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Sources: Medline, Embase, Oxford Medicine Online

Myofibrillar Myopathies and Cardiomyopathy

Summary

The term *myofibrillar myopathies* (MFMs) was proposed in 1996 as a descriptive term for a group of chronic neuromuscular diseases associated with common morphologic features, including an abnormal accumulation of intrasarcoplasmic proteins, the presence of vacuoles and a disorganization of the intermyofibrillar network beginning at the Z-disk.

In the Mayo Clinic series of 80 individuals with myofibrillar myopathy (MFM), the age of onset varied from two to 77 years. The age at diagnosis ranged from 11 to 82 years. *BAG3*-related myofibrillar myopathy (Bag3opathy) characteristically presents in the first or second decade of life and is typically fatal. Desminopathies may also present in the first decade of life, usually with cardiomyopathy. However, the majority of MFM presents after age 40 years.

Myofibrillar myopathy is characterized by slowly progressive weakness that can involve both proximal and distal muscles. Distal muscle weakness is present in about 80% of individuals and is more pronounced than proximal weakness in about 25%. A minority of individuals experience sensory symptoms, muscle stiffness, aching, or cramps. Peripheral neuropathy is present in about 20% of affected individuals. Overt cardiomyopathy can be a presenting manifestation or can appear during the evolution of myofibrillar myopathy in 15%-30% of affected individuals.

No known measures mitigate the slow but relentless progression of MFM. Corticosteroids have not been shown to be of benefit. Physical therapy, consisting of passive exercises, orthoses, and other supporting devices, is helpful in the more advanced cases. Respiratory support consisting of continuous (CPAP) or BiPAP ventilation, initially at night and later in the daytime, are indicated in patients with respiratory failure and signs of hypercapnea. Periodic monitoring of patients for appearance of cardiomyopathy should be done in all patients, and pacemaker and implantable cardioverter defibrillator should be considered in individuals with arrhythmia and/or cardiac conduction defects. Patients with progressive or life-threatening cardiomyopathy are candidates for cardiac transplantation. Affected pregnant women may need assistance during delivery if they have significant weakness of their abdominal muscles.

The table below identifies the MFM subtypes, inheritance pattern, age of onset and clinical features (taken from Kley, Rudolf; et al, 2016).

Gene/protein	Disease	Inheritance pattern	Age of onset	Main clinical features
DES/desmin	Desminopathy	Dominant, de novo	Early/middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency
	Desminopathy	Recessive	Infancy/childhood	
CRYAB/ α B-crystallin	α B-crystallinopathy	Dominant	Middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency, cataracts
	α B-crystallinopathy	Recessive	Infancy	Limb and axial stiffness and weakness, respiratory failure
MYOT/myotilin	Myotilinopathy	Dominant	Middle/late adulthood	Distal and proximal weakness, cardiopathy and respiratory insufficiency in a minority of patients
	Myotilinopathy	Recessive	Early/middle adulthood	Distal and proximal weakness, arrhythmia
ZASP/ZASP	ZASPopathy	Dominant	Middle/late adulthood	Distal > proximal weakness, cardiopathy and neuropathy in a minority of patients
FLNC/filamin C	MFM-filaminopathy	Dominant	Middle adulthood	Proximal > distal weakness, respiratory failure, cardiopathy in a subset of patients
BAG3/BAG3	BAG3 myopathy	De novo	Childhood	Proximal and distal weakness, respiratory insufficiency, hypertrophic cardiomyopathy, peripheral neuropathy
FHL1/FHL1	Reducing body myopathy, FHL1 myopathy	X-linked	Infancy/childhood, adulthood [rare]	Delayed motor milestones, proximal > distal weakness, scoliosis, contractures, rapid loss of ambulation, respiratory insufficiency, milder course in adult onset patients
TTN/titin	Hereditary myopathy with early respiratory failure (HMERF)	Dominant	Early-late adulthood	Distal, proximal and neck weakness, early respiratory insufficiency
PLEC/plectin	Epidermolysis bullosa simplex with muscular dystrophy (EBS-MD)	Recessive	Skin blistering since birth, myopathy in infancy/childhood, adulthood	Proximal and distal weakness, cardiomyopathy, cataracts, epidermolysis, nail and tooth abnormalities, brain abnormalities
ACTA1/ α -actin	MFM-actinopathy	De novo	Infancy	Upper limb > lower limb weakness, respiratory insufficiency, contractures
HSPB8/HSPB8	HSPB8 myopathy	Dominant	Early/middle adulthood	Distal > proximal weakness, peripheral motor neuropathy
DNAJB6/DNAJB6	Limb girdle muscular dystrophy 1D	Dominant	Middle adulthood	Distal and proximal weakness

Adapted from [1].

Sources:

Kley, Rudolf; Olive, Montse; Schroder, Rolf *New aspects of myofibrillar myopathies*. Current Opinion in Neurology. 29(5):628-634, October 2016.

Raymond D, Ozelius L. Myoclonus-Dystonia. 2003 May 21 [Updated 2012 Jan 26]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. URL: <https://www.ncbi.nlm.nih.gov/books/NBK1499/?report=reader> [Accessed 23/01/2017]

Udd B. Distal and myofibrillar myopathies. In: *Oxford Textbook of Neuromuscular Disorders*. Oxford, UK: Oxford University Press; 2014. <http://oxfordmedicine.com/view/10.1093/med/9780199698073.001.0001/med-9780199698073-chapter-27> . Accessed January 23, 2017.

Selcen D. Myofibrillar Myopathies. In: *Evaluation and Treatment of Myopathies*. Oxford, UK: Oxford University Press; 2014. <http://oxfordmedicine.com/view/10.1093/med/9780199873937.001.0001/med-9780199873937-chapter-5> . Accessed January 23, 2017.

1. Truncating FLNC Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies.

Author(s): Ortiz-Genga, Martín F; Cuenca, Sofía; Dal Ferro, Matteo; Zorio, Esther; Salgado-Aranda, Ricardo; Climent, Vicente; Padrón-Barthe, Laura; Duro-Aguado, Iria; Jiménez-Jáimez, Juan; Hidalgo-Olivares, Víctor M; García-Campo, Enrique; Lanzillo, Chiara; Suárez-Mier, M Paz; Yonath, Hagith; Marcos-Alonso, Sonia; Ochoa, Juan P; Santomé, José L; García-Giustiniani, Diego; Rodríguez-Garrido, Jorge L; Domínguez, Fernando; Merlo, Marco; Palomino, Julián; Peña, María L; Trujillo, Juan P; Martín-Vila, Alicia; Stolfo, Davide; Molina, Pilar; Lara-Pezzi, Enrique; Calvo-Iglesias, Francisco E; Nof, Eyal; Calò, Leonardo; Barriales-Villa, Roberto; Gimeno-Blanes, Juan R; Arad, Michael; García-Pavía, Pablo; Monserrat, Lorenzo

Source: Journal of the American College of Cardiology; Dec 2016; vol. 68 (no. 22); p. 2440-2451

