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Romanian Registry of Hypertrophic Cardiomyopathy – overview of general characteristics and therapeutic choices at a national level

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Introduction. Hypertrophic cardiomyopathy (HCM) is a disease with increased left ventricular (LV) wall thickness not solely explained by abnormal loading conditions, with great heterogeneity regarding clinical expression and prognosis. The aim of the present study was to collect data on HCM patients from different centres across the country, in order to assess the general characteristics and therapeutic choices in this population.

Methods. Between December 2014 and April 2017, 210 patients from 11 Romanian Cardiology centres were enrolled in the National Registry of HCM. All patients had to fulfil the diagnosis criteria for HCM according to the European Society of Cardiology guidelines. Clinical, electrocardiographic, imaging and therapeutic characteristics were included in a predesigned online file.

Results. Median age at enrolment was 55 ± 15 years with male predominance (60%). 43.6% of the patients had obstructive HCM, 50% non-obstructive HCM, while 6.4% had an apical pattern. Maximal wall thickness was 20.3 ± 4.8 mm (limits 15-37 mm) while LV ejection fraction was 60 ± 8%. Heart failure symptoms dominated the clinical picture, mainly NYHA functional class II (51.4%). Most frequent arrhythmias were atrial fibrillation (28.1%) and non-sustained ventricular tachycardia (19.9%). Mean sudden cardiac death risk score (SCD-RS) was 3.0 ± 2.3%, with 10.4% of the patients with high risk of SCD. However, only 5.7% received an ICD. Patients were mainly treated with beta-blockers (72.9%), diuretics (28.1%) and oral anticoagulants (28.6%). Invasive treatment of LVOT obstruction was performed in a small number of patients: 22 received myomectomy and 13 septal ablation. Cardiac magnetic resonance was reported in only 14 patients (6.6%).

Conclusions. The Romanian registry of HCM illustrates patient characteristics at a national level as well as the gaps in management which need improvement – accessibility to high-end diagnostic tests and invasive methods of treatment.

Key words: Hypertrophic Cardiomyopathy, Registry, Sudden death, Echocardiography, Arrhythmia.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inherited disease of the myocardium, affecting 1 in 500 of the general population [1]. According to the ESC guidelines, HCM is defined by an increased left ventricular (LV) wall thickness which cannot be exclusively explained by the presence of abnormal loading conditions [2]. HCM is characterized by a great heterogeneity regarding the clinical expression and prognosis, varying from heart failure manifestations, atrial fibrillation with its thromboembolic consequences to sudden cardiac death [3]. However, due to the progress made in understanding the natural history of the disease and the development of guidelines with recommendations regarding the diagnosis and treatment strategies, the prognosis of patients with HCM has improved, most of them having a normal life-expectancy [1].

The development of national registries is important in the case of such a heterogeneous and relatively rare disease as HCM because they put together a greater number of patients from a country or region, leading to a better understanding of the

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patient characteristics and the algorithms of diagnosis and treatment used at local level, as well as the identification of gaps in the application of current guidelines that need improvement

The aim of the present study was to collect data on HCM patients from different types of centres across the country, in order to assess the general characteristics and therapeutic choices in this patient population.

MATERIALS AND METHODS

Registry design

The registry RENCMH was developed in 2014 by the Romanian Society of Cardiology in order to observe the characteristics of Romanian HCM patients in terms of presentation and management. All included patients had to fulfil the diagnosis criteria for hypertrophic cardiomyopathy according to the European Society of Cardiology guidelines published in 2014 – the presence of a left ventricular wall thickness ≥ 15mm in one or more segments using any cardiac imaging technique, which is not explained solely by the loading conditions.

For each patient data was collected regarding personal and family history, clinical examination, ECG, echocardiography, other cardiac imaging techniques, Holter monitoring, genetic testing, as well as therapeutic management, all data being introduced online in an electronic database (www.rencmh.ro).

Patient data reporting was open to any Romanian cardiologist, based on volunteer online registration which was processed and accepted by a registry administrator.

