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REVIEW ARTICLE

Fetal Ventricular Hypertrabeculation/Noncompaction: Clinical Presentation, Genetics, Associated Cardiac and Extracardiac Abnormalities and Outcome

Claudia Stöllberger[1,3] · Christian Wegner[2] · Josef Finsterer[1]

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Abstract Left ventricular hypertrabeculation/noncompaction (LVHT) is a cardiac abnormality of unknown etiology. Aim of the review was to summarize the current knowledge about fetal LVHT, including clinical presentation, associated cardiac and extracardiac abnormalities and outcome. In 88 cases, LVHT was diagnosed by fetal echocardiography. In 36 %, no additional cardiac abnormalities were reported; in the remaining 64 %, one or more cardiac abnormalities were reported. Eight cases died prenatally, 17 were electively terminated, and 24 patients died after birth. Six patients were lost to follow-up, and 33 patients are alive at a mean age of 26 months. Surviving cases presented less frequently with fetal hydrops (13 vs. 62 %, $p = 0.0004$), complete heart block (27 vs. 78 %, $p = 0.0076$), more than three associated cardiac abnormalities (9 vs. 47 %, $p = 0.0008$) and more frequently with isolated LVHT (52 vs. 19 %, $p = 0.009$) than cases who died. Of the surviving patients, 16 received pharmacotherapy, three received pacemakers, eight underwent surgical procedures and four underwent heart transplantation. Postnatal regression of left ventricular hypertrophy and development of LVHT was found in four cases, improvement in cardiac function in two, and regression of right VHT in two. At autopsy, endocardial fibrosis was the most frequent abnormality in 92 %. Thirty-eight percentage of cases with fetal LVHT survived. Fetal and postnatal echocardiographic findings challenge the "embryonic pathogenetic" hypothesis of LVHT. Furthermore, fetal pathoanatomic findings like endocardial fibrosis might play a role in clarifying the still unsolved pathogenesis of LVHT.

Keywords Noncompaction · Echocardiography · Cardiomyopathy · Fetal echocardiography

Introduction

Left ventricular hypertrabeculation/noncompaction (LVHT), also termed "spongy myocardium" or "persisting sinusoids," is a cardiac abnormality of unknown etiology, classified as "primary genetic cardiomyopathy" by the American Heart Association or as "unclassified cardiomyopathy" by the European Society of Cardiology [15, 37]. LVHT is diagnosed in children as well as in adults and may be associated with normally sized and well-contracting as well as dilated and poorly contracting left ventricles [9]. LVHT may be associated with or without other congenital cardiac abnormalities. LVHT is diagnosed by pathoanatomic investigation, ventriculography, cardiac magnetic resonance imaging, cardiac computed tomography and, most frequently, echocardiography [20]. Echocardiographically, LVHT is characterized by an increased number of left ventricular trabeculae and a two-layered myocardial structure, with an outer compacted and an

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✉ Claudia Stöllberger
claudia.stoellberger@chello.at

Christian Wegner
christian.wegner@oeaw.ac.at

Josef Finsterer
fifigs1@yahoo.de

[1] Krankenanstalt Rudolfstiftung, Juchgasse 25, 1030 Vienna, Austria

[2] Vienna Institute of Demography of the Austrian Academy of Sciences, Wohllebengasse 12-14, 1040 Vienna, Austria

[3] Steingasse 31/18, 1030 Vienna, Austria

inner noncompacted layer [16, 20]. Different diagnostic criteria for LVHT are currently used. The most frequently used criteria are listed in Table 1 [11, 31, 51]. Hypertrabeculation/noncompaction (VHT) may also affect the right ventricle. Since the right ventricle is physiologically more trabeculated than the left ventricle, the distinction between normal and pathologic is difficult and there are no clear-cut diagnostic criteria in the literature.

Prenatal diagnosis of LVHT can be achieved by a standard fetal anatomic sonographic four-chamber view or by fetal echocardiography [3, 29]. Aim of the present review is to summarize the current knowledge about fetal LVHT, including clinical presentation, associated cardiac and extracardiac abnormalities and outcome.

