Clinical study of patients with hypertrophic cardiomyopathy

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Summary:

Background: Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease. Its morphologically divided into asymmetrical septal hypertrophy, symmetrical concentric hypertrophy and apical hypertrophy,and physiologically divided into obstructive HCM and non obstructive HCM according to the left ventricular outflow tract (LVOT) gradient at rest or with provocation. Several factors that increase risk of sudden cardiac death (SCD), the more risk factors a patient has, the greater the chance that the patient is exposed to sudden death and sufficient to warrant consideration for interventional therapy.

Objective: The aims of the study are to evaluate the clinical presentations, risk stratification and family screening of patients with HCM.

Patients and methods: This cross sectional study was performed in Ibn-Albitar hospital for cardiac surgery. We studied the prevalence of certain variables among seventy three patients with HCM from "June 2010 to April 2012" including the clinical triggers ,electrocardiographic (ECG) changes, ventricular and supraventricular arrhythmia by holter monitoring, morphological and physiological types of HCM by echocardiography, family screening and finally we assessed the risk factors for SCD and candidacy for interventional procedures.

Results: A total of seventy three patients, males to females ratio were 1.5:1 with a mean age of 34±26 (years). HCM was higher in patients younger than 45 years of age, 43(58.9%). Eighty seven percent were symptomatic and (12.3%) were asymptomatic diagnosed by family screening of first degree relatives with HCM. Family history of HCM was identified in (38.3%).Three quarter of patients had asymmetrical septal hypertrophy and (6.8%) had pure apical HCM. Abnormal ECG was found in(87.6%) mainly in the form of left ventricular hypertrophy(LVH)while 9 patients(12.3%) had normal ECG. Nonsustained ventricular tachycardia(NSVT) was found in(30.1%). Echocardiographically, systolic anterior motion(SAM) of the anterior mitral leaflet was seen in about half of patients and three patients (7.6%) had SAM without LVOT obstruction. About half of patients (49.4%) had resting and provocable LVOT obstruction and about half of obstructive type (47.2%) had LVOT gradient ≥50mmhg and are candidate for surgical or percutaneous intervention.

Conclusions: Most of our patients were symptomatic and significant number of patients had family history of HCM. Asymmetrical septal hypertrophy was the commonest morphological type of HCM. Relatively equal prevalence of obstructive and nonobstructive HCM and significant number of patients with the obstructive type had LVOT gradient ≥ 50mmhg who are candidate for surgical or trascatheter interventions.

Key word: clinical, hypertrophic, cardiomyopathy

Introduction:

Hypertrophic cardiomyopathy is a common genetic cardiovascular disease, the quintessential phenotype of HCM, to be about 0.2% (i.e., 1:500) in the general population(1).HCM is a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease (2). Clinically, HCM is usually recognized by maximal LV wall thickness ≥15mm.It is divided morphologically into three groups:1-Asymmetrical septal hypertrophy with a ratio of anterior or posterior septum to left ventricular posterior wall of 1.5:1 or greater.2-

symmetric hypertrophy, with a wide spectrum of wall thickening, from 3.5 to 4.5 cm thickness in all regions with severe cavity elimination to those with thickness of only 1.5 cm and near normal cavity dimensions.3- Apical HCM, defined as a ratio of 1.5:1 or greater in the apex comparing lower and upper ventricular wall thickness (3). Patients with apical HCM were further subdivided into two groups "pure" Apical HCM and"mixed" apical HCM(coexistent hypertrophy of the interventricular septum)(4) .

The pathophysiology of HCM is complex and consist of multiple interrelated abnormalities, including LVOT obstruction, diastolic dysfunction, mitral regurgitation,

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myocardial ischemia, and arrhythmias. It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction(2). Up to one third of patients with HCM will have obstruction under basal (resting) conditions (defined as gradients more than or equal to 30 mm Hg). Another one third or more of patients will have labile, physiologically provoked gradients (less than 30 mm Hg at rest and more than 30 mm Hg with physiologic provocation), The final one third of patients will have the nonobstructive form of HCM (gradients less than 30 mm Hg at rest and with provocation). Marked gradients more than or equal to 50 mm Hg, either at rest or with provocation, represent the conventional threshold for surgical or percutaneous intervention if symptoms cannot be controlled with medications(5).

