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Influence of centre expertise on the diagnosis and management of hypertrophic cardiomyopathy: A study from the French register of hypertrophic cardiomyopathy (REMY)

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ABSTRACT

Background: Our knowledge of hypertrophic cardiomyopathy (HCM) mainly originates from quarternary centres. The objective is to assess the current management of HCM patients in a large multicentre French register according to the level of expertise.

Methods and results: A total of 1431 HCM patients were recruited across 26 (11 expert and 15 non-expert) centres in REMY, a prospective hospital-based register of adult HCM patients. A sarcomeric origin was suspected in 1284 (89.7%) patients [261 (20.3%) with a reported gene mutation, 242 (18.8%) genotype-negative], while 107 (7.5%) had a diagnosis of non-sarcomeric HCM. Patients managed in non-expert centres were older ($P < 0.01$) and presented more often with NYHA III/IV class dyspnoea ($P < 0.01$), congestive heart failure ($P < 0.01$), low LEVF ($P < 0.01$), less often with a syncope history ($P < 0.01$) and lower LV obstruction ($P < 0.01$) than patients in expert centres. Genotype positive sarcomeric aetiologies were less frequent in non-expert centres ($P < 0.01$). The use of diagnostic and prognostic tests as cardiac MRI ($P < 0.001$), genetic ($P < 0.001$) and alpha-galactosidase A enzyme level testing ($P < 0.001$), Holter ECG ($P < 0.001$), and exercise test ($P < 0.001$), was lower in non-expert centres. Septal ablation procedures using alcohol ($P < 0.001$) or myectomy ($P < 0.001$) were more frequent in expert centres.

Conclusion: In real life practice, only a minority of HCM patients are identified as sarcomere positive as per genetic testing. The management of HCM patients varies according to the centre's level of expertise, with less access to diagnostic and prognostic tests in non-expert centres. Non-sarcomeric HCM may therefore be overlooked despite specific treatment in some aetiologies.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a the most prevalent inherited cardiomyopathy [1]. Our knowledge of the aetiologies [2], the underlying genetics [3] and prognosis factors [4] has substantially

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increased over the past decade [5]. Clinical management should follow the best evidence-based guidelines available. However, studies in the field of HCM originate mainly from tertiary or even quaternary centres and do not necessarily reflect practices in less experienced centres [6]. The magnitude of the gap between what should be done (as stated by the guidelines) and how patients are managed in daily practice has been poorly studied. Indeed, how patients with a HCM phenotype are investigated in terms of aetiology and risk classification has not been published when including non-expert centres [6].

To better appreciate real-life approaches and their adherence with the published current HCM guidelines in North America [7,8]and in Europe [9], we initiated, under the auspices of the French Society of Cardiology, a multicentre hospital-based register of HCM patients (REMY: REgister of hypertrophic cardioMYopathy). Expert centres, divided into referral and competent centres, are designated by a national institution in France in order to improve access to specialized patient care. We included here data on patients' profiles, aetiologies as stated by the clinician, investigations and management. Recruitment was independent of the recently published European HCM register [6].

2. Methods

2.1. Settings

The French Society of Cardiology aims at promoting disease-specific registers in order to better appreciate cardiovascular disease management and the consistency with contemporary guidelines. The REMY study, initiated in 2010, prospectively includes at the time of diagnosis or at follow-up in- or outpatients with a diagnosis of HCM. Twenty-six centres (see appendix) distributed across all French regions (13 teaching public hospitals, 13 non-teaching public or private hospitals) take part in REMY, an on-going register. A national institution ("La Haute Autorité de Santé") regulates healthcare delivery in France. In 2012, a document was launched alongside the French Society of Cardiology thereby identifying "referral" (quaternary) and "competent" (tertiary) centres for the management of HCM patients. The selection process of expert referral centres by the healthcare French authorities is rigorous, depending on presence of a multidisciplinary group of physicians and paramedics, quality of healthcare delivery, regional and national coordination of care, research, teaching and public information programs, and scientific productions in the field. The expert competent centres, which aim to manage patients closer to their home, are selected on their close interactions with a referral center and the use similar healthcare protocols and guidelines.

