Neuromuscular Disorders and Noncompaction Cardiomyopathy

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Introduction

Noncompaction cardiomyopathy (NCCM), also known as left ventricular hypertrabeculation (LVHT), has been repeatedly reported in patients with diseases of the skeletal muscle and rarely also in patients with diseases of the innervating neurons (neuromuscular disorders (NMDs)) [1]. The first patient with an NMD in whom LVHT was detected was reported in 1996 [2]. It was a 33 years old male with Becker muscular dystrophy (BMD) [2] in whom LVHT was accidentally detected when undergoing cardiologic diagnostic work-up for suspected heart failure [2]. During the following years, LVHT was additionally detected in a number of other NMDs (Table 3.1). Presence of an NMD in patients with LVHT has clinical implications. This chapter summarises and discusses previous and recent findings concerning patients with NMDs in whom LVHT was found and LVHT patients in whom an NMD was secondarily detected (Figs. 3.1 and 3.2).

History

After the first description of LVHT in a patient with BMD in 1996 [2], LVHT was consecutively described in a number of other NMDs. These include Barth syndrome [4], dystrobrevinopathy [6], mtDNA-related mitochondrial disorders (MIDs) [8],

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Table 3.1 NMDs in which LVHT has been described so far

NMD	Mutated gene	Reference
Becker muscular dystrophy (BMD)	*DMD*	[2, 3]
Barth syndrome	*G4.5/TAZ*	[4]
MIDs (biopsy, biochemistry positive)	uk	[5]
Dystrobrevinopathy	*DTNA*	[6, 7]
mtDNA-related MID (nonspecific)	mtDNA (*ND1, tRNA*)	[8]
Zaspopathy	*LDB3*	[7, 9–11]
Myotonic dystrophy 1	*DMPK*	[12–15]
mtDNA-related MID (LHON)	mtDNA (*ND1*)	[16, 17]
Laminopathy	*LMNA*	[18, 19]
Myoadenylat-deaminase deficiency	*AMPD1*	[20]
Duchenne muscular dystrophy (DMD)	*DMD*	[3, 21]
Hereditary neuropathy	*PMP22*	[22]
MYH7 myopathy	*MYH7*	[23, 24]
Myopathy with spherocytosis	uk	[25]
Myotonic dystrophy 2	*CNBP*	[26]
Oculopharyngodistal myopathy	uk	[27]
Glycogen storage disease IV	*Gbe1*	[28]
Fabry disease	*GLA*	[29, 30]
Duchenne carrier	*DMD*	[31]
Multiminicore disease	*RYR1*	[32]
Barth syndrome (carrier)	*G4.5/TAZ*	[33]
nDNA-related MID	*DNAJC19*	[34]
Congenital fiber type dysproportion	*MYH7B*	[35]
Glycogenosis IIb (Danon disease)	*LAMP2*	[36]
mtDNA-related MID (nonspecific)	mtDNA (*COX3*)	[37]
Non-specific muscular dystrophy	uk	[38]
Core myopathy	*TTN*	[39–42]
nDNA-related MID	*GARS*	[43]
nDNA-related MID	*SDHD*	[44, 45]
nDNA-related MID	*HADHB*	[46]
EBS with muscular dystrophy	*PLEC1*	[47]
nDNA-related MID	*MIPEP*	[48]
Walker-Warburg syndrome	*POMPT2*	[49]

NOP number of patients so far reported, *MID* mitochondrial disorder, *EBS* epidermiolysis bullosa simplex, *uk* unknown

zaspopathy [9], myotonic dystrophy 1 [12], laminopathy [18], myoadenylat-deaminase deficiency, *PMP22*-related hereditary neuropathy [22], *MYH7*-myopathy [50], myopathy with spherocytosis [25], myotonic dystrophy type-2 [26], oculopharyngodistal myopathy [27], glycogen storage disease-IV [28], Fabry disease [29], multiminicore disease [32], congenital fiber type dysproportion [35], Danon disease [36], nDNA-related MID [44, 46], epidermiolysis bullosa simplex with muscular dystrophy [47], metabolic myopathy due to *MIPEP* mutations [48], and Walker-Warburg syndrome due to *POMPT2* mutations (Table 3.1) [49]. NMDs in which LVHT occurs with a high prevalence are MIDs and Barth syndrome.

