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Review

Cardiomyopathies and Arrythmias in Neuromuscular Diseases

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Abstract: Neuromuscular diseases (NMDs) encompass various hereditary conditions affecting motor neurons, the neuromuscular junction, and skeletal muscles. These disorders are characterized by progressive muscle weakness and can manifest at different stages of life, from birth to adulthood. NMDs, such as Duchenne and Becker muscular dystrophies, myotonic dystrophy, and limb–girdle muscular dystrophies, often involve cardiac complications, including cardiomyopathies and arrhythmias. Underlying genetic mutations contribute to skeletal and cardiac muscle dysfunction, particularly in the *DMD*, *EMD*, and *LMNA* genes. The progressive nature of muscle deterioration significantly reduces life expectancy, mainly due to respiratory and cardiac failure. The early detection of cardiac involvement through electrocardiography (ECG) and cardiac imaging is crucial for timely intervention. Pharmacological treatment focuses on managing cardiomyopathies and arrhythmias, with an emerging interest in gene therapies aimed at correcting underlying genetic defects. Heart transplantation, though historically controversial in patients with muscular dystrophies, is increasingly recognized as a viable option for individuals with advanced heart failure and moderate muscle impairment, leading to improved survival rates. Careful patient selection and management are critical to optimizing outcomes in these complex cases.

Keywords: cardiomyopathy; implantable defibrillator; neuromuscular diseases; sudden death; pacemaker; heart transplantation

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1. Introduction

Neuromuscular diseases (NMDs) encompass a broad group of inherited disorders affecting motor neurons, peripheral nerves, neuromuscular junctions, and skeletal muscle. Inheritance patterns include X-linked recessive transmission predominantly impacting males, and autosomal recessive or dominant inheritance affecting both sexes. Clinically, NMDs are characterized by progressive muscular weakness and asthenia, with symptoms manifesting variably from neonatal stages to adulthood. The relentless progression of muscle degeneration often results in cramps, muscle stiffness, joint contractures, and chronic pain. Patients with NMDs demonstrate heightened susceptibility to comorbid conditions, particularly pulmonary diseases, with prognosis and life expectancy dependent

on disease type and severity. Cardiac and respiratory complications secondary to muscle impairment are primary contributors to mortality.

The NMD spectrum primarily includes peripheral neuropathies (e.g., neuropathies, amyotrophic lateral sclerosis, radiculopathies, plexopathies, neuropathies) and myopathies, such as dystrophinopathies (Duchenne muscular dystrophy and Becker muscular dystrophy), facioscapulohumeral dystrophy, Emery–Dreifuss muscular dystrophy, oculopharyngeal muscular dystrophy, limb–girdle muscular dystrophies, congenital muscular dystrophy, and various congenital, myofibrillar, distal, myotonic, and metabolic myopathies. Each subtype presents distinct clinical and molecular profiles, including glycogen storage disorders (e.g., Pompe and McArdle diseases), lipid storage disorders, mitochondrial myopathies, and unclassified myopathy [1].

Cardiac complications, including cardiomyopathies and arrhythmias, are prevalent in NMDs and are often progressive, leading to heart failure [2]. Early identification and regular follow-up to monitor preclinical disease stages are critical for improving outcomes in these patients [3].

Neuromuscular diseases involving cardiac manifestations typically affect skeletal muscle and include repeat nucleotide disorders (myotonic dystrophies, Friedreich's ataxia), laminopathies, desminopathies, dystrophinopathies, sarcoglycanopathies, and mitochondrial disorders.

The pathophysiological mechanisms underlying sudden death (SD) in NMDs are not fully elucidated; however, hypotheses include myocardial and conduction system fibrosis, membrane permeability alterations, and excessive sympathetic activity. In certain storage diseases, infiltrative material deposits within the conduction system may disrupt electrical signal propagation. Structural alterations frequently result in ventricular dilation, with dilated cardiomyopathy representing the terminal stage in diseases like DMD and BMD. Given the unique course of NMDs and their cardiac manifestations, specialized, regular follow-up is advised for optimal patient management, even in preclinical stages. The NMDs most associated with cardiopathies in general and arrhythmic issues, in particular, are the dystrophic forms. These are a group of hereditary diseases that affect skeletal muscles and, to varying degrees, the cardiac muscle. Cardiac manifestations include heart failure, atrioventricular and intraventricular conduction abnormalities, atrial and ventricular arrhythmias, and SD. Classically, dystrophies include Duchenne (DMD MIM #310200) and Becker (BMD MIM #300376) muscular dystrophies, Myotonic dystrophy type 1 (DM1 MIM #160900) and type 2 (DM2 MIM #602668), Emery–Dreifuss muscular dystrophy (EDMD1 #310300) and associated disorders, and limb–girdle muscular dystrophy (LGMDR1 MIM #253600—LGMDD1 MIM #603511). Limb–girdle muscular dystrophy (LGMD) represents a highly heterogeneous group of disorders, and not all subtypes exhibit a cardiac phenotype. Friedreich's ataxia (FRDA MIM #229300) is a mitochondrial disorder primarily affecting neural pathways and cardiac muscle [1]. While FRDA is most clinically renowned for its progressive, unremitting ataxia and neuromuscular decline, significant mortality occurs because of cardiomyopathy [4] (Table 1).