2.2. Inclusion criteria

Inclusion criteria were based on left ventricular (LV) hypertrophy (LVH) ≥15 mm in sporadic cases, and ≥13 mm[9] in the presence of a family history of HCM, using any imaging technique (echocardiography, cardiac magnetic resonance imaging (cMRI) or computed tomography (CT)] in adult patients ≥16 years after informed written consent. Patients with abnormal LV loading conditions (i.e., severe systemic hypertension or significant aortic stenosis ≤1cm^2) were excluded. Patients with an HCM phenotype were therefore eligible for inclusion, regardless the suspected aetiology or attempts to refine the causative diagnosis. The relevant government institution, *the National Commission Informatics and Liberty*, provided ethical clearance (CNIL agreement #909378).

2.3. Data collection

REMY uses an anonymized e-CRF hosted by the French Society of Cardiology, with prospective collection of clinical, imaging and laboratory data. The following characteristics are collected at inclusion: socio-demographic, echocardiographic features, investigations (e.g. laboratory tests, cMRI), genetic testing information, and history of predefined cardiovascular events, current medications, and invasive treatments. Echocardiographic parameters include maximal LV wall thickness (LVWT), LVH distribution, LV ejection fraction (LVEF) using the biplane Simpson's rule, maximal instantaneous LV outflow tract (LVOT) gradient either at rest or at provocation on Valsalva manoeuvre, and maximal antero-posterior left atrial (LA) diameter.

Practitioners were asked to fill in declared (or suspected) aetiologies. Predefined aetiologies include sarcomeric (clinically suspected or genetically confirmed), or non-sarcomeric HCM, as Anderson-Fabry disease (confirmed by genetics or enzyme testing in males), amyloidosis (senile, light-chain or familial, either confirmed by histology or genetics) and other phenocopies (e.g., PRKAG2 mutation). Genetic testing and the results (when available) are also collected. Of note, aetiology may be amended after inclusion. The number of genes tested was not included and genetics methods are left at the discretion of each participating centre. Variants of unknown significance are not collected. Prior cardiovascular events (e.g., history of sudden cardiac death (SCD), syncope, supra-ventricular and/or ventricular arrhythmias, heart failure, stroke) are also collected. The presence of an implantable cardiac defibrillator (ICD) implantation is collected at inclusion.

2.4. Statistical analysis

Descriptive data was reported for the entire study population. Results were reported as mean and standard deviation (SD) for normally distributed continuous variables; or as median and interquartile range (IQR) for non-normally distributed continuous variables and as numbers and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables using Student *t*-test, Wilcoxon-Mann-Whitney or ANOVA tests. Analysis was restricted to patients with no missing data. All data were verified and analysed at the Paris Cardiovascular Research Centre, INSERM 970, Paris, France, with the use of Statistical Analysis System software (SAS version 9.4).

3. Results

3.1. Description of the study population

A total of 1431 HCM patients were recruited from January 2010 to January 2016. Overall, 972 (67.9%) were male; mean age was 54.6 years (SD 16.5), with maximum LVWT of 20.3 (SD 4.9) mm and maximum LV gradient of 42.7 (SD 46.4) mmHg. Practioners suspected a sarcomeric origin in 1284 (89.7%) patients. Among these, 261 (20.3%) had a sarcomere gene mutation identified as pathogenic, 242 (18.9%) underwent genetic testing with negative results or identification of a genetic variant of unknown significance (gene negative suspected sarcomeric HCM), and 781 (60.8%) had either no gene testing or unknown results. One hundred and seven patients (7.5%) had a diagnosis of non-sarcomeric HCM. Non-sarcomeric aetiologies (or phenocopies) included amyloidosis in 67 out of 107 (62.6%) Anderson-Fabry disease in 18 (16.8%) mitochondrial disease in 3 (2.8%), PRKAG2 in 1, sarcoidosis in 1, hemochromatosis in 1, Noonan syndrome in 1, LEOPARD syndrome in 2 (all <0.01%), whilst specific non-sarcomeric aetiology remained either under investigation or with missing data in 13 (12.1%) patients. Finally, aetiology was missing in 40 (2.8%) patients.

