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CHILDHOOD HYPERTROPHIC CARDIOMYOPATHY: AN UNDERRECOGNIZED ENTITY

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is a known cause for sudden death in young adults and adults. It is also been increasingly recognized as an important underlying etiology in neonates and young children. Aim: to analyze the clinical profiles and to correlate with the histopathological features in 45 neonates and pediatric patients at autopsy. Material and methods: Retrospective study in 45 autopsy cases in whom unexplained left or both right and left ventricular hypertrophy were observed during gross examination of the organs. Detail histological studies were carried out in the multiple sections sampled form heart. Results: Clinically only one case was diagnosed as hypertrophic congenital heart disease, remaining cases had various clinical diagnoses including recurrent pneumonia. Grossly the heart weights were increased in all the cases with equal numbers of symmetrical and asymmetric ventricular hypertrophy. One third of the cases had associated cardiac anomaly. Microscopic examination showed classical histological features of HCM. There were myocardial fiber disarray with hypertrophied myocytes, anisonucleosis, streaky myocardial and perivascular fibrosis, patchy endocardial sclerosis and swollen endothelial cells of the perforating vessels. Conclusion- diagnosis of HCM may be difficult clinically. Autopsy may be considered in aa unresponsive and unexplained deaths. Histological features of HCM are characteristic to make the diagnosis.

KEYWORDS: Hypertrophic cardiomyopathy, autopsy, myofibre disarray, recurrent neonatal pneumonia, infantile pneumonia, septicemia.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is defined as the presence of unexplained left ventricular hypertrophy (LVH). Such LVH occurs in a non-dilated ventricle in the absence of other cardiac or systemic diseases capable of producing the observed magnitude of increased left ventricular (LV) wall thickness, such as long-standing hypertension, aortic stenosis, storage or infiltrative disorders. Reported incidence of unexplained HCM is approximately 1 in 500 in general population.[1] LVH often becomes apparent during adolescence or young adulthood around the onset of puberty.[2] Hypertrophy of LV can develop late in life, in infancy or in early childhood.[3] Pediatric cardiomyopathy (CM) is uncommon and includes heterogeneous group of disorders accounting for about half of all cardiac transplantations in children.[4] Reported studies of childhood CM reflected mainly accumulated experiences either in single institution,[5-8] single region [9,10] and one country.[11] Clinical features of HCM are reportedly variable, ranging from asymptomatic LVH to arrhythmias (atrial fibrillation as well as malignant ventricular arrhythmias) to refractory heart failure. Most common documented symptoms in young adult and adults are shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, pre-syncope and syncope. HCM is also an important cause for sudden cardiac death (SCD) and an important underlying etiology for heart failure in all age group.[12,13] HCM is increasingly recognized yet there is little data available regarding its prevalence, atypical clinical presentaiton and outcome of the disease. Main purpose of the present study was to analyze retrospectively the presenting clinical symptomatology, pathological features observed in the heart and other organs at autopsy in patients who were detected to have unexplained ventricular hypertrophy during routine heart review of hospital based clinical autopsy.

METHODOLOGY

We observed LV hypertrophy (LVH) in 45 cases over seven years' period (2010-2016) which were showing unaccountable LVH during routine organ review sessions. All these cases suspected to be cases of HCM