Diagnosis: The clinical diagnosis of HCM is conventionally made with cardiac imaging, at present most commonly with 2-dimensional echocardiography and increasingly with cardiac magnetic resonance imaging(CMR). Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM(6). A12-lead ECG is recommended in the initial evaluation and as a component of the screening algorithm for first-degree relatives of patients with HCM(6). Twenty-four hour ambulatory (Holter) electrocardiographic monitoring is recommended in the initial evaluation of patients with HCM who develop palpitation or lightheadedness and to detect ventricular tachycardia (VT) and identify patients who may be candidates for implantable cardiac defibrillator device(ICD) therapy(6). Transthoracic echocardiography(TTE) is recommended in the initial evaluation and as a component of the screening algorithm for family members of patients with HCM . Periodic (12 to 18 months) TTE screening is recommended for children of patients with HCM, starting by age 12 years(6). Although many patients have dynamic LVOT obstruction at rest, a significant number will have new or higher gradients after the Valsalva maneuver, inhalation of amyl nitrite, or during provocative exercise (5).

SCD Risk Stratification: All patients with HCM should undergo comprehensive SCD risk stratification at initial evaluation to determine the presence of the following:
1-Prior Personal History of Ventricular Fibrillation, SCD, or Sustained VT(7).
2-Family History of SCD(8).
3-Syncope(9).
4-Nonsustained Ventricular Tachycardia(10).
5-Maximum LV Wall Thickness(11).

Management: ICDs for secondary or primary prevention of sudden death in patients with risk factors(12). ;

drugs appropriate to control heart failure symptoms(2), surgical septal myectomy(13)or alcohol septal ablation(14) for progressive and drug-refractory heart failure caused by LVOT obstruction; heart transplantation for systolic (or less frequently intractable diastolic) dysfunction associated with severe unrelenting symptoms(15);and drug therapy or possibly radiofrequency ablation or surgical maze procedure for AF(16).

The aim of the study: To determine the clinical evaluation, risk stratification and family screening of patients with HCM.

Patients and Method:

This cross sectional study was performed in Ibn-Albitar hospital for cardiac surgery .We studied seventy three patients with HCM between "June 2010 to April 2012". Each patient had full history, clinical examination, ECG , 24 hours Holter study and echocardiography. Family screening and risk stratification for SCD were performed for all patients.

Definition of clinical variables: 1-Age(in years): we divided population into three groups, those < 45 years, those between 45and 60, and lastly those who are >60 year .2-Gender:divided into male and female.3-Clinical triggers: include history of chest pain ,dyspnea, palpitation, fatigue, presyncope, syncope and history of resuscitation from cardiac arrest .4-ECG: LVH was analyzed by Sokolow-Lyon index(17).5-24 hours Holter monitoring: to look for NSVT(defined as a run of≥3 consecutive ventricular beats at a rate of ≥120 beats/min, lasting<30 seconds),premature ventricular complex(PVCs) and paroxysmal atrial fibrillation(AF) (18).6-Echocardiography: Echocardiographic studies were performed with commercially available instruments PHILIPS (Envisor CHD). A complete M-mode and two-dimensional study was performed with parasternal and short axis views. The peak instantaneous LV outflow gradient at rest and with valsalva was estimated with continuous-wave Doppler. We evaluated the following variables: a-Maximal left ventricular wall thickness≥15mm in patients without HT, AS or athletes (6).b-Morphological types of HCM classified as asymmetrical septal hypertrophy(upper anterior septal to posterior wall ratio of 1.5:1) , symmetrical concentric HCM ,pure apical(defined as a ratio of 1.5:1 or greater in at least two of four measurements comparing lower and upper ventricular wall thickness), mixed apical HCM(19) and associated RVH(20).c-physiological types of HCM ,we divide HCM into obstructive and non obstructive HCM according to measurement of LVOT gradient by Doppler Echo. The obstructive type defined as LVOT gradient ≥30 mmhg at rest or with valsalva. LVOT gradient ≥ 50mmhg at rest or with valsalva was measured(6).Non obstructive type, the LVOT gradient < 30 at rest or with valsalva (5).d-SAM

(systolic anterior motion of mitral valve leaflet).h-MR≥ to 2+: defined by color flow Doppler(18). i- EF% j-Diastolic function depend on assessment of E/A ratio (21). 7-Family history: include history of HCM and history of SCD in first degree relative. Family screening was performed for first degree relatives with HCM depending on ECG and echocardiography(6).