Table 1. Major neuromuscular disease (NMD) musculoskeletal and cardiac phenotypes.

Neuromuscular Disease	Gene Variant	Musculoskeletal Phenotypes	Cardiac Phenotypes 1 (Cardiomyopathies)	Cardiac Phenotypes 2 (Arrhythmias, Conduction Abnormalities, SCD)	Age of Onset	Reference
Duchenne muscular dystrophy (DMD-MIM #310200)	*DMD*	Severe progressive muscle weakness	Dilated cardiomyopathy	Arrhythmias, conduction abnormalities	Childhood (3–6 years)	Bushby et al., 2010 [5]
Becker muscular dystrophy (BMD-MIM #300376)	*DMD*	Milder muscle weakness	Dilated cardiomyopathy	Ventricular arrhythmias, conduction issues	Adolescence (10–20 years)	Bushby et al., 2010 [5]
Emery–Dreifuss muscular dystrophy (EDMD1 to EMD 7) (EDMD1 MIM #310300)	*EMD*, *LMNA*	Joint contractures, muscle wasting	Dilated cardiomyopathy	Bradyarrhythmias, atrial fibrillation	Adolescence or early adulthood	Meune et al., 2006 [6]
Limb–girdle muscular dystrophy (LGMDR1-MIM #253600) (LGMDD1-MIM #603511)	Various (*CAPN3*, *DYSF*, *SGCA*, etc.)	Proximal muscle weakness	Variable cardiomyopathies	Arrhythmias, conduction disturbances	Variable (depends on subtype)	Mah et al., 2016 [7]
Myotonic dystrophy Type 1 e Type 2 (DM1 MIM #160900) (DM2 MIM #602668)	*DMPK* (DM1), *CNBP* (DM2)	Myotonia, progressive muscle weakness	Systolic–diastolic dysfunction (rare in DM2)	Atrial and ventricular arrhythmias, AV block	Variable (DM1 earlier than DM2)	Groh et al., 2012 [8]
Myofibrillar myopathies (MFMs)	Various (*DES*, *MYOT*, *CRYAB*, *FLNC*, etc.)	Progressive muscle weakness, distal > proximal, myofibrillar disorganization	Dilated cardiomyopathy; restrictive cardiomyopathy	Conduction block, atrial fibrillation, ventricular arrhythmias	Variable (childhood to adulthood)	Brodehl 2012 [9]
Friedreich's ataxia (FRDA MIM #229300)	*FXN* (*GAA* expansion)	Progressive ataxia, skeletal muscle involvement	Hypertrophic cardiomyopathy (progression to DCM)	T-wave inversions, conduction block, arrhythmias	Childhood or adolescence	Hanson et al., 2019 [4]

2. Genetics Basis

The genetic basis of neuromuscular diseases (NMDs) is highly complex, involving mutations across numerous genes critical to muscle structure, stability, and function. Below are the key genetic factors contributing to these disorders.

2.1. Dystrophinopathies

The DMD gene on the X chromosome encodes dystrophin, a protein that is essential for muscle fiber integrity. Mutations in this gene lead to two primary clinical phenotypes: Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). Duchenne muscular dystrophy, the more severe form, arises from frameshift mutations or large deletions that disrupt the reading frame, resulting in either absent or non-functional dystrophin. Becker muscular dystrophy, in contrast, is caused by in-frame mutations that permit the production of partially functional dystrophin, resulting in a comparatively milder phenotype [5].

2.2. Emery–Dreifuss Muscular Dystrophy (EDMD)

Emery–Dreifuss muscular dystrophy can be inherited in either an X-linked or autosomal dominant pattern. The X-linked form is associated with mutations in the EMD gene, which encodes emerin, a protein integral to nuclear membrane structure. The autosomal dominant form is linked to mutations in the *LMNA* gene, which encodes lamin A/C proteins that maintain nuclear envelope integrity. Mutations in these proteins compromise

nuclear structure and cellular stability, leading to progressive muscle weakness and cardiac conduction abnormalities [6].

2.3. Limb–Girdle Muscular Dystrophies (LGMDs)

LGMDs represent a genetically heterogeneous group of disorders involving mutations in various genes, such as *CAPN3* (encoding calpain-3), *DYSF* (encoding dysferlin), and *FKRP* (encoding fukutin-related protein). Each gene mutation affects muscle function through distinct mechanisms, including disruptions in muscle repair, membrane integrity, and the glycosylation of dystroglycan. Clinical presentations vary widely depending on the specific gene involved and the nature of the mutation [7].