Search Strategy and Selection Criteria

A literature search was carried out by systematically screening MEDLINE for publications with the key words "noncompaction" or "non-compaction" and "fetal" or "foetal" from 1990 to 2014. Reference lists and older references generated from initial papers were also considered. Clinical trials, longitudinal studies, case series and case reports were included. Articles in English, German and Polish language were considered.

Statistics

Group comparisons between cases who survived and cases who died were made by the two-sided Fisher exact test by using the statistical software package R [13].

Results

Cases with Prenatal Diagnosis of LVHT

We found 27 publications reporting the echocardiographic diagnosis of fetal LVHT comprising a total of 88 cases [1, 3, 4, 7, 12, 14, 17, 24, 28, 30, 32, 35, 38, 39, 41, 43–45, 47–49, 52, 55, 57, 58, 60, 62]. Eighty-four of these cases were singleton pregnancies. Twin pregnancies were reported three times [52, 58]. In 85 cases, LVHT was diagnosed by fetal echocardiography and postnatally confirmed by either echocardiography or autopsy. In the remaining three cases, LVHT was diagnosed only postnatally, but review of the fetal echocardiograms disclosed that LVHT was visible but had been overlooked [35, 38, 43].

The earliest report was published in 1995 [35]. Before the year 2000, only one further report was published [62]. Between 2000 to 2009, 29 cases (33 %) were published [1, 7, 12, 17, 24, 32, 38, 39, 43, 44, 48, 49]. Since 2010, 57 cases (65 %) were published [3, 4, 14, 28, 30, 41, 45, 47, 52, 55, 57, 58, 60]. The majority of the cases ($n = 49$, 56 %) were reported from hospitals in the USA [1, 3, 4, 7, 12, 17, 24, 30, 35, 38, 57, 58]. Nine cases were reported from China [52], eight cases from Canada [60], five cases from France [39, 62], five cases from Turkey [43], three cases form the UK [32, 48], two cases each from Italy and the Netherlands [28, 44, 45] and one case each from Ireland, Greece, Portugal, Japan and Belgium [14, 41, 47, 49, 55]. The ethnicity is only reported in three cases of African origin [32, 39, 47].

Indications for fetal echocardiography were an abnormal screening examination ($n = 22$, 25 %) [12, 30, 32, 35, 38, 39, 41, 43–45, 47, 49, 55, 57, 58, 62], fetal arrhythmia/bradycardia ($n = 7$, 8 %) [1, 7, 32, 39, 43] and family screening ($n = 2$, 2 %) [24, 39]. In the remaining 50 cases (57 %), the indications for echocardiography were not reported. The gestational week in which LVHT was diagnosed ranged from 15 to 38 weeks (see Table 1 in the ESM appendix). The gender was female ($n = 32$, 36 %), male ($n = 23$, 26 %) or not reported ($n = 33$, 38 %). Fetal hydrops, defined as abnormal accumulation of fluid in two or more fetal compartments, such as ascites, pleural effusion, pericardial effusion, and skin edema, was present in 29 cases (33 %) and absent in 42 cases (47 %), and in the remaining 17 cases (19 %), no information about hydrops is given. LVHT was associated with complete heart block in 30 cases (34 %) [3, 4, 7, 14, 17, 32, 47], sinus

Table 1 Echocardiographic criteria for left ventricular hypertrabeculation/noncompaction

References	Criteria
Chin et al. [11]	Two-layered structure with an epicardial compacted and endocardial noncompacted layer with *X*/*Y* ratio ≤0.5 at end diastole
Jenni et al. [31]	Two-layered structure with an epicardial compacted and endocardial noncompacted layer with NC/C ratio ≥2 at end systole; color Doppler evidence of intertrabecular recesses supplied by intraventricular blood, absence of coexisting cardiac structural abnormalities
Stöllberger et al. [51]	>3 trabeculations protruding from the left ventricular wall apically to the papillary muscle visible in one imaging plane at end diastole; two-layered myocardium with NC/C ratio ≥2 at end systole; intertrabecular spaces perfused from the ventricular cavity, as visualized on color Doppler imaging

bradycardia in seven cases (8 %) [3, 17, 24, 32, 52, 62], supraventricular tachycardia in five cases (6 %) [39, 43, 62] and AV block II in three cases [1, 3].