3.2. Comparison according to HCM aetiology

On univariable analysis, patients with non-sarcomeric HCM were significantly older ($P < 0.01$), more often male ($P = 0.02$), had higher NYHA class ($P < 0.01$), lower LVEF ($P < 0.01$), and less LV obstruction ($P < 0.01$) than patients with sarcomeric (either suspected or genetic positive) HCM (Table 1). Non-sarcomeric HCM were non-obstructive (i.e., maximum LV gradient <30 mmHg) in all cases but two (one patient with Fabry disease and one patient with AL amyloidosis).

Patients with gene positive sarcomeric HCM were significantly younger (mean age 46.47 years (15.99)) ($P < 0.01$), presented with more frequent family history of HCM ($P < 0.01$) or a family history of sudden cardiac death ($P < 0.01$) when compared to the other groups. Ventricular arrhythmias were more frequent among patients with gene positive sarcomeric HCM ($P < 0.01$). Patients with gene negative or no genetic testing but still suspected sarcomeric aetiology by the practioners had higher LV gradients than patients with gene positive sarcomeric HCM ($P < 0.01$).

Patients with gene positive sarcomeric HCM were significantly younger ($P < 0.01$) and had more often a family history of HCM ($P < 0.01$) or SCD ($P < 0.01$) when compared to those without genetic results but still suspected by the clinician as being of sarcomeric aetiology. On the other hand, the latter were in higher NYHA class ($P = 0.04$), had more angina ($P < 0.01$), and LV obstruction ($P = 0.01$) than gene positive sarcomeric HCM patients.

Among patients with available genetic testing, patients with positive sarcomere gene mutation(s) were significantly younger ($P < 0.01$), had more family history of HCM ($P < 0.01$) or of SCD ($P < 0.01$) than those with negative results. Gene negative HCM patients presented more often with angina ($P < 0.01$) than those with gene positive sarcomeric HCM. New York heart association classification did not differ according

Table 1
Comparison of patients' characteristics according to sarcomere versus non-sarcomere aetiologies (only patients with a definite non-sarcomeric aetiology were considered).

All patients	Gene positive sarcomeric HCM	Gene negative suspected sarcomeric HCM	Suspected Sarcomeric: no genotype or missing data	Non-sarcomeric HCM	Missing data or not confirmed	ANOVA P value
N = 1431	N = 261	N = 242	N = 781	N = 107	N = 40	
Age: mean (SD), years	46.47 (15.99)	56.41 (16.40)	53.16 (15.05)	63.23 (14.66)	59.53 (12.96)	<0.001
Male sex, N (%)	169 (64.75)	516 (66.07)	171 (70.66)	82 (76.64)	34 (85.00)	0.02
NYHA class, N (%)*						
I	119 (45.77)	273 (35.97)	96 (40)	23 (22.33)	14 (38.89)	<0.001
II	108 (41.54)	324 (42.69)	101 (42.08)	39 (37.86)	14 (38.89)	
III	31 (11.92)	142 (18.71)	41 (17.08)	35 (33.98)	6 (16.67)	
IV	2 (0.77)	20 (2.64)	2 (0.83)	6 (5.83)	2 (5.56)	
Angina, N (%)**	53 (20.38)	246 (32.24)	70 (29.17)	15 (14.29)	10 (26.32)	<0.001
Syncope, N (%)***	69 (26.44)	224 (28.75)	56 (23.24)	14 (13.46)	8 (21.05)	0.01
Supra-ventricular arrhythmias, N (%)§	71 (27.41)	228 (29.65)	57 (23.85)	42 (40.00)	11 (28.95)	0.05
Ventricular arrhythmias, N (%)§§	54 (20.85)	145 (18.93)	37 (15.55)	13 (12.62)	6 (15.79)	0.29
Congestive heart failure, N (%) §§§	15 (7.89)	91 (13.96)	17 (8.63)	31 (33.33)	6 (27.27)	<0.01
Family history of HCM, N (%)ø	179 (69.92)	224 (30.07)	78 (33.62)	12 (12.12)	0 (0.00)	<0.001
Family history of SCD, N (%)øø	87 (38.50)	124 (17.64)	41 (27.15)	7 (7.22)	6 (18.18)	<0.001
LVEF, median (IQR)øøø	68.00 (63.00–72.00)	65.00 (60.00–70.00)	69.00 (64.00–73.00)	55.00 (45.00–65.00)	61.00 (52.00–67.00)	<0.001
Maximum LVWT, median (IQR) †	20.00 (17.00–24.00)	19.00 (17.00–22.00)	19.00 (17.00–22.00)	18.00 (16.00–21.00)	18.00 (16.00–21.00)	<0.01
LV obstruction ≥30 mmHg, N (%) ††	27 (10.47)	54 (6.99)	12 (5.08)	4 (3.81)	1 (2.63)	0.09
Maximum LV gradient, median (IQR) †††	15.00 (7.00–58.00)	33.00 (8.00–80.00)	20.00 (7.80–70.00)	1.54 (0.00–5.00)	10.00 (6.00–22.00)	<0.001
LA diameter (mm), mean (SD)i	41.95 (9.90)	42.65 (8.34)	41.12 (8.07)	45.03 (8.34)	41.99 (9.08)	0.01