2.4. Myotonic Dystrophy

The most prevalent form of myotonic dystrophy, DM1, is caused by a CTG trinucleotide repeat expansion in the 3′ untranslated region of the *DMPK* gene. This repeat expansion results in toxic RNA aggregates that interfere with RNA splicing factors, causing widespread disruptions in RNA processing and cellular function. Clinical severity in DM1 correlates with repeat length, with larger expansions associated with earlier onset and more severe disease manifestations [10].

2.5. Myofibrillar Myopathies (MFMs)

MFMs are characterized by progressive muscle weakness and structural abnormalities within muscle fibers. Key genes implicated include DES (encoding desmin), *CRYAB* (encoding alphaB-crystallin), and *MYOT* (encoding myotilin). Mutations in the *DES* gene, encoding for the intermediate filament protein desmin, may cause skeletal and cardiac myopathies; the histopathological hallmark of many but not of all *DES* mutations is abnormal cytoplasmic desmin aggregation in (cardio)myocytes. The disease phenotypes of these mutations are clinically heterogeneous, ranging from isolated myopathy, dilated cardiomyopathy with or without skeletal muscle disorder, and hypertrophic, restrictive, or arrhythmogenic right ventricular cardiomyopathy [9,11,12].

Desmin-related myopathy could be also caused by mutations in *CRYAB*, encoding the small heat shock protein αB-crystallin, a binding partner of desmin filaments. The salt bridges between arginine 120 and aspartate 109 are affected by mutations in the *CRYAB* gene leading to the formation of cytoplasmic aberrant alpha-B-Crystallin aggregates with desmin [13].

DES arrhythmogenic cardiomyopathy (ACM) presents with left dominant or biventricular disease, high penetrance, and a high burden of adverse cardiovascular outcomes. Male sex, NSVT, and LVEF < 50% are associated with the occurrence of cardiovascular events and provide an initial basis for risk stratification in this patient population [14].

Filamin-C, encoded by *FLNC* (MIM #102565), is the predominant isoform expressed in skeletal and heart muscle. Dominant mutations causing myopathies, such as myofibrillar myopathy type 5 (MFM; MIM #609524) and distal myopathy type 4 (MIM #614065), have previously been described [15,16]. Mutations in *FLNC* have been identified in families with hypertrophic cardiomyopathy (HCM) [17] and familial dilated cardiomyopathy (DCM) [18]. Brodehl et al. present genetic and functional evidence showing that FLNC is a gene associated with restrictive cardiomyopathy (RCM). Although RCM is a rare cardiomyopathy, the observation of two independent families suggests that novel variants in FLNC linked to RCM may be more prevalent than previously anticipated [19].

Understanding the genetic foundations of these disorders aids in diagnosis and the development of targeted therapies, improving predictive accuracy for affected patients.

2.6. Friedreich's Ataxia (FRDA)

Friedreich's ataxia (FRDA) is caused by GAA trinucleotide repeat expansions in the *FXN* gene, leading to a deficiency in frataxin, a mitochondrial protein critical for oxidative phosphorylation and iron–sulfur cluster assembly. Frataxin deficiency impairs mitochondrial function, increases reactive oxygen species (ROS), and causes iron misdistribution, resulting in mitochondrial dysfunction and reduced cellular energy production.

Frataxin deficiency in the heart leads to iron accumulation, oxidative damage, fibrosis, and myocardial hypertrophy. These factors contribute to hypertrophic cardiomyopathy and reduced myocardial reserve, changes which are often detectable via late gadolinium enhancement during cardiac MRI. These pathological changes drive cardiomyocyte apoptosis, inflammation, and progressive cardiac dysfunction.

Cardiomyopathy in FRDA is primarily driven by mitochondrial dysfunction and oxidative damage rather than iron deposition. Current research focuses on understanding frataxin's role in cellular homeostasis and developing targeted therapeutic strategies [9–13].

2.7. Gender Differences and Genotype-Phenotype Correlations

Specific *LGMD* subtypes exhibit gender-specific phenotypic differences. For instance, calpain-3 mutations often present with more severe symptoms in males, while dysferlin mutations may have a more pronounced clinical impact in females.

These differences underscore the importance of considering sex as a factor in genetic expression and disease progression. Identifying specific mutations not only aids in the subclassification of muscular dystrophies but also enhances the ability to predict clinical outcomes and personalize treatment strategies. For example, patients with dystrophin mutations may respond differently to therapeutic interventions than those with lamin A/C mutations, necessitating individualized management approaches [20].

3. Primary and Secondary Arrhythmogenesis in NMDs

Cardiac involvement in neuromuscular diseases (NMDs) poses significant clinical challenges, especially in the context of arrhythmias, which can manifest as the primary features of the disease or as secondary complications. The pathogenesis of rhythm disturbances in NMDs is complex, encompassing cellular, structural, and systemic disruptions.

3.1. Cellular Mechanisms of Arrhythmogenesis

One central mechanism underlying arrhythmogenesis in NMDs is the disruption of intracellular ion transport. Mutations affecting calcium-handling proteins lead to the dysregulation of calcium homeostasis, resulting in early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). These factors predispose myocardial tissue to activity being triggered. This ion imbalance is crucial in the susceptibility to tachyarrhythmias observed in conditions such as Duchenne muscular dystrophy [21,22].