In two cases, VHT was confined to the right ventricle exclusively [1, 52]. In 29 further cases (33 %), both ventricles were affected [3, 7, 12, 14, 24, 28, 32, 38, 39, 41, 43, 48, 49, 52, 55, 57, 58, 60, 62]. In the remaining 57 cases (65 %), VHT was confined to the left ventricle. Left ventricular systolic function was described as normal in 17 cases (19 %), as moderately reduced in 19 cases (22 %) and as poor in 11 cases (13 %), and unreported in the remaining 41 cases (47 %).

In 32 cases (36 %), no additional cardiac abnormalities were reported [1, 3, 28, 30, 32, 35, 38, 39, 41, 43, 44, 48, 49, 52, 57, 60, 62]. In three further cases, LVHT was associated with a left atrial thrombus [43], myocardial calcification [45] and restrictive cardiomyopathy [24]. In the remaining 53 cases (60 %), one or more structural cardiac abnormalities were reported. The most frequent abnormalities are listed in Table 2. In one case each were reported a single atrium [52], tricuspid stenosis [58], mitral atresia [3], crisscross atrioventricular valves [3], hypoplastic aortic valve [3], aorto-left ventricular tunnel [38], pulmonary regurgitation [43] and an atrial septal defect [38].

Associated with LVHT were abnormalities of the great vessels: interrupted inferior vena cava ($n = 8$) [3], interrupted aortic arch ($n = 1$) [3], coarctation of the aorta ($n = 2$) [3, 30], hypoplastic aortic arch ($n = 1$) [3] and left superior vena cava ($n = 2$) [3].

Extracardiac abnormalities associated with fetal LVHT were hypoplastic lungs ($n = 3$) [7, 47, 52], abdominal heterotaxia ($n = 1$) [7], omphalocele ($n = 2$) [7, 32], polysplenia ($n = 2$) [7, 47], bilateral hydronephrosis ($n = 2$) [32, 39], multicystic kidneys ($n = 1$) [32], hypoplastic/dysplastic kidneys ($n = 3$) [47, 52], absent gallbladder ($n = 1$) [32], extrabiliary atresia ($n = 1$) [32], hepatopathy ($n = 1$) [60], mild developmental delay ($n = 1$) [38], single umbilical artery ($n = 1$) [39], microcephaly ($n = 1$) [39], Toriello–Carey syndrome ($n = 1$) [44], broad forehead ($n = 1$) [49], flat nose ($n = 1$) [49], low-set ears ($n = 1$) [49] and multiple anomalies ($n = 2$) [60]. Genetic or metabolic abnormalities associated with LVHT were mitochondrial disorders ($n = 4$) [12, 14, 57, 60], *MYH7* mutations ($n = 3$) [28, 41], and 1 p 36 deletion ($n = 1$) [60].

Eight cases (9 %, female $n = 2$, male $n = 3$, gender unknown $n = 3$) died prenatally [7, 17, 24, 41, 43, 47], with confirmation of LVHT at autopsy in four cases [7, 24, 41, 47]. Of these eight cases, LVHT was associated with structural cardiac and extracardiac abnormalities in four cases [7, 17, 47], with restrictive cardiomyopathy in one case [24], and it was isolated in the remaining three cases [41, 43]. In one fetus with isolated LVHT, a de novo mutation in the *MYH7* gene was detected [41].

Seventeen fetuses (19 %) were electively terminated (female $n = 2$, male $n = 5$, gender unknown $n = 10$) [3, 17, 39, 44, 52, 60, 62], with confirmation of LVHT at autopsy in 11 cases [39, 52, 62]. In five cases, LVHT was associated with significant structural cardiac abnormalities [3, 17, 52], and in two further cases, it was associated with mitral and tricuspid valve regurgitation [39]. In further five cases, LVHT was associated with multiple extracardiac abnormalities including Toriello–Carey syndrome [44, 52, 60, 62]. In the remaining five cases, pregnancy was terminated only because of LVHT [52, 62].