on gross examination of the heart and were subjected to histological examination of representative tissue blocks sampled from different parts of the heart. Exclusion criteria - cases who were found to have congenital heart disease, systemic vasculitis, chronic kidney diseases, known hypertension, clinical diagnosis of arrhythmia induced cardiac dysfunction, administration of corticosteroid or anthracycline, systemic metabolic or neuromuscular disorders or maternal diabetes. Available medical records of the enrolled cases were reviewed. Diagnostic criteria used in the present study for HCM were modification of the criteria described by the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.[14] The guideline stated that " a morphologic diagnosis is based on the presence of a hypertrophied and non-dilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident in a patient (usually 15 mm in an adult or the equivalent relative to body surface area in children)". The present study population included neonates, infants and children. Grossly the observations of the heart were recorded as follows - external appearance including appearances of the apex, left border and anterior and posterior surfaces of the left ventricle, LV cavity along inflow and outflow tracts, papillary muscle, length of chordea tendinea and its orientation with the mitral valve leaflets, appearances of LV cavity in the apical slice made at the level of base of papillary muscles. Ventricular wall hypertrophy was graded subjectively into mild, moderate and mark. Right ventricular (RV) wall thickness was also commented upon. Tissue blocks were sampled from both the ventricles inclusive the posterior wall, inter-ventricular septum, and LV and RV along outflow tracts inclusive of aortic and pulmonary valves, along inflow tracts inclusive mitral and tricuspid valves. On histology, we evaluated pattern and extend myocyte disarray, individual myocyte fibre hypertrophy/atrophy, anisonucleosis, degree of interstitial/myocardial fibrosis, intra-myocardial blood vessel, fat infiltration, endocardial thickening and any other histological variance from normal. We also performed special stains like Masson's trichrome (MT) and Elastic Van Giesen (EVG) to assess extend of fibrosis and elastosis. The junction between interventricular septum and ventricular free walls where disarray occurs naturally were excluded from the study. Demographic profiles of patients, clinical diagnosis and histopathological findings were evaluated.

RESULTS

Of the total of 2507 autopsy cases reviewed during 2010 to 2016, there were 45(1.8%) cases which had unaccountable left ventricular hypertrophy with the gross impression of HCM. These cases were still birth, neonates, infants and children who had predominant presentation with respiratory tract infection with septicemia and septic shock. Two thirds of the cases were male and one third was female. Clinical diagnoses of the cases are given in Table 1. Sepsis and septic shock related to pneumonia were the commonest clinical diagnosis and all these patients had terminal multi-organ failure. The youngest live born patient was a neonate who also had facial dysmorphism and deformed limbs born at 33 weeks of gestation. The oldest case was a ten years old male child who had presented with sepsis and septic shock. There were six patients who had multiple non-cardiac skeletal deformities like facial dysmorphism, spina bifida, recto-urethral fistula, arthrogryposis and umbilical hernia. Only in one case, ante-mortem diagnosis of HCM who was a neonate born at 40 weeks. Gestational age of still births is given in table 1.

Table 1: Distribution of the cases based on clinical diagnosis.

	Clinical diagnosis	Age range at presentation	Sex		Number (%)
			male	females	
1.	Sepsis, septic shock with multiorgan failure	1 day - 3 years	11	1	12 (26.6)
2.	Liver disease	6 months - 2years	3	3	6 (13.3)
3.	Multiple non-cardiac skeletal congenital malformations	1 day - 3 day	2	4	6 (13.3)
4.	Severe birth asphyxia	2 - 24 hours	4	1	5 (11.1)
5.	Intrauterine fetal death	Fresh still birth at 34 to 39 weeks of gestations	1	3	4 (8.8)
6.	Metabolic disorders	8 day and 11 months	2	0	2 (4.4)
7.	Meconium aspiration syndrome	6 hours and 3 day	1	1	2 (4.4)
8.	Hydrops fetalis	Fresh still birth and 20 hours	1	1	2 (4.4)
9.	Primary immunodeficiency	2 years 6 months	1	0	1 (2.2)
10.	Chronic Myeloid Leukemia with blast crisis	3 years	1	0	1 (2.2)
11.	Hypertrophic congenital heart disease	1 day	1	0	1 (2.2)
12.	Patent ductus arteriosus	3 day	1	0	1 (2.2)
13.	Arrhythmia	1 year 9 months	1	0	1 (2.2)
14.	Storage disorder	1 year	0	1	1 (2.2)
	Total		30	15	45 (100)

There was gross increased in the heart weight in the index 45 cases compared to normal heart for the age (Table 2). Group of the cases depicted in the first row in Table 2 were intra-uterine fetal death and fresh still births at 33 to 40 weeks of gestation.

Table 2: Gross weight of the hearts in different age groups of our cases.

