Human Pathology (2013) **44**, 133–141

ELSEVIER

Human PATHOLOGY

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Original contribution

Diagnostic contribution of left ventricular endomyocardial biopsy in patients with clinical phenotype of hypertrophic cardiomyopathy☆,☆☆

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Received 25 January 2012; revised 19 April 2012; accepted 20 April 2012

Keywords:
Endomyocardial biopsy;
Hypertrophic cardiomyopathy;
Infiltrative diseases;
Left ventricular hypertrophy;
Storage diseases

Summary Hypertrophic cardiomyopathy phenotype is shared by heterogeneous entities. The purpose of the study was to evaluate the diagnostic role of left ventricular endomyocardial biopsy. One hundred fifty-one consecutive patients with unexplained left ventricular hypertrophy and normal/elevated QRS voltages or left bundle-branch block underwent left ventricular endomyocardial biopsy because of associated left ventricular dysfunction (37%), presence of sporadic form of left ventricular hypertrophy (32%), or patient desire for a definite diagnosis (31%). Biopsy samples were processed for histology and electron microscopy. Blood samples were collected for histologically oriented gene analysis of major sarcomeric (*MYH7*, *MYBPC3*, *TNNT2*, *TPM1*) and lysosomal (*LAMP2*, *PRKAG2*, α-galactosidase A) proteins. Histology showed changes consistent/compatible with hypertrophic cardiomyopathy in 124 patients: myocardial storage disease in 18 due to Fabry disease in 12 and glycogen-storage disease in 6 and myocardial infiltrative disease in 9 because of amyloidosis in 7 and sarcoidosis in 2. Gene analysis was positive in 67% of patients with hypertrophic cardiomyopathy (*MYH7* mutation in 36, *MYBP* in 29, *TNNT2* in 14, and *TPM1* in 5) and in 83% of patients with lysosomal storage disease (α-galactosidase A mutation in 12, *PRKAG2* in 2, and *LAMP2* in 1). In patients with hypertrophic cardiomyopathy phenotype, left ventricular endomyocardial biopsy is safe and may recognize infiltrative/storage diseases in up to 18% of evolving and sporadic cases.

1. Introduction

There is increasing evidence that the clinical profile of hypertrophic cardiomyopathy (HCM) may include heterogeneous entities with different treatment options and prognosis [1,2]. These include various mutations of sarcomeric proteins [3] as well as several types of storage and infiltrative heart muscle diseases [4-7]. Particularly for Fabry disease and glycogen storage disease due to *LAMP2*

☆ Funding sources: This work was supported by the Telethon grant no. GGP08167, grant no. RF-2009-1511346, and grant no. RBFR081CCS from the Italian Ministry of Health.

☆☆ Disclosures: There are no conflicts of interest related to the article.

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http://dx.doi.org/10.1016/j.humpath.2012.04.023

and *PRKG2* gene mutation, the clinical manifestation may be confined to the heart and have similarities to the sarcomeric form of HCM. However, the findings of left ventricular hypertrophy (LVH) with the imaging tools available do not provide specific diagnosis and require additional investigations.

In this context, imaging techniques such as 2-dimensional echocardiography [8] and cardiac magnetic resonance [9] can provide useful hints; however, the findings these tools provide are not yet specific enough to not require additional investigations. A possible diagnostic option can be genetic screening that combines gene analysis of sarcomeric proteins with that of major lysosomal enzymes [10]. This approach is, however, expensive, time consuming, and necessarily limited to some predefined entities. On the other hand, prompt recognition of specific myocardial disorders responsible of LVH is crucial because the affected subjects may benefit from a personalized treatment, including enzyme replacement therapy, steroids, and immunosuppressive or alkylating agents [11,12]. In this setting, the role of endomyocardial biopsy has been recently evaluated by both European and American Societies of Cardiology [13], and indication for its use has been restricted to patients with HCM and heart failure where the suspicion of a storage/infiltrative disease is consistent and noninvasive tests are inconclusive.

The present study reports the histologic findings of a large series of patients with clinical phenotype of HCM submitted over a 20-year period for left ventricular (LV) endomyocardial biopsy.

2. Materials and methods

2.1. Patient population

From January 1989 to December 2008, 151 consecutive patients (97 male, 54 female; mean age, 44.2 ± 15.9 years) with a diagnosis of HCM were submitted to cardiac catheterization, coronary angiography, LV angiography, and LV endomyocardial biopsy. The diagnosis of HCM was based on the presence of unexplained and pronounced LVH (maximal wall thickness ≥ 15 mm as defined by echocardiography) and normal/elevated QRS voltages or left bundle-branch block. Part of the patient population was included in a previously published study [14]. Patterns of hypertrophy were defined in accordance with previously published methods [15].