Twenty-four patients (27 %) died after birth, thereof 22 patients (92 %) in the postnatal period [3, 4, 17, 32, 60], with confirmation of LVHT at autopsy ($n = 6$) [1, 3, 7, 12, 13, 17, 24, 29, 32, 35, 62]. The gender of the 22 patients

Table 2 Cardiac abnormalities of cases in whom fetal echocardiography detected ventricular hypertrabeculation/noncompaction

Abnormality	Number of cases	References
Atrioventricular septal defect	$n = 29$	[3, 4, 7, 17, 47]
Double-outlet right ventricle	$n = 23$	[3, 4, 17]
Left atrial isomerism	$n = 21$	[3, 4, 7, 17, 47]
Pulmonary stenosis	$n = 13$	[3, 14, 17, 52]
Dextrocardia	$n = 9$	[3]
Malposed great arteries	$n = 9$	[3, 17]
Mitral regurgitation	$n = 9$	[3, 28, 32, 39, 43, 58]
Tricuspid regurgitation	$n = 8$	[3, 28, 32, 39, 43]
Ventricular septal defect	$n = 6$	[12, 14, 17, 38, 52, 55]
Aortic valve stenosis	$n = 6$	[3, 17]
Pulmonary atresia	$n = 4$	[3, 58]
Right ventricular hypertrophy	$n = 5$	[3, 43]
Partial anomalous pulmonary venous return	$n = 3$	[17]
Right ventricular hypoplasia	$n = 3$	[3]

was female in 10 cases, male in six cases and unknown in the remaining six patients. In 19 of these 22 cases (86 %), LVHT was associated with structural cardiac and extracardiac abnormalities, and in only three cases, LVHT was isolated [32, 60]. Two further patients died within the first year of life: one female patient with mitochondriopathy at age 7 months because of a respiratory infection and the other female patient with structural cardiac abnormalities at age 2 months because of sudden death [43, 57].

Thirty-three patients (38 %, females $n = 14$, males $n = 9$, gender unknown $n = 10$) are reported to be alive [1, 3, 4, 12, 14, 17, 19, 28, 30, 32, 35, 38, 39, 43, 45, 48, 49, 52, 55, 58, 60]. The age at survival is reported in 18 cases and ranges between 15 days to 10 years with a mean age of 26 months (see Table 1 in the ESM appendix).

Six patients (7 %, females $n = 2$, gender unknown $n = 4$), all with significant cardiac and extracardiac abnormalities, were lost to follow-up [3].

In 33 cases (38 %), information about the family was reported. Familial LVHT was reported in seven (21 %) of these cases: LVHT of the mother, two brothers and one cousin ($n = 2$) [39], LVHT of the mother ($n = 2$) [60], LVHT and Ebstein's anomaly of the father ($n = 1$) [38], LVHT and MYH7 mutation of the grandmother, father and brother ($n = 1$) [28], and LVHT of a half sister ($n = 1$) [24]. Further reported familial diseases comprise consanguinity of the parents ($n = 2$) [43, 49], miscarriages of four siblings ($n = 1$) [45], a brother with Toriello–Carey syndrome ($n = 1$) [44], death of three uncles of metabolic disorder in childhood ($n = 1$) [49], cardiac murmur of the father in childhood ($n = 1$) [7], unspecified cardiac problems of the mother in childhood ($n = 1$) [57], father with dilated cardiomyopathy and MYH7 mutation ($n = 1$) [28], sibling with transposition of the great arteries ($n = 1$) [43], grandmother with systemic Lupus erythematodes and mother with ankylosing spondylitis ($n = 1$) [32], mother with Ebstein's anomaly ($n = 1$) [35] and mother with arterial hypertension ($n = 1$) [47]. In six cases, healthy parents are reported [14, 32, 38, 55], an "unremarkable family history" in four cases [43], no history of cardiac disease in one further case [12] and normal electrocardiograms of the parents in one case [1]. In further four patients, normal echocardiograms of the first-degree relatives ($n = 2$) [58] and of the mother ($n = 2$) are reported [30, 38]. Consanguinity of the parents is reported in two cases [43, 49]. In the remaining 55 cases, no information about the family is given. No information about neurologic or neuromuscular problems in the families is given.

