GLOBAL CARDIOLOGY SCIENCE & PRACTICE

OPEN ACCESS

Review article

Neuromuscular diseases with hypertrophic cardiomyopathy

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INTRODUCTION

Neuromuscular disorders are frequently associated with cardiac abnormalities, even in pediatric population[1]. Cardiac involvement includes both structural changes and conduction disease. In general, HCM is a rare manifestation of neuromuscular diseases[2].

Autosomal dominant inheritance with mutations in sarcomeric genes are described in about 60% of young adults and adult population with HCM. Other genetic disorders, such as inherited metabolic and neuromuscular diseases and other chromosome abnormalities are responsible of 5–10% of HCM in adults[3]. We review the most frequent neuromuscular diseases related with HCM.

MITOCHONDRIAL DYSFUNCTION

Often, mitochondrial diseases in newborns and infants can lead to heart, skeletal muscle and central nervous system abnormalities due to, in most cases, alterations in nuclear DNA[4]. Late onset manifestations are related with single-organ affectation in adults and mtDNA mutations are most frequent than nuclear DNA mutations[5,6]. Concerning cardiac phenotype, concentric HCM with rapid evolution to dilated and hypokinetic cardiomyopathy is frequent within mitochondrial diseases[4]. Genetics and skeletal biopsy is mandatory in patients with mitochondrial disease suspicion[7]. Early encephalopathy in infants and cardiomyopathy are associated with a worst prognosis[4,6,7]. There is no specific treatment for this group of diseases, but some agents have being studied for treating mitochondrial diseases (agents increasing electron transfer chain function, energy buffer, antioxidants, restoration agents of nitric oxide production, cardiolipin protectors and agents enhancing mitochondrial biogenesis)[8]. In patients with CoQ10 deficiency, ubiquinone can improve both electronic transfer chain function and clinical manifestations[7].

Friedreich's ataxia

Friedreich's ataxia (FA) is a multisystem autosomal recessive disease involving mitochondrial function due mutations in *FXN* gene, located on chromosome 9q, which encodes a 210 amino acid Frataxin protein. GAA triplet repeat expansion in intron 1 of FXN occurs in 96–98% of FA patients, with alleles containing 66 to 1300 GAA triplet repeats[9]. Earlier disease is related with larger numbers of GAA repeats and more rapid disease progression[10].

https://doi.org/10.21542/gcsp.2018.27

Received: 11 May 2018
Accepted: 15 June 2018

Cite this article as: Cesar S. Neuromuscular diseases with hypertrophic cardiomyopathy, Global Cardiology Science and Practice 2018:27 https://doi.org/10.21542/gcsp.2018.27

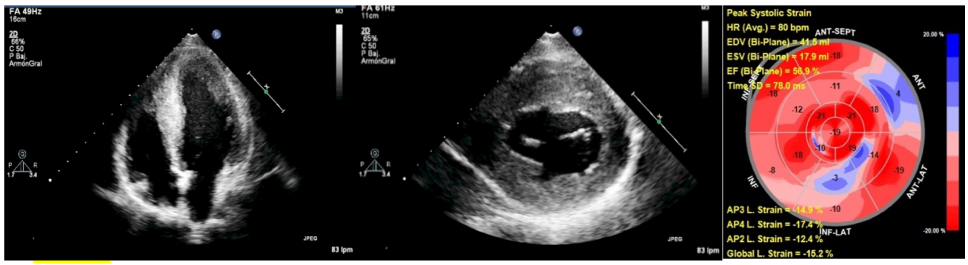

Figure 1. Echocardiography from a FA patient with HCM. The images show an apical 4 chamber with left ventricle HCM (mid-septal and apical regions) and left ventricle short axis image with concentric HCM. The last image shows regional dysfunction and decreased longitudinal strain analyzed with speckle-tracking myocardial strain.

These abnormalities generate oxidative cellular stress and enzyme deficiency due to iron-sulfur clusters, which is the cause of respiratory chain dysfunction[11]. FA is characterized by progressive limb and gait ataxia, but other features such as spasticity absent lower limb reflexes, impaired vibration sense and proprioception, scoliosis have been described. HCM is a very frequent finding and heart failure is the most common cause of death. Patient with FA and HCM have an early onset within the first or second decades with a poor correlation with the neurological level of disability[12,13].