Statistical analysis

The statistical analysis was made using IBM SPSS Statistics 23.0 (IBM Corporation, USA, 2015). Univariate analysis was performed for both continuous and categorical variables. Continuous variables were expressed as mean ± SD, while categorical variables were reported as percentages.

RESULTS

Data collection

Between December 2014 and April 2017, 210 patients from eleven Romanian Cardiology centres were enrolled in the National Registry of Hypertrophic Cardiomyopathy. There were an average 19 ± 38 inclusion per centre, and the median of 5 with limits between 1 and 130 patients per centre. The number of doctors who participated was 16 (Fig. 1).

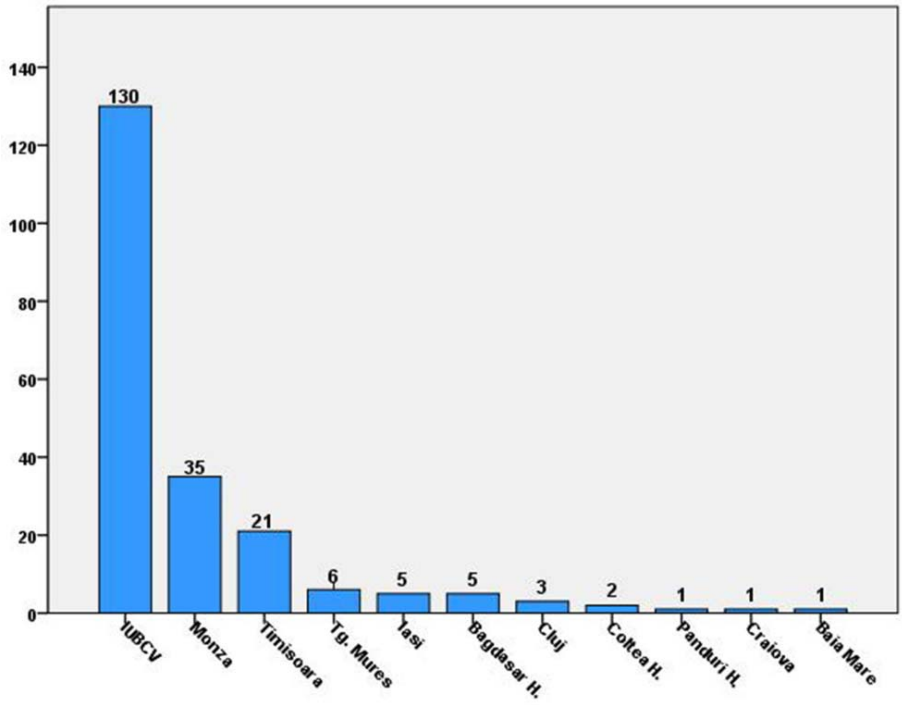

Figure 1. Number of enrolled patients per centre.

Demographic characteristics

The mean age at enrolment was 55 ± 15 years (limits between 15 and 85 years) with women being older than men (mean age 59 ± 14 years and 53 ± 15, respectively) in our cohort (p value = 0.03) (Table 1).

Table 1
General characteristics of the patients

Age at enrolment	55 ± 15
Males	126 (60)
Family history of sudden cardiac death	30 (14.3)
NYHA	
Class I	25 (11.9)
Class II	108 (51.43)
Class III	35 (16.67)
Class IV	1 (0.48)
Angina	60 (28.57)
Palpitations	97 (46.19)
Fatigability	110 (52.38)
Syncope	21 (10)

Values are given as n (%) or mean ± SD

Regarding the distribution according to sex, there was a male predominance, accounting for 60% of the enrolled patients.

Family history

Thirty patients (14.3%) of all patients reported a history of sudden cardiac death in their families.

Symptoms

The majority of enrolled patients (n = 169, 80.5%) reported heart failure symptoms, with more than half (n = 108, 51.4%) being in New York Heart Association (NYHA) functional class II. Other frequent symptoms among the patients were palpitations (n = 97, 46.2%), angina (n = 59, 28.6%) and atypical chest pain (n = 40, 19%) (Fig. 2).