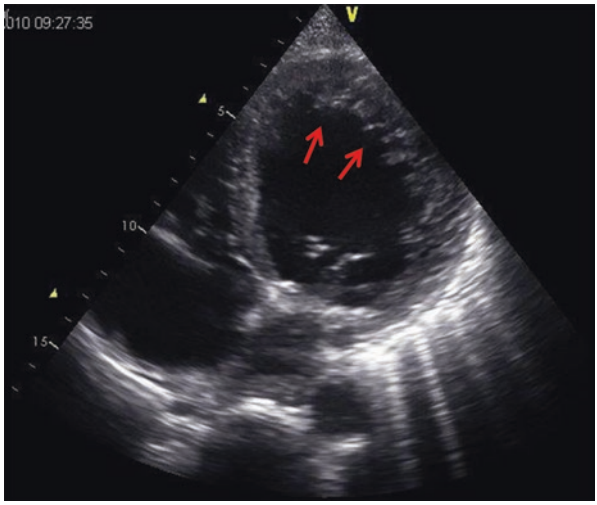

Fig. 3.1 Echocardiographic apical four-chamber view showing a dilated left ventricle with hypertrabeculation/noncompaction of the left ventricular apex and lateral wall

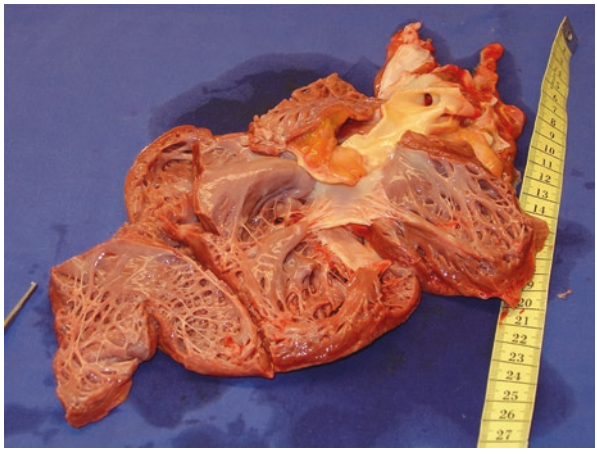

Fig. 3.2 Autopsy specimen showing hypertrabeculation of the posterior, lateral and apical segments in a patient with Duchene muscular dystrophy

Mutated Genes Associated with LVHT and NMD

DMD

Mutations in the *DMD* gene may be asymptomatic or symptomatic. Clinical manifestations include Duchenne muscular dystrophy (DMD), one of the most prevalent muscular dystrophies in children, Becker muscular dystrophy (BMD), a milder form of DMD, and isolated dilated cardiomyopathy (DCM). Since the *DMD* gene is located on the X-chromosome, female carriers of a *DMD* mutation may also manifest clinically, depending on the random inactivation of the mutated/non-mutated chromosome. In DMD, BMD patients, and DMD-carriers, cardiac involvement is a common phenotypic feature. Most frequently, cardiac involvement includes conduction defects, arrhythmias,

and DCM [51]. Only in single patients carrying a *DMD* mutation has LVHT been reported. The first patient carrying a *DMD* mutation and presenting with LVHT was a patient with BMD [2]. In 2005 the first patient with DMD and LVHT was reported [21]. In 2012 LVHT was reported for the first time in a female carrier of a *DMD* mutation [52]. Occurrence of LVHT in Duchenne carriers was confirmed in another case report [31]. In a study of 186 DMD/BMD patients, aged 4–64 years, from Japan, even 35 (19%) presented with LVHT [3]. Left ventricular function was worse among the 35 LVHT DMD/BMD patients compared to the 151 DMD/BMD patients without LVHT [3]. Over a follow-up of 46 months, on the average, left ventricular function deteriorated much quicker among the DMD/BMD patients with than without LVHT [3]. Additionally, the death rate during the follow-up period was much higher in the LVHT group (37% vs. 14.6%) [3]. In a study of 151 DMD patients from Italy, LVHT was detected in 15 patients (10%) [53]. In a study of 15 genetically confirmed DMD-carriers the rate of LVHT was 40% on cardiac MRI (cMRI) upon application of the Peterson criteria and 13% upon application of the Grothoff criteria [54]. One third of the females had systolic dysfunction and 60% had late gadolinium enhancement (LGE) [54].

G4.5/TAZ

The *G4.5/TAZ* gene encodes a protein, which is involved in the remodeling of cardiolipin. Tafazzin is highly expressed in the skeletal muscle and the myocardium [55]. Mutations in the *G4.5/TAZ* gene cause various different phenotypes, such as Barth syndrome, DCM, hypertrophic cardiomyopathy (HCM), endocardial fibroelastosis, and isolated LVHT. Barth syndrome is clinically characterised by the triad of DCM (or HCM, LVHT, or fibroelastosis), myopathy, and neutropenia [55]. Additional features include growth delay, exercise intolerance, cardiolipin abnormalities, and 3-methyl-glutaconic aciduria. The first report about LVHT in a patient with Barth syndrome dates back to 1997, when Bleyl et al. reported LVHT in 6 of 6 patients with Barth syndrome [4]. After this first description of LVHT in patients with Barth-syndrome [4], LVHT has been repeatedly reported in these patients and is now regarded as a hallmark of the disease [55]. Since Barth syndrome is an X-linked disorder, females transmit the disease and may be clinically unaffected or mildly affected. Also female carriers of the *G4.5/TAZ* mutation manifest in the heart. In 2012, LVHT was first described in a female carrier of Barth syndrome [33]. *G4.5/TAZ* mutations may show broad intra- and inter-familial phenotypic heterogeneity from severe Barth syndrome to asymptomatic LVHT with mild myopathy [56]. In rare cases, the hallmarks of the disease may be absent and patients may initially present only with growth retardation or mild myopathy [57]. In a study of 39 Japanese patients with LVHT, a pathologic variant was found in 16 genes [58]. In this study, *G4.5/TAZ* was the gene second most frequently mutated in LVHT patients (n = 6) after *MYH7* [58]. In a study of 36 pediatric patients with LVHT, two patients carried a *G4.5/TAZ* mutation [59]. In a Japanese study of 79 patients with LVHT, a TAZ mutation was detected in 2 of them [7]. When investigating a cohort of 34 patients with Barth syndrome, LVHT was diagnosed in 53% of them [60].