Additionally, sodium and potassium channel function alterations can impact depolarization and repolarization processes, creating a substrate for arrhythmias. The interplay between these ion channel disruptions and inherent muscle pathology underscores the primary nature of some arrhythmias in NMDs [23].

3.2. Degeneration of the Conduction System

Another prominent feature of certain NMDs, such as myotonic dystrophy types 1 and 2, is the degeneration of the cardiac conduction system. Histopathological studies frequently reveal fibrofatty infiltration and progressive fibrosis of the His–Purkinje system and sinoatrial node [23]. These changes lead to conduction delays and blocks and an increased propensity for bradyarrhythmias and atrioventricular blocks.

3.3. Structural and Extracellular Changes

The structural remodeling of the myocardium, often marked by interstitial fibrosis, significantly contributes to arrhythmogenic risk in NMDs. Fibrotic tissue disrupts normal electrical conduction, creating zones of conduction heterogeneity that facilitate reentrant circuits. This mechanism is particularly relevant in DMD and BMD, of which myocardial fibrosis is an established hallmark [24].

Extracellular matrix remodeling, influenced by dysregulated matrix metalloproteinases (MMPs) and their inhibitors, further complicates the myocardial architecture. These changes promote fibrotic deposition and contribute to an inflammatory milieu that exacerbates electrical instability [23].

3.4. Secondary Arrhythmogenesis and Heart Failure

Secondary arrhythmias in NMDs often develop as the disease progresses to involve dilated cardiomyopathy and heart failure. The associated ventricular remodeling and neurohormonal activation—including the renin–angiotensin–aldosterone system (RAAS) and heightened sympathetic activity—further destabilize the electrical environment. This increases automaticity and reentry phenomena, significantly raising the risk of atrial and ventricular arrhythmias [8,23].

3.5. Interaction with Primary Cardiomyopathies

The relationship between primary cardiomyopathies and arrhythmias in patients with NMDs is intricate and contributes significantly to clinical outcomes. In many cases, the development of cardiomyopathy exacerbates the risk of arrhythmias due to changes in the myocardial substrate, such as hypertrophy, fibrosis, and ventricular dilation. These structural changes create an environment predisposed to electrical instability and arrhythmogenic events. Studies have shown that patients with more severe cardiomyopathy involvement exhibit higher incidences of arrhythmias, including ventricular tachycardia (VT) and atrial fibrillation (AF). The interplay between NMD-related myocardial pathology and primary cardiomyopathies underscores the need for comprehensive management strategies that address both the muscular and cardiac components of the disease [8,23].

3.6. Clinical Implications and Management

Understanding the mechanisms underlying primary and secondary arrhythmogenesis is fundamental to developing targeted management strategies for NMD patients. Clinical management may involve the use of antiarrhythmic medications, though these must be carefully selected to minimize adverse effects given the complex cardiac environment in NMDs. Device-based therapies, such as implantable cardioverter-defibrillators (ICDs) and pacemakers, are frequently indicated to prevent sudden cardiac death in high-risk individuals [24].

A comprehensive cardiac care plan for NMD patients should include routine electrocardiograms (ECGs), Holter monitoring, and electrophysiological (EP) studies to detect and address conduction abnormalities and arrhythmias early.

The complex interplay between cellular dysfunction, conduction system degeneration, and structural myocardial remodeling highlights the dual nature of arrhythmogenesis in NMDs. Effective management must address primary and secondary arrhythmic mechanisms to optimize clinical outcomes and reduce arrhythmic mortality in this population.

4. Clinical Manifestations and Diagnosis of Arrhythmias

Arrhythmias in patients with neuromuscular diseases (NMDs) exhibit a broad spectrum of clinical manifestations, ranging from asymptomatic episodes identified during

routine monitoring to symptomatic events such as palpitations, syncope, or sudden cardiac arrest [8]. The age of onset and arrhythmia type can vary considerably across NMD subtypes. For instance, ventricular arrhythmias often emerge during adolescence in patients with Duchenne muscular dystrophy (DMD), while patients with conditions like myotonic dystrophy may present with conduction abnormalities earlier in life [23,25]. Diagnostic approaches include electrocardiograms (ECGs), Holter monitoring, and electrophysiological (EP) studies, which are instrumental in characterizing the underlying arrhythmogenic substrate and informing treatment strategies.

Thorough clinical evaluation and detailed history-taking are essential for identifying arrhythmias, particularly in diseases where subtle symptoms might otherwise go unnoticed. Key factors such as a family history of cardiac disease, muscle weakness, and systemic involvement should prompt more extensive cardiac evaluation. In disorders like Emery–Dreifuss muscular dystrophy (EDMD), the early recognition of signs such as atrial paralysis or junctional escape rhythms can be critical for patient outcomes [23].