Publication Date: Dec 2016

Publication Type(s): Journal Article

Abstract: Filamin C (encoded by the FLNC gene) is essential for sarcomere attachment to the plasmatic membrane. FLNC mutations have been associated with myofibrillar myopathies, and cardiac involvement has been reported in some carriers. Accordingly, since 2012, the authors have included FLNC in the genetic screening of patients with inherited cardiomyopathies and sudden death. The aim of this study was to demonstrate the association between truncating mutations in FLNC and the development of high-risk dilated and arrhythmogenic cardiomyopathies. FLNC was studied using next-generation sequencing in 2,877 patients with inherited cardiovascular diseases. A characteristic phenotype was identified in probands with truncating mutations in FLNC. Clinical and genetic evaluation of 28 affected families was performed. Localization of filamin C in cardiac tissue was analyzed in patients with truncating FLNC mutations using immunohistochemistry. Twenty-three truncating mutations were identified in 28 probands previously diagnosed with dilated, arrhythmogenic, or restrictive cardiomyopathies. Truncating FLNC mutations were absent in patients with other phenotypes, including 1,078 patients with hypertrophic cardiomyopathy. Fifty-four mutation carriers were identified among 121 screened relatives. The phenotype consisted of left ventricular dilation (68%), systolic dysfunction (46%), and myocardial fibrosis (67%); inferolateral negative T waves and low QRS voltages on electrocardiography (33%); ventricular arrhythmias (82%); and frequent sudden cardiac death (40 cases in 21 of 28 families). Clinical skeletal myopathy was not observed. Penetrance was >97% in carriers older than 40 years. Truncating mutations in FLNC cosegregated with this phenotype with a dominant inheritance pattern (combined logarithm of the odds score: 9.5). Immunohistochemical staining of myocardial tissue showed no abnormal filamin C aggregates in patients with truncating FLNC mutations. Truncating mutations in FLNC caused an overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature sudden death. Prompt implantation of a cardiac defibrillator should be considered in affected patients harboring truncating mutations in FLNC. Copyright © 2016 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Database: Medline

2. Myofibrillar and distal myopathies

Author(s): Palmio J.; Udd B.

Source: Revue Neurologique; Oct 2016; vol. 172 (no. 10); p. 587-593

Publication Date: Oct 2016

Publication Type(s): Journal: Review

Abstract: Distal myopathies and myofibrillar myopathies are both rare subcategories of muscle diseases. Myofibrillar myopathies are genetically heterogeneous group of diseases characterized by distinctive histopathology of abnormal protein aggregations and myofibrillar disintegration. All genes causing myofibrillar myopathy encode proteins that either reside in or associate with the Z-disc. Distal myopathies are also genetically heterogeneous muscular dystrophies in which muscle weakness presents distally in the feet and/or hands. A subgroup of distal myopathies, desminopathy, distal myotilinopathy, ZASPopathy and alpha-B crystallin-mutated distal myopathy, belong to myofibrillar myopathies and show similar pathological changes in muscle biopsies. Common features of these diseases are dominant inheritance and adult-onset of symptoms starting in the feet and slowly progressing to encompass other muscle groups. Cardiomyopathy is not a common feature in distal MFM myopathies. Copyright © 2016 Elsevier Masson SAS

Database: EMBASE

3. Cardiac arrhythmia and late-onset muscle weakness caused by a myofibrillar myopathy with unusual histopathological features due to a novel missense mutation in FLNC.

Author(s): Avila-Smirnow, D; Gueneau, L; Batonnet-Pichon, S; Delort, F; Bécane, H-M; Claeys, K; Beuvin, M; Goudeau, B; Jais, J-P; Nelson, I; Richard, P; Ben Yaou, R; Romero, N B; Wahbi, K; Mathis, S; Voit, T; Furst, D; van der Ven, P; Gil, R; Vicart, P; Fardeau, M; Bonne, G; Behin, A

Source: Revue neurologique; Oct 2016; vol. 172 (no. 10); p. 594-606

Publication Date: Oct 2016

Publication Type(s): Journal Article Review

Abstract: Myofibrillar myopathies (MFM) are mostly adult-onset diseases characterized by progressive morphological alterations of the muscle fibers beginning in the Z-disk and the presence of protein aggregates in the sarcoplasm. They are mostly caused by mutations in different genes that encode Z-disk proteins, including DES, CRYAB, LDB3, MYOT, FLNC and BAG3. A large family of French origin, presenting an autosomal dominant pattern, characterized by cardiac arrhythmia associated to late-onset muscle weakness, was evaluated to clarify clinical, morphological and genetic diagnosis. Muscle weakness began during adult life (over 30 years of age), and had a proximal distribution. Histology showed clear signs of a myofibrillar myopathy, but with unusual, large inclusions. Subsequently, genetic testing was performed in MFM genes available for screening at the time of clinical/histological diagnosis, and desmin (DES), α B-crystallin (CRYAB), myotilin (MYOT) and ZASP (LDB3), were excluded. LMNA gene screening found the p.R296C variant which did not co-segregate with the disease. Genome wide scan revealed linkage to 7q.32, containing the FLNC gene. FLNC direct sequencing revealed a heterozygous c.3646T>A p.Tyr1216Asn change, co-segregating with the disease, in a highly conserved amino acid of the protein. Normal filamin C levels were detected by Western-blot analysis in patient muscle biopsies and expression of the mutant protein in NIH3T3 showed filamin C aggregates. This is an original FLNC mutation in a MFM family with an atypical clinical and histopathological presentation, given the presence of significantly focal lesions and prominent sarcoplasmic masses in muscle biopsies and the constant heart involvement preceding significantly the onset of the myopathy. Though a rare etiology, FLNC gene should not be excluded in early-onset arrhythmia, even in the absence of myopathy, which occurs later in the disease course. Copyright © 2016 Elsevier Masson SAS. All rights reserved.

4. Myofibrillar myopathies: State of the art, present and future challenges

Author(s): Behin A.; Wahbi K.; Laforet P.; Stojkovic T.; Becane H.-M.; Duboc D.; Eymard B.; Salort-Campana E.; Verschueren A.; Franques J.; Attarian S.; Pouget J.; Richard P.; Carlier R.-Y.; Carlier P.; Maisonnobe T.; Maues De Paula A.; Figarella-Branger D.; Nelson I.; Bonne G.; Vicart P.; Udd B.; Romero N.

Source: Revue Neurologique; Oct 2015; vol. 171 (no. 10); p. 715-729

Publication Date: Oct 2015

Publication Type(s): Journal: Article

Abstract: Myofibrillar myopathies (MFM) have been described in the mid-1990s as a group of diseases sharing common histological features, including an abnormal accumulation of intrasarcoplasmic proteins, the presence of vacuoles and a disorganization of the intermyofibrillar network beginning at the Z-disk. The boundaries of this concept are still uncertain, and whereas six genes (DES, CRYAB, LDB3/ZASP, MYOT, FLNC and BAG3) are now classically considered as responsible for MFM, other entities such as FHL1 myopathy or Hereditary Myopathy with Early Respiratory Failure linked to mutations of titin can now as well be included in this group. The diagnosis of MFM is not always easy; as histological lesions can be focal, and muscle biopsy may be disappointing; this has led to a growing importance of muscle imaging, and the selectivity of muscle involvement has now been described in several disorders. Due to the rarity of these myopathies, if some clinical patterns (such as distal myopathy associated with cardiomyopathy due to desmin mutations) are now well known, surprises remain possible and should lead to systematic testing of the known genes in case of a typical histological presentation. In this paper, we aim at reviewing the data acquired on the six main genes listed above as well as presenting the experience from two French reference centres, Paris and Marseilles. Copyright © 2015 Elsevier Masson SAS.