DTNA

The *DTNA* gene encodes for alpha-dystrobrevin, a component of the dystrophin-associated protein complex (DPC), which consists of dystrophin and several integral and peripheral membrane proteins, including dystroglycans, sarcoglycans, syntrophins, and alpha- and beta-dystrobrevin. *DTNA* mutations are associated with various congenital heart defects and LVHT. *DTNA* mutations were first described in association with LVHT by Ichida et al. in 2001 [6]. In a study of 70 Japanese patients with LVHT (20 familial and 59 sporadic cases), a *DTNA* mutation was found in only 1 family [7]. In a study of transgenic mice carrying an overexpressed *DTNA* mutation, deep trabeculations were found in addition to DCM with systolic dysfunction [61].

Mutated Genes Causing Mitochondrial Disorders (MIDs)

mtDNA Genes

mtDNA genes encode for subunits of respiratory chain complexes, for tRNAs, and for rRNAs. Of the 37 mtDNA genes, 4 have been reported in association with LVHT [1]. LVHT has been particularly reported in patients carrying mutations in *ND1* [62, 63]. In a Tunisian 16 years old female with hypothyroidism, work-up for cardiac compromise revealed tricuspid insufficiency, DCM, Ebsteins's anomaly, a superior caval vein draining into the coronary sinus, and LVHT [63]. The patient carried the homoplasmic variant m.3308T>C in the ND1 gene [63]. Studying mtDNA from 20 LVHT patients, a mtDNA mutation in the *ND1* gene was found in two of them [62]. In a study of 32 patients with a genetically confirmed MID (mitochondrial myopathy, n = 8, CPEO, n = 14, MELAS, n = 7, KSS, n = 2, MERRF, n = 1), 1 patient presented with LVHT due to a mutation in the *ND4* gene [64]. Isolated LVHT in a patient with Leber's hereditary optic neuropathy (LHON) has been first reported by Finsterer et al. in 2001 [16]. LHON in this patient was due to the variant m.3460G>A in the *ND1* gene [16]. Upon a family screening, LVHT was also detected in the brother of the index case, who also carried the *ND1* mutation m.3460G>A [17]. In a patient with mitochondrial myopathy due to the m.3243A>G mutation in *tRNA(Leu)* and nail-patella syndrome due to a *LMX1B* mutation, LVHT was detected [65]. Cardiac disease additionally included complete heart block, requiring pacemaker implantation [65]. Studies of the myocardium for mitochondrial changes from 6 LVHT patients revealed a *COX3* mutation in one of them [37].

nDNA Genes

GARS

Glycyl-tRNA synthetase (GARS) is an aminoacyl-tRNA synthetase (ARS) that links the amino acid glycine to its corresponding tRNA prior to protein translation and is one of three bifunctional ARS that are active within both the cytoplasm and mitochondria [43]. Dominant mutations in *GARS* manifest phenotypically as

hereditary neuropathy or spinal muscular atrophy [43]. In a 12 years old female with exercise-induced myalgias persistent elevation of serum lactate and alanine, and periventricular leucencephalopathy, LVHT was detected upon screening for cardiac involvement [43]. The cause of the MID was a compound heterozygous mutation in the *GARS* gene [43].

HADHB

HADHB encodes for the beta-subunit of the mitochondrial trifunctional protein, an enzyme of the fatty acid beta-oxidation, which is built up of 4 alpha-subunits and 4 beta-subunits. Clinical manifestations of *HADHB* mutations are heterogeneous. The most severe phenotype is characterised by CMP, lactic acidosis, hypoketotic hypoglycemia, and neonatal death [46]. LVHT has been reported only in one *HADHB* mutation carrier so far [46]. This patient was a fetus (third pregnancy of a Turkish lady) who's initial fetal echocardiography revealed biventricular hypertrophy, mild ventricular enlargement, but normal systolic and diastolic function. During the further pregnancy the fetus developed pleural effusions and edema due to systolic dysfunction [46]. After birth the child presented with severe lactic acidosis, being resistant to any therapy. Post-natal echocardiography revealed severely reduced systolic function and LVHT. The patient died shortly after birth without undergoing autopsy but genetic work-up of skin fibroblasts revealed a *HADHB* mutation [46]. The consanguineous parents did not exhibit phenotypic features of a MID and did not allow testing for the mutation [46].