Histologically, left ventricle cellular hypertrophy, diffuse fibrosis and focal myocardial necrosis have been described[12].

Echocardiographic hallmark is a concentric LV hypertrophy with absence of left ventricular outflow tract obstruction, but eccentric hypertrophy might be present (Figure 1)[13–15].

Diastolic function is mildly impaired, with pseudo-normal diastolic pattern described in some series. Contrary to other diseases that cause concentric hypertrophy pattern with a sparkling granular texture (e.g., amyloidosis), atrial enlargement and pericardial effusion are rare in FA[3,13]. LV fibrosis is described and has been related with progressive LV thinning and dilatation[16]. Despite left ventricular ejection fraction being preserved in many patients, regional myocardial analysis with speckle-tracking can show regional dysfunction or decreased values of global longitudinal strain, as reported previously[17,18]. End-stage patients with FA can develop a reduced ejection fraction with hypokinesia and slight LV dilatation (Figure 2)[11].

The QRS duration in most FA patients, is normal even with significant LV hypertrophy. T-wave abnormalities are very frequent, especially in left precordial leads[13].

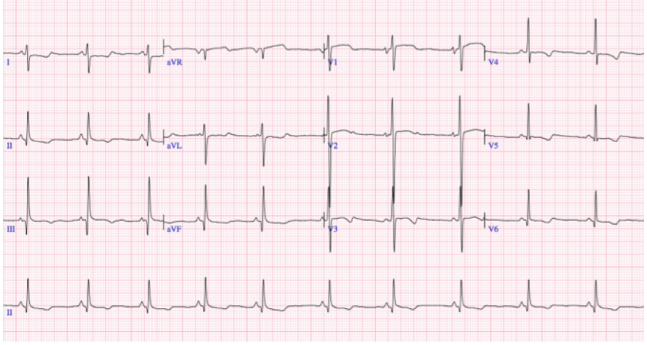

Figure 2. FA patient with HCM. ECG shows LVH data and repolarization abnormalities.

Supraventricular arrhythmias such as AV reentry tachycardia, atrial fibrillation and atrial flutter are described[12,19].

There is no specific treatment for HCM in FA patients. Management of heart failure symptoms (salt restriction, diuretic therapy), ACE inhibitors or angiotensin II receptor blockers may be beneficial in long-term treatment[20]. Treatment of atrial arrhythmias is mandatory, because the important atrial role to LV filling and cardiac output[14]. The drug idebenone acts as a transporter in the electron transport chain and has been advocated for use in FA following studies showing mild diastolic improvement and reduction LVH[21,22]. However, further trials have shown no benefit.

Cardiac transplantation is not commonly performed, due to advanced impairment of both motor skills and muscle strength.

Barth syndrome and other 3-methylglutaconic (3-MGA) aciduria disorders

Barth syndrome (type II 3-MGA-aciduria), is characterized with skeletal myopathy, neutropenia, growth retardation and 3-metylglutaconic aciduria. It is associated with both HCM/LVNC and DCM phenotypes.[8,23].

Barth syndrome is an X-linked autosomal recessive disease caused by *TAZ* gene mutations. This gene encodes for tafazzin, an acyl-transferase that catalyzes cardiolipin remodelling in the inner mitochondrial membrane[24]. Barth syndrome causes heart failure, arrhythmias and sepsis in male newborns and infants (Figure 3)[23].

Other 3-methylglutaconic aciduria diseases related with HCM are TMEM70 mutations (type IV 3-MGA-aciduria)[25].

Sengers syndrome presents in two forms of the disease - a lethal neonatal form characterized by severe HCM, cataract, skeletal myopathy, lactic acidosis[25–27] and a more benign adult form. It is caused by mutations in AGK gene that encodes for the mitochondrial acylglycerol kinase.