The indication to perform an endomyocardial biopsy study was essentially based on acute clinical deterioration (37%), an unhelpful family history (sporadic disease, relatives unapproachable or dead) (32%), and the patient's request to have a definite disease diagnosis (31%) because there were familial cases of sudden death and no evidence of liver, renal, or skeletal muscle damage nor skin lesions or corneal opacities. Our institution is a tertiary referral center dedicated to the study of different types of heart muscle diseases including HCM in adults.

2.2. Cardiac magnetic resonance imaging

Beginning in 2000, all patients underwent cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement [14]. End-diastolic volume, end-systolic volume, stroke volume, and LV ejection fraction (LVEF) were calculated. The volume of hyperenhanced tissue was also calculated on short-axis images.

2.3. Cardiac catheterization and endomyocardial biopsy

All invasive studies were performed after patient written informed consent and approval by the ethical committee of our institution. All patients were submitted to cardiac catheterization, coronary and LV angiography, and endomyocardial biopsy. Pretreatment with aspirin 0.8 g twice a day in the 24 hours preceding the study was adopted to avoid biopsy-related systemic embolization.

Biopsies were performed in the septal-apical region of the LV, drawing 6 or 8 samples per patient. Myocardial specimens were processed for histology, electron microscopy, and molecular biology. Control angiography was obtained soon after biopsy to rule out possible damage of LV wall. Blood samples were drawn at the end of catheterization for genetic screening and immunologic/serologic studies.

2.4. Histologic and ultrastructural studies

Five-micrometer-thick sections from paraffin-embedded blocks were stained with hematoxylin-eosin, Miller elastic Van Gieson, and Masson trichrome and examined by light microscopy. Sections from frozen samples were stained with periodic acid–Schiff (PAS) and Sudan black for assessment of glycolipid storage material. For ultrastructural evaluation, glutaraldehyde-fixed samples were embedded in an Epon resin. Additional stainings, such as Congo red and Pearl's, were performed when an infiltrative disease was suspected. In cases of Congo red positivity, immunohistochemical typing of amyloid protein was performed. Immunohistochemistry for the characterization of inflammatory infiltrates was carried out as previously described [16]. The diagnosis of myocarditis was established in the presence of inflammatory infiltrates (≥ 14 leucocytes or >7 CD3+ cells/mm^2) associated with necrosis of the adjacent myocytes, in accord with the Dallas criteria. Extent of fibrous tissue and of myocyte disarray was evaluated by means of a computer-assisted image analyzer, using the Lucia G software (version 4.82; Nikon, Tokyo, Japan).

2.5. Screening of myocardial specimens for viral genomes

Two frozen myocardial specimens from each patient with histologic evidence of myocarditis were used for polymerase

chain reaction (PCR) and reverse transcriptase PCR analysis as previously described [17]. Ten primer pairs were used to detect cardiotropic virus DNA and RNA. The purified PCR products were sequenced directly on an automated ABI Model 310 A sequencer (Applied Biosystems, Carlsbad, CA). Blood samples of patients whose myocardium was infected by a viral agent were analyzed by PCR for the presence of the same virus.

2.6. Genetic studies

Genomic DNA was isolated from peripheral blood lymphocytes using the QIAmp DNA Mini kit (Qiagen, Hilden, Germany). We analyzed the coding regions and the exon-intron boundaries of the *MYH7*, *MYBPC3*, *TNNT2*, and *TPM1* genes in patients with histologic evidence of HCM; the *PRKG2* and *LAMP2* genes in patients with glycogen-storage disease; and the α-galactosidase A gene in patients with glycosphyngolipid deposits as previously described [18].

2.7. Statistical analysis

Categorical data were presented as absolute frequencies and percent values, and quantitative measurements, as mean ± SD. The 4 groups of patients were compared by Kruskal-Wallis analysis of variance for the quantitative variables. The categorical variables among groups were compared by the χ^2 test. $P \leq .05$ was considered statistically significant.

3. Results

Clinical, echocardiographic, and histologic data of the patient population and their correlations are reported in Table 1. Electrocardiographic, echocardiographic, cardiac magnetic resonance, and histopathology images are shown in Figs. 1, 2, and 3.

3.1. Cardiac magnetic resonance imaging

Cardiac magnetic resonance was performed in 73 patients (48%) and confirmed the LV morphological and functional data observed at echocardiography. No specific cardiac signals distinguishing HCM from infiltrative or storage diseases were observed. Gadolinium contrast enhancement showed the presence of late enhancement in 43 patients (59%). Focal late enhancement areas were variably localized in the LV wall, but the patterns observed were not sufficiently specific to provide a definite diagnosis of the underlying disease.