Advanced imaging modalities, particularly cardiac magnetic resonance (CMR), provide valuable insights into myocardial fibrosis and enable the more accurate stratification of arrhythmic risk [26]. Integrating clinical findings with diagnostic data supports a comprehensive management approach tailored to each neuromuscular condition (Table 2).

Table 2. Cardiac screening recommendations in NMDs.

Neuromuscular Disease	Age to Start Screening	Monitoring Frequency	Methodology	Phenotype
Duchenne muscular dystrophy (DMD)	At time of diagnosis	Every 2 years until age 10, annually after age 10	ECG, echocardiogram, MRI	Progressive muscle weakness, cardiomyopathy, scoliosis
Becker muscular dystrophy (BMD)	At time of diagnosis	Annually after age 10	ECG, echocardiogram, MRI	Milder muscle weakness, dilated cardiomyopathy
Myotonic dystrophy (DM1, DM2)	From age 18	Annually, or based on symptoms	ECG, electrophysiological study if needed	Myotonia, arrhythmias, cardiac conduction abnormalities
Emery–Dreifuss muscular dystrophy (EDMD)	From age 20 or earlier if symptomatic	Every 1–2 years, continuous monitoring for patients with PM	ECG, echocardiogram	Joint contractures, muscle wasting, bradyarrhythmias
Limb–girdle muscular dystrophy (LGMD)	Variable	Annually, based on specific form	ECG, echocardiogram	Proximal muscle weakness, variable cardiac involvement

5. Management Strategies and Prognostic Significance

The management of arrhythmias in patients with neuromuscular diseases (NMDs) requires a multidisciplinary approach tailored to the type and severity of the arrhythmia and the specific neuromuscular condition. Pharmacologic treatments, including beta-blockers and antiarrhythmic agents, are frequently employed to control and to reduce arrhythmic episodes [27]. However, careful consideration is needed due to potential side effects and interactions with other medications required for managing the neuromuscular disease.

Device-based interventions, such as pacemakers and implantable cardioverter-defibrillators (ICDs), are fundamental in managing patients at elevated risk of sudden

cardiac death. Pacemakers are particularly beneficial in cases with significant bradyarrhythmias or conduction blocks, whereas ICDs are indicated for preventing life-threatening ventricular arrhythmias [24].

Cardiac resynchronization therapy (CRT) may be considered for patients with progressive heart failure and intraventricular conduction delays. CRT has been shown to improve cardiac function and reduce the overall burden of arrhythmias, thereby contributing to improved patient outcomes [8,23].

Routine follow-up with comprehensive cardiac monitoring, including regular ECGs, Holter monitoring, and periodic electrophysiological (EP) studies, is essential to assess disease progression and arrhythmic risk. Genetic counselling and assessment should also be incorporated into long-term management to evaluate familial risk and provide personalized care strategies for affected individuals [8].

From a prognostic perspective, early intervention in arrhythmia management is crucial. Effective monitoring and treatment can significantly reduce morbidity and enhance the quality of life for patients with NMDs. Collaborative care involving cardiologists, neurologists, and electrophysiologists supports a comprehensive approach to managing these complex cases, ensuring that all aspects of the disease are addressed [28,29].

6. Duchenne and Becker Muscular Dystrophies

Muscular dystrophies constitute a heterogeneous group of genetic disorders that variably affect skeletal and cardiac muscles. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) account for over 80% of all muscular dystrophy cases [5,21]. Both disorders result from X-linked recessive mutations in the dystrophin gene (*DYS*) located on chromosome Xp21.2, leading to dystrophin deficiency in cardiac and skeletal muscles. Although most mutations are inherited, spontaneous mutations contribute to approximately 30% of DMD cases [30]. DMD is more common, presents earlier, and is more severe than BMD, occurring in approximately 1 in 5000 male births [7], whereas BMD has an incidence of 1 in 19,000 male births [31]. Immunohistochemical analyses reveal an absence of dystrophin in DMD, while in BMD, dystrophin is present, but in an abnormal quantity or with an abnormal quality. Diagnostic evaluation includes the measurement of creatine phosphokinase (CPK) levels, which are elevated 50 to 200 times above average in DMD and 10 to 35 times higher in BMD. Early symptoms often include gait disturbances and difficulty climbing stairs, with ambulation typically lost by age 12 in DMD patients. Cardiac and respiratory involvement commonly exacerbates the prognosis of DMD, although mechanical ventilation has significantly improved survival rates in recent decades [25,26,32]. BMD typically presents later and with less severe symptoms than DMD. Diagnosis usually occurs around age 5, when children display a wide-based gait, an equinus foot position, and calf hypertrophy and require Gowers' maneuver—using arms on the knees to rise—to compensate for lower limb weakness. Walking difficulties generally manifest between ages 10 and 12, followed by complications such as scoliosis, cardiomyopathy, and restrictive respiratory insufficiency. The progression of DMD is severe, leading to fatal cardiorespiratory failure in young adulthood. BMD progresses more slowly, often allowing for an average life expectancy.