Statistical analysis:Standard statistical analysis was done using SAS program run in IBM computer. Proportion was tested by using the number (No.) and percent (%) for most clinical variables and Mean± SD for some of echocardiographic variables.

Results:

A total of seventy three patient of HCM had a mean age of 34±26(years) with arange of 13-70 years. Table 1 shows distribution of the studied sample according to their age and gender. Males to females ratio were 1.5:1. HCM was higher in patients < 45 year of age, 43(58.9%).

Table 1: The distribution of the studied sample according to the age and gender

Gender					
Male		Female		Total	%
N	%	N	%		
25	56.8	18	62	43	58.9
16	36.3	5	17.2	21	28.7
3	6.8	6	20.7	9	12.3
44	100	29	100	73	100

Table 2 shows the clinical triggers of patients with HCM. Sixty four(87.6%) patients were symptomatic and 9(12.3%) were asymptomatic diagnosed by family screening of first degree relatives with HCM. Dyspnea and fatigue were the most common symptoms.

Table 2: Clinical triggers of patients with HCM

Clinical Variable	N	%
Asymptomatic	9	12.3
Chest pain	16	21.9
Dyspnea	34	46.5
Syncope	20	27.4
Presyncope	26	35.6
Palpitation	24	32.8
Fatigue	32	43.8
Cardiac arrest	1	1.3

Table 3 shows first degree family screening of patients with HCM. Nine patients (12.3%) were diagnosed by family screening (Echocardiography) while all of them were asymptomatic and had normal ECG with different morphological types of HCM.

Table 3: Family screening of patients with HCM

| Gender					
Male		Female		Total	%
N	%	N	%		
25	56.8	18	62	43	58.9
16	36.3	5	17.2	21	28.7
3	6.8	6	20.7	9	12.3
44	100	29	100	73	100

Table 4 shows morphological types of HCM by echocardiography. Three quarter of patients had asymmetrical septal hypertrophy.

Table 4: Morphological types of HCM by echocardiography

Types	N	%
Asymmetrical septal hypertrophy	55	75.3
Symmetrical concentric hypertrophy	13	17.8
Pure apical HCM	5	6.8
Mixed apical HCM	2	2.7
Associated RVH	3	4.1

Abnormal ECG was found in 64(87.6%) patients, while 9(12.3%) had normal ECG. The majority had LVH. One patient had Mobitz type II AV block and had dual chamber pacemaker was inserted. Seven patients (9.5%) had giant T-wave and those were the patients with pure and mixed apical HCM. Twenty four hours holter monitoring reveal that PVCs was the commonest finding 56(76.7%), NSVT 22(30.1%), paroxysmal AF 3(4.1%) and 15(20.5%) had normal holter.

Figure1: Show the frequency of obstructive versus nonobstructive HCM. About half of patients 36(49.4%) had resting and provocable LVOT obstruction.
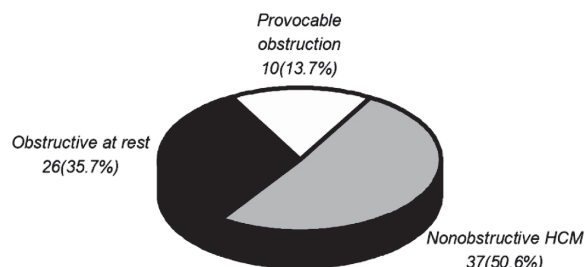

Figure 1:The frequency of obstructive versus nonobstructive HCM

Table 5 shows the frequency of LVOT gradient in patients with obstructive HCM. About half of them(47.2%) with LVOT gradient ≥ 50mmhg at rest and with valsalva. SAM was seen in about half of patient and three patients (7.6%) had SAM without LVOT obstruction. Three patients (4.1%) had associated mid ventricular obstruction with gradient of ≥ 60mmhg.