3.2. Cardiac catheterization and endomyocardial biopsy

Cardiac catheterization showed normal coronary arteries in all patients. Systolic function was normal or hyperkinetic in 63% of the cases and hypokinetic (LVEF <50%) in 37% of them. LV endomyocardial biopsy was normally well tolerated; a major complication was registered in 1 patient (0.6%), consisting of transient headache and visual disturbances, interpreted as brain microembolization that disappeared within 2 hours after rapid mannitol infusion (200 mL in 15 minutes). No bleeding complications related to the high-dose aspirin pretreatment were reported.

3.3. Histology, electron microscopy, and molecular biology

Severe hypertrophy (up to 60 μm in diameter) of myocardiocytes associated with some perinuclear halo and replacement fibrosis was observed in 124 (82%) of 151 patients studied, and in 58.5% of them, myocyte disarray was also evident. These pathologic changes were suggestive of HCM. In these patients, some wall thickening of intramural arterioles was commonly reported and was particularly pronounced and associated with lumen narrowing in many subjects manifesting chest pain. Among the 124 patients with HCM, 51 had a reduced LV contractility. Remarkably, 28 of the 51 and 12 of the 18 studied because of ventricular tachycardia had histologic evidence of active lymphocytic myocarditis with less than 7 CD3+ inflammatory cells/mm^2 of myocardial tissue, focally associated with necrosis of the adjacent myocytes.

In 50% of patients with HCM/myocarditis, a viral genome (enterovirus in 3, adenovirus in 5, influenza A virus in 3, Epstein-Barr virus in 2, hepatitis C in 1) was identified by PCR of frozen endomyocardial samples. In 18 patients, myocardiocytes were hypertrophied but regularly arranged, containing large intracytoplasmic vacuoles, which were PAS and Sudan black positive in 12 patients and PAS positive in 6. Electron microscopy showed that these vacuoles consisted of single-membrane-bound myelin bodies, suggesting glycosphyngolipid accumulation in the first instance, and of huge areas of cytosolic glycogen sometimes surrounded by a double membrane (autophagosomes) in the second case. These findings were highly suggestive for Fabry disease and glycogen storage disease, respectively. Notably, the patient with brain embolism at LV endomyocardial biopsy, despite pretreatment with antiplatelet drugs, had histology of Fabry disease.

In 7 patients, myocytes showed cell atrophy and a remarkable increase in fibrous tissue as well as of an interstitial apple-green substance under polarized light after Congo red staining consistent with amyloid deposition. Amyloid was often observed around and inside vessel walls, sometimes contributing to lumen narrowing. Amyloid was confirmed by immunohistochemistry, which was positive for κ or λ light chain (AL type) in 6 cases and transthyretin in 1. Finally, in the last 2 patients, the major histologic changes were those of granulomatous infiltrates with some epithelioid and giant cells suggestive of myocardial sarcoidosis.

Table 1 Clinical/echocardiographic data of patient population compared with the histologic substrate denoting HCM, glycogen, or glycolipid storage disease, and infiltrative myocardial disease