MIPEP

The *MIPEP* gene encodes for the mitochondrial intermediate peptidase, an enzyme representing a critical component of the human mitochondrial protein import machinery, involved in the maturation of nuclear-encoded mitochondrial OXPHOS-related proteins (precursor processing) [66]. The mitochondrial intermediate peptidase is a mitochondrial pre-sequence protease, which processes about 70% of all mitochondrial pre-proteins that are encoded in the nucleus and imported post-translationally to mitochondria [48]. Mutations in the mitochondrial intermediate pre-sequence protease MIP/Oct1 have been recently found to cause a syndrome characterised by developmental delay, epilepsy, metabolic myopathy, severe hypotonia, cataracts, infantile death, and LVHT [48]. Muscle biopsy in three patients carrying *MIPEP* mutations from four unrelated families revealed moderate fiber size variation, type-1 fiber predominance, increased subsarcolemmal oxidative activity, increased number of mitochondria, pleomorphism of mitochondria on electron microscopy, marked increase in lipid droplets, increase in glycogen stores, membrane-bound glycogen deposits, and aggregation of mitochondria [48]. LVHT was found in two of the four patients so far reported [48]. In patient-1 LVHT was associated with WPW-syndrome and in patient-2 LVHT was associated with DCM [48]. Patient-1 was alive at age 4.5 years at the last follow up, having developed muscle hypertonia and dystonic movements. Patient-2 had died from intractable seizures at age 2 years [48].

SDHD

SDHD encodes for a subunit of complex-II of the respiratory chain. In a male neonate who had died 1 day after birth, post-mortem examination revealed HCM and LVHT [44]. Biochemical examination of the muscle revealed severe complex-II deficiency [44]. Genetic work-up revealed a recessive mutation in the *SDHD* gene [44].

DNAJC19

DNAJC19 encodes for a mitochondrial chaperone, located at the inner mitochondrial membrane. Mutations in this gene have been only rarely reported. The initial description is about a Hutterite family with DCM and ataxia [67]. LVHT in association with *DNAJC19* variants has been first described by Ojala et al. in 2012 in two Finnish brothers who additionally presented with DCM, microcytic anemia, male genital anomalies, and methyl-glutaconic aciduria [34].

Non-genetically Confirmed MID

Since the diagnosis of MIDs is challenging and not in each family a causative mutation can be detected, the diagnosis is often not genetically confirmed and based only on evidence, resulting from the phenotype, the lactate stress test, histochemical findings, and the biochemical results. Several cases of MIDs and LVHT without genetic confirmation have been reported. This is the case in a 31 years old female with mitochondrial myopathy in whom also LVHT was detected [68]. In a study of 113 pediatric patients with a MID, diagnosed upon the biochemical defect and in 11.5% upon a genetic defect, 13% (15 patients) had LVHT [69]. In a 6 weeks-old male with succinate-dehydrogenase deficiency, diagnosed upon muscle biopsy, echocardiography revealed not only DCM but also LVHT [67]. In a patient with complex-II deficiency LVHT has been reported in addition to DCM, failure to thrive, generalised hypotonia, and developmental delay [45]. The patient presented additionally with DCM, failure to thrive, hypotonia, and developmental delay [45]. In a study of 89 MID patients, diagnosed upon immunehistochemical and biochemical investigations, 33% had cardiac involvement [70]. In 3 of these patients, LVHT was detected [70]. In a female fetus, LVHT and AV-block 3 were diagnosed at 22 weeks' gestation [71]. Post-natally HCM and ventricular septal defects were additionally found and she received a pacemaker [71]. Muscle biopsy revealed a complex-I defect [71]. In a study of 220 patients with LVHT, a putative MID, diagnosed upon clinical, electromyographic, muscle bioptic findings, and lactate stress testing, was found in 19 patients [72]. The first MID patient in whom LVHT was detected was a 68 years male in whom muscle biopsy was indicative of a MID and in whom ventriculography, carried out during coronary angiography, revealed LVHT [5]. When studying 36 pediatric patients with LVHT, MID was diagnosed upon muscle biopsy findings in 5 [59]. Altogether, at least 62 MID patients with LVHT (mtDNA mutation: n = 8, nDNA mutation: n = 7, histochemical or biochemical evidence: n = 47) have been reported. Thus, MIDs seem to the NMD most frequently presenting with LVHT.

LDB3

LDB3 encodes for the Z-band alternatively spliced PDZ-motif protein (ZASP). ZASP is one of the major components of the Z-disc proteins in skeletal and cardiac muscle and plays an important role in stabilising the Z-disc through its PDZ-mediated interaction with alpha-actin-2 (ACTN2) and F-actin [10]. Mutations in *LDB3* manifest phenotypically as DCM, sudden cardiac death (SCD) myopathy, or LVHT [10]. LVHT has been first reported in three patients carrying a *LDB3* variant by Vatta et al. (Table 3.1) [9]. Additionally, LVHT was described in two patients with zaspopathy described by Xi et al. [10]. Xing et al. screened 79 patients with LVHT for mutations in *DTNA, SNTA1*, *FKBP1A*, and *LFB3*, and found a *LDB3* mutation in four of them [7].

