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Cardiac evaluation in patients with neuromuscular diseases

Diagnostyka kardiologiczna u chorych z chorobami nerwowo-mięśniowymi

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Abstract

Cardiac involvement in neuromuscular disease most often manifests with cardiomyopathy, atrioventricular conduction disturbances, and supraventricular and ventricular tachyarrhythmias, accompanied by heart failure in some patients. The phenotype of cardiac involvement, and to a large extent also the symptoms and the timing of their occurrence, depend on the genetic background of the neurological disease, hence the importance of genetic testing. Knowledge of the proper neurological diagnosis supported by genetic testing results allows for targeted cardiological investigations. Non-invasive imaging modalities (echocardiography, cardiac magnetic resonance) and cardiac rhythm monitoring using electrocardiography allow the assessment of myocardial involvement progression and implementation of appropriate treatment. In addition, they enable identification of asymptomatic patients at an early disease stage and prevention of future sudden cardiac death.

Key words: muscular dystrophy, cardiomyopathies, conduction disorders, dystrophinopathies, laminopathies, myotonic dystrophy

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Introduction

Neuromuscular diseases (NMD) are a wide group of disorders with varying clinical phenotypes. Peripheral muscle dysfunction is often accompanied by abnormal myocardial structure and function, particularly in patients with various types of muscular dystrophy. In the recent decades, our knowledge on the genetic defect underlying most muscular dystrophies has expanded significantly. Of interest, the same mutations may be associated with various phenotypes, including isolated cardiomyopathies without peripheral muscular symptoms [1]. In most muscular dystrophies, cardiac involvement manifests as various types of cardiomyopathy, with or without symptomatic heart failure, atrioventricular conduction disturbances, and atrial and ventricular tachyarrhythmias (Table 1). Cardiac involvement manifesting during childhood or in the first three decades of life is typical for many NMD. However, cardiac symptoms may also develop much later, or precede the diagnosis of NMD in some relatively low-symptomatic neurological syndromes. Some NMD are associated with a high risk of sudden cardiac death (SCD). Others, despite evidence of advanced cardiac involvement, are not associated with an increased SCD risk, and the cause of death is usually respiratory failure or other organ damage. In addition to appropriate neurological phenotypic characterization, an attempt to make the genetic diagnosis is of key importance in NMD. Early detection of mutations predisposing to the development of cardiomyopathy or conduction disturbances should prompt appropriate investigations and prevention of life-threatening arrhythmia. Of note, with non-invasive modalities to evaluate myocardial function, such

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Table 1. Most common types of neuromuscular disease and associated cardiac complications

NMD type	Molecular defect	Mode of inheritance	Cardiac involvement		
			Cardiomyopathy	AV conduction disturbances	Arrhythmia
DMD	Dystrophin	XR	DCM	Rare	Common mild
BMD	Dystrophin	XR	DCM	Rare	Common
EDMD 1	Emerin	XR	CM	Common	Common
EDMD 2	Lamin A/C	AD	DCM	Common	Common
DM 1	Protein kinase	AD	Rarely HCM/DCM	Common	Common
LGMD 1B	Lamin A/C	AD	DCM	Common	Common
LGMD 2E	B-sarcoglycan	AR	DCM	Common	Common
FA	Frataxin	AR	HCM	Rare	Common

NMD — neuromuscular disease; DMD — Duchenne muscular dystrophy; BMD — Becker muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; FA — Friedreich ataxia; CM — cardiomyopathy; DCM — dilated cardiomyopathy; HCM — hypertrophic cardiomyopathy; XR — X-linked; AD — autosomal dominant; AR — autosomal recessive; AV — atrioventricular