Variables	Total (n = 151)	HCM (n = 124)	GSD (n = 6)	GLSD (n = 12)	IMD (n = 9)	*P*
Age (y), mean ± SD	44.2 ± 15.9	41.4 ± 12.3	26.0 ± 13.8	43.5 ± 7.47	49.2 ± 5.11	.003
Sex, n (%)						.206
Male	91 (60.2)	76 (61.2)	2 (33.4)	8 (83.3)	5 (55.5)	
Female	60 (39.7)	48 (38.8)	4 (66.6)	4 (16.7)	4 (44.5)	
Age at onset of symptoms (y), mean ± SD	25.4 ± 10.5	22.8 ± 7.7	21.8 ± 13.8	40.7 ± 5.38	47.5 ± 7.7	<.001
FH HCM, n (%)						.004
Yes	92 (60.9)	76 (61.3)	5 (83.4)	10 (83.4)	1 (11)	
FH SCD, n (%)						.018
Yes	26 (17.2)	23 (18.2)	4 (67)	1 (8.3)	1 (11)	
FH PHF, n (%)						<.001
Yes	13 (8.6)	6 (4.8)	2 (33)	4 (33)	1 (11)	
NYHA functional class, n (%)						<.001
I	55 (36.4)	53 (42.4)	1 (16.6)	1 (8.3)	0 (0.0)	
II	54 (35.8)	42 (33.8)	4 (66.6)	7 (58.3)	1 (11.1)	
III	37 (24.5)	27 (21.8)	1 (16.6)	3 (25.0)	6 (66.7)	
IV	5 (3.3)	2 (1.6)	0 (0.0)	1 (8.3)	2 (22.2)	
ECG changes, n (%)						<.001
Increased ECG voltages	132 (87.4)	116 (93.5)	4 (66.6)	12 (100)	0 (0)	
Normal ECG voltages	8 (5.3)	3 (2.4)	2 (33.3)	0 (0)	3 (33.3)	
Left bundle-branch block	11 (7.3)	5 (4.0)	0 (0)	0 (0)	6 (66.6)	
Ventricular arrhythmias, n (%)						.008
Lown grade 03	101 (66.8)	86 (69.4)	0 (0.0)	8 (66.7)	7 (78)	
Lown grade 4a	24 (15.9)	16 (12.9)	4 (66.7)	3 (25.0)	1 (11)	
Lown grade 4b	26 (17.2)	22 (17.7)	2 (33.3)	1 (8.3)	1 (11)	
Atrial fibrillation, n (%)						.264
Yes	27 (17.8)	19 (15.3)	1 (16.7)	4 (33.3)	3 (33.3)	
Maximal wall thickness, mean ± SD	23.5 ± 5.6	24.5 ± 5.8	22. 0 ± 6.7	21. 9 ± 5.9	23.8 ± 5.6	.382
Pattern of hypertrophy, n (%)						<.001
Asymmetric septal	96 (63.5)	89 (71.8)	1 (16.6)	5 (41.7)	1 (16.6)	
Concentric	50 (33.1)	31 (25.0)	5 (83.4)	6 (50.0)	8 (83.4)	
Apical	5 (3.3)	4 (3.2)	0 (0.0)	1 (8.3)	0 (0.0)	
LV EDD (mm), mean ± SD	41.8 ± 6.8	41.2 ± 6.0	41.8 ± 7.5	42.6 ± 4.3	40.1 ± 4.6	.792
LV ESD (mm), mean ± SD	22.8 ± 5.4	21.9 ± 6.2	22.1 ± 8.3	19.4 ± 3.2	22.3 ± 3.6	.571
LVEF (%), mean ± SD	61.2 ± 11.4	61.7 ± 10.4	60.0 ± 6.0	60.8 ± 6.1	61.4 ± 5.1	.969
Fractional shortening (%), mean ± SD	46.8 ± 7.7	47.3 ± 7.5	46.4 ± 7.8	46.0 ± 4.4	45.4 ± 4.9	.819
LA maximal volume (mL), mean ± SD	79.0 ± 19.6	78.0 ± 18.7	77.1 ± 14.0	76.4 ± 12.4	82.4 ± 19.1	.889
Mitral regurgitation, n (%)						.012
Absent	104 (68.8)	92 (74.2)	3 (49.9)	6 (50.0)	3 (33.3)	
Mild	28 (18.5)	16 (12.9)	2 (33.3)	5 (41.7)	5 (55.6)	
Moderate	19 (12.5)	16 (12.9)	1 (16.6)	1 (8.3)	1 (11.1)	
β-Blockers, n (%)						<.001
Yes	94 (62.2)	92 (74.2)	1 (16.6)	1 (8.3)	0 (0.0)	
Verapamil, n (%)						.009
Yes	52 (34.4)	50 (40.3)	0 (0.0)	2 (16.6)	0 (0.0)	
Amiodarone, n (%)						.004
Yes	46 (90.1)	31 (25.0)	5 (83.4)	5 (41.6)	5 (55.5)	
ACE inhibitors, n (%)						<.0001
Yes	34 (22.5)	18 (14.5)	5 (83.4)	5 (41.6)	6 (66.7)	
Diuretics, n (%)						<.0001
Yes	44 (29.1)	25 (20.1)	4 (66.7)	8 (66.7)	7 (77.8)	

Table 1 (*continued*)

Variables	Total (n = 151)	HCM (n = 124)	GSD (n = 6)	GLSD (n = 12)	IMD (n = 9)	*P*
Enzyme replacement therapy, n (%)						<.0001
Yes	12 (7.9)	0 (0.0)	0 (0.0)	12 (100)	0 (0.0)	
Steroids/alkylating agents, n (%)						<.0001
Yes	9 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (100)	

Abbreviations: GSD, glycogen; GLSD, glycolipid storage disease; IMD, infiltrative myocardial disease; FH, family history; SCD, sudden cardiac death; PHF, premature heart failure; NYHA, New York Heart Association; EDD, end-diastolic diameter; ESD, end-systolic diameter.
NOTE. *P* value refers to comparison among the 4 groups. For the quantitative variables, it refers to the Kruskal-Wallis analysis of variance; for the categorical variables, the χ^2 test.