6.1. Cardiac Involvement in Duchenne and Becker Muscular Dystrophy

Cardiac involvement can be a primary clinical manifestation in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD), with incidence increasing with age and often preceding skeletal muscle involvement. Studies estimate that 25% of boys with DMD exhibit cardiac involvement by age 6, 59% exhibit this by age 10, and that over 90% of individuals older than 18 exhibit this issue, with nearly universal cardiac involve-

ment in advanced age. Improved survival rates due to reductions in respiratory failure through mechanical ventilation have highlighted the impact of cardiac complications in these patients [33]. The underlying myocardial damage is characterized by the progressive replacement of cardiac muscle cells with fibrofatty tissue, resulting in a loss of contractile capacity. In certain families, cardiomyopathy can develop without the accompanying skeletal muscle symptoms [34]. Current guidelines recommend cardiac screening every two years for DMD patients up to age ten, with annual scanning thereafter.

Patients with Duchenne muscular dystrophy (DMD) typically develop dilated cardiomyopathy (DCM), although severe skeletal muscle weakness may obscure its clinical recognition (Figure 1). Additionally, thoracic deformities can complicate cardiovascular assessment in these patients. Cardiomyopathy in DMD generally manifests during childhood, around six years of age, or during adolescence. It is characterized by early myocardial fibrosis, supraventricular and ventricular arrhythmias, and progressive systolic dysfunction. In advanced stages, often by early adulthood, left ventricular dilatation can progress to end-stage heart failure.

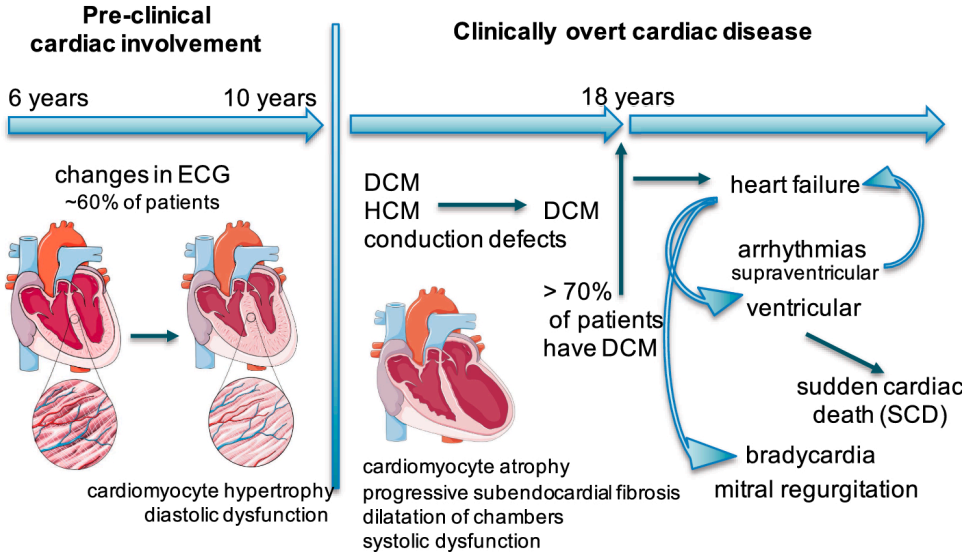

Figure 1. Cardiac involvement in DMD [35].

In Becker muscular dystrophy, more than 70% of patients develop dilated cardiomyopathy (DCM), which typically develops later in life, most commonly during the 4th or 5th decade. Once DCM is diagnosed, it often progresses rapidly, setting BMD apart from Duchenne muscular dystrophy (DMD). The severity of cardiac involvement in BMD frequently progresses to become the primary cause of mortality [7,31,36].

6.2. Electrocardiographic Abnormalities and Arrhythmias

Electrocardiography (ECG) should be systematically included in the clinical management of patients with Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) (Figures 2–4). Most patients present with abnormal ECG findings, typically including deep and narrow inferolateral Q waves, right bundle branch block, and repolarization abnormalities [37,38]. These electrocardiographic features correlate with the observation of fibrosis in the basal posterior wall of the heart and the conduction system. ECG abnormalities are thought to precede echocardiographic findings, although no direct correlation between ECG and echocardiographic changes has been confirmed.

In a study of 131 DMD patients, 78.6% exhibited abnormal ECGs, with specific findings including elevated R waves in V1 in 29.7% of cases, pathological Q waves in V6 in 21.3% of cases, QS complexes in the lateral leads in 37.4% of cases, repolarization abnormalities in 54.9% of cases, and right bundle branch conduction disturbances in 55.7% of cases [33,34,39].