Age group	Number (%)	Weight range in grams (normal range)	Mean heart weight in grams (normal mean weight)
33 to 40 weeks of gestational age	11	12-26 (10.2-18.9)	18.27 (15.7)
Neonates (day 1 to 30 days)	17	17.5-40 (17-20)	24.26 (18.5)
Infants (1 month to12 months)	10	20-58 (20-44)	52.25 (32.1)
Children (1 to 3 years of age)	7	60-155 (45-124)	96.2 (78.4)

The external and internal appearances of the hearts are shown in Fig. 1. In all our cases, hypertrophy was noted mainly involving LV free wall and septum. There were three cases that had shown septal hypertrophy with RV hypertrophy; another nine cases showed combination of LVH, septal hypertrophy and RVH. All these 12 cases were in anteroseptal category. Six cases were considered in septal hypertrophy category and 5 cases with LVH, septum hypertrophy, and apical hypertrophy were considered in anteroseptal-lateral category. We have 22 (48.8%) cases of symmetrical hypertrophy and 23 (51.1%) cases of asymmetric hypertrophy [six (13.3%) septal hypertrophy; five (11.1%) anteroseptal and lateral hypertrophy; and 12 (26.6%) anteroseptal]. In asymmetric hypertrophy, localization and degree of the hypertrophy were variable. The ventricular free wall thickness varied from 0.5 cm to 1.26 cm and septal thickness varied from 0.4 cm to 1.2 cm. In present study, 14 had small (~ 2 mm) patent foramen ovale, 3 cases with patent ductus arteriosus (PDA) and 1 case with PDA and transposition of great arteries (TGA) (Table 3).

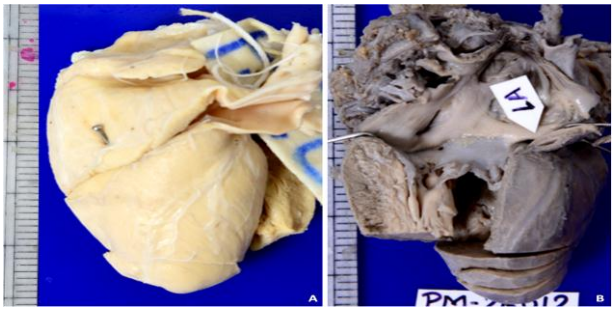

Fig. 1: Gross photographs of hearts. A: shows the anterior view of the heart showing enlarged left ventricle indicated by shifting of the interior interventricular sulcus towards the right and left ventricle forming the apex. B: shows the cut open view of left inflow highlighting the hypertrophied left ventricular posterior wall and grossly hypertrophied posterior papillary muscle almost filling up the left ventricular cavity and grossly shortened chordea tendinea.

Table 3: Cases with other anomalies.

S. No.	Congenital heart disease	Number of patients	Age (range)	Sex	
				Male	Female
1	Patent foramen oval	14	33wk-15day	8	6
2	PDA	3	34wk, new born, 1 day	1	2
3	One case of ASD, PDA and transposition of great arteries (TGA)	1	1day	0	1

Histology: On microscopic examination all cases showed disarray of myocardial fibers with hypertrophy of myocytes, anisonucleosis, streaky myocardial fibrosis, perivascular fibrosis, patchy endocardial thickening by fibrosis and stromal deposition of loose myxomatous material (Fig. 2). Affected myofibrils showed more than double the size of the normal cardiac myocytes with nuclear enlargement and hyperchromasia. The extent of disarray was variable. Eight cases showed additional findings of discoloration of the myocardium on gross examination suggesting myocardial infarction (MI). Microscopic examination of these affected areas showed histological changes in the form of eosinophilic myofibrils, loss of cellular detail and nuclei, atrophic thin myofibres, myocytolysis mainly along the sub-endocardium and extravasated red blood cells with minimum few scattered inflammatory cells. Intramural arteries showed thickening of the wall by smooth muscle proliferation and increased amount of collagen within adventitia (Fig. 2).