We compared the characteristics of cases who survived with the cases who died pre- or postnatally and excluded cases who were electively terminated or lost to follow-up. Cases who survived presented less frequently with fetal hydrops than cases who died (13 vs. 62 %, $p = 0.0004$). Cases who survived had more frequent isolated LVHT than cases who died (52 vs. 19 %, $p = 0.009$) and less frequent more than three associated cardiac abnormalities than cases who died (9 vs. 47 %, $p = 0.0008$). Complete heart block was more frequent in cases who died than in cases who survived (78 vs. 27 %, $p = 0.0076$).

Cases with Fetal Echocardiography but Only Postnatal Diagnosis of LVHT

Additionally, we found 16 publications of 18 cases (females $n = 6$, males $n = 11$, gender unknown $n = 1$) in whom fetal echocardiography was carried out in gestational weeks 18–37 (mean 26 weeks) but did not show LVHT, whereas LVHT was diagnosed at a mean postnatal age of 176 days (1-1460) by echocardiography ($n = 15$) [5, 6, 18, 22, 25, 27, 34, 38, 42, 43, 46, 54, 59, 61] or by autopsy ($n = 3$) [6, 23, 56]. Indications for fetal echocardiography were an abnormal screening examination ($n = 6$) [18, 23, 27, 34, 46, 54], fetal arrhythmia/bradycardia ($n = 2$) [42, 61] and family screening ($n = 1$) [25], and indications were not reported in the remaining nine cases. In six cases, VHT affected also the right ventricle [6, 15, 27, 54, 56, 59]. In six cases, LVHT was associated with fetal arrhythmia (complete heart block $n = 2$, bradycardia $n = 2$, tachycardia $n = 1$, WPW syndrome $n = 1$) [18, 27, 42, 46, 54, 56]. In five cases, fetal hydrops was present [6, 22, 23, 46, 56]. Left ventricular systolic function in the fetal echocardiogram was normal in seven cases, moderately reduced in four cases, poor in five cases and not reported in the remaining two cases.

In six cases, no additional cardiac abnormalities except LVHT were reported [5, 6, 18, 27, 42, 46]. In the remaining 12 cases, one or more structural cardiac abnormalities were reported: pulmonary stenosis ($n = 4$) [34, 56, 59, 61], tricuspid regurgitation ($n = 3$) [22, 34, 54], ventricular septal defect ($n = 3$) [25, 38, 43], mitral regurgitation ($n = 2$) [6], tricuspid stenosis ($n = 1$) [23], premature closure of the arterial duct ($n = 1$) [22], aortic valve dysplasia ($n = 1$) [56] and atrial septal defect ($n = 1$) [59].

Extracardiac abnormalities reported in these 18 cases were psychomotor delay and respiratory insufficiency ($n = 1$) [5], Arnold-Chiari malformation and facial dysmorphism ($n = 1$) [38], and hepatomegaly ($n = 1$) [42]. Genetic or metabolic abnormalities were Xq28 mutations ($n = 3$) [6], mitochondriopathy ($n = 1$) [18], *MYBPC3* gene mutation ($n = 1$) [25] and trisomy 22 ($n = 1$) [59].

Of these 18 cases, one was electively terminated [23], three died in the postnatal period [34, 42, 56], one died at the age of 28 weeks [6], and the remaining 13 cases (72 %) are reported to be alive [5, 6, 18, 22, 25, 27, 38, 43, 46, 54, 59, 61].

In 11 cases (61 %), information about the family was reported. Familial LVHT was reported in four (22 %) of these cases [6, 34]. Further familary aspects comprise death of a sibling because of a cardiac anomaly ($n = 1$) [18], a sibling with tricuspid atresia ($n = 1$) [43], hypertrophic cardiomyopathy of the mother ($n = 1$) [25] and gestational diabetes of the mother ($n = 1$) [46]. In two cases, a negative family screening is reported [5, 38]. Consanguinity of the parents is reported in one case [43]. In the remaining seven cases, no information about the family is given. No information about neurologic or neuromuscular problems in the families is given.