Database: EMBASE

5. Phenotypic variability of Pro209Leu BAG3 mutations: Cardiomyopathy, demyelinating neuropathy and a long QT syndrome

Author(s): Kostera-Pruszczyk A.; Potulska-Chromik A.; Kaminska A.; Ploski R.; Sadurska E.; Karolczak J.; Redowicz M.; Pruszczyk P.

Source: Neuromuscular Disorders; Oct 2015; vol. 25

Publication Date: Oct 2015

Publication Type(s): Journal: Conference Abstract

Abstract: Myofibrillar myopathies (MFM) are a group of genetically heterogeneous disorders characterized by myofibrillar degeneration. Accumulation of numerous Z-disc proteins, such as alphaB-crystallin, desmin, or myotilin, is a morphological hallmark of MFM. Most MFM patients present in early adulthood with progressive limb muscle weakness or cardiomyopathy. Although distal muscles are frequently involved in MFM patients and may mimic neuropathy, sensory-motor polyneuropathy is a rare feature. Cardiac dysfunction can present as arrhythmia due to A-V block, restrictive or dilated cardiomyopathy. We report a sporadic case of a 15-year-old girl with demyelinating polyneuropathy (with cv in median/ulnar motor nerves 38 m/s) accompanied by long QT and, later in the course of her disease, by restrictive cardiomyopathy. She had pes equinovarus, mild distal muscle weakness and decreased vibration sensation, areflexia, and rigid spine. LQT was confirmed by Holter ECG. In 90% of the recorded tracings QT was prolonged with maximal QTc 578 ms. Muscle biopsy confirmed desmin, alphaB-crystallin storage at Z-disc. Genetic testing demonstrated heterozygous mutation Pro209Leu (c.626C > T) in exon 3 of BAG3 gene, causing neuropathy with restrictive cardiomyopathy. No mutation in known LQT syndrome genes was found.

This is the second reported patients with BAG3 mutation and LQT. We postulate that LQT could be a part of the clinical spectrum of Pro209Leu BAG3 mutations.

Database: EMBASE

6. Mutations in filamin C cause familial restrictive cardiomyopathy

Author(s): Brodehl A.; Ferrier R.; Greenway S.C.; Brundler M.; Yu W.; Alvarez N.; Giuffre M.; Gerull B.

Source: Canadian Journal of Cardiology; Oct 2015; vol. 31 (no. 10)

Publication Date: Oct 2015

Publication Type(s): Journal: Conference Abstract

Abstract:BACKGROUND: Restrictive cardiomyopathy (RCM) is characterized by increased stiffness of the ventricles, impaired diastolic filling with preserved systolic function. Familial RCM is a rare condition and mainly caused by mutations sarcomere proteins and desmin. Filamin C (FLNC) is a muscle specific protein which provides the mechanical link between the extracellular matrix, the plasma membrane and the actin cytoskeleton. Mutations in FLNC are known to cause myofibrillar myopathy (MFM) and most recently suggested to be associated with hypertrophic cardiomyopathy (HCM). Purpose: In families with autosomal dominant RCM we excluded mutations in all known genes for RCM and aimed to identify and validate a novel cause of the disease. METHODS: Cardiovascular assessment was done in all available family members after the index case was diagnosed with early onset RCM leading to heart transplantation. Genetic studies via next generation sequencing (NGS) have been performed followed by segregation analysis in affected family members. Explanted heart tissue has been evaluated by histology and immunohistochemistry. Functional analysis of mutated FLNC proteins were carried out in cultured cells and analyzed by immunocytochemistry. RESULTS: The index case presented with heart failure at the age of 13 years requiring heart transplantation a year later. Cardiac assessment showed an impaired diastolic filling pattern, enlarged atria, normal systolic LV-function and wall thicknesses suggesting restrictive cardiomyopathy. Subsequently other family members were diagnosed with signs of RCM. Years later her 2 year old daughter also required heart transplantation due to RCM. Genetic studies via Next Generation Sequencing (NGS) found a unique variant in FLNC (p.S1624L) segregating with the disease. Histopathology and immunohistochemistry revealed FLNC specific cytoplasmic aggregates. Further expression of mutant FLNC proteins in C2C12 and H9C2 cells showed perinuclear and cytoplasmic aggregates not observed in wild-type FLNC transfected cells. Finding of a second mutation in a different family with RCM discovered by NGS confirmed the involvement of FLNC in the genetic aetiology of RCM. CONCLUSION: Mutations in FLNC are a novel cause of familial autosomal dominant RCM. It demonstrates the powerful strategy of NGS to uncover novel genetic causes for familial diseases.

Database: EMBASE

7. Developmental Alterations in Heart Biomechanics and Skeletal Muscle Function in Desmin Mutants Suggest an Early Pathological Root for Desminopathies.

Author(s): Ramspacher, Caroline; Steed, Emily; Boselli, Francesco; Ferreira, Rita; Faggianelli, Nathalie; Roth, Stéphane; Spiegelhalter, Coralie; Messaddeq, Nadia; Trinh, Le; Liebling, Michael; Chacko, Nikhil; Tessadori, Federico; Bakkers, Jeroen; Laporte, Jocelyn; Hnia, Karim; Vermot, Julien

Source: Cell reports; Jun 2015; vol. 11 (no. 10); p. 1564-1576

Publication Date: Jun 2015

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Abstract:Desminopathies belong to a family of muscle disorders called myofibrillar myopathies that are caused by Desmin mutations and lead to protein aggregates in muscle fibers. To date, the initial pathological steps of desminopathies and the impact of desmin aggregates in the genesis of the disease are unclear. Using live, high-resolution microscopy, we show that Desmin loss of function and Desmin aggregates promote skeletal muscle defects and alter heart biomechanics. In addition, we show that the calcium dynamics associated with heart contraction are impaired and are associated with sarcoplasmic reticulum dilatation as well as abnormal subcellular distribution of Ryanodine receptors. Our results demonstrate that desminopathies are associated with perturbed excitation-contraction coupling machinery and that aggregates are more detrimental than Desmin loss of function. Additionally, we show that pharmacological inhibition of aggregate formation and Desmin knockdown revert these phenotypes. Our data suggest alternative therapeutic approaches and further our understanding of the molecular determinants modulating Desmin aggregate formation. Copyright © 2015 The Authors. Published by Elsevier Inc. All rights reserved.