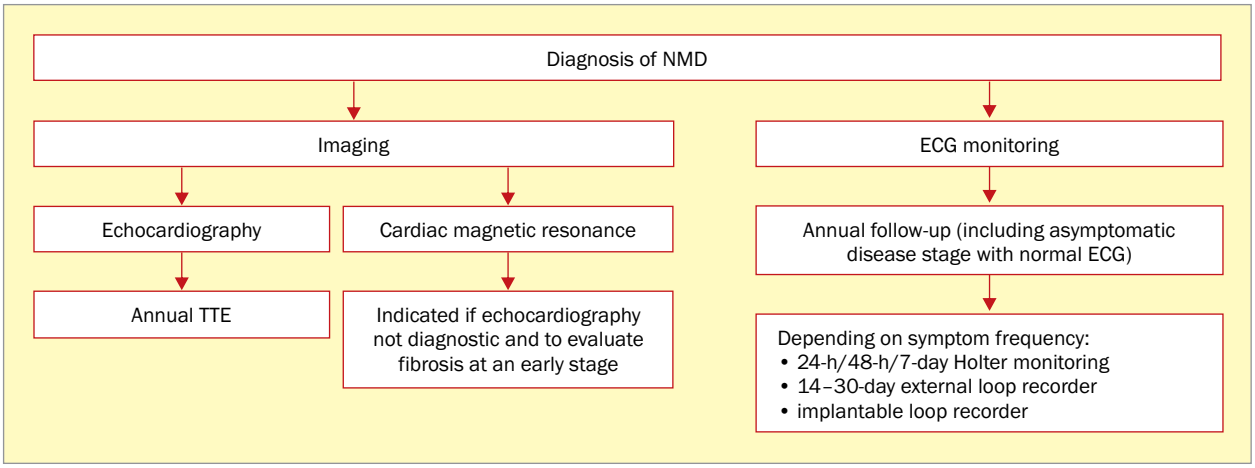

Figure 1. Suggested cardiac evaluation following the diagnosis of neuromuscular disease (NMD); TTE — transthoracic echocardiography; ECG — electrocardiogram

as echocardiography, cardiac magnetic resonance (CMR) and electrocardiography (ECG), it is possible to identify cardiac dysfunction prior to any cardiovascular symptoms [2] (Figure 1). In the present review, we focused on selected issues related to cardiac involvement in dystrophinopathies, laminopathies, and myotonic dystrophy (DM).

Dystrophinopathies

Duchenne muscular dystrophy (DMD) is the most common NMD. It is an X-linked disorder with the incidence of 1:3600–1:9300 births among males. The genetic defect usually involves deletion of multiple exons of the dystrophin gene on chromosome X. Due to frame shift, dystrophin is virtually absent. In Becker muscular dystrophy (BMD), dystrophin gene mutation usually does not lead to frame shift and the gene is translated, leading to a partially functional protein, although present in lesser amounts. This results in a much milder clinical course of muscular dystrophy, and usually much later onset of cardiomyopathy. The incidence of BMD is also much lower (1:18,000).

DMD

Myocardial involvement in DMD manifests with dilated cardiomyopathy (DCM). The mean age at the onset of systolic dysfunction is about 14 years [3], and development of heart failure symptoms is usually delayed, which may be explained by limited activity of the patients. Cardiac investigations should be initiated at the time of the diagnosis of DMD [4] and should also target mutation carriers, *i.e.*, mothers and sisters of DMD patients, as systolic dysfunction and evidence of myocardial fibrosis can usually be identified in them in the fifth decade of life [5]. Despite severe systolic

dysfunction present in DMD, ventricular arrhythmia is less frequent than might be expected, which may be partially explained by lower sympathetic tone in these patients. Atrioventricular conduction disturbances, typical for some NMD, are also very rare in this disorder.

BMD

In most patients with BMD, initial manifestations of cardiac involvement develop after 20 years of age but they are present in 70% of patients by the age of 40 [6]. The clinical phenotype is of DCM with varying severity of heart failure symptoms. The clinical course of BMD is much less predictable compared to DMD. There is no simple correlation between the severity of DCM and peripheral muscle involvement. In addition, the risk of SCD seems higher in BMD compared to DMD, which may only be partially explained by earlier development of respiratory failure in DMD, potentially leading to earlier death. As a result, patients with BMD-related cardiomyopathy are much more often referred for implantation of a cardioverter-defibrillator (ICD).

Laminopathies

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of NMD (incidence about 1:100,000 births) characterized by an early presence of joint contractures, slowly progressing muscle weakness and associated atrioventricular conduction disturbances. The underlying genetic defect may involve various proteins of the nuclear envelope. Several subtypes have been defined, and the most common ones are EDMD 1 due to emerinopathies (caused by mutations in the *EMD* gene) and laminopathies (caused by mutations in the *LMNA* gene).