HCM: hypertrophic cardiomyopathy. LVWT: left ventricular wall thickness. SCD: sudden cardiac death. LA: left atrial. SD, standard deviation. IQR, interquartile range.
* Missing data in 31 cases.
** missing data in 23 cases.
*** missing data in 6 cases. §Includes atrial fibrillation or flutter; missing data in 19 cases.
§§ Includes sustained and non-sustained ventricular tachycardia, ventricular fibrillation, missing data in 25 cases.
§§§ Defined as NYHA III or IV with need of loop diuretics, missing data in 263 cases.
ø Missing data in 60 cases.
øø Missing data in 215 cases.
øøø LVEF, left ventricular ejection fraction, missing data in 37 cases.
† Maximum LVWT (left ventricular wall thickness), missing data in 20 cases.
†† Missing data in 33 cases.
††† Missing data in 389 cases.
i Missing data in 196 cases.

to the genetic results (P = 0.34), nor did congestive heart failure (P = 0.79).

In gene positive sarcomeric HCM, LVH involved predominantly the septum (upper septum: 20 (7.9%); all septum; 132 (52.4%); septum and anterior wall: 76 (30.2%), while it was confined to the lateral or apical walls in 16 (6.4%) and concentric in 8 (3.2%) patients. In patients with non-sarcomeric HCM, LVH was moderate (maximal LVWT≤20 mm) in 62 (59.1%) and predominantly concentric in 83 (82.2%) of the cases.

Investigations differed between patients with suspected sarcomeric HCM and suspected non-sarcomeric HCM (regardless their gene status). Patients with sarcomeric HCM underwent more often Holter ECG monitoring (P < 0.01), exercise ECG (P < 0.01) or exercise peak VO2 consumption assessment (P < 0.01) and genetic testing (P < 0.01) while non-sarcomeric HCM patients underwent more myocardial biopsies (P < 0.01).

3.3. Patients' characteristics and management according to the centres' level of expertise

Two referral centres took part in the study, alongside 9 competent centres, and 15 non-expert centres. Mean number of patients included was: 243 (SD 330) in referral centres, 91 (SD 119) in competent centres, and 9 (SD 22) in non-expert centres. Patients' characteristics according to the centres' level of expertise are depicted in Table 2. Patients managed in non-expert centres were older (P < 0.01), presented more often with NYHA III/IV dyspnoea (P < 0.01), congestive heart failure (P < 0.01), lower LEVF (P < 0.01), less history of syncope (P < 0.01), and less severe LV obstruction (P < 0.01) than patients admitted to expert (reference or competent) centres. There were less gene positive sarcomeric HCM patients in non-expert centres (P < 0.01) than in expert centres.