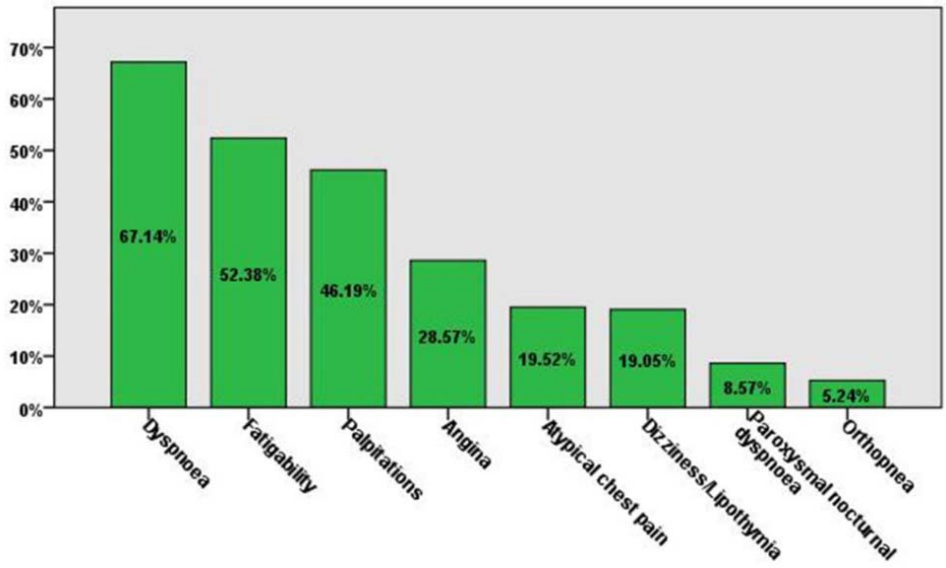

Figure 2. Distribution of symptoms in the enrolled patients.

Electrocardiogram

An electrocardiogram was performed for each patient, the most frequent anomalies being the presence of left ventricular hypertrophy voltage criteria (n = 140, 66.7%), ST segment depression (n = 90, 42.9%), deep inverted T waves >10 mV (n = 63, 42.9%) and Q waves (n = 27, 12.9%). Fifty-nine patients (28.1%) were in atrial fibrillation. Almost 20% of all patients had a conduction anomaly, the most frequent being left bundle branch block (n = 22, 10.5%) and right bundle branch block (n = 13, 6.2%).

Ambulatory 24 hours ECG monitoring was performed in 136 patients (64.8%), in 27 (19.9%) of them being recorded episodes of non-sustained ventricular tachycardia.

Echocardiography

The mean maximum left ventricular wall thickness was 20.3 ± 4.8 mm (limits between 15 and 37 mm). The right ventricular wall thickness was recorded only for 43 patients (20.5%), 30 of them presenting right ventricular hypertrophy (right ventricular wall thickness ≥ 6 mm). The mean LV

ejection fraction was 60 ± 8% with the mean end-diastolic volume of 102.4 ± 40.4 mL and the mean end-systolic volume of 38.8 ± 26.3 mL. The left atrium was frequently dilated with a mean antero-posterior diameter of 45.3 ± 7.7 mm and a mean volume of 101.6 ± 49.4 mL (Table 2).

The LV outflow tract gradient (LVOT) was recorded for 140 patients: 48 patients (34.3%) had a LVOT gradient ≥50 mmHg at rest, 13 patients (9.3%) developed high gradient during the Valsalva maneuvre only, while 79 patients (56.4%) had a LVOT gradient < 50 mmHg both at rest and during Valsalva. Thus, 61 patients (43.6%) had the obstructive form of HCM, 70 patients (50%) nonobstructive HCM, while 9 patients (6.4%) the apical form of HCM.

Mitral valve abnormalities were common among the included patients, being described in 47.1% of them. The systolic anterior motion (SAM) of the mitral valve was the most frequent (36.7%), followed by the presence of thickened chordae tendineae (16.7%) and abnormal papillary muscles (13.3%). Mitral regurgitation was described in 90% of all patients, in most cases being grade 1 (30%) and grade 2 (36.7%).