EDMD 1

EDMD 1 is an X-linked disorder. The clinical course is initially mild. Sometimes the correct neurological diagnosis is only made after an advanced atrioventricular block develops in a young man without conventional cardiovascular risk factors. Atrioventricular conduction disturbances are usually accompanied by junctional escape rhythm and atrial standstill, often preceded by low-amplitude atrial fibrillation (AF) [7]. In the early disease phase (usually second to third decade of life), patients require cardiac pacing without a defibrillator, as the risk of malignant ventricular arrhythmia is initially not high [6]. With disease progression, fibrosis may progress and involve not only atria but also ventricles, ultimately leading to the typical DCM phenotype. At that stage, the risk of ventricular arrhythmia is high enough to warrant consideration of ICD implantation. The disease is associated with significant atrial enlargement, predisposing to supraventricular arrhythmia. As a result, the risk of thromboembolic complications including ischaemic stroke is significantly increased [8].

EDMD 2

This type of dystrophy is usually characterized by an autosomal dominant mode of inheritance. A defect in the lamin *A/C* gen may also lead to a phenotype of isolated DCM with particularly poor prognosis resulting from a high rate of SCD. A similar genetic defect was identified in one type of limb-girdle muscular dystrophy (LGMD 1B) [9]. The neurological phenotype is the same in both most common forms of EDMD, while the cardiac presentation varies. EDMD 2 is usually characterized by DCM with a relatively modest left ventricular chamber enlargement despite severe systolic dysfunction, accompanied by atrioventricular conduction disturbances. This type of EDMD is associated with a high risk of tachyarrhythmia-related SCD, usually due to ventricular fibrillation (VF) [6]. In all patients with this type of muscular dystrophy, SCD risk should be evaluated using available tools including dedicated calculators [10, 11] (Table 2).

Myotonic dystrophy

Myotonic dystrophy is one of the most common (incidence 1:8,000 births) muscular dystrophies, most typically manifesting with myotonia, or impaired muscle relaxation, which accompanies muscle weakness and atrophy, and symptoms from other organ systems (glaucoma, frontal hair loss, hormonal disturbances). The mode of inheritance is autosomal dominant. The risk of cardiac complications depends on the type of DM.

DM 1

In the more common type 1, the defect involves the *DMPK* gene coding for a protein kinase, and it is characterized by trinucleotide triplet expansion. Genetic anticipation can be seen, with increasing symptom severity in successive generations due to prolongation of repeated sequences. In this type of DM, cardiac involvement is seen in about 80% of patients. Atrioventricular and intraventricular conduction disturbances are most commonly accompanied by supraventricular and ventricular tachyarrhythmias [12] (Table 1). Cardiomyopathy, usually of the DCM phenotype, is relatively rare.

DM 2

In this type, the defect involves the *CNBP* gene which encodes a zinc finger protein. Trinucleotide triplet expansion is also present but without evident genetic anticipation. The clinical presentation is more heterogeneous compared

Table 2. Evaluation of the risk of life-threatening tachyarrhythmia in laminopathies (from [10])

Parameter	Evaluation
Gender [M/F]	Higher risk in men
Non-missense *LMNA* gene mutation [yes/no]	Insertions, deletions, truncation mutations, abnormal splicing
AVB [no/1st degree AVB/advanced AVB]	The highest degree of AVB should be taken into account. First-degree AVB is defined as PR interval ≥ 0.2 s, and advanced AVB is defined as second-degree Mobitz II AVB or third-degree AVB (but not second-degree Mobitz I AVB)
nsVT [yes/no]	≥ 3 ventricular beats ≥ 120/min and duration < 30 s during Holter ECG monitoring for a minimum of 24 h
LVEF [%]	Echocardiographic measurement

M — male; F — female; AVB — atrioventricular block; nsVT — nonsustained ventricular tachycardia; LVEF — left ventricular ejection fraction; ECG — electrocardiography

to type 1 but usually milder, with a lower risk of cardiac involvement which is seen in up to 10–20% cases. Typical cardiac manifestations include first-degree atrioventricular block and bundle branch blocks [13].

Cardiac tests in patients with NMD

Imaging is necessary to identify myocardial involvement, assess its progression, and select patients for implantation of cardiac devices. Echocardiography or CMR is recommended upon the diagnosis of NMD due to the possibility of an low-symptomatic course of cardiac involvement. If no abnormalities are found, imaging should be repeated anually or ever 1–5 years [4, 14]. Due to concomitant chest deformities and poor acoustic windows, mostly in DMD, echocardiography is often not fully diagnostic and CMR is warranted. The latter modality is also dedicated for patients with identified mutations but no abnormalities found on echocardiography. To detect supraventricular or ventricular arrythmia that may be associated with a risk of SCD, follow-up ECG monitoring should be performed annually since the diagnosis of NMD [4, 15]. Depending on the frequency of symptoms suggesting arrhythmia which was not recorded in conventional ECG, options include 24-hour, 48-hour, or 7-day Holter ECG monitoring, 14- to 30-day monitoring with an external loop recorder, or an implantable loop recorder [15] (Table 3).