The use of cardiac imaging varied across the centres' levels of expertise, with less cardiac MRI (P < 0.01), CT- cardiac scans (P < 0.001), and coronary angiograms (P < 0.01) in non-expert centres (Table 3). In less experienced hospitals, patients underwent less genetic testing (P < 0.01) or alpha-galactosidase enzyme A level measurement (P < 0.01) than in expert centres. Overall, the use of genetic testing increased throughout the study period, whereas alpha-galactosidase A enzyme level testing did not change substantially over time (data not shown). Prognostic tests such as 24-h Holter ECG monitor (P < 0.001) and exercise testing (P < 0.01) were also underused in non-expert centres. Myocardial biopsy was more frequently performed in non-expert hospitals (P < 0.01).

Medical and non-medical management in terms of medication and interventions differed according to the level of expertise (Supplementary Table 1). Patients in referral centres were more frequently under gradient reduction medications: betablockers (P < 0.01), Verapamil (P

Table 2
Patients' characteristics according to the centres' level of expertise.

	Reference centre N = 486	Competent centre N = 821	Non-expert centre N = 124	Univariable P value
Age: mean (SD), years	54.81 (16.77)	53.34 (16.06)	62.63 (16.21)	<0.001
Male sex: N (%)	316 (65.02)	565 (68.82)	91 (73.39)	0.14
NYHA class, N (%)*				<0.001
I	138 (28.81)	344 (42.95)	43 (36.44)	
II	203 (42.38)	349 (43.57)	34 (28.81)	
III	126 (26.3)	100 (12.48)	29 (24.58)	
IV	12 (2.51)	8 (1)	12 (10.17)	
Angina, N (%)**	190 (39.34)	182 (22.64)	22 (18.49)	<0.001
Syncope, N (%)***	156 (32.30)	198 (24.21)	17 (13.93)	<0.001
Supra-ventricular arrhythmias, N (%)§	173 (35.97)	188 (23.30)	48 (39.34)	<0.001
Ventricular arrhythmias, N (%)§§	114 (23.90)	116 (14.36)	25 (21.01)	<0.001
Congestive heart failure, N (%) §§§	86 (19.63)	47 (7.51)	27 (30.00)	<0.001
Family history of HCM, N (%)ø	148 (30.71)	327 (42.52)	18 (15.79)	<0.001
Family history of SCD, N (%)øø	81 (16.80)	170 (27.69)	14 (12.28)	<0.001
LVEF, median (IQR)øøø	65.00 (60.00–70.00)	68.00 (62.00–74.00)	58.00 (45.00–64.00)	<0.001
Maximum LVWT (mm), median (IQR)†	19.00 (17.00–22.00)	19.00 (17.00–23.00)	18.00 (16.00–22.00)	0.27
LV obstruction ≥30 mmHg, N (%)††	33 (6.83)	53 (6.58)	12 (9.92)	0.30
Maximum intra-LV gradient, median (IQR)†††	70.00 (27.00–100.0)	12.00 (6.00–45.00)	0.00 (0.00–31.00)	<0.001
LA diameter (mm), mean (SD) ¡	44.45 (8.74)	40.90 (8.34)	44.71 (8.35)	<0.001
Gene positive sarcomeric HCM, N (%)¡¡	73 (15.15)	184 (23.03)	4 (3.64)	<0.001

HCM: hypertrophic cardiomyopathy. LVWT: left ventricular wall thickness. SCD: sudden cardiac death. LA: left atrial. SD, standard deviation. IQR, interquartile range.
* Missing data in 33 cases.
** missing data in 25 cases.
*** missing data in 8 cases.
§ Missing data in 0 cases.
§§ Missing data in 27 cases.
§§§ Missing data in 277 cases.
† Missing data in 22 cases.
†† Missing data in 22 cases.
††† Missing data in 398 cases.
ø Missing data in 26 cases.
øø Missing data in 221 cases.
øøø Missing data in 46 cases.
¡ Missing data in 201 cases.
¡¡ Missing data in 40 cases.

Table 3
Investigations undertaken at enrolment according to the participating centres' level of expertise.