Database: Medline

8. BAG3 myofibrillar myopathy presenting with cardiomyopathy.

Author(s): Konersman, Chamindra G; Bordini, Brett J; Scharer, Gunter; Lawlor, Michael W; Zangwill, Steven; Southern, James F; Amos, Louella; Geddes, Gabrielle C; Kliegman, Robert; Collins, Michael P

Source: Neuromuscular disorders : NMD; May 2015; vol. 25 (no. 5); p. 418-422

Publication Date: May 2015

Publication Type(s): Case Reports Journal Article

Abstract:Myofibrillar myopathies (MFMs) are a heterogeneous group of neuromuscular disorders distinguished by the pathological hallmark of myofibrillar dissolution. Most patients present in adulthood, but mutations in several genes including BCL2-associated athanogene 3 (BAG3) cause predominantly childhood-onset disease. BAG3-related MFM is particularly severe, featuring weakness, cardiomyopathy, neuropathy, and early lethality. While prior cases reported either neuromuscular weakness or concurrent weakness and cardiomyopathy at onset, we describe the first case in which cardiomyopathy and cardiac transplantation (age eight) preceded neuromuscular weakness by several years (age 12). The phenotype comprised distal weakness and severe sensorimotor neuropathy. Nerve biopsy was primarily axonal with secondary demyelinating/remyelinating changes without "giant axons." Muscle biopsy showed extensive neuropathic changes that made myopathic changes difficult to interpret. Similar to previous cases, a p.Pro209Leu mutation in exon 3 of BAG3 was found. This case underlines the importance of evaluating for MFMs in patients with combined neuromuscular weakness and cardiomyopathy. Copyright © 2015 Elsevier B.V. All rights reserved.

Database: Medline

9. When myopathy breaks the rules: A late-onset distal presentation

Author(s): Newby R.; Jamieson S.; Alty J.; Udd B.

Source: BMJ Case Reports; Apr 2015; vol. 2015

Publication Date: Apr 2015

Publication Type(s): Journal: Article

Available in full text at [BMJ Case Reports](#) - from Highwire Press

Abstract: Myopathies typically present with proximal or generalised muscle weakness, but it is important for clinicians to recognise they may also have other distributions. This paper describes a case of distal myopathy that was confirmed genetically as ZASP (Z-band alternatively spliced PDZ motif-containing protein) myofibrillar myopathy (MFM). MFMs are particularly topical because the genetic basis of several have recently been established, enabling diagnosis of conditions previously labelled 'idiopathic myopathy', and shedding new light on their pathophysiology. This paper describes a purely distal lower limb phenotype of ZASP MFM, the pathophysiology of ZASP and other MFMs, and the differential diagnosis of late-onset distal symmetrical weakness. The case includes several learning points: ZASP MFM is a new diagnosis; it should be included in differential diagnoses for late-onset myopathy, especially if there is a distal pattern or autosomal dominant inheritance; testing for cardiomyopathy is recommended, and a genetic test is now available.

Database: EMBASE

10. Repeated radiofrequency ablation of atrial tachycardia in restrictive cardiomyopathy secondary to myofibrillar myopathy.

Author(s): Stöllberger, Claudia; Gatterer, Edmund; Finsterer, Josef; Kuck, Karl-Heinz; Tilz, Roland Richard

Source: Journal of cardiovascular electrophysiology; Aug 2014; vol. 25 (no. 8); p. 905-907

Publication Date: Aug 2014

Publication Type(s): Research Support, Non-u.s. Gov't Case Reports Journal Article

Available in full text at [Journal of Cardiovascular Electrophysiology](#) - from John Wiley and Sons

Available in full text at [Journal of Cardiovascular Electrophysiology](#) - from EBSCOhost

Abstract: Myofibrillar myopathy is characterized by nonhyaline and hyaline lesions due to mutations in nuclear genes encoding for extra-myofibrillar or myofibrillar proteins. Cardiac involvement in myofibrillar myopathy may be phenotypically expressed as dilated, hypertrophic, or restrictive cardiomyopathy. Radiofrequency ablation of atrial fibrillation and flutter has so far not been reported in myofibrillar myopathy. We report the case of a young female with myofibrillar myopathy and deteriorating heart failure due to restrictive cardiomyopathy and recurrent atrial fibrillation and atrial tachycardias intolerant to pharmacotherapy. Cardiac arrhythmias were successfully treated with repeat radiofrequency ablations and resulted in regression of heart failure, thus postponing the necessity for cardiac transplantation. © 2014 Wiley Periodicals, Inc.

Database: Medline

11. Cardiomyopathy in neurological disorders.

Author(s): Finsterer, Josef; Stöllberger, Claudia; Wahbi, Karim

Source: Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology; 2013; vol. 22 (no. 5); p. 389-400

Publication Date: 2013

Publication Type(s): Journal Article Review

Abstract:According to the American Heart Association, cardiomyopathies are classified as primary (solely or predominantly confined to heart muscle), secondary (those showing pathological myocardial involvement as part of a neuromuscular disorder) and those in which cardiomyopathy is the first/predominant manifestation of a neuromuscular disorder. Cardiomyopathies may be further classified as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or unclassified cardiomyopathy (noncompaction, Takotsubo-cardiomyopathy). This review focuses on secondary cardiomyopathies and those in which cardiomyopathy is the predominant manifestation of a myopathy. Any of them may cause neurological disease, and any of them may be a manifestation of a neurological disorder. Neurological disease most frequently caused by cardiomyopathies is ischemic stroke, followed by transitory ischemic attack, syncope, or vertigo. Neurological disease, which most frequently manifests with cardiomyopathies are the neuromuscular disorders. Most commonly associated with cardiomyopathies are muscular dystrophies, myofibrillar myopathies, congenital myopathies and metabolic myopathies. Management of neurological disease caused by cardiomyopathies is not at variance from the same neurological disorders due to other causes. Management of secondary cardiomyopathies is not different from that of cardiomyopathies due to other causes either. Patients with neuromuscular disorders require early cardiologic investigations and close follow-ups, patients with cardiomyopathies require neurological investigation and avoidance of muscle toxic medication if a neuromuscular disorder is diagnosed. Which patients with cardiomyopathy profit most from primary stroke prevention is unsolved and requires further investigations. Copyright © 2013 Elsevier Inc. All rights reserved.

Database: Medline

12. When your heart is flutter and you're weak at the knees: A case report

Author(s): Davidson A.; Longman C.; Farrugia M.

Source: Journal of Neurology, Neurosurgery and Psychiatry; Nov 2013; vol. 84 (no. 11)

Publication Date: Nov 2013

Publication Type(s): Journal: Conference Abstract

Available in full text at [Journal of neurology, neurosurgery, and psychiatry](#) - from Highwire Press

Available in full text at [Journal of Neurology, Neurosurgery and Psychiatry](#) - from ProQuest

Abstract:A 49 year old gentleman presented to Neurology with a 10 year history of deteriorating mobility. He described an evolving bilateral foot drop from his mid-thirties, with progressive symptoms affecting his left hand, manifesting as difficulties performing fine tasks such as snapping his fingers. He also had bilateral sensorineural deafness. He was known to cardiology with a tachy-brady syndrome which had evolved into persistent atrial fibrillation not requiring a pacemaker. His mother had Alzheimer's disease, with a "shuffling gait". His brother suffered from childhood polio. On examination, he was dysarthric, with wasting and weakness of the interossei and thenar eminence in both hands. There was wasting of the calf muscles and of tibialis anterior, with normal arched feet. Weakness was present at hips, knees and ankles with marked symmetrical weakness of ankle dorsiflexion bilaterally. Investigations showed normal CK with a myopathic pattern on EMG.