3.4. Genetic studies

Gene mutations known to be associated with HCM, including 5 new genetic defects previously reported by the authors [18], were identified in 84 (67%) of 124 patients with a definite histologic diagnosis of HCM. In particular, mutations in the *MYH7* gene have been identified in 36 patients, in the *MYBP* gene in 29 cases, in the *TNNT2* gene in 14 subjects, and in the *TPM1* gene in 5. In the 12 patients with glycosphyngolipid storage disease, mutations of the α-galactosidase A gene was always detected, with a high prevalence (5 patients) of N215S. In the 6 patients with glycogen storage disease, sequencing analysis of the *LAMP2* and *PRKG2* genes was positive in only 3 cases, with mutation in the first gene for 1 patient and in the second for 2.

3.5. Therapeutic considerations

A specific treatment consisting of enzyme replacement therapy in patients with Fabry disease and of steroids and/or alkylating agents in patients with AL type amyloidosis or sarcoidosis was possible in 20 (74%) of 27 patients found to be affected by storage or infiltrative myocardial diseases.

4. Discussion

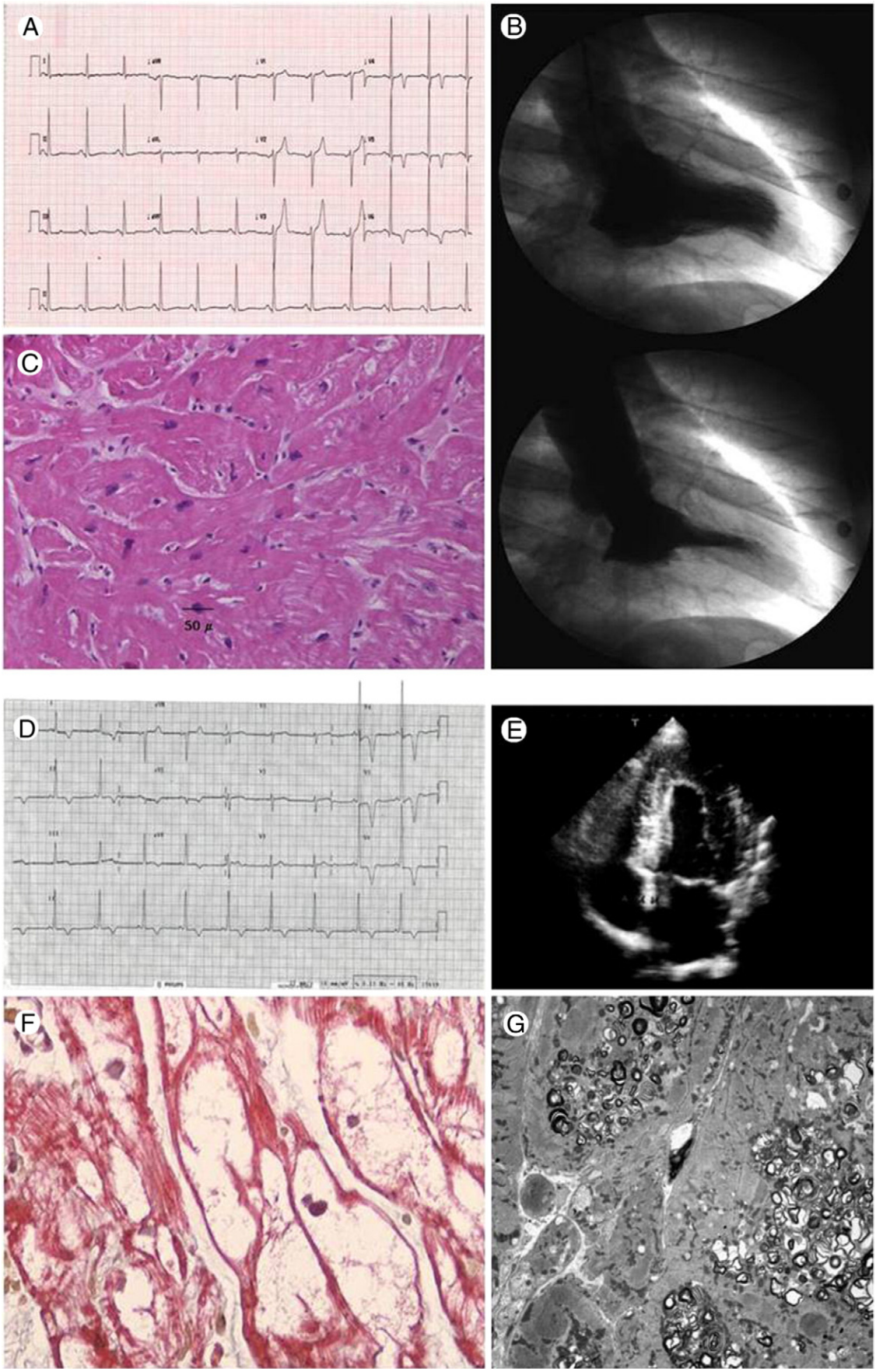
Real prevalence of specific myocardial diseases in patients presenting with HCM phenotype is actually unknown because of the limited diagnostic impact of imaging techniques, the incomplete knowledge of all genes giving rise to LVH, and the occurrence of infiltrative and storage diseases mimicking HCM. In particular, both echocardiography and cardiac MRI with late gadolinium enhancement can recognize signals of tissue damage, but the patterns obtained are not sufficiently specific to provide a definite diagnosis of myocardial disease. Gene analysis can miss up to 50% of HCM patients as well as the cardiac variant of both glycogenosis (specifically due to *LAMP2* and *PRKAG2* gene mutation) and Fabry disease. The infiltrative diseases of the myocardium may coexist with preserved systolic function and normal electrocardiographic (ECG) voltages. In addition, the presence of left bundle-branch block may hinder the recognition of the expanded interstitial space that, in patients with normal intraventricular conduction, results in low ECG voltages.