	Reference centre N = 486	Competent centre N = 821	Non-expert centre N = 124	Univariable P value
Holter ECG, N (%)*	383 (80.80)	567 (73.26)	58 (50.43)	<0.001
Cardiac MRI, N (%)**	325 (69.15)	528 (69.38)	59 (51.75)	<0.01
Cardiac CT scan, N (%)***	92 (19.45)	11 (2.34)	11 (9.65)	<0.001
Exercise ECG, N (%)§	301 (64.59)	537 (77.04)	18 (15.52)	<0.001
VO2 max, N (%)§§	102 (21.98)	215 (47.25)	5 (4.42)	<0.001
Coronary angiogram, N (%)§§§	244 (52.81)	45 (9.57)	13 (11.61)	<0.001
Genetic testing, N (%)†	177 (37.42)	484 (59.39)	12 (11.01)	<0.001
BNP or NT-pro-BNP, N (%)	315 (64.81)	525 (63.95)	98 (79.03)	0.01
Creatine kinase, N (%)††	261 (74.36)	298 (65.21)	50 (47.62)	<0.001
Alpha-galactosidase A enzyme testing, N (%)†††	45 (13.89)	70 (8.79)	5 (4.81)	0.01
Alpha-galactosidase A enzyme testing in males ≥30 yo, N (%)°	4 (9.76)	46 (11.11)	4 (8.00)	0.78
Proteinuria level, N (%)°°	124 (38.87)	74 (18.23)	13 (13.40)	<0.001
Creatinine level, N (%)°°°	401 (99.50)	397 (94.30)	117 (97.50)	<0.001
Electrophysiological investigations, N (%)¡	27 (5.83)	22 (4.67)	5 (4.35)	0.67
Myocardial biopsy, N (%)¡¡	35 (7.38)	8 (1.71)	46 (39.66)	<0.001

* Missing data in 68 cases.
** Missing data in 86 cases.
*** Missing data in 374 cases.
§ Missing data in 152 cases.
§§ Missing data in 399 cases.
§§§ Missing data in 387 cases.
† Missing data in 34 cases.
†† Missing data in 518 cases.
††† Missing data in 207 cases.
° Missing data in 73 cases.
°° Missing data in 609 cases.
°°° Missing data in 487 cases.
¡ Missing data in 382 cases.
¡¡ Missing data in 372 cases.

< 0.01) and/or Dispopyramide (P < 0.01). Also, patients underwent more interventions aimed at reducing intra-ventricular obstruction in expert centres: septal alcohol ablation (P < 0.01) or septal myectomy (P < 0.01), or mitral valve procedures (P < 0.01). Implantable cardiac defibrillators were equally inserted in expert and non-expert centres, ranging between 11.32% and 12.40% of patients at inclusion, respectively (P = 0.42).

4. Discussion

This is the first prospective study assessing the management of HCM across 26 institutions with different levels of expertise of a single European country, expertise being established by the national healthcare services. The diagnosis of sarcomeric or non-sarcomeric causes, the latter being diagnosed with an increasing frequency [10], is essential, as specific treatments may exist such as enzyme replacement therapy as in Anderson-Fabry's disease. International recommendations for management of HCM are available [8,9], focusing on exclusion of non-sarcomeric causes and SCD risk stratification among patients with sarcomeric HCM. How guidelines translate in real-life medical practice remains poorly investigated beyond expert centres [6].

Most importantly, we demonstrate that the vast majority of HCM patients do not necessarily have a definite aetiological diagnosis. Tertiary or quaternary centres may present results in homogenously tested study populations whereas registers reflect more accurately real-life medical practice. Here, barely one fifth of the study population has a genotype positive diagnosis of sarcomeric HCM whilst suspected in the vast majority of patients, mainly due to little use of genetic testing or pending genetic results. Also, among patients who underwent genetic testing with available results, almost half had negative results. This is in keeping with the yield of contemporary genetic testing ranging from 35% to 47% in previous reports [11,12].

4.1. Investigations: diagnostic, prognostic tests, and treatment

A large number of diagnostic procedures were underused in our population. Alpha-galactosidase A enzyme testing, essential to rule out Anderson-Fabry's disease [13,14]as advised by the recent European guidelines in males above 30 years [9], was seldom performed (<10%). Similarly, access to genetic testing and counselling was low whereas recommended in adults according to the latest ESC guidelines in order to optimize first-degree family screening [9]. Important tests to refine risk stratification for ventricular arrhythmias or heart failure as heart failure biomarkers [15], cMRI looking for late gadolinium enhancement [16,17],or exercise testing (either ECG, echocardiogram or VO2 max) [18] were used in less than two thirds of the patients.