His ECG showed atrial fibrillation with left bundle branch block and echocardiography demonstrated biatrial enlargement. Given his presentation and family history a muscle biopsy was performed. This revealed numerous atrophic fibers and an increase in internal nucleation, with scattered cytoplasmic vacuoles. There was also a mild increase in type 1 fibre and abnormal Desmin staining. Sequencing of the VCP (valosin containing protein) gene did not identify any abnormality. Then sequencing of the DES (Desmin) gene was performed and identified a mis-sense mutation c.1346A>C (p.Lys449Thr), diagnosing a desminopathy. Desminopathy is part of the myofibrillar myopathies (MFMs). They are a group of muscular dystrophies, associated with myofibrillar disorganisation and accumulation of myofibrillar degradation products. Diagnosis is via muscle pathology and electron microscopy. Inheritance can be autosomal dominant, autosomal recessive, X-linked and rarely sporadic. Age of onset can vary between third and seventh decades. Patients present with progressive muscle weakness which can be distal, limb-girdle or scapuloperoneal in distribution. Cardiomyopathy may precede muscle weakness and cardiac arrhythmias may occur. Respiratory insufficiency, including diaphragm paralysis, peripheral neuropathy and spinal rigidity can be associated with some subsets. Desmin is a 53kDa intermediate filament which is involved in the formation of cellular cytoskeleton. Over 40 mutations have been described, the majority clustering in the alpha-helical head domain but there is also newer evidence that mutations in the "tail" region can lead to similar phenotypes.¹⁻⁴ Recognising MFMs is important because of their myriad of implications. Although there is no active treatment for the muscular dystrophy, cardiac and respiratory interventions can be used. Furthermore, it is crucial to identify family members at risk and counsel them appropriately.

Database: EMBASE

13. Autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7 is caused by a DES mutation.

Author(s): Hedberg, Carola; Melberg, Atle; Kuhl, Angelika; Jenne, Dieter; Oldfors, Anders

Source: European journal of human genetics : EJHG; Sep 2012; vol. 20 (no. 9); p. 984-985

Publication Date: Sep 2012

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available in full text at [European Journal of Human Genetics](#) - from National Library of Medicine

Available in full text at [European Journal of Human Genetics : EJHG](#) - from ProQuest

Available in full text at [European Journal of Human Genetics](#) - from Nature Publishing Group

Abstract: Using exome sequencing we searched for the genetic cause of autosomal dominant myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy (ARVC) in a Swedish family. A heterozygous C-to-T transition, c.1255C>T, p.Pro419Ser in the desmin gene on chromosome 2q35, was identified. Previous studies had demonstrated linkage to chromosome 10q22.3, but no causative mutation had been found in that region. Sanger sequencing of DNA from 17 family members confirmed the heterozygous c.1255C>T desmin mutation in seven out of ten family members that had been classified as affected in the previous study. Our new results demonstrate the usefulness of next-generation sequencing, and the diagnostic difficulties with some forms of dominantly inherited muscle diseases as they can display a wide clinical and morphological variability even within a given family.

Database: Medline

14. High cardiovascular morbidity and mortality in myofibrillar myopathies due to DES gene mutations: a 10-year longitudinal study.

Author(s): Wahbi, Karim; Béhin, Anthony; Charron, Philippe; Dunand, Murielle; Richard, Pascale; Meune, Christophe; Vicart, Patrick; Laforêt, Pascal; Stojkovic, Tanya; Bécane, Henri Marc; Kuntzer, Thierry; Duboc, Denis

Source: Neuromuscular disorders : NMD; Mar 2012; vol. 22 (no. 3); p. 211-218

Publication Date: Mar 2012

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Abstract:To determine incidence and type of major cardiac adverse events in patients with mutated desmin (DES) gene, we retrospectively reviewed baseline medical information, and examined the long-term outcomes of 28 DES patients (17 men, baseline mean age=37.7±14.4 years [min=9, max=71]) from 19 families. Baseline studies revealed skeletal muscle involvement in 21 patients and cardiac abnormalities in all but one patient. Over a mean follow-up of 10.4±9.4 years [min=1, max=35], cardiac death occurred in three patients, death due to cardiac comorbidities in two, one or more major cardiac adverse events in 13 patients. Among the 19 patients with mild conduction defects at baseline, eight developed high-degree conduction blocks requiring permanent pacing. Cardiac involvement was neither correlated with the type of DES mutation nor with the severity of skeletal muscle involvement. Our study underscores that in DES patients in-depth cardiac investigations are needed to prevent cardiac conduction system disease. Copyright © 2011 Elsevier B.V. All rights reserved.

Database: Medline

15. Restrictive cardiomyopathy as a cardiac manifestation of myofibrillar myopathy.

Author(s): Finsterer, Josef; Stöllberger, Claudia; Höftberger, Romana

Source: Heart & lung : the journal of critical care; 2011; vol. 40 (no. 5); p. e123

Publication Date: 2011

Publication Type(s): Case Reports Journal Article

Abstract:Restrictive cardiomyopathy (RCM) has been repeatedly reported as a cardiac manifestation of certain neuromuscular disorders, but only in single patients with myofibrillar myopathy (MFMP). In a 19-year-old woman with a history of short stature, tiptoe-walking since childhood, fixed joint contractures, severe scoliosis requiring surgical correction, elevated levels of creatine kinase, and RCM, MFMP was diagnosed based on her clinical presentation, her elevated muscle enzymes and a muscle biopsy. An electrocardiogram showed an atrioventricular-block I, paroxysmal sinus-tachycardia, biphasic P-waves, right-axis deviation, abnormal repolarization, and episodes of supraventricular tachycardia. Echocardiography confirmed her RCM. Her respiratory function was markedly reduced, despite surgical correction of her severe scoliosis at age 14 years. After an aggravation of heart failure because of atrial flutter, the patient profited from successful cardioversion and diuretics. Electrocardiographic abnormalities such as atrial flutter and RCM represent cardiac manifestations of MFMP. Cardioversion can be successful, and oral anticoagulation may prevent cardioembolic events. Copyright © 2011 Elsevier Inc. All rights reserved.

Database: Medline

16. Myofibrillar myopathies

Author(s): Selcen D.

Source: Neuromuscular Disorders; Mar 2011; vol. 21 (no. 3); p. 161-171

Publication Date: Mar 2011

Publication Type(s): Journal: Review

Abstract:Myofibrillar myopathies represent a group of muscular dystrophies with a similar morphologic phenotype. They are characterized by a distinct pathologic pattern of myofibrillar dissolution associated with disintegration of the Z-disk, accumulation of myofibrillar degradation products, and ectopic expression of multiple proteins and sometimes congophilic material. The clinical features of myofibrillar myopathies are more variable. These include progressive muscle weakness, that often involves or begins in distal muscles but limb-girdle or scapuloperoneal distributions can also occur. Cardiomyopathy and peripheral neuropathy are frequent associated features. EMG of the affected muscles reveals myopathic motor unit potentials and abnormal irritability often with myotonic discharges. Rarely, neurogenic motor unit potentials or slow nerve conductions are present. The generic diagnosis of myofibrillar myopathies is based on muscle biopsy findings in frozen sections. To date, all myofibrillar myopathy mutations have been traced to Z-disk-associated proteins, namely, desmin, alphaB-crystallin, myotilin, ZASP, filamin C and Bag3. However, in the majority of the myofibrillar myopathy patients the disease gene awaits discovery. © 2010 Elsevier B.V.