DMPK

DMPK encodes for the dystrophia myotonia protein kinase, of which the specific function is unknown. However, there are indications that the enzyme has signalling and regulatory functions by interaction with other proteins, such as myosin phosphatase. The most well-known mutation in the *DMPK* gene is an intronic CTG-repeat expansion >49, clinically manifesting as myotonic dystrophy type-1 (MD1). Severity of MD1 correlates with the size of the CTG-expansion. Thus, the phenotype varies from an asymptomatic or only mildly manifesting condition to severe multisystem disease with early death shortly after birth (congenital myotonic dystrophy). The longer the CTG-expansion, the more likely becomes MD1 a multisystem disease, affecting all body tissues but particularly skeletal muscle, myocardium, endocrine organs, and the brain. Cardiac involvement in MD1 is frequent and mainly includes CMP and ventricular arrhythmias [13]. CMP may manifest as HCM, DCM, or as LVHT. LVHT has been first reported in 2004 by Stöllberger et al. [12]. Since then at least 25 other MD1 patients with LVHT have been described [12–15]. In a study of 40 MD1 patients, LVHT was detected in 35% of them (n = 14) [13].

LMNA

The *LMNA* gene encodes for lamin A/C, an intermediate filament protein associated with the inner nuclear membrane [73]. *LMNA* mutations result in abnormal cell signalling, which includes increased signalling by extracellular signal-regulated kinase-1 and kinase-2 and other mitogen-activated protein kinases, protein kinase B/mammalian target of rapamycin complex-1, and transforming growth factor-β [73]. Characteristic of *LMNA* mutations are that they show strong phenotypic heterogeneity manifesting as Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy (LGMD), myofibrillar myopathy, DCM with conduction system disease, atrial fibrillation, or malignant ventricular arrhythmias, Dunnigan-type familial partial lipodystrophy, mandibulo-acral dysplasia, Hutchinson-Gilford progeria syndrome,

restrictive dermopathy, or as autosomal recessive Charcot-Marie-Tooth disease type-2 [74]. LVHT in association with *LMNA* mutations has been first reported by Hermida-Prieto et al. in a single patient in 2004 [18]. Two Chinese patients carrying *LMNA* mutations and presenting with LVHT have been reported by Liu et al. in 2016 [19]. Unfortunately, it is unclear if these two patients also manifested in the skeletal muscles. LVHT in association with *LMNA* mutations has been also reported in 3 patients from the USA but again it remains unclear if these patients had an NMD or not [75]. In a study of 9 patients from 8 families carrying *LMNA* mutations, only 1 presented with LVHT. Phenotypic heterogeneity was broad among the 9 patients [74]. In a study of 68 LVHT patients mutations in the LMNA gene were found in 5% of the cases but of the 68 patients only 2 patients had an NMD [76].

AMPD1

AMPD1 encodes for the myo-adenylate deaminase, an enzyme involved in deamination of AMP molecules. *AMPD1* has a widespread expression, particularly in type-I muscle fibers, smooth muscle fibers, and in neurons. Mutations in AMPD1 may be asymptomatic, may cause myalgias, rhabdomyolysis, or metabolic myopathy, manifesting with fatigue, cramps, muscle pain, or recurrent myoglobinurea. *AMPD1* variants have been associated with coronary heart disease or heart failure. Only in a single patient with AMPD1 associated myopathy has LVHT been reported [20]. The patient was a 53 years old male presenting with easy fatigability, myalgias since boyhood, and recurrently elevated creatine-kinase [20]. Holter-ECG showed nocturnal sinus-bradycardia and echocardiography showed myocardial thickening in addition to LVHT [20]. LVHT was confirmed by cardiac MRI.

MYH7

MYH7 encodes for the beta-myosin heavy chain, a sarcomeric protein predominantly expressed in the skeletal muscle and the myocardium. It mainly occurs in slow-twitch fibers (type-I-fibers). Mutations in *MYH7* were identified in patients with HCM, DCM, Laing distal myopathy, myosin storage myopathy, and axial myopathy (dropped head, camptocormia) [77]. Only in single patients have *MYH7* mutations been reported in patients with myopathy and LVHT simultaneously [23, 24, 77]. Myopathy together with LVHT was first described by Ruggiero et al. in 2013 [24]. In this study, three members of an Italian family presented with Laing-like distal myopathy and LVHT. Muscle biopsy showed fiber-type disproportion. Mild distal myopathy was also reported in a female with LVHT carrying a *MYH7* mutation [23]. Other members of the index patient's family presented with myopathy plus anginal chest pain, impaired relaxation, or DCM [23]. In a cohort of 21 Italian patients with MYH7 myopathy, 5 had LVHT [77]. It has not been reported if the 3 previously reported Italian patients [24] were included in this cohort or not.