A systematic biopsy study on this syndrome has not been provided so far because of the assumption of the rare incidence of specific entities and of the inability to provide alternative therapeutic measures in opposition to the possible risks deriving from an invasive procedure. The present study reports the investigational results of LV endomyocardial biopsy in a large series of patients with unexplained LVH suggestive of HCM because of pronounced ECG voltages and LV mass. The invasive study was often prompted by peripheral centers because of impaired LV function (37%), a sporadic form of the disease (32%), or subjects with a family history of sudden death requiring a definite histologic assessment of their disorder (31%).

This study offers possible insights on the different entities that may lead to the HCM phenotype, the limits of actual imaging techniques, and the necessity to consider alternative diagnostic strategies including expanded genetic studies and ultimately LV endomyocardial biopsy.

LV endomyocardial biopsy has been preferred to right ventricle endomyocardial biopsy to obtain the best chances to investigate the site of cardiac hypertrophy and to overcome the misleading disarray of the cardiomyocytes linked to the spatial organization of right ventricle trabeculations. In this regard, diagnostic cardiomyocyte disarray was observed in 58.5% of patients, suggesting the ability of LV endomyocardial biopsy to pick up biopsy material from the middle LV layer where characteristic changes are usually located in HCM.

Unexpectedly, a storage or an infiltrative myocardial disease was observed in 18% of study population, and for 74% of them, a specific treatment consisting of enzyme replacement therapy (for Fabry disease) or a steroid/alkylating therapy (for AL amyloidosis and sarcoidosis) could be identified. Remarkably, no systemic evidence of the disease could be recognized in the storage disease cohort because the cardiac variant of Fabry disease often associated with the N215S mutation of α-galactosidase A [19,20] as well as glycogen cardiomyopathy due to mutation of *LAMP2* or *PRKAG2* genes can provide clinical manifestations confined to the heart [3,4]. As far as cardiac amyloidosis is concerned, ECG voltages were misleadingly normal or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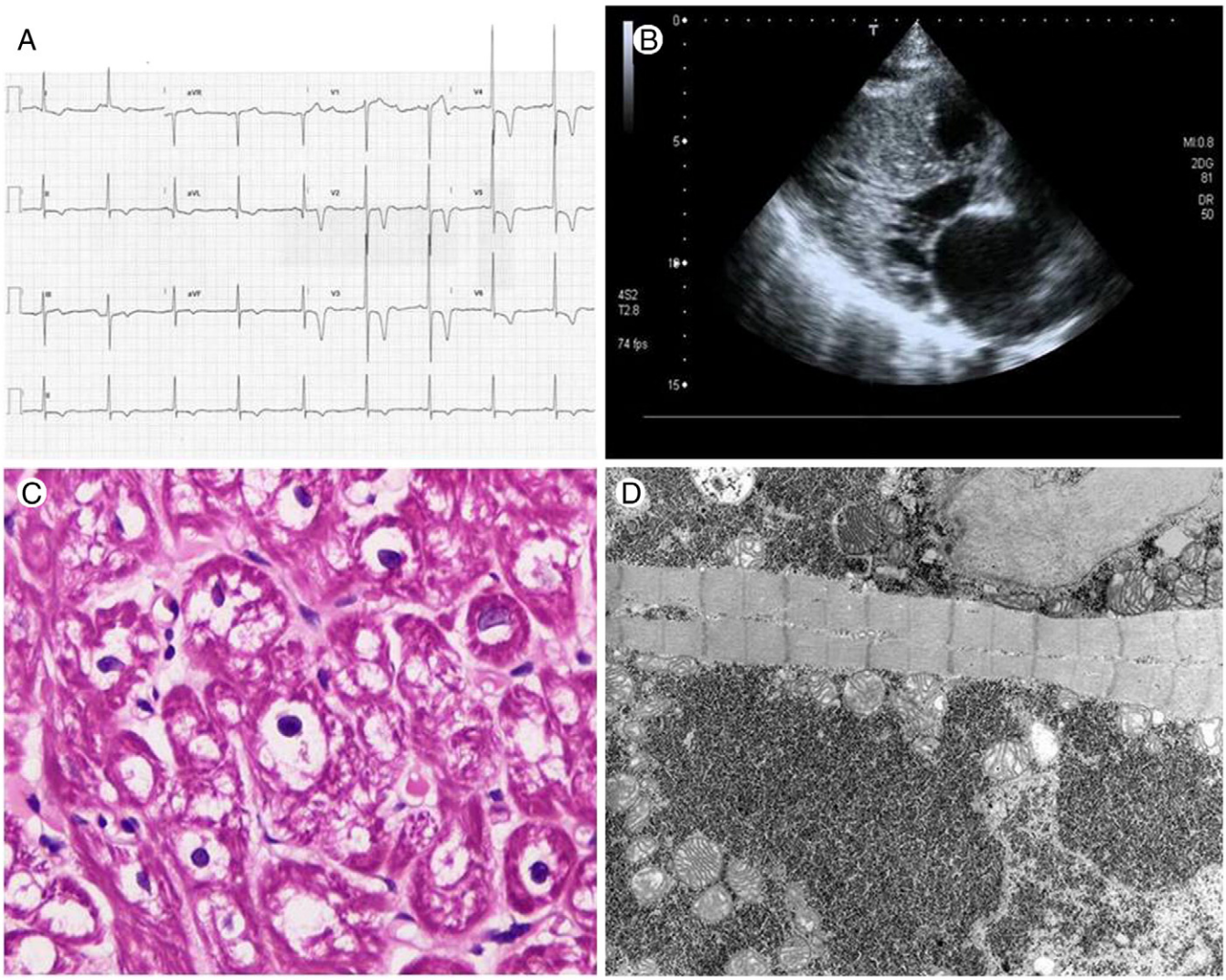