Database: EMBASE

17. End-stage cardiac disease as an initial presentation of systemic myopathies: case series and literature review.

Author(s): Katzberg, Hans; Karamchandani, Jason; So, Yuen T; Vogel, Hannes; Wang, Ching H

Source: Journal of child neurology; Nov 2010; vol. 25 (no. 11); p. 1382-1388

Publication Date: Nov 2010

Publication Type(s): Case Reports Journal Article Review

Abstract:Life-threatening cardiomyopathy is associated with certain systemic myopathies and usually presents as an end-stage progression of the disease. However, cardiac symptoms can sometimes precede muscle weakness. The authors reviewed medical records from 2003 to 2008 on patients attending their neuromuscular clinic and identified patients who initially presented with an end-stage cardiomyopathy and were later diagnosed with a specific muscle disease through muscle biopsy. They report 5 cases of children who initially presented with cardiomyopathies without neuromuscular symptoms. The cardiac symptoms were so severe that 4 of them required cardiac transplantation and 1 died prior to transplantation. Review of muscle pathology confirmed the diagnoses of Becker muscular dystrophy, myofibrillar myopathy, mitochondrial myopathy with cytochrome oxidase deficiency, Danon disease, and glycogen storage disease. The authors conclude that cardiomyopathy can be the initial presentation of a wide spectrum of systemic myopathies. Careful evaluation of neuromuscular systems should be carried out in patients presenting with end-stage cardiomyopathies.

Database: Medline

18. Myofibrillar myopathies.

Author(s): Selcen, Duygu

Source: Current opinion in neurology; Oct 2008; vol. 21 (no. 5); p. 585-589

Publication Date: Oct 2008

Publication Type(s): Research Support, N.i.h., Extramural Journal Article Review

Available in full text at [Current Opinion in Neurology](#) - from Ovid

Abstract: The aim of this communication is to provide an up-to-date overview of myofibrillar myopathies. The most important recent advance in the myofibrillar myopathies has been the discovery that mutations in Z band alternatively spliced PDZ-containing protein and filamin C, as well as in desmin, alphaB-crystallin and myotilin, result in similar pathologic alterations in skeletal muscle that are typical of myofibrillar myopathy. Despite the increasing genetic heterogeneity, the clinical and morphologic phenotypes are remarkably homogeneous. The typical clinical manifestation is slowly progressive proximal, distal or both proximal and distal limb muscle weakness. Cardiomyopathy can be associated and is sometimes the presenting finding. Peripheral neuropathy also occurs in some patients. In every myofibrillar myopathy, there is abnormal accumulation of an array of proteins at ectopic sites as well as accumulation of degraded myofibrillar proteins forming large aggregates. The key issue now is to analyze the molecular mechanisms underlying the cascade of events that destroy the myofibrillar architecture and trigger the aberrant expression of multiple proteins. Several disease genes have recently been recognized in myofibrillar myopathies. So far, the disease proteins identified are components of or chaperone for the Z-disk. In each case, the molecular defect leads to a stereotyped cascade of structural events in the muscle fiber.

Database: Medline

19. Atrial fibrillation/flutter in myopathies

Author(s): Finsterer J.; Stollberger C.

Source: International Journal of Cardiology; Aug 2008; vol. 128 (no. 3); p. 304-310

Publication Date: Aug 2008

Publication Type(s): Journal: Review

Abstract: With improved screening of patients with primary and secondary myopathies and more comprehensive investigations it turns out that an increasing number of patients with myopathies develops cardiac disease (cardiac involvement), before or after onset of the neuromuscular abnormalities. Cardiac involvement in myopathies manifests within the myocardium or the cardiac conduction system with impulse generation or conduction disturbances. An increasingly recognized rhythm abnormality in these patients is atrial fibrillation/flutter (AFI/AFL), which carries an increased risk for stroke embolism and represents an absolute indication for oral anticoagulation (OAC). Primary myopathies, in which AFI/AFL has been described so far include dystrophinopathies, Emery-Dreifuss muscular dystrophy, facio-scapulo-humeral muscular dystrophy, limb girdle muscular dystrophies, congenital myopathies, myofibrillar myopathies, myotonic dystrophies, glycogenoses, mitochondrial disorders, Barth syndrome, McLeod syndrome, and non-specific myopathies. Secondary myopathies, in which AFI/AFL has been described comprise polymyositis, dermatomyositis, colchicine-induced myopathy, and hyperthyroid myopathy. Myopathies most commonly associated with AFI/AFL are myotonic dystrophy and Emery-Dreifuss muscular dystrophy. Information about the frequency of stroke/embolism in these patients is rudimentary but there are indications that it is not increased in these patients. Only a few patients with AFI/AFL receive OAC to prevent from stroke/embolism. Patients with myopathy and AFI/AFL require thorough surveillance. If additional cardiovascular risk factors develop, OAC should be considered as in patients with other causes of AFI/AFL. © 2008 Elsevier Ireland Ltd. All rights reserved.

Database: EMBASE

20. Myofibrillar myopathy with arrhythmogenic right ventricular cardiomyopathy 7: corroboration and narrowing of the critical region on 10q22.3.

Author(s): Kuhl, Angelika; Melberg, Atle; Meinl, Edgar; Nürnberg, Gudrun; Nürnberg, Peter; Kehrer-Sawatzki, Hildegard; Jenne, Dieter E

Source: European journal of human genetics : EJHG; Mar 2008; vol. 16 (no. 3); p. 367-373

Publication Date: Mar 2008

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available in full text at [European Journal of Human Genetics : EJHG](#) - from ProQuest

Available in full text at [European Journal of Human Genetics](#) - from Nature Publishing Group

Abstract:Several years ago, autosomal dominant myofibrillar myopathy (MFM) in combination with arrhythmogenic right ventricular cardiomyopathy (ARVC7) was tentatively mapped to a 10.6-Mbp (million base pairs) region on chromosome 10q22.3 between D10S605 (78.9 Mbp) and D10S215 (89.5 Mbp) in a Swedish family assuming that ARVC7 was allelic with cardiomyopathy, dilated 1C (CMD1C). To date, neither the genetic defect in ARVC7 nor CMD1C has been reported. In a comprehensive follow-up study we re-examined and confirmed the previous linkage data for ARVC7 using a high-density single nucleotide polymorphism marker panel from Affymetrix (Human Mapping 10K Array). No other regions with significant evidence for linkage were discovered. The critical interval was narrowed down to 4.27 Mbp between D10S1645 and D10S1786. This reduced the total number of candidate genes to 18 of which 17 (RAI17, PPIF, C10ORF56, SFTPA1, SFTPA2, SFTPA1B, SFTPA2B, SFTPD, C10ORF57, PLAC9, ANXA11, MAT1A, DYDC1, DYDC2, C10ORF58, TSPAN14 and SH2D4B) are shared with the CMD1C region. No disease-causing mutation was found in their coding regions. Moreover, metavinculin (VCL) and ZASP/cypher (LDB3) proximal and distal to this linked region were excluded by sequence analysis. To search for submicroscopic and intragenic deletions by PCR, we generated hybrid cell lines carrying only the affected or normal chromosome 10 homolog. All sequence tagged sites and exons were present on both homologs. We speculate that regulatory mutations in 1 of the 18 genes from 10q22.3 are responsible for a heterogenous spectrum of clinically distinct myodegenerative disorders, affecting both skeletal and cardiac muscles to variable degrees.

