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Cardiomyopathy in neurological disorders

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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.

1. Introduction

Cardiomyopathies (CMPs) are generally characterised by abnormal structure, dimension, or function of the left or right ventricular myocardium in the absence of arterial hypertension, coronary heart disease, valve abnormalities, or congenital heart disease [1]. CMPs may be hereditary or acquired and either confined to the heart or may represent cardiac involvement in systemic disease. Diagnosis of CMP relies on clinical, electrocardiographic, echocardiographic, coronary angiographic, or genetic findings. Complications of CMPs may include neurological disease and neurological disease may be accompanied by CMP. This review aims at summarising and discussing recent findings concerning the neurological implications in CMPs.

2. Classification of CMPs

There is no binding classification of CMPs but the frequently used classification of the American Heart Association classifies CMPs as primary (solely or predominantly confined to heart muscle), secondary [those showing pathological myocardial involvement as part of a neuromuscular disorder (NMD)] and those in which cardiomyopathy is the first/predominant manifestation of a NMD [2]. The European Society of Cardiology, on the contrary, differentiates according to the etiology between primary (familial, genetic, hereditary) CMPs and secondary (non-familial, acquired) CMPs [1]. Among the hereditary as well as acquired forms, hypertrophic CMP (HCM), dilated CMP (DCM), restrictive CMP (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified CMPs are further delineated [1]. Primary unclassified CMPs include left ventricular hypertrabeculation (noncompaction) and secondary unclassified CMPs include Takotsubo-CMP ("broken heart" syndrome). Some of the CMPs may be either acquired or primary, such as CMP due to amyloidosis (Tables 1 and 2) [1]. In primary CMPs the mutated gene may be known or unknown [1].

3. Neurological disease and CMPs

CMPs may be related to neurological disease twofold. CMPs may either secondarily cause neurological disease or may represent

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the cardiac manifestation of an exclusively or predominantly neurological disease.

3.1. Neurological complications of CMPs

Concerning the first group, CMPs may cause cerebrovascular events, such as some types of vertigo or syncope, transitory ischemic attack (TIA), ischemic stroke, cerebral bleeding, or vascular dementia, due to systolic dysfunction, arrhythmias, arterial hypertension, or embolic events from intracardiac thrombus formation.

3.2. Neurological disorders manifesting with CMPs

Neurological disorders most frequently associated with CMP are primary (hereditary) or secondary (acquired) neuromuscular disorders (NMDs). Primary NMDs more frequently go along with CMPs than secondary NMDs. NMDs may be accompanied by all types of CMPs but most frequently HCMs, DCMs, and left ventricular hypertrabeculation (LVHT) can be found in NMDs. The cause of CMP in NMDs is unknown, but there are indications that isoforms of mutated muscle proteins causing muscle disease are also expressed in the myocardium [3].

4. Hypertrophic CMP

4.1. Definition and diagnostic criteria

HCM is present if there is left ventricular myocardial thickening >15 mm, with or without normal systolic function, in the absence of any other disease producing wall thickening (Fig. 1). HCM may be non-obstructive or obstructive (Table 2). Hypertrophy of the left ventricular myocardium may be symmetric or asymmetric. Asymmetric myocardial thickening frequently affects the interventricular septum, the mid-ventricular myocardium (MVHC) or the outflow tract. If myocardial thickening predominantly affects the apex, the apical form of HCM (aHCM) is present. Non-obstructive HCM may turn into obstructive HCM and vice versa. In some cases, HCM converts into DCM with progression of the disease [4].

Table 1
Classification of CMPs (modified according to Elliott et al. 2008 [1])

HCM	DCM	ARVC	RCM	Unclassified
Familial				
Unknown gene	Unknown gene	Unknown gene	Unknown gene	LVHT
Sarcomeric protein mutations	Sarcomeric protein mutations	Intercalated disc proteins	Sarcomeric proteins	
ß myosin heavy chain	Z-band (LIM protein, TCAP)	Plakoglobin	Troponin I	
Cardiac myosin binding prot.	Cytoskeletal genes	Desmoplakin	Essential light chain myosin	
Cardiac troponin I	Dystrophin	Plakophilin 2	Familial amyloidosis	
Troponin-T	Desmin	Desmogelin 2	Transthyretin	
a-tropomyosin	Metavinculin	Desmocollin 2	Apolipoprotein	
Essential myosin light chain	Sarcoglycan complex	Cardiac ryanodine receptor	Desminopathy	
Regulatory myosin light chain	CRYAB	RyR2	Pseudoxanthoma elasticum	
Cardiac actin	Epicardin	Transforming growth factor	Hemochromatosis	
a-myosin heavy chain	Nuclear membrane	TGFb3	Anderson-Fabry disease	
Titin	Lamin A/C	Glycogenosis		
Troponin C	Emerin			
Muscle LIM protein	Intercalated disc proteins			
Glycogen storage disease	Mitochondrial disorder			
Pompe				
PRKAG2,				
Forbes				
Danon				
Lysosomal storage disease				
Anderson–Fabry				
Hurler's				
Disorders of fatty acid metabolism				
Carnitine deficiency				
Phosphorylase B-kinase deficiency				
Mitochondrial disorders				
Syndromic HCM				
Noonan's syndrome				
LEOPARD syndrome				
Friedreich's ataxia				
Beckwith–Wiedermann syndrome				
Swyer's syndrome				
Other				
Phospholamban promoter				
Familial amyloid				
Non-familial				
Obesity	Myocarditis (infective/toxic/immune)	Inflammatory	Amyloid	Takotsubo-CMP
Infants of diabetic mothers	Kawasaki disease	Scleroderma		
Athletic training	Eosinophilic (Churg Strauss syndrome)	Endomyocardial fibrosis		
Amyloid (AL/prealbumin)	Viral persistence	Carcinoid heart disease		
	Drugs	Metastasis		
	Pregnancy	Radiation		
	Endocrine	Drugs (anthracyclines)		
	Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia			
	Alcohol			
	Tachycardiomyopathy			