Table 2
Echocardiographic characteristics of the patients

LA anteroposterior diameter (mm)	45.3 ± 7.7
LA volume (mL)	101.6 ± 49.4
LV end-diastolic volume (mL)	102.4 ± 40.4
LV end-systolic volume (mL)	38.8 ± 26.3
LV ejection fraction (%)	60 ± 8
LV maximum wall thickness (mm)	20.3 ± 4.8

Values are given as mean ± SD

Other diagnostic methods

Cardiac magnetic resonance was performed and reported in only 14 patients (6.6%).

Coronary angiography was performed in 87 patients (41.4%): 8 patients (9.2%) presented muscular bridges, all on the left anterior descending artery and 17 patients (19.5%) had atherosclerotic lesions (5.7% on the circumflex artery, 2.3% on the right coronary artery and 11.5% had multiple lesions).

Genetic testing was reported in 7 patients – one patient was diagnosed with Friedreich ataxia, while in 6 cases no mutation was found.

Sudden cardiac death risk score

The mean sudden cardiac death (SCD) risk score was 3.2 ± 2.8% (limits between 0.67% and 24.16%). The majority of patients had a low risk of SCD (as defined by SCD 5 years risk < 4%) (138, 80.2%), while 18 (10.5%) had a high risk (as defined by SCD 5 years risk ≥ 6%) and 16 (9.3%) an intermediate risk. The most common factors among the patients associated with SCD were: the LVOT obstruction (36.2%), nonsustained ventricular tachycardia (14.3%), the family history of SCD (14.8%) and unexplained syncope (10%).

Pharmacological treatment

Most of the patients (72.9%) received a beta-blocker, while only 4.8% were on a calcium channel blocker (verapamil). Diuretics were given in 28.1% of the patients and mineralocorticoid receptor antagonists (spironolactone) in 15.7%. Antiarrhythmic drugs (amiodarone) were used in 18.1% of the patients and 28.6% of the total number of patients required oral anticoagulant treatment (Table 3).

Table 3
Pharmacological and invasive methods of treatment

Pharmacological treatment	
Beta-blockers	153 (72.9)
Calcium channel blockers – verapamil	10 (4.8)
Amiodarone	38 (18.1)
Diuretics	59 (28.1)
Mineralocorticoid receptor antagonists – spironolactone	33 (15.7)
Oral anticoagulants	60 (28.6)
Invasive treatment	
Alcohol septal ablation	13 (6.1)
Surgical septalmyectomy	22 (10.5)
ICD implantation	12 (5.7)
Pacemaker implantation	22 (10.5)

Values are given as n (%)

Invasive treatment

Invasive methods of reducing the LV outflow obstruction were used in a small number of patients: 13 patients (6.1%) were treated by alcohol septal ablation, while 22 patients (10.5%) underwent a surgical septal myectomy accompanied, in 13 of them (7.1%), by mitral valve repair. Only 12 patients (5.7%) received an implantable cardioverter defibrillator (ICD), while 22 patients (10.5%) required a pacemaker.

DISCUSSION

The present paper describes the clinical, imaging, ECG and therapeutic characteristics of a

registry HCM population from Romania, allowing the assessment of gaps from the guidelines and need for further education or tests availability.

The general characteristics of the patients in our registry were similar to those published in the EURObservational Research Programme (EORP) cardiomyopathy pilot, as well as the long-term registry [4, 5]. The mean age at enrolment was similar (55 ± 15 years in our study *vs*. 53.4 + 15.88 years in EORP registry), as well as the male predominance (60% vs. 59.3%). The mean age at enrolment was higher for women, consistent with the results of a previous multicentre study, which has proposed as a possible explanation for this the existence of certain endocrine or genetic factors which delay the phenotypic expression of HCM in women [6]. Only 14.3% of the patients reported a family history of sudden cardiac death, the percentage being lower to the one in EORP registry (21.1%) [5]. This can be explained by the difficult access to medical facilities in the past and the incomplete information of the patients regarding the diseases of their relatives.