Fig. 2 Cardiac glycogenosis. Increased ECG voltages (A) and massive LVH (B, echocardiographic LV long-axis view) secondary to huge intracytoplasmic vacuoles (C, hematoxylin and eosin; original magnification ×200) containing large cytosolic areas of glycogen accumulation (D, transmission electron microscopy) in a female, 27-year-old patient affected by cardiac glycogenosis.

with left bundle-branch block, whereas the immunologic studies were elusive, reporting κ or λ monoclonal light chains in the urine sediment after cardiac histologic indications or mutated transthyretin produced by liver in a familial form of cardiac amyloid.

No distinctive clinical and/or echocardiographic/MRI findings could be established among the various histologic forms of LVH, although Fabry disease and infiltrative myocardial disease tended to have a late (>35 years) manifestation, whereas glycogen storage disease typically manifested an early expression (often before 20 years) [21,22].

In terms of procedural risks, LV endomyocardial biopsy had a low rate (0.6%) of transient complications, consisting of brain microembolism promptly resolved by mannitol infusion. In general, systemic embolism was prevented by 24 hours of pretreatment with high-dose aspirin, and notably, the case reporting cerebral ischemia was affected by Fabry disease, where endocardial fat deposition in addition to recognized platelet hyperactivity could have overcome the aspirin effect.

Finally, a positive genetic screening although histologically oriented was obtained in 100% of patients with

Fig. 1 Comparison between Fabry disease and HCM. Increased ECG voltages (A) and LV mass (B, angiographic LV diastolic and systolic view) in a patient (male, 33 years old) with severe hypertrophy and disarray of cardiomyocytes (C, hematoxylin and eosin staining) consistent with a diagnosis of HCM. Similar high QRS voltages (D) and LV mass (E, echocardiographic LV apical 4-chamber view) are evident in a 35-year-old male patient with Fabry disease (α-galactosidase A gene mutation N215S). At histology and electron microscopy, regularly arranged, large, and vacuolated cardiomyocytes (F, Masson trichrome; original magnification ×200) because of glycosphyngolipid accumulation (G, transmission electron microscopy) are evident.