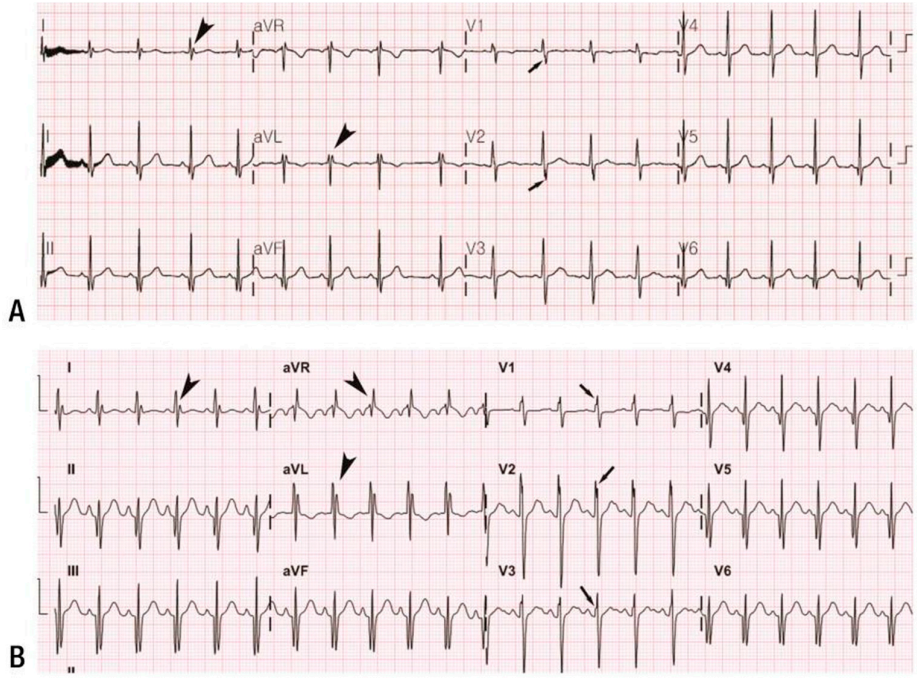

Figure 2. (**A**) The electrocardiography (ECG) of an 11-year-old patient showing the fragmentation of the QRS complex at I, aVL, V1, and V2, and (**B**) follow-up ECG in a 14-year-old patient showing increased the prevalence of fragmented QRS (I, aVR, aVL, V1, V2, and V3). Different types of notched and fragmented QRS patterns are indicated by arrowheads (RSr′, rSr′, and rSR′) and arrows (notched R upstroke and notched S downstroke) [40].

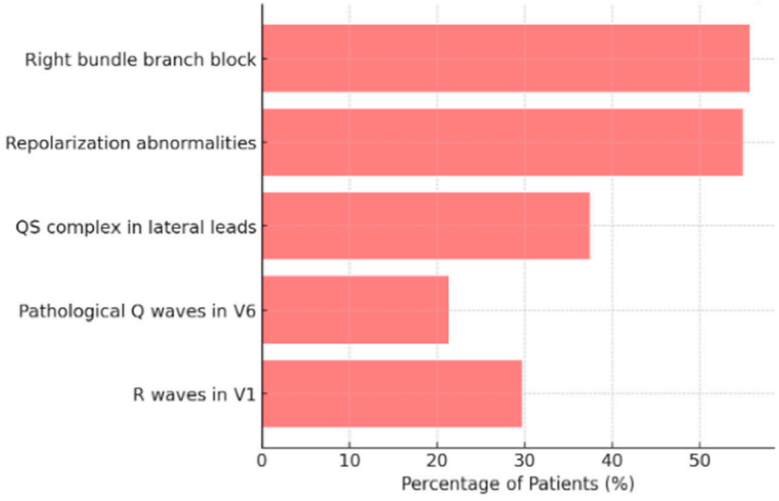

Figure 3. The distribution of ECG abnormalities in Duchenne muscular dystrophy patients.

Figure 4. Contrast CMR images of patients with BMD in the following order (from left to right): two short-axis views, a 3-chamber-view, and a 4-chamber view, demonstrating the transmural pattern of LGE in the LV free wall representing myocardial damage (white arrows). In addition, this patient presented with ECG changes typically seen in muscular dystrophy (R/S ratio $\geq$ 1.0 in lead V1, a deep Q-wave in leads I, II, aVL, and V5-V6, or complete right bundle branch block) [41].

6.3. Cardiac Imaging in Duchenne Muscular Dystrophy

Imaging modalities used for assessing cardiac involvement in Duchenne muscular dystrophy (DMD) include echocardiography and cardiac magnetic resonance imaging (MRI). Echocardiography in DMD patients often reveals regional kinetic abnormalities in the basal posterior wall, left ventricular dilation, and overall reduced systolic function. Current guidelines recommend performing an echocardiogram at diagnosis or from age 6, with follow-up every 1 to 2 years until age 10. After age 10, annual echocardiograms are advised in order to monitor left ventricular function. However, echocardiography can be technically challenging in DMD patients due to chest wall deformities [42].

MRI enables more precise assessment of left ventricular size and function and can detect the presence of fibrosis [43]. Consequently, MRI is recommended at diagnosis and annually after age ten unless contraindicated. However, the use of MRI in pediatric patients presents challenges due to the need for sedation, high costs, and limited accessibility.