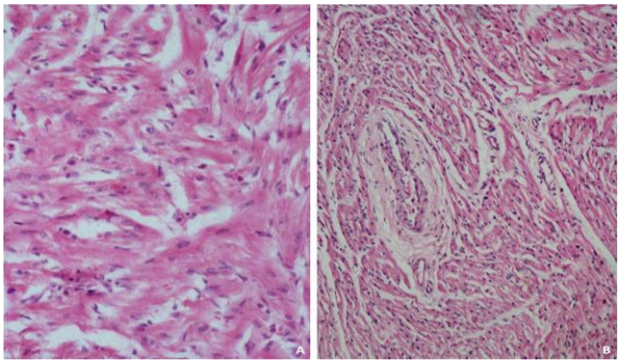

Fig. 2: representative photomicrograph of left ventricular myocardium. A: shows the characteristic diagnostic disarray of cardiac myocytes associated with anisonucleiosis and increased amount of intercellular collagen. B: show the prominent intramyocardial blood vessel with increased adventitial collagen amongst the disarray cardiac myocytes.

DISCUSSION

Diagnosis of HCM in these 45 autopsy cases were based on gross morphological features supported by the characteristics microscopic features. Out of these 45 cases, only one case was diagnosed clinically as HCM. Phadke et al[15] also documented similar distribution of symmetric and asymmetric cases of HCM. Maron at al[16] reported that sudden death in HCM was observed in wide age distribution. Majority of our cases were neonates and young children. Neonatal and childhood HCM is a well established condition though there is limited data and it has been reported to be associated with maternal diabetes,[17-19] osteogenesis imperfect,[20] neonatal Noonan syndrome,[21] and Danon disease[22] and in families of individual having HCM.[23] Available data suggest that sudden death especially in young adults and athletes is cardiac arrhythmia.[24,25] Only one case in our was documented to have arrhythmia during life. Teare et al[26] showed that disease with asymmetric basal and septal hypertrophy causes obstruction of left ventricular outflow at sub aortic level. Majority of our cases being fetal and neonates suggest disease evolvement to start at early fetal life. One study also had documented fetal HCM.[27] Similarly Zielinsky et al[28] reported fetal hypertrophic cardiomyopathy in 39 cases by prenatal echocardiography and majority of the mothers were diabetic. HCM is one condition where more than 400 different gene mutations and mutations of different genes have been documented in 50% to 70% of cases.[29]

Van Noorden and co-workers[30] introduced a semi quantitative approach for the diagnosis of HCM based on histological features like myocyte hypertrophy, disarray and interstitial fibrosis. Bulkley et al[31] reported myofibril disarray in the junction between interventricular septum and ventricular free walls in normal hearts. Hence, we have not taken into consideration the myocyte disarray in these foci. Few studies reported that myofibre disarray as a highly sensitive and specific marker for HCM only when considered in a quantitative rather than a qualitative fashion.[12,32] Using a planimetric method to measure the percentage area of septal disorganization, these studies showed a cut point of 5% to be the best to distinguish patients with HCM from those with other cardiac diseases. Subsequently, another study had shown that extent of muscle disarray does not differ much amongst the sections from the septum and the ventricular free wall in HCM.[33]

A quantitative approach in the diagnosis of HCM may be difficult due to variable amount and extent of distributions of the disarray, myocytes hypertrophy and fibrosis. Hence, endomyocardial biopsies will have both false negative and false positive results in the diagnosis of HCM. In this respect, studies in autopsy cases have the advantages of examining many sections taken from different select areas of the ventricles. Phadke et al[15] demonstrated significant myofibers disarray (~5%) in 40% to 50% cases in an average of twenty sections studied from one normal hearts. Not only myofibers disarray is diagnostic for HCM but also myocytes hypertrophy, interstitial myocardial fibrosis and vasculopathy along with gross features. O'Hanlon et al demonstrated varying degrees of fibrosis in myocardium to be an independent predictor of adverse outcome in HCM.[34]

To conclude, diagnosis of HCM clinically is difficult in asymptomatic patients, as these patients may have varied clinical manifestations in non-cardiac organs. A diagnosis may only be established with strong clinical and morphological suspicion with utilization of the available radiological approach. Quantitative assessment of myocardial fiber disarray along with other histological features in a heart with LVH is indeed pathognomonic for the diagnosis of HCM. The importance of histological examination may be emphasized especially in the setting unaccountably hypertrophied left ventricle or in cases with sudden death. Autopsy should be considered in unexplained cases of sudden death for the diagnosis of HCM.

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