Drug therapy in patients with cardiac involvement in NMD

Few data are available to support the use of typical drug therapy recommended in heart failure or asymptomatic left ventricular systolic dysfunction in patients with NMD-related cardiomyopathies. There is some evidence indicating that angiotensin-converting enzyme (ACE) inhibitors and corticosteroids (used to improve muscle strength and prevent cardiomyopathy) are warranted in patients with DMD. However, most recommendations are based on extrapolating data from the general population of patients with heart failure of various aetiology to the NMD populations. Currently, ACE inhibitors are recommended in all patients with NMD and reduced left ventricular ejection fraction (LVEF) and should be considered in boys above 10 years of age with DMD for the primary prevention of DCM [4].

There is a consensus that beta-blockers should be used in patients with NMD and existing systolic dysfunction, and in patients with cardiac arrhythmia to relieve symptoms related to tachyarrythmias. However, beta-blockers are generally not recommended solely for the prevention of systolic dysfunction or symptomatic heart failure in patients without existing left ventricular systolic dysfunction.

Based on promising data on the effectiveness of combined aldosterone antagonist and ACE inhibitor treatment in patients with DMD and concomitant left ventricular systolic dysfunction, such a combination should be considered in patients with DMD/BMD who fulfil the above criterion. It may also be considered in those with preserved systolic function and myocardial fibrosis identified in CMD [4]. Of note, the above recommendations apply only to patients with dystrophinopathies.

Similarly, glucocorticosteroids may be considered to delay progression of cardiac involvement in a limited population of patients with DMD.

Based on the current recommendations, anticoagulation in NMD should be limited to patients with established indications for such treatment (*e.g.*, presence of an intracardiac thrombus), and may be considered in patients with documented AF. The role of commonly used scoring systems for the risk of thromboembolic complication, and of novel oral anticoagulants has not been established in the NMD population. In the clinical practice, patients above 30 years of age with EDMD and concomitant AF, atrial flutter or atrial standstill receive anticoagulation due to markedly increased stroke risk regardless of the risk estimation using the CHA_2DS_2-VASc score (Table 4).

Table 3. The 2005 European Society of Cardiology (ESC) recommendations of arrhythmia treatment in patients with neuromuscular disease (from [15])

Recommendation	Class of recommendations	Level of evidence
Annual follow-up is recommended in patients with muscular dystrophies, even in the concealed phase of the disease when patients are asymptomatic and the ECG is normal	I	B
It is recommended that patients with NMD who have ventricular arrhythmia are treated in the same way as patients without NMD	I	C
Permanent pacemaker implantation is recommended in patients with NMD diseases and third--degree or advanced second-degree AVB at any anatomical level	I	B
Permanent pacemaker implantation may be considered in patients with DM type 1 (Steinert disease), Kearns–Sayre syndrome or LGMD with any degree of AVB (including first-degree) in consideration of the risk of rapid progression	IIb	B
The use of an ICD may be considered in DM type 1 (Steinert disease), EDMD and LGMD type 1B when there is an indication for pacing and evidence of ventricular arrhythmias	IIb	B

ECG — electrocardiography; NMD — neuromuscular disease; AVB — atrioventricular block; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy

Table 4. Indications for cardiac treatment in patients with neuromuscular disease

Type of therapy		Indicated	May be considered	Not recommended
Drug therapy	ACEI	LVEF ≤ 35% DMD > 10 years of age		
	MRA	DMD/BMD + LV systolic dysfunction (in combination with ACEI)	DMD/BMD + preserved LV systolic function when fibrosis present on CMR	
	BB	Systolic dysfunction, symptomatic tachyarrhythmia		Prevention of systolic dysfunction, symptomatic HF without systolic dysfunction
	GCS		DMD + to delay progression of cardiac involvement	
	AC	Depending on the risk of thromboembolic complications; documented intracardiac thrombus; documented AF or atrial flutter	EDMD + AF, atrial flutter, atrial standstill > 30 years of age	
Conventional pacing		Symptomatic bradyarrhythmia, AV conduction disturbances (absolute indications: asymptomatic third degree or second degree Mobitz II AV block)	DM 1, LGMD, EDMD + symptomatic second degree Mobitz I or first degree AV block	
Cardiac device	ICD	Symptomatic HF with NYHA class II–III symptoms, LV systolic dysfunction, LVEF ≤ 35%, high SCD risk		
	CRT	QRS ≥ 130 ms + LBBB (in SR) particularly in EDMD, BMD, DM 1	QRS ≥ 130 ms without LBBB (in SR) or with AF	
Ventricular assist device			Destination therapy in selected situations in DMD	
Cardiac transplantation		Mild changes in peripheral muscle, preserved respiratory function		