Our results in terms of investigations are similar to the recently published European register led by international experts in HCM [6]. In the European register, baseline data was collected among 1739 HCM patients, among other cardiomyopathies, across 69 centres in 18 countries. Structural and financial reasons may be accountable for a lower proportion of patients offered genetic testing in the EURObservational Research Programme of the European Society of Cardiology (46.4%). However, only 66.9% of participants underwent a Holter ECG monitor in the European register [6]. Therefore, structural or economic reasons may not be the only reasons for poor adherence to current European guidelines.

The majority (~80%) of patients received beta-blockers as a first line therapy. This is strikingly high given that only one third presented with LVOT obstruction, that barely one out of ten developed heart failure, and that less than one out of five had ventricular arrhythmias. Our findings are however consistent with those of the European pilot register where beta-blockers were given in 78% of patients included in the first part of the study [19], and in 74% of the subsequent larger HCM cohort recently published [6].

4.2. Comparison of patients' characteristics according to the underlying aetiology

Approximately 8% of adult patients with HCM had a non-sarcomeric underlying aetiology in the current cohort, while the pilot register of the European Society of Cardiology reported a lower incidence of non-sarcomeric HCM (5.3%) [19] and a recent two-centre cohort (1697 patients) a greater proportion (24%) of phenocopies [10]. In the current study, the proportion of non-sarcomeric HCM may have been underestimated as demonstrated by the low percentage of patients tested for alpha-galactosidase A enzyme. In spite of the underuse of tests allowing a differential diagnosis, the proportion of patients with amyloidosis and Anderson-Fabry disease were similar to previously published cohorts [14,20], and the predominance of amyloidosis followed by Anderson-Fabry disease hence confirmed among non-sarcomeric HCM aetiologies [10].

As previously reported, gene positive sarcomeric HCM patients were younger, with more family history of HCM or SCD, and less LV obstruction than gene negative or non-sarcomeric HCM patients [12]. Strikingly, practitioners did not modify the underlying suspected "sarcomeric" aetiology for patients with negative genetic testing. Patients with suspected but not genetically confirmed "sarcomeric" HCM had more LV obstruction than genotype positive participants, suggesting that obstructive HCM remains a synonym of sarcomeric HCM for the vast majority of cardiologists. Patients with non-sarcomeric HCM, and those who are gene positive differ drastically. Patients' profile in the group with suspected sarcomeric origin but no genetic testing are somehow in the continuum between gene positive and gene negative HCM, in terms of age, family history and heart failure. Our results suggest that a number of patients who are stated as "sarcomeric" HCM may actually be phenocopies. The knowledge in the field of cardiovascular genetics has considerably changed over the past decade [3] with over 80 gene panels now available in France with no extra-charge for the patient but increasing complexity in its analysis [21]. Lack of family history, older age at diagnosis decreases the likelihood of a pathogenic mutation in sarcomeric genes [12], as demonstrated here. Our results outline the heterogeneity of the condition, and the need to further our understanding of this complex phenotype.

4.3. Patients' characteristics and management according to the centres' level of expertise

In our study, many non-expert centres took part, although including fewer patients per centre. Patients' characteristics significantly differed according to the level of expertise. In expert (reference and competent centres according to the French health authority classification), patients were younger, less symptomatic as per NHYA class, had higher LVEF and more often family history of HCM than in non-expert centres. These results are somehow similar to the EURObservational Research Programme of the European Society of Cardiology's results [6]. Indeed, the pilot register was started by core of ESC leading centres [19]. The number of participating centres increased substantially in the second phase, somehow implying various levels of expertise [6]. These centres remain part of a supra-national network and practitioners may have an interest in HCM. In the second phase of the European register, patients were older (median age 49.0 versus 46.0 years old) with less family history of cardiomyopathy (34.4% versus 46.4%). Likewise, expert centres had a higher proportion of familial disease in our study thereby allowing diagnosis at a younger age [6]. Also, patients seen in expert centres were more likely to present with LVOT obstruction and therefore underwent more frequently treatments such as beta-blockers and gradient reduction interventions as septal alcohol ablation or surgical myectomy. The differences in the baseline characteristics of patients in expert versus non-expert centres may be explained by referral bias. Older patients with heart failure are more likely to present with non-sarcomeric (i.e., phenocopies) HCM. Access to specialized diagnostic testing and

care may therefore be denied on the grounds of age and heart failure, preventing a number of patients the benefit of optimal care.