Postnatal Development of the Surviving Cases

Forty-six of the patients (43 %) were reported to be alive 0.5–120 months (mean 28 months) after birth [1, 5, 6, 12, 14, 18, 19, 22, 25, 27, 28, 30, 32, 35, 38, 39, 45, 46, 49, 54, 55, 58, 59, 61]. Their characteristics are reported in Table 2 of the ESM appendix. In 16 (35 %) of these 46 cases, it is only reported that they were alive, but no age is given [3, 4, 17, 43, 48, 52, 60]. Three patients (7 %) received pacemakers [1, 14, 27], four patients (9 %) underwent heart transplantation [3, 6, 25, 60], eight patients (17 %) underwent one or more interventional or surgical cardiac procedures [17, 28, 30, 38, 58, 59, 61], 16 further patients (35 %) were treated with pharmacotherapy only [5, 6, 12, 18, 22, 32, 38, 39, 43, 46, 49, 54, 55, 58], and in 15 patients (33 %), it is not reported whether they received any therapy. Follow-up echocardiographic examinations disclosed postnatal changes in seven cases (15 %): regression of left ventricular hypertrophy and development of LVHT (acquired LVHT) in four cases (9 %) [5, 18, 22, 25], improvement in cardiac function in two cases (4 %) [28, 38] and regression of right VHT in two cases (4 %) [38, 54]. In none of the cases, disappearance of LVHT has been reported.

Delayed psychomotor development was reported in seven cases (15 %) 12–84 months (mean 43 months) after birth [5, 6, 14, 28, 38, 46].

Findings at Autopsy

In 27 cases (fetal diagnosis of LVHT $n = 21$, postnatal diagnosis of LVHT $n = 6$), autopsy was carried out after terminated pregnancy ($n = 12$), intrauterine demise ($n = 4$), death within the first 7 days after birth ($n = 8$), death after 7 months ($n = 1$) and heart transplantation ($n = 2$) [3, 6, 7, 23–25, 32, 34, 39, 41, 47, 52, 56, 62]. In 13 of these 27 cases, detailed reports of the autopsy are available. Apart from trabeculations, endocardial fibrosis or fibroelastosis was the most frequently reported abnormality in 12 of these 13 cases (92 %) [6, 7, 23–25, 32, 39, 41, 47, 56, 62]. Additionally, abnormal myocardiocytes were reported in four cases [6, 32, 34], dystrophic myocardial calcifications and multiple intraventricular thrombi in one case each [24, 39].

Discussion

Fetal diagnosis of VHT was once considered difficult or unreliable [6, 62]. Technical improvements in ultrasound equipment and advances in operator training have increased the detection of abnormal heart structure during routine obstetric scanning, allowing referral for specialist diagnosis and counseling [29]. Successful antenatal detection of LVHT has been well documented and has been achieved as early as 15 weeks of gestation [3]. Diagnostic criteria for the prenatal diagnosis of LVHT have been established which are similar to the criteria used for adults as listed in Table 1: multiple trabeculations and recesses, distinct compacted and noncompacted layers and a noncompaction/compaction ratio $\geq$2.0 during systole [3]. Awareness of echocardiographers and technical improvements are probably the reasons for the increase in publications about fetal LVHT since the beginning of the twenty-first century.

Despite these advances in the diagnosis of fetal LVHT, we know neither its prevalence nor whether its distribution differs between ethnicities. That the majority of cases (56 %) with fetal LVHT were reported from the USA may be rather explained by advanced prenatal care, lower threshold for publications and good quality of technical ultrasound equipment than by ethnic differences.

Fetal LVHT was frequently (60 %) reported to be associated with other congenital complex malformations including atrioventricular defects, double-outlet right ventricle, valvular atresias and transposition of the great arteries. Most probably, these malformations contributed to cardiac problems which initiated fetal echocardiography. Fetuses with structural cardiac defects and LVHT have a poorer prognosis than isolated LVHT cases.