Respiratory chain-related disorders

Respiratory chain disorders are clinically and genetically heterogenous group. Gene mutations of complex-I respiratory chain subunits in mtDNA and nuclear DNA have been related with HCM.[4,5] Patients could have epilepsy, ataxia, muscle weakness, neurosensorial deafness, lactic acidemia and hypoglycemia[28].

Other mutations in II-complex respiratory chain subunits in nuclear DNA have been related with HCM, DCM and LVNC. Mutations have also been identified in SDH genes (*SDHA* and *SDHD* genes). Muscular weakness, ataxia, seizures, ophthalmoplegia, pigmentary retinitis, optic atrophy and lactic acidosis are manifestations of these patients[29].

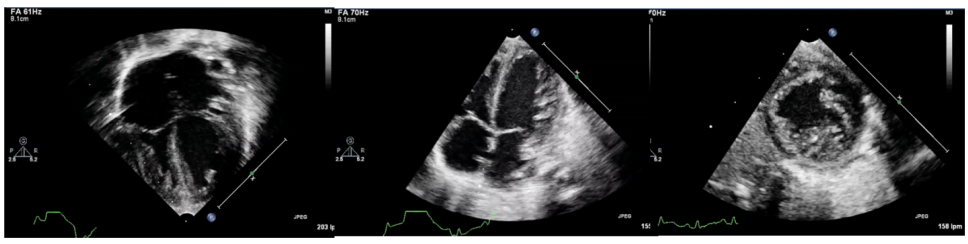

Figure 3. Echocardiography of a newborn diagnosed with Barth syndrome. 1) 4 chamber view shows biventricular hypertrophy, 2) shows mixed non-compaction and LV hypertropphy and 3) short axis view shows postero-apical non compaction.

Stroke-like episodes, epilepsy, hypoglycemia, lactic acidosis and optic atrophy have been related with or without HCM, DCM and histiocytoid cardiomyopathies in cases of mutations in *MTCYB* gene that encodes cytochrome-b protein in III-complex respiratory chain[30].

Finally, other disorders related with IV-complex respiratory chain have been associated with HCM, DCM and histiocytoid cardiomyopathy. Genes encoding subunits of IV-complex in mtDNA and nuclear mtDNA, such as *COX6B*, and genes encoding assembly factors in the IV-complex respiratory chain, such as *COX10*, *SCO1*, *COA6* and *SURF*, have been described[31,32].

tRNA and rRNA-related disorders

Mitochondrial tRNA gene mutations cause HCM, DCM and histocytoid cardiomyopathy with or without multiorgan involvement. MERRF (Myoclonus epilepsy and ragged red fibers) and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), due to mutations in *MTTK* and *MTTL1* genes respectively, are examples of this group[33,34]. Mutations in *MTRNR2* gene, encoding mitochondrial ribosome protein 16S, have been related with HCM[35]. Other mutations in rARN genes, such as *MRPL44*, and mutations in *TSFM*, have been related with HCM and multiorgan syndrome[36,37].

Mitochondrial depletion DNA syndromes

These disorders have in common a significant drop in mitochondrial DNA in affected tissues. Mutations in *TYMP* (also called *ECGF1*) gene can lead to reduced levels of thymidine phosphorylase enzyme activity, which is found in Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE). Clinical manifestations of MNGIE are progressive gastrointestinal dysmotility, cachexia, ptosis/ophthalmoplegia, leukoencephalopathy, demyelinating peripheral neuropathy. There is no hard evidence for HCM but ECG analysis showed left ventricular hypertrophy in some cases[38].

CoQ10 biosynthesis deficiency

Mutations in genes encoding biosynthesis of CoQ10 (*COQ2*, *COQ9* and *PDSS1* genes) can lead to CoQ10 deficiency, that can be related with encephalopathy, skeletal myopathy, ataxia and nephrotic syndrome. Isolated HCM or associated with other multi-organ affectation have been associated with mutations in *COQ2*, *COQ4*, *COQ9* genes[39].