Table 5: Frequency of LVOT gradient in studied sample with obstructive HCM.

	LVOT gradient(mmhg)					
	LVOT 30-49 mmhg at rest		LVOT30-49mmhg with valsalva		LVOT≥50mmhg at rest and with valsalva	
Obstructive HCM	N	%	N	%	N	%
	9	25	10	27.8	17	47.2
Total	36	100	36	100	36	100

Figure 2 shows the frequency of risk factors for SCD in studied sample with HCM. Of the total 73 patients, Thirty seven (50.6%) had risk factors for SCD and non sustained VT was the most prevalent one.
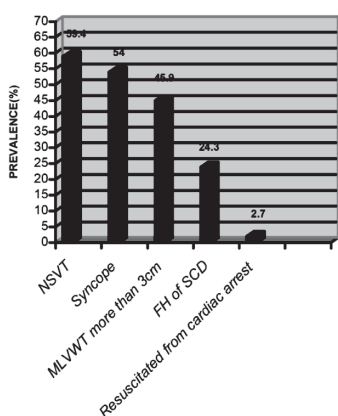
Figure 2: Frequency of risk factors for SCD among studied sample with HCM

Discussion:
This study focused on clinical evaluation, risk stratification and family screening of patients with HCM by history, examination, ECG, Echocardiography and Holter monitoring. Although HCM is a relatively common genetic cardiac disease, it's apparent that a substantial proportion of patients with this disease are not diagnosed clinically, many for whom timely recognition would be of substantial benefit to their clinical courses. The present study estimated that high prevalence of disease in male and in patients younger than 45year of age and this agreed with study done by Elliott PM et al(22) and study done by Maron MS

et al(5),but the mean age of our study group was slightly lower than that of previous studies. Our data substantiate that most patients with HCM continue to be diagnosed largely on the basis of overt clinical presentations that virtually mandate diagnostic studies such as echocardiography, including the onset of cardiac symptoms (i.e., chest pain and exertional dyspnea) as well as cardiovascular events such as syncope, atrial fibrillation, or cardiac arrest. The present study demonstrates that large number of the studied sample are symptomatic (87.6%) with clinical triggers that brought the patient to our hospital. (12.3%) of patient who were asymptomatic were diagnosed with family screening by echocardiography .Only one patient was resuscitated from cardiac arrest and these are similar to study done by Adabag AS et al(23). Regarding family screening of patients with HCM in our study reveals that (38.3%) had family history of HCM while (12.3%) had family history of SCD and this result partly agrees with study done by Efthimiadis GK et al who found that the family history of HCM was detected in (33.1%) and family history of SCD was detected in (10%) of patients (18). This reflects the importance of family history and family screening of all first degree relative with HCM for early diagnosis and risk stratification to prevent SCD. The limitation of this study is lack of genetic screening (24). The distribution of LVH in HCM by 2D echocardiography divide HCM in our study into asymmetrical septal hypertrophy(75.3%) which is the commonest type including (anterior, posterior and basal septal hypertrophy) and this results was comparable to study done by Klues HG et al(25) and study done by Leonard M et al(19). Pure apical HCM was found in (6.8%) in our study while mixed apical HCM was detected in(2.7%) which is considered large percentage compared with Klues HG et al study on American population who found that pure apical HCM constitute (3.2%) of studied sample while the results were near the results of Yan L et al in Chine's population who found that both pure and mixed apical HCM were detected in (16%) of studied sample(26). Georgios K Efthimiadis et al reported a case of isolated RVH(27) which is rare type of HCM while in our study we report 3cases (4.1%) of associated RVH with asymmetrical or concentric HCM. In our study almost (12.3%) of patients presenting with demonstrable echocardiographic evidence of HCM had a normal ECG at the time of diagnosis, and this results agreed with study done by McLeod CJ et al who demonstrated that normal ECG does not exclude the presence of HCM but suggests a mild manifestation of the disease and in this subset of patients with normal ECG-HCM appears to exhibit a less severe phenotype with better cardiovascular outcomes(28). The present study demonstrates a broad spectrum of ventricular and supraventricular arrhythmias occurring particularly on