A frequent way of presentation of HCM patients is represented by heart failure symptoms secondary to the presence of LVOT obstruction, diastolic dysfunction or atrial fibrillation [7]. The patient enrolled in our registry had a more advanced heart failure symptomatology compared to the results of EORP registry: the majority of patients in the Romanian registry were in NYHA functional class II (51.43%), while 16.67% were in NYHA functional class III. In comparison, in the EORP registry, the majority were in NYHA functional class I (32.7.4%) and II (49.9%) [5]. This can be the result of later presentation to the hospital for diagnosis, a more difficult access to healthcare facilities for people coming from rural areas, as well as a possible lower compliance to the medical treatment.

Atrial fibrillation (AF) is a common arrhythmia which complicates the natural history of HCM, the risk of occurrence being 4- to 6-fold greater than in the general population [8]. In our study the prevalence of AF was 28.1%, somewhat higher than the value reported in a systematic review in 2014 (22.45% with 95% CI 20.13% to 24.77%) [9]. In the EORP registry a history of atrial fibrillation was reported in 26.6% of the enrolled patients [5]. The main predictors of developing AF in HCM patients are left atrial size, age and NYHA functional class [8]. The mean antero-posterior diameter of the left atrium in our registry was 45.3 ± 7.7 mm, somewhat higher than the result of the Italian registry of HCM (42±9mm), which could explain the higher prevalence of AF in our study (28.1% and 18%, respectively) [10, 11].

The European Society of Cardiology guidelines published in 2014 recommend a 48-hour ambulatory ECG monitoring at the initial assessment of patients with HCM in order to determine the SCD risk, as well as the thromboembolic risk [2]. In our registry only 64.7% of the patients had an ambulatory ECG monitoring, a significantly lower percentage than in the EORP pilot registry (79.4%), but similar to the one reported in the long term registry (66.9%). Non-sustained ventricular tachycardia, a factor associated with an increase in the SCD risk, was reported in 19.8% of the patients. The percentage varies in other previously published studies from 19.6% to 31% [12, 13].

Of the patients included in our registry, 34.3% had a significant LVOT gradient (≥ 50 mmHg) at rest, in a similar range than reported in a previous study (37%) [14]. Overall, the obstructive form of HCM was reported in 43.6% of the patients, a significantly smaller percentage than the figure reported in the literature (70%) [14]. This difference could be explained by the fact that the registry only included dynamic gradient provocation by the Valsalva maneuvre, but not exercise stress echocardiography in patients without obstruction at rest, which has a reduced sensitivity (40%) for detecting the presence of an exercise-induced LVOT gradient [14].

Cardiac magnetic resonance is a complementary imagistic method in evaluating patients with HCM. It has a higher spatial and temporal resolution and brings valuable information regarding the cardiac structure, function as well as the presence of myocardial fibrosis, which is associated with an increased risk of developing major adverse events [15, 16]. In our group of patients cardiac magnetic resonance was performed in only 6.6% of them, in comparison with the EORP registry where this imagistic method was used in 33.8% of the HCM patients. The ESC guidelines for HCM management recommend using cardiac MRI in all HCM patients with inadequate echocardiography window (class I, level of evidence B indication), as well as in all patients for extensive assessment of structure and function (class IIa, level of evidence B indication) [2]. The low accessibility to cardiac magnetic resonance in Romania, as proven by this registry, is caused by the fact that there are few centres where this type of investigation is performed, as well as its high costs.

Based on current guidelines, genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives (class I indication, level of evidence B) [2]. However, genetic testing was very rarely reported in RENCMH patients (7, 3.3%), proving the very low accessibility to certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations in the Romanian public health system.

The pharmacological treatment remains the main approach in the management of HCM, targeting the symptomatology, LVOT obstruction and the arrhythmias [17]. The use of different classes of drugs in our study was similar to the EORP registry: beta-blockers 72.9% *vs*. 74.4%, diuretics 28.1% *vs*. 31.4%, oral anticoagulants 28.6% *vs*. 27.2% [5].