X-LINKED RECESSIVE MUSCULAR DYSTROPHIES

Dystrophinopathies

The most frequent X-linked muscular dystrophies are Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)[40]. Mutation in the *DMD* gene leads to an absence of functional protein in DMD, whereas BMD shortened dystrophin or reduced amount is detected. Weakness of leg, pelvic and shoulder girdle muscles starts in early childhood. Cardiac involvement in BMD may precede the skeletal muscle weakness. Dilated cardiomyopathy is the final cardiac phenotype, but hypertrophic phenotype is described within female carriers of dystrophinopathy and diastolic dysfunction followed by eccentric hypertrophy are described[41–43]. There are few reports in BMD patients with hypertrophic cardiomyopathy[44]. Abnormal circumferential strain is described in DMD patients despite normal ejection fraction and pre-symptomatic stage[45]. Cardiovascular complications are a leading cause of morbidity and mortality in DMD patients[41].

There is no specific treatment for cardiomyopathy in dystrophinopathies (Figures 4 and 5). Some evidence suggests cardiac benefits with early treatment with ACE inhibitors, improving long-term cardiac outcomes[41].

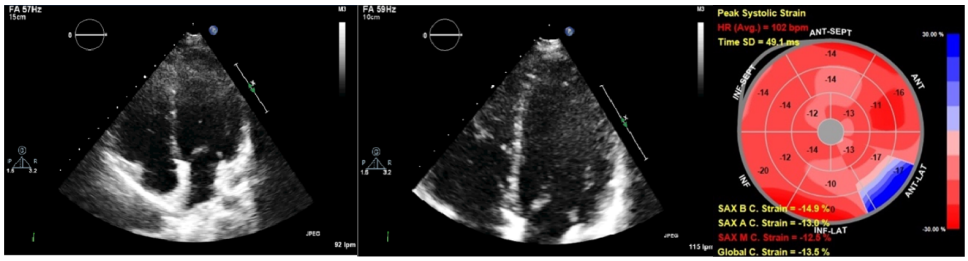

Figure 4. Echocardiography from a pediatric Duchenne muscular dystrophy patient. Note the left ventricle image with slight thickened interventricular septum and heterogeneous echogenicity. The last image shows regional dysfunction and decreased global circumferential strain based on speckle-tracking.

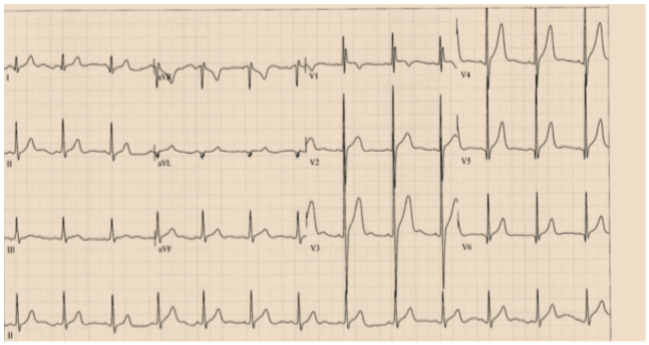

Figure 5. BMD patient with cardiomyopathy. ECG shows LVH data, short PR interval and J point elevation in V2-V4 leads.

Emery-Dreifuss muscular dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is a rare hereditary disease characterized by early joint contractures of Achilles tendons, elbows and rigid spine, childhood onset of muscle weakness and wasting and adult-onset cardiac disease (arrhythmias, cardiomyopathy). EDMD can be transmitted X-linked (mutations in *EMD* gene) or autosomal (mutations in *LMNA* gene). Mutations in *EMD* gene can lead to abnormalities in emerin protein, which is a component of the nuclear envelope[46,47]. Other mutations in *FHL1* gene are described in some families with X-linked EDMD, some of them with HCM[46].

MYOTONIC DYSTROPHIES

Myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM-1), or Steinert disease, is a genetic disease due to an expansion of CTG triplet in *DMPK* gene on chromosome 19. DM-1 is multisystemic disease with autosomal dominant transmission and incomplete penetrance. Myotony and muscle weakness are the main clinical manifestations but both cardiovascular and respiratory system are also involved[48]. Arrhythmias are the second cause of death in DM-1 patients, most of them suffering sudden cardiac death[49]. About cardiac involvement, concentric HCM are described in these patients, mainly detected in adults. Other structural findings are DCM and LVNC[50].