ACEI — angiotensin-converting enzyme inhibitors; LVEF — left ventricular ejection fraction; DMD — Duchenne muscular dystrophy; MRA — mineralocorticoid receptor antagonists; BMD — Becker muscular dystrophy; LV — left ventricle; CMR — cardiac magnetic resonance; BB — beta-blockers; HF — heart failure; GCS — glucocorticosteroids; AC — anticoagulants; AV — atrioventricular; DM — myotonic dystrophy; LGMD — limb-girdle muscular dystrophy; EDMD — Emery-Dreifuss muscular dystrophy; AF — atrial fibrillation; ICD — implantable cardioverter-defibrillator; NYHA — New York Heart Association; SCD — sudden cardiac death; CRT — cardiac resynchronization therapy; LBBB — left bundle branch block; SR — sinus rhythm

Conventional pacing

Candidates for permanent cardiac pacing include patients with symptomatic bradycardia due to sinus node disease or atrioventricular block [15]. In the population with NMD, atrioventricular conduction disturbances are more common in patients with EDMD, DM and LGMD, and cardiac pacing should be considered at the initial manifestation (usually below 30 years of age). It should be remembered, however, that pacemaker implantation in patients with EDMD does not protect from stroke due to the occurrence of AF or atrial standstill. In patients with bradycardia and AF, rate adaptive ventricular pacing should be preferred over dual-chamber pacing.

Implantable cardiac devices (cardioverter defibrillator, cardiac resynchronization therapy)

Typical indications for ICD implantation for primary prevention of SCD are present in optimally managed patients with symptomatic heart failure with New York Heart Association (NYHA) class II–III symptoms and left ventricular systolic dysfunction with LVEF ≤ 35% [16]. In general, the same indications apply to the NMD population. The final decision, however, should also take into account specific circumstances in these patients, including life expectancy, potentially futile care in end-stage disease, risk of procedural complications, and the risk of inappropriate ICD interventions. The neurological diagnosis, genetic defect, or even mutation type in a given patient should also be considered, as these may indicate a particularly high SCD risk. In summary, ICD implantation should be considered in selected patients with DMD, BMD, EDMD 2, LGMD 1B, DM 1, and Friedreich ataxia, taking into account the above risk factors. Cardiac resynchronization therapy (CRT) may be considered in patients with indications for permanent pacing, systolic dysfunction, and predicted high percentage of pacing, particularly in EDMD, BMD, and DM 1.

Other options

In some patients, particularly with EDMD 2, LGMD 1B and BMD, cardiac transplantation may be considered if peripheral muscle changes are not advanced and respiratory function is preserved. There are also single reports of the use of ventricular assist devices as destination therapy in patients with DMD. Integrated palliative care is recommended in end-stage heart failure.

Summary

Most patients with NMD are at risk of cardiac involvement. Precise neurological diagnosis is vital for early determination of this risk and implementation of appropriate treatment, including therapies to delay the development of cardiomyopathy. Early imaging using echocardiography or CMR and systematic monitoring of the progression of myocardial involvement are necessary to guide decisions regarding initiation of drug treatment and therapies to prevent SCD. The risk of cardiac complications, and thus management may vary significantly depending on the underlying genetic defect despite similar or even identical phenotypic presentation. Both effective drug therapy and invasive procedures that modify outcomes in many NMD are currently available. Neurological units involved in the diagnosis and management of NMD should cooperate with adequately prepared cardiologists experienced in managing NMD patients.

Conflict of interest(s)

The authors declare no conflicts of interests.