ambulatory (Holter) ECG, for example,(76%)of our patients had PVCs ranging from frequent PVCs to couplets . NSVT was demonstrated in (30.1%) of our studied sample and this agreed with study done by Adabag AS et al (10) and he associated the presence of arrhythmias on 24-h holter with severe disease expression. . He found that NSVT and couplets were more common in HCM patients with advanced symptoms (NYHA functional classes III or IV), and NSVT was significantly more common in association with extreme LV hypertrophy . The latter finding is relevant to recent observations that relate extreme LV hypertrophy to a greater likelihood of sudden death in HCM. The ambulatory Holter ECG has been an important component of the outpatient evaluation and risk stratification of HCM patients; therefore absence of these arrhythmia more reliably defined those patients at low risk who deserve reassurance regarding their prognosis. Paroxysmal atrial fibrillation was detected in (4.1%) of the patients, Adabag AS et al reported that its occurrence correlated with older age , advanced symptoms (NYHA functional classes III or IV) and enlarged left atrium (10). Regarding echocardiographic variables of our study reveals that SAM was detected in (53.4%) of patient which is already present at rest or provoked with valsalva and this result agreed with study done by Leonard M.et al.(19). Maron BJ et al reported that (15%) had SAM of the mitral valve, but without evidence of basal outflow obstruction by doppler imaging(29) while our study revealed this feature in (7.6%) of patients. Our study revealed that LVOT obstruction(gradient ≥ 30 mmhg at rest and with valsalva) was detected in about half of patients (49.4%) which are slightly less than study done by Maron MS et al who revealed that of those patients in whom valsalva did not provoke a gradient, (15%) developed an exercise gradient of 30 to 49 mm Hg, and (25%) had an exercise gradient ≥50 mm Hg; Therefore, the valsalva maneuver had a sensitivity of only 40% for identifying the presence of an exercise-induced outflow gradient(5). In patients with both avalsalva-induced and an exercise-induced gradient, the outflow obstruction generated during the valsalva maneuver significantly underestimated the magnitude generated during exercise(5). Maron et al in 2003 and Elliott et al in 2006 support the finding that patients with HCM presenting with an LVOTO gradient of ≥30 mm Hg have a relative risk for SCD of about twofold that of nonobstructed patients. They found that relief of outflow tract obstruction through surgical myectomy is associated with very low rates of SCD . A limitation to using LVOT obstruction as an independent risk marker is that the obstruction in HCM is dynamic and highly variable from hour to hour(6). Around half of patients with obstructive HCM had LVOT gradient ≥ 50mmh at rest and with valsalva and regarded

a significant percentage of patients who are candidate for surgical or percutaneous interventions according to guideline of management of HCM(6).Almost all patients in studied sample were stratified according to risk factor for SCD for prevention of sudden death in those patients and their relatives. Half of our patients had risk factors for SCD. The most prevalent risk factor was NSVT (59.4%). Syncope was found in (54%) of patients with risk factors for SCD and regarded as the most warning symptoms that require further evaluation and this corresponded with study done by Elliot PM et al(22). MLVWT≥30mm was detected (45.9%) in our studied sample. Spirito P et al, demonstrated that the magnitude of hypertrophy is directly related to the risk of sudden death and is a strong and independent predictor of prognosis. Multiple risk factors ≥2 were found in (56.7%) of patients with risk factors for SCD, Elliot PM et al, demonstrates that patients with multiple risk factors have a substantially increased risk of SCD sufficient to warrant consideration for prophylactic therapy(22).

Conclusions:
Most of patients with HCM were symptomatic; syncope was the most warning symptom and large number of patients had family history of HCM. Abnormal ECG was found in a majority of patient and the LVH was the most prominent feature. PVCs were the most common ventricular arrhythmias and NSVT was the most warning arrhythmia by Holter monitoring. Asymmetrical septal hypertrophy was the commonest morphological type of HCM. Relatively equal prevalence of obstructive and nonobstructive HCM of our studied sample.

Authors Contributors:
Dr.Amjad R. Bairam and Dr.Alaa A.Al-Kinani Performing and doing study conception , study design, acquisition of data analysis, interpretation of data, drafting of manuscript and critical revision.
Dr. Mahmood R. Al –Haleem and Dr.Ghazi A.Jawhar participate in acquisition of data analysis

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