MYOFIBRILLAR MYOPATHIES

Myofibrillar myopathies (aggregate myopathies) are a genetically heterogeneous diseases with manifestation in both skeletal and cardiac muscle. Focal dissolution of

myofibrils and aggregation of degraded myofibrillar products into inclusions containing desmin and other proteins have been found close to Z-disc.

Mutations in desmin (*DES*), alpha-aB crystallin (*CRYAB*), myotilin (*MYOT*), Z band alternatively spliced PDZ-containing protein (*ZASP*), filamin C (*FLNC*) and Bcl-2-associatged athanogene-3 (*BAG3*) are responsible for different phenotypes of myofibrillar myopathy[53].

The most common myofibrillar myopathy is caused by *DES* gene mutations (Desminopathy) and typically cause skeletal myopathy and cardiomyopathy (dilated and restrictive cardiomyopathy, HCM, AV block and arrhythmogenic cardiomyopathy are also described)[51].

AlphaB-crystallinopathy is an infrequent subtype of myofibrillar myopathy, caused by a mutation in *CRYAB* gene, and clinically characterized by proximal upper limb and distal lower limb weakness, velopharyngeal muscles, respiratory failure, HCM and lens opacities[52].

Myotilinopathy is caused by mutations in *MYOT* gene and is characterized by late-onset disorder with distal weakness of lower limbs or limb-girdle weakness. Peripheral neuropathy, respiratory failure and HCM are rare associated findings[52].

ZASPopathy can be related with very late-onset symptoms, similar to myotilinopathies, but peripheral neuropathy and HCM have been described[52]. Filaminopathy related with myofibrillar myopathy is an adult-onset proximal weakness with both respiratory and cardiac abnormalities[52]. BAG3 mutations associated with myofibrillar myopathy is a rare disease characterized by rapid progressive limb and axial muscle weakness, HCM and respiratory insufficiency[52].

OTHER RARE NEUROMUSCULAR DISORDERS RELATED WITH HCM

Limb girdle muscular dystrophy

Limb girdle muscular dystrophies are a group of neuromuscular disorders characterized by proximal muscular weakness and wasting of the arms and legs. Within autosomal recessive inheritance group, HCM with or without skeletal muscle manifestations has been described in Limb Girdle 1C (autosomal dominant inheritance, mutation in *CAV3* gene) and 2J (autosomal recessive inheritance, mutation in *TTN* gene)[53,54].

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHMD) affects facial, shoulder girdle, and sometimes peroneal muscles. FSHMD is caused by a deletion of an integral number of 3.3kb tandem repeats from the subtelomeric region on chromosome 4q35. FSHMD has been related with HCM in some publications[51,55].

Congenital myopathies

Within congenital myopathies, HCM has been described in Nemaline myopathy type 3, related with mutations in Alpha-actin, alpha tropomyosin and nebulin gene with a general autosomal recessive inheritance pattern[56]. Multiminicore disease (rigid spine syndrome), an autosomal recessive disease related with ryanodine receptor gene and selenoprotein N1 gene mutations, has been associated with HCM and RCM[53,56].

Primary carnitine deficiency

Classic initial presentation of primary carnitine deficiency is hypoketotic hypoglycemic encephalopathy, with hepatomegaly, elevation of transaminases and hyperammonemia. Muscle weakness and cardiomyopathy can be present in these patients, which could

be both dilated or hypertrophic cardiomyopathy. Mutations in *SLC22A5* gene have been related with primary carnitine deficiency[57].