Database: Medline

21. Primary myopathies and the heart.

Author(s): Finsterer, Josef; Stöllberger, Claudia

Source: Scandinavian cardiovascular journal : SCJ; Feb 2008; vol. 42 (no. 1); p. 9-24

Publication Date: Feb 2008

Publication Type(s): Journal Article Review

Abstract:Myopathies are frequently not confined to the skeletal muscles but also involve other organs or tissues. One of the most frequently affected organ in addition to the skeletal muscle is the heart (cardiac involvement, CI). CI manifests as impulse generation or conduction defects, focal or diffuse myocardial thickening, dilation of the cardiac cavities, relaxation abnormality, hypertrophic, dilated, restrictive cardiomyopathy, apical form of hypertrophic cardiomyopathy, noncompaction, Takotsubo phenomenon, secondary valve insufficiency, intra-cardiac thrombus formation, or heart failure with systolic or diastolic dysfunction. CI occurs in dystrophinopathies, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, limb girdle muscular dystrophies,

laminopathies, congenital muscular dystrophies, myotonic dystrophies, congenital myopathies, metabolic myopathies, desminopathies, myofibrillar myopathy, Barth syndrome, McLeod syndrome, Senger's syndrome, and Bethlem myopathy. Patients with myopathy should be cardiologically investigated as soon as their neurological diagnosis is established, since supportive cardiac therapy is available, which markedly influences prognosis and outcome of CI in these patients.

Database: Medline

22. Conspicuous involvement of desmin tail mutations in diverse cardiac and skeletal myopathies.

Author(s): Bär, Harald; Goudeau, Bertrand; Wälde, Sarah; Casteras-Simon, Monique; Mücke, Norbert; Shatunov, Alexey; Goldberg, Y Paul; Clarke, Charles; Holton, Janice L; Eymard, Bruno; Katus, Hugo A; Fardeau, Michel; Goldfarb, Lev; Vicart, Patrick; Herrmann, Harald

Source: Human mutation; Apr 2007; vol. 28 (no. 4); p. 374-386

Publication Date: Apr 2007

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Intramural Case Reports Journal Article

Available in full text at [Human Mutation](#) - from ProQuest

Available in full text at [Human Mutation](#) - from John Wiley and Sons

Abstract: Myofibrillar myopathy (MFM) encompasses a genetically heterogeneous group of human diseases caused by mutations in genes coding for structural proteins of muscle. Mutations in the intermediate filament (IF) protein desmin (DES), a major cytoskeletal component of myocytes, lead to severe forms of "desminopathy," which affects cardiac, skeletal, and smooth muscle. Most mutations described reside in the central alpha-helical rod domain of desmin. Here we report three novel mutations--c.1325C>T (p.T442I), c.1360C>T (p.R454W), and c.1379G>T (p.S460I)--located in desmin's non-alpha-helical carboxy-terminal "tail" domain. We have investigated the impact of these and four--c.1237G>A (p.E413K), c.1346A>C (p.K449T), c.1353C>G (p.I451M), and c.1405G>A (p.V469M)--previously described "tail" mutations on in vitro filament formation and on the generation of ordered cytoskeletal arrays in transfected myoblasts. Although all but two mutants (p.E413K, p.R454W) assembled into IFs in vitro and all except p.E413K were incorporated into IF arrays in transfected C2C12 cells, filament properties differed significantly from wild-type desmin as revealed by viscometric assembly assays. Most notably, when coassembled with wild-type desmin, these mutants revealed a severe disturbance of filament-formation competence and filament-filament interactions, indicating an inherent incompatibility of mutant and wild-type protein to form mixed filaments. The various clinical phenotypes observed may reflect altered interactions of desmin's tail domain with different components of the myoblast cytoskeleton leading to diminished biomechanical properties and/or altered metabolism of the individual myocyte. Our in vitro assembly regimen proved to be a very sensible tool to detect if a particular desmin mutation is able to cause filament abnormalities. Published 2007 Wiley-Liss, Inc.

Database: Medline

23. Prevalence of desmin mutations in dilated cardiomyopathy

Author(s): Taylor M.R.G.; Slavov D.; Ku L.; Carniel E.; Haubold K.; Ferguson D.; Graw S.L.; Zhu X.; Sucharov C.C.; Long C.S.; Bristow M.R.; Mestroni L.; Di Lenarda A.; Sinagra G.; Boucek M.M.; Cavanaugh J.; Lavori P.

Source: Circulation; Mar 2007; vol. 115 (no. 10); p. 1244-1251

Publication Date: Mar 2007

Publication Type(s): Journal: Article

Available in full text at [Circulation](#). - from Ovid

Available in full text at [Circulation](#) - from Highwire Press

Abstract:BACKGROUND - Desmin-related myofibrillar myopathy (DRM) is a cardiac and skeletal muscle disease caused by mutations in the desmin (DES) gene. Mutations in the central 2B domain of DES cause skeletal muscle disease that typically precedes cardiac involvement. However, the prevalence of DES mutations in dilated cardiomyopathy (DCM) without skeletal muscle disease is not known. METHODS AND RESULTS - Denaturing high-performance liquid chromatography was used to screen DES for mutations in 116 DCM families from the Familial Dilated Cardiomyopathy Registry and in 309 subjects with DCM from the Beta-Blocker Evaluation of Survival Trial (BEST). DES mutations were transfected into SW13 and human smooth muscle cells and neonatal rat cardiac myocytes, and the effects on cytoskeletal desmin network architecture were analyzed with confocal microscopy. Five novel missense DES mutations, including the first localized to the highly conserved 1A domain, were detected in 6 subjects (1.4%). Transfection of DES mutations in the 2B domain severely disrupted the fine intracytoplasmic staining of desmin, causing clumping of the desmin protein. A tail domain mutation (Val459Ile) showed milder effects on desmin cytoplasmic network formation and appears to be a low-penetrant mutation restricted to black subjects. CONCLUSIONS - The prevalence of DES mutations in DCM is between 1% and 2%, and mutations in the 1A helical domain, as well as the 2B rod domain, are capable of causing a DCM phenotype. The lack of severe disruption of cytoskeletal desmin network formation seen with mutations in the 1A and tail domains suggests that dysfunction of seemingly intact desmin networks is sufficient to cause DCM. © 2007 American Heart Association, Inc.