Invasive methods of reduction the LVOT obstruction were used in a small proportion of patients [18]. The alcohol septal ablation was performed in 6.1% patients, the percentage being somewhat higher than in EORP long-term registry (4%), while the percentage of those who underwent surgical septal myectomy was significantly higher (10.5% and 4.6%, respectively) [4]. The higher proportion of patients who benefited from surgical therapy of LVOT obstruction in our registry is due to the fact that most of them are reported by one high-volume and high-expertise centre for this procedure.

Regarding the prevention of SCD, even though 10.4% of the patients had a high risk, only 5.7% received an ICD, in comparison with EORP registry where 19.9% received an ICD for either primary or secondary prophylaxis [5].

Study limitations

The patients enrolled in the Romanian registry for HCM came from various centres both of tertiary and secondary care. The voluntary nature related to registries enrollment can bias the interpretation of data, as they mainly come from higher-volume, academic centres.

Even though a self-explanatory electronic chart was created to be filled for each patient, the data were incomplete in some cases. In addition, it is a transversal study which could not assess the disease progression, as well as the need for further, more invasive treatment in time.

As mentioned before, the registry lacked a file on exercise test as a tool for assessing functional class and obtaining higher LVOT gradients in patients appearing to have non-obstructive HCM.

CONCLUSIONS

The Romanian registry for HCM illustrates the patient characteristics at a national level, the extent to which the European guidelines are applied and the aspects in the disease management which need improvement – the accessibility to diagnostic tests (ambulatory ECG monitoring, cardiac magnetic resonance, genetic testing) and invasive methods of treatment (ICD, alcohol septal ablation and surgical septal myectomy).

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

* The first 2 authors had equal contributions.

Introducere. *Cardiomiopatia hipertrofică (CMH) este o afecțiune caracterizată de creşterea grosimii peretelui ventriculului stâng (VS) care nu este explicată doar de condiții anormale de încărcare, cu o mare heterogenitate în ceea ce priveşte expresia clinică şi prognosticul. Scopul studiului a fost de a colecta date despre pacienții cu CMH din diferite centre din țară pentru a analiza caracteristicile generale şi alegerile terapeutice în această populație.*

Metode. *Între decembrie 2014 şi aprilie 2017, 210 pacienți din 11 centre române de cardiologie au fost înrolați în Registrul Național de CMH. Toți pacienții au întrunit criteriile de diagnostic pentru CMH conform ghidurilor Societății Europene de Cardiologie. Caracteristicile clinice, electrocardiografice, imagistice şi terapeutice au fost incluse într-un formular online.*

Rezultate. *Vârsta medie la înrolare a fost 55±15 ani cu o predominanță a sexului masculin (60%). 43.6% dintre pacienți au avut forma obstructivă de CMH, 50% forma non-obstructivă, în timp ce 6.4% au avut forma apicală. Grosimea maximă a pereților VS a fost 20.3±4.8 mm (limite 15-37mm), în timp ce fracția de ejecție a VS a fost 60±8%. Simptomele de insuficiență cardiacă au dominat tabloul clinic, în special clasa funcțională NYHA II (51.4%). Cele mai frecvente aritmii au*

fost fibrilația atrială (28.1%) şi tahicardia ventriculară nesusținută (19.9%). Scorul mediu de risc de moarte subită a fost 3.0 ± 2.3%, cu 10.4% dintre pacienți având un risc crescut de moarte subită. Doar 5.7% dintre pacienți au primit un defibrilator implantabil. Pacienții au fost tratați în special cu beta-blocante (72.9%), diuretice (28.1%) şi anticoagulante orale (28.6%). Tratamentul invaziv al obstrucției tractului de ejecție al ventriculului stâng a fost realizat în cazul unui număr mic de pacienți: 22 dintre aceştia au efectuat miomectomie şi 13 ablație septală cu alcool. Investigarea prin rezonanță magnetică cardiacă a fost raportată doar pentru 14 pacienți (6.6%).

***Concluzii**. Registrul român pentru CMH ilustrează caracteristicile pacienților la nivel național precum şi aspectele care necesită îmbunătățire în ceea ce priveşte managementul acestei afecțiuni – accesibilitatea la teste diagnostice moderne şi metode invazive de tratament.*

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