REFERENCES

[1] Finsterer J, Stöllberger C. Cardiac involvement in primary myopathies. *Cardiology*. 2000;94:1–11.
[2] Coats CJ, Elliott PM. Genetic biomarkers in hypertrophic cardiomyopathy. *Biomark Med [Internet]*. 2013;7(4):505–16. Available from: http://www.futuremedicine.com/doi/10.2217/bmm.13.79.
[3] Task A, Elliott PM, Uk C, Anastasakis A, Germany MAB, Germany MB, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J [Internet]*. 2014;35(39):2733–79. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehu284.
[4] Scaglia F. Clinical spectrum, and morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics [Internet]*. 2004;114(4):925–31. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2004-0718.
[5] Limongelli G, Tome-Esteban M, Dejthevaporn C, Rahman S, Hanna MG, Elliott PM. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. *Eur J Heart Fail*. 2010;12(2):114–21.
[6] Limongelli G, D'Alessandro R, Maddaloni V, Rea A, Sarkozy A, McKenna WJ. Skeletal muscle involvement in cardiomyopathies. *J Cardiovasc Med*. 2013;14(12):837–61.
[7] Schwartz ML, Cox GF, Lin AE, Korson MS, Perez-Atayde A, Lacro RV, et al. Clinical approach to genetic cardiomyopathy in children. *Circulation*. 1996;94:2021–38.
[8] El-Hattab AW, Zarante AM, Almannai M, Scaglia F. Therapies for mitochondrial diseases and current clinical trials. *Mol Genet Metab [Internet]*. 2017;122(3):1–9. Available from: http://dx.doi.org/10.1016/j.ymgme.2017.09.009.
[9] Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich' s ataxia: autosomal recessive disase caused by an intronic GAA triplet repeat expansion. *Science (80-)*. 1996;271(5254):1423–7.
[10] Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: A cross-sectional analysis of baseline data. *Lancet Neurol*. 2015;14(2):174–82.
[11] Pousset F, Legrand L, Monin M, Ewenczyk C. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol*. 2016;72(11):1334–41.
[12] Weidemann F, Liu D, Hu K, Florescu C, Niemann M, Herrmann S, et al. The cardiomyopathy in Friedreich's ataxia — new biomarker for staging cardiac involvement. *Int J Cardiol*. 2015;194:50–7.
[13] Weidemann F, Störk S, Liu D, Hu K, Herrmann S, Ertl G, et al. Cardiomyopathy of Friedreich ataxia. *J Neurochem*. 2013;126(SUPPL.1):88–93.
[14] Mark Payne R, Wagner GR. Cardiomyopathy in Friedreich Ataxia: clinical findings and research. *J Child Neurol*. 2012;27(9):1179–86.
[15] Weidemann F, Rummey C, Bijnens B, Störk S, Jasaityte R, Dhooge J, et al. The heart in Friedreich ataxia: Definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. *Circulation*. 2012;125(13):1626–34.
[16] Raman SV, Phatak K, Hoyle JC, Pennell ML, McCarthy B, Tran T, et al. Impaired myocardial perfusion reserve and fibrosis in Friedreich ataxia: A mitochondrial cardiomyopathy with metabolic syndrome. *Eur Heart J*. 2011;32(5):561–7.
[17] Dedobbeleer C, Rai M, Donal E, Pandolfo M, Unger P. Normal left ventricular ejection fraction and mass but subclinical myocardial dysfunction in patients with Friedreich's ataxia. *Eur Heart J Cardiovasc Imaging*. 2012;13(4):346–52.
[18] St John Sutton M, Ky B, Regner SR, Schadt K, Plappert T, He J, et al. Longitudinal strain in friedreich ataxia: A potential marker for early left ventricular dysfunction. *Echocardiography*. 2014;31(1):50–7.
[19] Lynch DR, Regner SR, Schadt KA, Friedman LS, Lin KY, Sutton MGSJ. Management and therapy for cardiomyopathy in Friedreich's ataxia. *Expert Rev Cardiovasc Ther*. 2012;10(6):767–77.
[20] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW WC. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society. *Circulation*. 2017;1–75.
[21] Kipps A, Alexander M, Colan SD, Gauvreau K, Smoot L, Crawford L, et al. The longitudinal course of cardiomyopathy in friedreich's ataxia during childhood. *Pediatr Cardiol*. 2009;30(3):306–10.
[22] Giovanni DS, Valeria P, Bahaa F, Majid AF. *Monitoring Cardiac Function During Idebenone Therapy in Friedreich's Ataxia*. 2015:1–5.
[23] Dudek J, Maack C. Barth syndrome cardiomyopathy. *Cardiovasc Res*. 2017;113(4):399–410.
[24] Xu Y, Malhotra A, Ren M, Schlame M. The enzymatic function of tafazzin. *J Biol Chem*. 2006;281(51):39217–24.
[25] Wortmann SB, Kluijtmans LA, Engelke UFH, Wevers RA, Morava E. The 3-methylglutaconic acidurias: What's new? *J Inherit Metab Dis*. 2012;35(1):13–22.