Database: EMBASE

24. Cardiovascular manifestations of myofibrillar myopathy.

Author(s): El Menyar, Ayman A; Bener, Abdulbari; Al Suwaidi, Jassim

Source: Anadolu kardiyoloji dergisi : AKD = the Anatolian journal of cardiology; Dec 2004; vol. 4 (no. 4); p. 336-338

Publication Date: Dec 2004

Publication Type(s): Journal Article Review

Abstract:Myofibrillar myopathy (MFM) is a rare autosomal dominant disorder characterized by cardiac and skeletal myopathy. Either of these can dominate in the clinical picture. It is associated with cardiomyopathy, arrhythmia and/or atrioventricular (AV) conduction defects. Myofibrillar myopathy is often an overlooked disorder because of its variable clinical presentation. We highlight the various cardiovascular manifestations of MFM that have been reported in the literature and address the importance of considering this syndrome in young patients presenting with idiopathic cardiomyopathy and/or AV conduction defects.

Database: Medline

25. Myofibrillar myopathy: clinical, morphological and genetic studies in 63 patients.

Author(s): Selcen, Duygu; Ohno, Kinji; Engel, Andrew G

Source: Brain : a journal of neurology; Feb 2004; vol. 127 ; p. 439-451

Publication Date: Feb 2004

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available in full text at [Brain](#) - from Highwire Press

Available in full text at [Brain](#) - from Oxford University Press ; Collection notes: To access please select Login with Athens and search and select NHS England as your institution before entering your NHS OpenAthens account details.

Available in print at [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#) - from Brain : A Journal of Neurology

Abstract:The term myofibrillar myopathy (MFM) was proposed in 1996 as a non-committal term for a pathological pattern of myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins that include desmin, alphaB-crystallin (alphaBC), dystrophin and congophilic amyloid material. Subsequent studies revealed dominant mutations in desmin and alphaBC in some MFM patients, and clinical differences between kinships. We here review the clinical, structural and genetic features of 63 unrelated patients diagnosed as having MFM at the Mayo Clinic between 1977 and 2003. The age of onset was 54 +/- 16 years (mean +/- SD). Weakness was both proximal and distal in 77% and proximal only in 13%. Cardiomyopathy was diagnosed in 16%. Electro myography revealed a myopathic pattern associated with abnormal electrical irritability; 13 patients had abnormal nerve conduction studies but four of these had long-standing diabetes. The abnormal muscle fibres are best identified in trichrome-stained sections as harbouring amorphous, granular or pleomorphic hyaline structures, and vacuoles containing membranous material. The hyaline structures are strongly congophilic. Semiquantitative analysis in each case indicates that among the abnormal fibres, an average of 90, 75, 75, 70 and 70% abnormally express myotilin, desmin, alphaBC, dystrophin and beta-amyloid precursor protein, respectively. Therefore, immunostains for these proteins, and especially for myotilin, are useful adjuncts in the diagnosis of MFM. Electron microscopy shows progressive myofibrillar degeneration commencing at the Z-disk, accumulation of degraded filamentous material and entrapment of dislocated membranous organelles in autophagic vacuoles. In all patients, we searched for mutations in desmin and alphaBC, as well as in telethonin, a Z-disk-associated protein, or in syncoilin, which together with plectin links desmin to the Z-disk. Two of the 63 patients carry truncation mutations in the C-terminal domain of alphaBC, four carry missense mutations in the head or tail region of desmin, and none carries a mutation in syncoilin or telethonin. Thus, MFM is morphologically distinct but genetically heterogeneous. Further advances in defining the molecular causes of MFM will probably come from linkage studies of informative kinships or from systematic search for mutations in proteins participating in the intricate network supporting the Z-disk.

Database: Medline

26. Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene

Author(s): Dalakas M.C.; Semino-Mora C.; Sivakumar K.; Park K.-Y.; Lee H.S.; Goldfarb L.G.

Source: New England Journal of Medicine; Mar 2000; vol. 342 (no. 11); p. 770-780

Publication Date: Mar 2000

Publication Type(s): Journal: Article

Available in full text at [New England Journal of Medicine](#) - from Massachusetts Medical Society ; Notes: Please select 'Login via Athens or your institution' and enter your OpenAthens username and password.

Available in full text at [New England Journal of Medicine, The](#) - from ProQuest

Abstract:Background: Myofibrillar myopathies are a heterogeneous group of inherited or sporadic skeletal myopathies associated with cardiomyopathy. Among the myofibrillar proteins that accumulate within the muscle fibers of affected patients, the one found most consistently is desmin, an intermediate-filament protein responsible for the structural integrity of the myofibrils. Skeletal and cardiac myopathy develops in mice that lack desmin, suggesting that mutations in the desmin gene may be pathogenic. Methods: We examined 22 patients from 8 families with dominantly inherited myofibrillar or desmin-related myopathy and 2 patients with sporadic disease and analyzed the desmin gene for mutations, using complementary DNA (cDNA) amplified from muscle-biopsy specimens and genomic DNA extracted from blood lymphocytes. Restriction-enzyme analysis was used to confirm the mutations. Expression vectors containing normal or mutant desmin cDNA were introduced into cultured cells to determine whether the mutant desmin formed intermediate filaments. Results: Six missense mutations in the coding region of the desmin gene that cause the substitution of an amino acid were identified in 11 patients (10 members of 4 families and 1 patient with sporadic disease); a splicing defect that resulted in the deletion of exon 3 was identified in the other patient with sporadic disease. Mutations were clustered in the carboxy-terminal part of the rod domain, which is critical for filament assembly. In transfected cells, the mutant desmin was unable to form a filamentous network. Seven of the 12 patients with mutations in the desmin gene had cardiomyopathy. Conclusions: Mutations in the desmin gene affecting intermediate filaments cause a distinct myopathy that is often associated with cardiomyopathy and is termed 'desmin myopathy.' The mutant desmin interferes with the normal assembly of intermediate filaments, resulting in fragility of the myofibrils and severe dysfunction of skeletal and cardiac muscles. (C) 2000, Massachusetts Medical Society.

Database: EMBASE

DISCLAIMER: Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

Strategy 121113

#	Database	Search term	Results
1	EMBASE	("myofibrillary myopathy").ti,ab	4
2	EMBASE	("Myofibrillar myopath*").ti,ab	389
3	EMBASE	(1 OR 2)	391
4	EMBASE	(cardiomyopath*).ti,ab	86578
5	EMBASE	exp CARDIOMYOPATHY/	129512
6	EMBASE	(4 OR 5)	139941
7	EMBASE	(3 AND 6)	99
8	Medline	("Myofibrillar myopath*").ti,ab	224
9	Medline	exp CARDIOMYOPATHIES/	81316
10	Medline	(cardiomyopath*).ti,ab	56935
11	Medline	(9 OR 10)	104936
12	Medline	(8 AND 11)	65
13	Medline	(cardi* OR heart).ti	465617
14	Medline	(8 AND 13)	6
15	EMBASE	(cardi* OR heart).ti	832304
16	EMBASE	(3 AND 15)	35