bottom wall of right ventricular is also observed
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Discussion

HCM is a heterogeneous disease, in general caused by mutations in genes encoding cardiac sarcomeric proteins [2,10]. Although supraventricular and ventricular tachyarrhythmias are a common but manageable complication [2], AV block is a very rare finding [4-9]. As previously reported [8], and presently described, prolonged QRS duration and abnormal His-Purkinje system conduction may result in complete AV block. In previous reports, patients had paroxysmal syncopal or persistent complete AV block with resuscitated cardiac arrest, and a pacemaker was implanted in all of them, except one [9]. Fananapazir et al. demonstrated abnormal His-Purkinje conduction in 23% of HCM patients who survived sudden cardiac death [11], and Barriales-Villa et al. reported 3.5% of 451 HCM patients with 2nd or 3rd degree AV block [12]. This suggests that some patients may have syncope and sudden death related to complete AV block, or torsades de pointes following AV block [13]. As presently described however, sudden death, even in patients with AV block considered at low-risk, may also be caused by ventricular fibrillation. From this point of view, it is important to point out that our patient had none of the current recognized HCM risk markers. It would have make sense to consider a pacemaker rather than a defibrillator according to guidelines [2]. However, the utility of LGE for detecting myocardial fibrosis is well established: its prognostic value has been described and significant relationships with sudden cardiac death have been demonstrated [2,3]. In the present case, follow-up confirmed that assessment of LGE may have the potential to improve risk stratification in HCM. To the best of our knowledge, this is the first report of a rare association of AV conduction disease and ventricular fibrillation in a non-obstructive HCM patient.
The pathophysiology of AV block in human HCM is unknown. In human’s with complete AV block, it has been generally assumed that the wide escape-beat QRS complexes may be attributed to lesions in the distal portion of the AV bundle or bilateral lesions of the bundle branches, and that the narrow QRS complexes may be associated with lesions in the approaches to the AV node, in the AV node itself, or in the proximal portion of the AV bundle. The site of the block in the present case was both localized at supra- and infra-Hisian level, and it can be hypothesized an overall progressive degenerative and fibrotic changes of AV conduction pathways, as suggested by the marked LGE in the LV septal and antero-basal walls on cardiac MRI, indicative of fibrosis. The degenerative process may result in disrupitive lesions of the AV bundle and the beginning of the bundle branches. In our patient, not only did the large areas of fibrosis located within the interventricular septum constitute the electrophysiological substrate for ventricular fibrillation, but they also provoked extensive damage to the conduction system, eventually leading to high-degree AV block. This mechanical hypothesis is supported by animal studies. Indeed, Kaneshige et al. examined histologically the cardiac conduction system of 13 HCM feline with complete AV block [14]. Marked degeneration and fibrous replacement of the AV conduction system were consistently observed in the combined regions of the branching portion of AV bundle and the upper portion of the left bundle branch. These changes were associated with extensive fibrosis of the central fibrous body and endocardial and myocardial fibrosis in the upper border of the ventricular septum. The assumption of genetics, which is increasingly associated with occurrence of some type of conduction disturbances, can also be mentioned despite the fact that no specific mutation concerning AV block was identified in a study on the genetics of HCM [15].

Disclosure of interest: The authors declare that they have no competing interest.

Supplementary data
Supplementary data associated with this article can be found, in the online version, at: https://doi.org/10.1016/j.lpm.2018.11.012.

References