More frequently than mutation carriers with LVHT plus NMD, patients with LVHT and a *MYH7* mutation but without neurological investigation have been

reported. In a study of 190 patients with LVHT from the USA, 8 were found to carry a *MYH7* variant. Though cardiologists did not report muscle symptoms, it remains unknown if any of the included patients manifested also in the skeletal muscle [39]. This uncertainty remains since the patients were not systematically referred to the neurologist and since these patients obviously had not exhibited muscular manifestations [39]. In a study of 102 patients with LVHT, *MYH7* mutations were detected in 19 of them [58]. Unfortunately, these patients were not systematically referred for neuromuscular evaluation. In a study of 57 Chinese patients with LVHT, 6 carried a mutation in the *MYH7* gene [78].

CNBP/ZNF9

CNBP/ZNF9 encodes for a protein of which the function is unknown but which is mainly expressed in the heart and muscle. Intron-1 of the gene contains the complex repeat motif $(TG)_n(TSGT)_n(CCTG)_n$. Expansion of this motif between >75 and up to 11,000 repeats causes myotonic dystrophy type-2 (MD2). MD2 is a multisystem disorder manifesting mainly in the muscle, eyes, and endocrine organs. Most patients present with myotonia, cataract, diabetes, and elevated, follicle stimulating hormone. Cardiac involvement may occur and includes ventricular arrhythmias and DCM [79]. Only in a single patient with MD2 has LVHT been reported so far [26]. This was a 61 years male with DCM and apical hypertrabeculation [26]. Additionally, the patient presented with hand myotonia and progressive limb muscle weakness evolving for >20 years. He also had diabetes mellitus and an isolated elevation of gamma-glutamyl transpeptidase [26].

GLA

GLA encodes for alpha-galactosidase, an enzyme which cleaves the terminal galactose from ceramide trihexoside. Mutations in the gene result in accumulation of ceramide trihexoside in neurons, ganglia, myocardiocytes, kidney, and the smooth muscle cells. The phenotype of alpha-galactosidase deficiency is known as Fabry's disease, of which the severity correlates with the residual enzyme activity, being 1–17%. Cardiac involvement in Fabry's disease includes HCM, conduction defects, ectasia of arteries, and myocardial infarction. LVHT has been reported in Fabry's disease only once so far. A 32 years old female was found to carry a *GLA* mutation upon a family screening. She did not manifest clinically with the disease but echocardiography revealed typical hypertrabeculation of the mid-ventricular and the apical segments of the left ventricular myocardium [29].

RYR1

RYR1 encodes for the ryanodine receptor-1, also known as skeletal muscle calcium release channel or skeletal muscle-type ryanodine receptor. The gene is mainly expressed in the skeletal muscle. Mutations in RYR1 manifest phenotypically

heterogeneously as multiminicore myopathy, atypical periodic paralysis, distal myopathy, centronuclear myopathy, central core disease, arthrogryposis multiplex congenital, or as malignant hyperthermia susceptibility. Cardiac disease in carriers of RYR1 mutations is rare despite expression of *RYR1* also in cardiomyocytes [80]. SCD has been reported in patients with malignant hyperthermia susceptibility due to *RYR1* mutations. Only a single patient with multiminicore myopathy due to a *RYR1* mutation has been reported in whom also LVHT was detected [36]. The patient was a 16 years old Turkish male with myopathic face, weakness and hypotonia of the limb muscles with proximal predominance, and hyperlordosis [36]. Electromyography was myopathic and muscle biopsy showed multiminicore myopathy [36]. Echocardiography showed slightly enlarged cardiac cavities, mildly reduced ejection fraction, and typical LVHT of the apex [36].

MYH7B

The *MYH7B* gene belongs to the *MYH* gene family, which, in humans, also includes the *MYH6* and *MYH7* genes, both clustered on chromosome 14 [35]. The *MYH7B* gene encodes for the myosin heavy chain 7B, which is particularly expressed in the skeletal and the cardiac muscle [35]. Very low expression was observed in the brain, testes, ovary, liver, and blood [35]. Mutations in the *MYH7B* gene have been only rarely reported. In a single Italian family, a *MYH7B* mutation manifested in the skeletal muscle as congenital fiber type disproportion [35]. In four of the family members screening for cardiac involvement revealed LVHT. The 10 year old index patient presented with myopathy manifesting with proximal muscle weakness, scoliosis, and amyotrophy. She had a history of hypotonia, poor sucking, and persistent crying since birth. Persistent arterial duct and patent foramen ovale resolved spontaneously [35]. In addition to LVHT, the index case presented with long-QT, myocardial thickening, repolarisation abnormalities, and reduced systolic function [35]. Interestingly, the index patient additionally carried a mutation in the *ITGA7* gene [35], which, however, was not made responsible for the phenotype. Other patients with myopathy and LVHT due to a mutation in the *MYH7B* gene have not been reported.