Streszczenie

Zajęcie mięśnia sercowego w przebiegu chorób nerwowo-mięśniowych najczęściej objawia się pod postacią kardiomiopatii, zaburzeń przewodnictwa przedsionkowo-komorowego oraz tachyarytmii nadkomorowych i komorowych, przebiegających niekiedy z niewydolnością serca. Fenotyp zajęcia serca, a w dużej mierze również objawy i czas ich wystąpienia, zależą od podłoża genetycznego choroby neurologicznej, dlatego należy podkreślić istotę badań genetycznych. Znajomość właściwego rozpoznania neurologicznego popartego wynikiem badań genetycznych pozwala na ukierunkowaną diagnostykę kardiologiczną. Nieinwazyjne badania obrazowe (echokardiografia, rezonans magnetyczny serca) oraz monitorowanie rytmu serca za pomocą elektrokardiografii pozwalają na ocenę progresji zajęcia mięśnia sercowego i wdrożenie odpowiedniego leczenia. Co więcej, umożliwiają wychwycenie pacjentów bezobjawowych na wczesnym etapie choroby i prewencję wystąpienia nagłego zgonu sercowego w przyszłości.

Słowa kluczowe: dystrofia mięśniowa, kardiomiopatie, zaburzenia przewodnictwa, dystrofinopatie, laminopatie, dystrofia miotoniczna

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Commentary

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The article "Cardiac evaluation in patients with neuromuscular diseases" deals with an important issue in specialist cardiology practice. Individuals with neuromuscular diseases are a heterogeneous group of patients with various clinical presentation in terms of both neurological symptoms and potential cardiovascular complications.

While the knowledge on specific neuromuscular disorders is well established among the neurologists, in the cardiology practice these patients may be collectively referred to as "patients with dystrophy", without detailed differentiation between different types. Obviously, this may be sometimes justified and explained by the organization of health care, as the duration of the diagnostic workup from the suspicion of neuromuscular disease to the genetic diagnosis is usually long. The authors briefly present the most important aspects of cardiac investigations and therapeutic possibilities in the most important and most common neuromuscular diseases, including Duchenne and Becker muscular dystrophies, Emery-Dreifuss muscular dystrophy, and myotonic dystrophy type 1 (Steinert disease) and type 2.

Cardiac involvement in myotonic dystrophies deserves a more detailed discussion. Indeed, the most dangerous consequences of cardiac involvement in myotonic dystrophy type 1 include advanced atrioventricular conduction disturbances, with or without prior first degree atrioventricular block present for many years. It should be stressed that sudden cardiac death in patients with myotonic dystrophy type 1 is most commonly associated with advanced or complete atrioventricular block. In contrast, tachyarrhythmias are less frequent in Steinert disease but may also contribute to poor prognosis. Established risk factors for sudden cardiac death in this population should be borne in mine, *i.e.*, non-sinus rhythm (particularly atrial fibrillation), PR interval prolongation > 240 ms, QRS duration > 120 ms, intermittent second- and third-degree atrioventricular block, and corrected QT interval > 450 ms. A history of bradycardia-induced ventricular fibrillation is also considered an indication for prompt cardioverter-defibrillator implantation in some countries, especially in patients with left ventricular systolic dysfunction.

As indicated by the authors, the risk of cardiac involvement in myotonic dystrophy type 2 is lower compared to type 1. Our experience indicates that atrioventricular and interventricular conduction disturbances are much less common, while supraventricular and ventricular arrhythmia is significantly more common in type 2 (except for atrial fibrillation which often accompanies myotonic dystrophy type 1, as also reported by others). For a proper understanding of cardiovascular complications of myotonic dystrophy type 2, it should be remembered that this disorder often manifests later in life. Hence, cardiac involvement related to the underlying neuromuscular disorder may coexist with pathologies resulting from normal aging and concomitant conditions such as diabetes type 2 which is typical for this type of dystrophy, thyroid disorders, or hypertension which is ubiquitous in later years of life.

The value of the article also stems from the discussion of the practical aspects of the proposed cardiac investigation, and a figure that clearly presents suggested cardiac investigations following the diagnosis of neuromuscular disease. It should be noted that a patient with neuromuscular disorder should have a good quality 12-lead electrocardiogram (ECG) recorded during each follow-up visit, with careful evaluation of all necessary parameters including corrected QT interval. Unfortunately, obtaining a good quality tracing is not always easy, and some patients are reluctant to undergo ECG recording due to their limited mobility. Patients with neuromuscular disorders are usually regularly followed-up by neurologists, while cardiac evaluation is usually performed after the genetic diagnosis is established, and only occasionally afterwards. It is thus important, as also highlighted in the commented article, that these patients should also undergo regular cardiological controls, optimally in specialized tertiary care centres cooperating with neurology experts.

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