Early detection of LVHT and associated structural abnormalities is crucial because LVHT may indicate a poor prognosis [3]. However, it has to be stressed that 38 % of cases with fetal diagnosis of LVHT survived and psychomotor delay is only reported in a minority of them (seven of 46 cases). Additionally, an improvement in cardiac function with pharmacotherapy or interventions has been reported in several cases. Thus, the fetal diagnosis of LVHT per se does not seem to be justified as an argument for termination of pregnancy.

No congenital anomalously originating coronary arteries have been reported in patients with a prenatal diagnosis of LVHT. This is surprising in view of the frequently

mentioned, although not proven, pathogenetic concept that LVHT is due to a developmental disturbance of the myocardium. The embryonic development of the coronary vasculature is closely associated with the compaction process of the myocardium, and thus, it could be expected that coronary anomalies occur more frequently in patients with LVHT [53].

The embryonic pathogenesis of LVHT is further challenged by the findings of four cases in whom repeated echocardiographic examinations documented that LVHT was not present at birth but developed postnatally [5, 18, 22, 25]. Furthermore, several cases with repeated ultrasound investigations during pregnancy showed that features of LVHT were visualized only later in pregnancy [28, 30, 32, 45, 49]. It is uncertain whether these observations reflect technical difficulties in viewing the fine noncompacted structure of the heart in early stages of fetal development or whether LVHT developed later. Additionally, it is unknown whether LVHT has been overlooked during examination of the fetus or developed postnatally in the cases whose fetal echocardiographies showed no LVHT and in whom LVHT was diagnosed only after birth [6, 23, 27, 34, 38, 42, 43, 46, 54, 56, 59, 61].

In contrast to the predominant left ventricular involvement of VHT seen in adults, the fetal cases frequently (33 %) display biventricular involvement. The high incidence of right ventricular VHT may be related to the right ventricular dominant fetal circulation. The fetal right ventricle perfuses the umbilical arteries. Postnatal follow-up investigations in two patients show that right ventricular VHT had decreased and right ventricular function had improved [38, 54]. This could be due to the fact that after birth, right ventricular dominance decreases with a fall in pulmonary vascular resistance and normalization of pulmonary artery pressures.

The higher prevalence of females in fetal VHT cases is at variance with cohort studies from infants [8] and adults in whom the prevalence of males is higher than that of females [2, 26, 36, 40, 51]. The cause for this phenomenon is unknown.

A further, so far unexplained, finding is the high prevalence (92 %) of endocardial fibrosis in the cases that underwent pathoanatomic investigation. Endocardial fibrosis is a frequently found abnormality in adults and children with LVHT [11, 21, 33]. Endocardial fibrosis may enhance the detection rate of LVHT since the endocardial boundary and the trabeculations become more clearly visible when investigating the heart by ultrasound. Endocardial fibrosis in LVHT is considered an aging phenomenon, which is rather unlikely in the fetus. It is unclear whether endocardial fibrosis develops due to immunologic reactions, whether it is the consequence of local blood flow abnormalities or whether it is induced by hemodynamic and mechanical factors around the trabeculated myocardium [50]. Endocardial fibrosis may lead to diastolic dysfunction, restrictive filling pattern of the left ventricle and heart failure. Involvement of the cardiac conduction system by the endocardial fibrosis might promote arrhythmia [33]. Probably, the endocardium plays a role in the pathogenesis of LVHT: Animal experiments have shown that endocardial Notch1 plays a crucial role in regulating ventricular trabeculations and that Fkbp1a-mediated regulation of Notch1 plays an important role in intercellular communication between endocardium and myocardium, which is crucial in controlling the formation of the ventricular walls [10]. Thus, there is a need to investigate more precisely the role of the endocardium in LVHT pathogenesis.

In conclusion, findings of LVHT in the fetus and postnatal period challenge the embryonic hypothesis in several aspects. The follow-up data are unfortunately rare; thus, the information about the prognosis of fetal LVHT is incomplete. Furthermore, fetal pathoanatomic findings like endocardial fibrosis might play a role in clarifying the still unsolved pathogenesis of LVHT.

Conflict of interest None.

Ethical standard Since the work is a review of cases published in the literature by several authors, no informed consent of the patients was feasible and therefore was not obtained.

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