LAMP2

LAMP2 encodes for the lysosome-associated membrane glycoprotein-2. LAMP2 provides selectins with carbohydrate ligands and plays a role in the protection, maintenance, and adhesion of the lysosome and possibly also in tumour cell metastasis. Mutations in the *LAMP2* gene cause Danon disease, also known as glycogen storage disease IIb, an X-linked lysosomal glycogen storage disorder, which is clinically characterised by HCM, myopathy, and intellectual decline. LVHT in Danon disease has been reported only in a single patient so far. The patient was a 19 years old mildly mentally retarded male in whom LVHT was detected after a syncope during a basketball game at age 14 years [36]. At age of 16 year, he developed heart

failure. Despite immediate treatment, heart failure became intractable and the patient underwent heart transplantation. For immunosuppression he received tacrolimus, daclicumab, prednisone, and mycophenolate mofetil. After transfer to the ward, the patient developed muscle weakness why he underwent muscle biopsy. Upon muscle biopsy, Danon disease was suspected and sequencing of the *LAMP2* gene revealed a causative mutation [36].

TTN

The *TTN* gene is the largest of the human genes so far detected. It encodes for titin, a giant protein, which is mainly expressed in the striated muscles and cardiac muscle [40]. Mutations in the *TTN* gene manifest with marked phenotypic heterogeneity. Heterozygous *TTN* truncating mutations have been reported as a major cause of dominant DCM, HCM, cardiac septal defects, isolated LVHT, Emery-Dreifuss muscular dystrophy, distal myopathy, or arthrogryposis [40]. However, relatively few *TTN* mutations and phenotypes are known, and the pathophysiological role of titin in cardiac and skeletal muscle conditions is incompletely understood. Myopathy plus LVHT has been reported in a single family carrying a *TTN* mutation so far [40]. In a study of 190 patients with LVHT, a *TTN* mutation was detected in 14 of them [39]. In a three-generation family with autosomal dominant CMP due to a *TTN* mutation, LVHT was detected in 7 family members [41]. In a single child with bradycardia and LVHT, mutations in the *RYR2, CASQ2*, and *TTN* gene respectively were discovered, [42]. In the latter three studies it is unclear if these LVHT patients had been investigated for NMD.

PLEC1

PLEC1 encodes for plectin, a linker protein involved in cytoskeletal organisation, which is particularly expressed in epithelia, skeletal muscle, and myocardium [47]. *PLEC1* mutations manifest phenotypically with broad heterogeneity, including epidermiolysis bullosa simplex (EBS), EBS plus muscular dystrophy, and pyloric atresia. EBS plus muscular dystrophy is characterised by skin fragility and late-onset muscular dystrophy, but significant phenotypic heterogeneity can occur [47]. Even the dermatological manifestations vary regarding severity and include neonatal skin fragility and mucosal vulnerability resulting in tracheal and urethral tract complications [47]. Muscular dystrophy is similarly variable in onset and severity, characterised by diffuse limb muscle weakness with onset between infancy and 4th decade of life. LVHT has been reported only in a single carrier of a *PLEC1* mutation [47]. This was an 18 years old Afro-American male with blistering at the elbows at birth, being subsequently diagnosed as EBS. Developmental delay and first muscular manifestations were observed at age of 2 years [47]. By age of 4 years, the patient had lost the ability to rise from the floor and to walk stairs independently [47]. Since age of 10 years, he was wheel-chair bound. Work-up for cardiac involvement an age17 years by cMRI revealed LVHT.

POMPT2

POMPT2, together with *POMPT1*, encodes for the protein-O-manosyl-transferase, which is involved in the glycosylation of alpha-dystroglycan [49]. Hypoglycosilation of alpha-dystroglycan results in dystroglycanopathies of which Walker-Warburg syndrome (WWS) is the most severe. WWS is a rare autosomal recessive congenital muscular dystrophy (CMD) clinically characterised by eye and brain abnormalities. WWS is genetically heterogeneous and may not only be caused by *POMPT2* mutations but also by mutations in the *FKTN, FKRP, POMGnT1, POMGnT2, ISPD, B3GNT1,* or *LARGE1* genes respectively [49]. Cardiac involvement is infrequent in WWS [81]. Only 1 WWS patient with coarctation of the aorta has been reported. The only patient in whom LVHT has been reported so far was a neonate with facial dysmorphism (hypertelorism, low set ears, frontal bossing, micro-retrognathia), laterally displaced nipples, hypospadias, and muscle hypotonia [49]. ECG in this patient showed incomplete left bundle branch block, left ventricular hypertrophy, and T-wave inversion. Echocardiography revealed an atrial septal defect, shunting left-to-right, a muscular ventricular septal defect, and LVHT [49]. At an age of 4 months the patient experienced a cardiogenic shock due to congestive heart failure and recurrent episodes of cardiac arrest, the last one being unresponsive to resuscitation. Heart failure and conduction defects were attributed to LVHT [49].

Diagnostic Work-Up of NCCM

For a comprehensive diagnostic work-up, we refer to Chap. 2 of this title.