Access to highly specialized diagnostic testing may be explained at a European level by structural differences and economic differences between participating countries at each national level [6]. In our context, the French social security covers for all recommended tests, as cMRI, alpha-galactosidase A enzyme, or genetic testing. Underuse of these tests by non-expert centres may be explained either by lower access to laboratories within their network, or by less adherence to current guidelines. The lower use of Holter-ECG in non-expert centres, which is crucial in terms of SCD stratification in patients with sarcomeric HCM, is in favour of less knowledge and/or compliance to current guidelines [9]. On the other hand, access to expert cMRI may be restricted to high volume centres in many parts of Europe. Late gadolinium enhancement quantification may be highly informative for SCD stratification in sarcomeric HCM [17], while T1 mapping may be used for non-sarcomeric diagnosis [22]. Myocardial biopsy was frequently performed in non-expert centres (~40% of patients), whereas its indication is debatable in the management of HCM given that the risks may outweigh the benefits in most cases [9]. In amyloidosis, other sites are usually available for histology alongside cardiac MRI and genetic testing. Myocardial biopsy is therefore not a frontline diagnostic test.

Reasons for a lower compliance to current guidelines in the management of HCM in non-expert centres are therefore likely to be due to less knowledge of the current guidelines and to a limited-access to a multidisciplinary approach including genetics and cardiac multi-modality imaging, highlighting the need for dedicated multidisciplinary HCM teams. Unlike other countries, the French social security allows to attend hospitals outside the local facilities. Referral to expert (tertiary or quaternary) centres is therefore not limited from an economic perspective. However, collaborations between general hospitals and university-affiliated hospitals may lack. The formal organization of disease-specific collaborations may improve the referral of HCM patients to expert centres with the possibility of joint follow-up.

4.4. Strengths and limitations

This study is the first large multi-centre HCM register that assesses the contemporary patient profiles and management practices across hospitals with various levels of expertise. We provide valuable data on how patients are actually managed and highlight the pitfalls of contemporary practice. This cohort was set independently of the European Cardiomyopathy Registry recently published [6,19], making comparisons possible. Similar to many observational studies [19], only a minority of patients have a definitive genetic diagnosis for a variety of reasons: mostly not done, underway or negative results with methods that vary from one centre to another (e.g., number of genes tested). Indeed, a minority of patients with suspected sarcomeric HCM had a genetic confirmation of the condition. We did not explore the possibility of multiple gene variants due to the methods of our study: a large multicentre register with a 6-year inclusion period and the heterogeneity of panels used [21]. The yield of genetic testing remains however similar to that of other single-centre genetic focused studies [12]. Our study bears other limitations, as the epidemiological representation of the condition in France. Many patients are managed in private practice with no referral to the hospital. Also, our register was not sampled as to be representative of the French territory. It is a voluntary register and all cardiology centres were offered the opportunity to take part. Follow-up data to assess outcomes according to medical practice needs further assessment.

5. Conclusions

In contemporary France, the vast majority of HCM patients have no genetic confirmation of the underlying aetiology. The phenotype of HCM patients varies according to the level of expertise with older and more heart failure patients in non-expert centres. Expertise is associated with higher compliance to contemporary guidelines in terms of diagnostic and prognostic testing. Non-sarcomeric HCM may be overlooked, especially among non-experts, despite specific treatments in some aetiologies. A network allowing referral to expert centres is warranted, although impact on prognosis needs further assessment.

Conflicts of interest

Dr. Hagège has served as an advisor to Amicus, Gilead, Myokardia, Sanofi Genzyme.

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Appendix A. Supplementary data

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