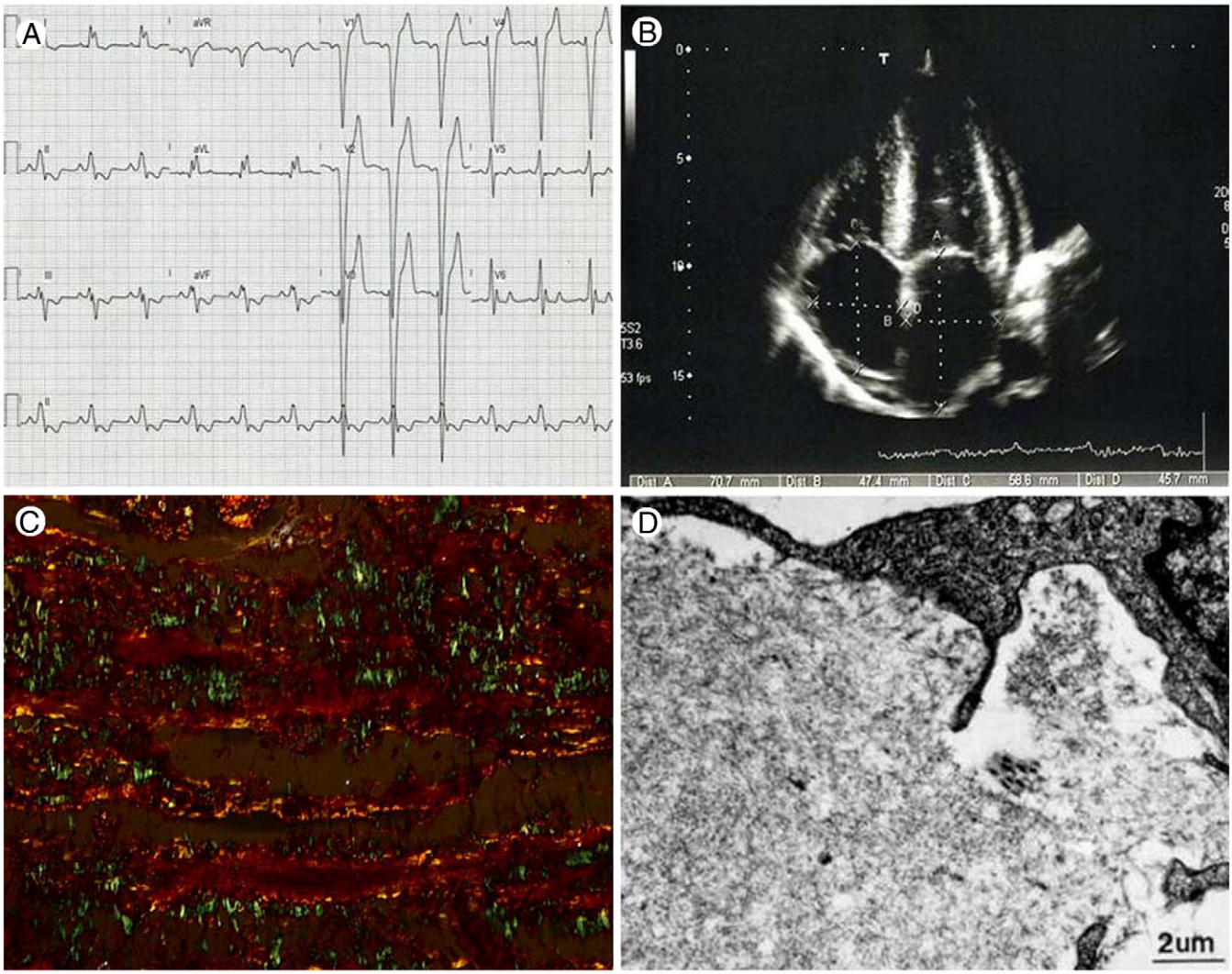

Fig. 3 Cardiac amyloidosis. Patient with left bundle-branch block (A) and LVH (B, echocardiographic LV apical 4-chamber view) due to interstitial accumulation of an apple-green birefringent material after Congo red staining (C) consisting of large deposits of β-fibrils (D, transmission electron microscopy), suggestive of cardiac amyloidosis.

Fabry disease but in only 67% of the HCM cohort and 50% of subjects with glycogen cardiomyopathy, suggesting that the gene approach can miss a consistent number of patients with genetic forms of LVH and all patients with myocardial infiltration.

In conclusion, in patients with HCM phenotype, LV endomyocardial biopsy is safe and may recognize an infiltrative or storage disease in up to 18% of the cases. It may direct genetic studies and suggest the more appropriate treatment.

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