[26] Haghighi A, Haack TB, Atiq M, Mottaghi H, Haghighi-Kakhki H, Bashir RA, et al. Sengers syndrome: Six novel AGK mutations in seven new families and review of the phenotypic and mutational spectrum of 29 patients. *Orphanet J Rare Dis*. 2014;9(1).
[27] Mayr JA, Haack TB, Graf E, Zimmermann FA, Wieland T, Haberberger B, et al. Lack of the mitochondrial protein acylglycerol kinase causes sengers syndrome. *Am J Hum Genet [Internet]*. 2012;90(2):314–20. Available from: http://dx.doi.org/10.1016/j.ajhg.2011.12.005.
[28] Bernier FP, Boneh A, Dennett X, Chow CW, Cleary MA, Thorburn DR. Diagnostic criteria for respiratory chain disorders in adults and children. *Neurology*. 2002;59(9):1406–11.
[29] Alston CL, Ceccatelli Berti C, Blakely EL, Oláhová M, He L, McMahon CJ, et al. A recessive homozygous p.Asp92Gly SDHD mutation causes prenatal cardiomyopathy and a severe mitochondrial complex II deficiency. *Hum Genet*. 2015;134(8):869–79.
[30] Mancuso M, Nesti C, Ienco EC, Orsucci D, Pizzanelli C, Chiti A, et al. Novel MTCYB mutation in a young patient with recurrent stroke-like episodes and status epilepticus. *Am J Med Genet Part A*. 2014;164(11):2922–5.
[31] Darin N, Moslemi AR, Lebon S, Rustin P, Holme E, Oldfors A, et al. Genotypes and clinical phenotypes in children with cytochrorne-c oxidase deficiency. *Neuropediatrics*. 2003;34(6):311–7.
[32] Ghosh A, Pratt AT, Soma S, Theriault SG, Griffin AT, Trivedi PP, et al. Mitochondrial disease genes COA6, COX6B and SCO2 have overlapping roles in COX2 biogenesis. *Hum Mol Genet*. 2016;25(4):660–71.
[33] Wang YX, Le WD. Progress in diagnosing mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *Chin Med J (Engl)*. 2015;128(13):1820–5.
[34] Goodfellow JA, Dani K, Stewart W, Santosh C, McLean J, Mulhern S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: An important cause of stroke in young people. *Postgrad Med J*. 2012;88(1040):326–34.
[35] Liu Z, Song Y, Li D, He X, Li S, Wu B, et al. The novel mitochondrial 16S rRNA 2336T>C mutation is associated with hypertrophic cardiomyopathy. *J Med Genet*. 2014;51(3):176–84.
[36] Distelmaier F, Haack TB, Catarino CB, Gallenmüller C, Rodenburg RJ, Strom TM, et al. MRPL44 mutations cause a slowly progressive multisystem disease with childhood-onset hypertrophic cardiomyopathy. *Neurogenetics*. 2015;16(4):319–23.
[37] Emperador S, Bayona-Bafaluy MP, Fernández-Marmiesse A, Pineda M, Felgueroso B, López-Gallardo E, et al. Molecular-genetic characterization and rescue of a TSFM mutation causing childhood-onset ataxia and nonobstructive cardiomyopathy. *Eur J Hum Genet*. 2016;25(1):153–6.
[38] Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, et al. Mitochondrial neurogastrointestinal encephalomyopathy: An autosomal recessive disorder due to thymidine phosphorylase mutations. *Ann Neurol*. 2000;47(6):792–800.
[39] Smith AC, Ito Y, Ahmed A, Schwartzentruber JA, Beaulieu CL, Aberg E, et al. A family segregating lethal neonatal coenzyme Q 10 deficiency caused by mutations in COQ9. *J Inherit Metab Dis*. 2018.
[40] Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol [Internet]*. 2018 a;17(3):211–2. Available from: http://dx.doi.org/10.1016/S1474-4422(18)30024-3.