LVHT or NCCM is usually diagnosed accidentally on echocardiography [82]. In the young age group, patients are usually referred for syncopes or palpitations whereas in the older age groups patients are usually referred for heart failure [82]. However, there are groups of patients at risk having LVHT in a higher frequency than the general population. These risk groups include patients with chromosomal defects, NMD, black Africans, pregnant females, and athletes. This is why patients of these at-risk groups need to be systematically investigated for LVHT and, vice versa, patients with LVHT require work up for chromosomal defects and NMDs. A shortcoming in the work-up of patients with LVHT, however, is that often they are not investigated for associated non-cardiac disease or the genetic background. Since NMDs are frequently only mildly manifesting or even subclinical, neurologists specialised in NMDs need to be involved. For cardiologists who diagnose LVHT, neuromuscular features are frequently not evident why the NMD often goes undetected. For this reason, all patients with LVHT should be seen by a neurologist. Vice versa, all patients with an NMD should be referred to the cardiologist as soon as the diagnosis is established or even when it is suspected, to assess if cardiac involvement is present and if the patient requires cardiac therapy. Diagnosing the NMD in a LVHT patient may be challenging since the NMD may be absent, subclinical, or only mildly manifesting. In these cases, the NMD may be easily overlooked, particularly if the patient was not thoroughly investigated. Why mutations in certain genes

manifest with or without NMD is poorly understood. An example for the variable expression is the *LMNA* gene. LVHT has been repeatedly reported in patients carrying *LMNA* mutations [18, 19, 75], but only in a few patients LGMD has been reported.

Treatment of NCCM

For a comprehensive overview, we refer to Chaps. 5, 6 and 9 of this title.

Treatment of LVHT in patients with an NMD is not at variance compared to patients with LVHT but without an NMD. LVHT is asymptomatic in the majority of the cases but may be complicated by intertrabecular thrombus formation leading to cardiac thombo-embolism, heart failure, or ventricular arrhythmias, potentially leading to SCD. Primary prevention of cardio-embolism by oral anticoagulation is not indicated in patients with asymptomatic LVHT plus an NMD. However, if LVHT is associated with severe heart failure, or atrial fibrillation, oral anticoagulation is indicated. Oral anticoagulation should be also applied for secondary prevention of cardiac thrombo-embolism if a LVHT patient has a previous history of stroke/embolism. Heart failure in LVHT with NMD requires the same established therapy as heart failure in other patients (i.e. ACE-inhibitors, beta-blockers, diuretics). In case malignant ventricular arrhythmias are detected, implantation of an implantable cardioverter defibrillator (ICD) should be considered. To detect ventricular arrhythmias in LVHT patients with an NMD, either repeated 24-h or longer Holter recordings are necessary. In case of unclear clinical presentation, implantation of a reveal-recorder should be considered. If implantation of an ICD is indicated but not immediately feasible, application of a wearable cardioverter defibrillator should be recommended. Primary and secondary prevention of malignant ventricular arrhythmias is achieved by implantation of an ICD.

Outcome

There are only few studies available investigating the outcome of NMD patients with LVHT. In a study of 220 LVHT patients of whom 134 had a NMD, predictors of mortality on multivariate analysis were increased age, heart failure, atrial fibrillation, bradycardia, and presence of a NMD [72]. Thus, presence of an NMD in LVHT patients seems to have a strong impact on the outcome of these patients.

Conclusions

NCCM or LVHT is a morphological cardiac abnormality associated with an increased risk of intraventricular thrombus formation, heart failure, and ventricular arrhythmias with SCD. LVHT has a low prevalence in the general population but an increased prevalence among patients with a NMD and chromosomal defects.

Among these groups, LVHT is most prevalent in NMDs. LVHT may occur in some patients with a certain NMD type but not in the majority of the patients. Also, in LVHT patients with a certain mutated gene only some will manifest also with a NMD. Though LVHT has been reported in association with a number of mutated genes, which manifest as pure NMD or NMD with multiorgan disease, a causal relation has not been established yet since these mutations have been also described in association with an NMD but without LVHT. These genes include *DMD*, *TAZ, DTNA, mtDNA genes (ND1, tRNA(Leu), COX3, ND4), LDB3, DMPK, LMNA, AMPD1, PMP22, MYH7, CNBP, GLA, RYR1, DNAJC19, MYH7B, LAMP2, TTN, GARS, SDHD, HADHB, PLEC1, MIPEP*, and *POMPT2*. A causal relation between mutations in these genes and the occurrence is rather unlikely since only a limited number of patients carrying these mutations present with LVHT, since mutations in many different genes cause the same morphological abnormality, and since a causal relation between any of these mutations and LVHT has not been proven yet. Since LVHT is associated with complications, it is essential to detect the abnormality, to monitor it adequately, and to initiate adequate measures when indicated. Thus, all patients with an NMD need to be prospectively investigated for LVHT, and all patients with LVHT need to be prospectively investigated for NMD. Concerning the primary prevention of complications from LVHT, no consensus has been reached so far. Detection of an associated genetic defect in a patient with LVHT does not alter cardiac therapy but may influence the symptomatic treatment of the neuromuscular manifestations. Thus, it is nonetheless useful to test LVHT patients for concomitant genetic defects, despite absence of a causal relation between LVHT and any of the so far detected genetic defects associated with LVHT. There is a general need to encourage and conduct studies about the prevalence of LVHT in different NMDs worldwide and about the pathogenetic relation between NMDs and LVHT.

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