[41] Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol [Internet]*. 2018 b;17(4):347–61. Available from: http://dx.doi.org/10.1016/S1474-4422(18)30025-5.
[42] Mavrogeni S, Markousis-mavrogenis G, Papavasiliou A. Cardiac involvement in Duchenne and Becker muscular dystrophy. *World J Cardiol*. 2015;7(7):1–14.
[43] Finsterer J, Cripe L. Treatment of dystrophin cardiomyopathies. *Nat Publ Gr [Internet]*. 2014;11(3):168–79. Available from: http://dx.doi.org/10.1038/nrcardio.2013.213.
[44] Ok YP, Ahn Y, Woo SP, Ji HL, Hyung WP, Ju HK, et al. Rapid progression from hypertrophic cardiomyopathy to heart failure in a patient with Becker's muscular dystrophy. *Eur J Heart Fail*. 2005;7(4):684–8.
[45] Ryan TD, Taylor MD, Mazur W, Cripe LH, Pratt J, King EC, et al. Abnormal circumferential strain is present in young duchenne muscular dystrophy patients. *Pediatr Cardiol*. 2013;34:1159–65.
[46] Gueneau L, Bertrand AT, Jais J, Salih MA, Stojkovic T, Wehnert M, et al. Mutations of the FHL1 gene cause Emery-Dreifuss muscular dystrophy. 2009;338–53.
[47] Brown CA, Scharner J, Felice K, Meriggioli MN, Tarnopolsky M, Bower M, et al. Novel and recurrent EMD mutations in patients with Emery-Dreifuss muscular dystrophy, identify exon 2 as a mutation hot spot. *J Hum Genet [Internet]*. 2011;56(8):589–94. Available from: http://dx.doi.org/10.1038/jhg.2011.65.
[48] Gomes L, Pereira T, Martins L. Cardiovascular profile in myotonic dystrophy type 1: Analysis of a case series in a specialized center. *Rev Port Cardiol [Internet]*. 2014;33(12):765–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25481780.
[49] Finsterer J, Stöllberger C, Maeztu C. Sudden cardiac death in neuromuscular disorders. *Int J Cardiol [Internet]*. 2016;203:508–15. Available from: http://dx.doi.org/10.1016/j.ijcard.2015.10.176.
[50] Fragola PV, Luzi M, Calo L, Antonini G, Borzi M, Frongillo D, et al. Cardiac involvement in myotonic dystrophy. *Am J Cardiol [Internet]*. 1994;74(10):1070–2. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7977052.
[51] Finsterer J, Stöllberger C. Primary myopathies and the heart. *Scand Cardiovasc J*. 2008;42(1):9–24.
[52] Olivé M, Kley R, Goldfarb L. Myofibrillar myopathies. *Curr Opin Neurol*. 2013;26(5):527–35.

[53] Finsterer J, Stöllberger C, Wahbi K. Cardiomyopathy in neurological disorders. *Cardiovasc Pathol [Internet]*. 2013;22(5):389–400. Available from: http://dx.doi.org/10.1016/j.carpath.2012.12.008.
[54] Finsterer J, Ramaciotti C, Wang CH, Wahbi K, Rosenthal D, Duboc D, et al. Cardiac findings in congenital muscular dystrophies. *Pediatrics*. 2010;126(3):538–45.
[55] Finsterer J, Stöllberger C, Meng G. Cardiac involvement in facioscapulohumeral muscular dystrophy. *Cardiology*. 2005;103(2):81–3.
[56] Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, et al. Management of cardiac involvement associated with neuromuscular diseases: A scientific statement from the American Heart Association. *Circulation*. 2017;136:200–231.
[57] Lahrouchi N, Lodder EM, Mansouri M, Tadros R, Zniber L, Adadi N, et al. Exome sequencing identifies primary carnitine deficiency in a family with cardiomyopathy and sudden death. *Eur J Hum Genet*. 2017;25(6):783–7.