6.4. Ventricular Arrhythmias, Sudden Death, and the Use of an Implantable Defibrillator

The percentage of deaths attributed to arrhythmias in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) remains uncertain. Ventricular arrhythmias and sudden death are believed to play a role in these disorders, similar to that seen in other forms of non-ischemic dilated cardiomyopathies. The use of implantable cardioverter-defibrillators (ICDs) is well established for preventing sudden cardiac death in patients with a left ventricular ejection fraction (LVEF) below 35%; however, its role in patients with DMD-related cardiomyopathy is not yet well defined. Current guidelines discourage the use of ICDs in patients with a life expectancy of less than one year.

7. Myotonic Dystrophy Type 1 and Type 2

Myotonic dystrophy is an autosomal dominant systemic disease that affects multiple organs, including the heart. Clinically, it is characterized by asthenia, myotonia, and skeletal muscle atrophy. Based on distinct mutations, the disease is divided into two forms: type 1 (*DM1*), Steinert's disease, and type 2 (*DM2*), or proximal myotonic myopathy.

DM1 is caused by the expansion of a cytosine–thymine–guanine (*CTG*) repeat in a non-coding region of the DMPK gene on chromosome 19 (*19q13.3*). This expansion is inherited in a way that may increase with each generation, often worsening clinically in successive generations. DM1 is the second most common kind of muscular dystrophy after Duchenne muscular dystrophy and is the most common in adults, with an incidence of approximately 1 in 8000.

DM2 involves a mutation that expands a *CCTG* repeat in the *ZNF9* gene on chromosome 3 (3q21). Although its incidence is estimated to be around 1 in 20,000, it is likely underdiagnosed. In both DM1 and DM2, abnormal DNA amplification leads to defects in the synthesis of the gap junction protein GJA1, and recent studies have reported the overexpression of calcium channel proteins such as *CACNA1C* [37,38,44,45].

In DM1, cardiac involvement occurs in 60-80% of cases and is characterized by myocyte degeneration, fatty infiltration, and fibrosis. These issues primarily affect conduction tissue and, less frequently, atrial and ventricular myocytes. Cardiac involvement can lead to systolic–diastolic dysfunction, though symptomatic left ventricular dysfunction is seen in only 10–15% of patients. Cardiac involvement in DM2 is much less frequent (10–25%) and tends to present later in life.

Progressive neuromuscular respiratory failure is the leading cause of death in myotonic dystrophy, with sudden cardiac death being the second most common cause. Sudden death risk is higher in DM1, affecting about one-third of patients, while it is notably lower in DM2 [42,46,47].

7.1. Arrhythmic Risk

Given the high incidence of conduction system involvement in myotonic dystrophy type 1 (DM1), it was initially hypothesized that sudden death (SD) was primarily due to atrioventricular block (AVB). However, observations in DM1 patients with pacemakers revealed a high incidence of ventricular tachycardia and fibrillation (VT/VF), suggesting that ventricular arrhythmias also play a significant role. Consequently, stratifying AVB and arrhythmic risk is crucial in DM1 patient management.

Proposed clinical markers for risk stratification include the age of symptom onset, the severity of muscle involvement, and the number of CTG repeats [48]. Efforts have focused on combining clinical and electrocardiographic criteria to enhance predictive accuracy. In a study involving 171 DM1 patients, significant predictors of SD included a history of palpitations, arterial hypertension, right bundle branch block, and bifascicular block [49]. A 2015 study further identified atrial tachyarrhythmias, a PR interval > 240 ms on ECG, intraventricular conduction abnormalities, and any degree of AVB as predictors of SD. Notably, up to 25% of patients with atrioventricular conduction disturbances also have a family history of SD [50,51].

7.2. Role of ECG in Arrhythmic Risk Stratification

ECG plays a critical role in diagnosing and stratifying sudden death (SD) risk in patients with myotonic dystrophy type 1 (DM1). Prolonged PR intervals and QRS durations correlate with the extent and distribution of the conduction system lesions observed at autopsy [52]. A review of 18 studies involving 1,828 DM1 patients reported first-degree AVB in 30% of patients, a QRS duration > 120 ms in 20% of patients, frequent premature ventric-

ular contractions (PVCs) in 15% of patients, and non-sustained ventricular tachycardia (VT) in 4% of patients [53]. In another unselected DM1 cohort, 65% of patients demonstrated abnormal ECG findings, with first-degree AVB in 42% of patients, right bundle branch block in 3% of patients, left bundle branch block in 4% of patients, and non-specific intraventricular conduction delays in 12% of patients [54]. Conduction abnormalities worsen with age, are more frequent, and occur earlier in DM1 than in DM2 [55]. Notably, up to 18% of DM1 patients may exhibit a "Brugada-like" pattern after sodium channel blocker loading [56]. While the role of this test in arrhythmic risk stratification is uncertain, it is worth considering if class 1 drugs are needed to treat conditions like myotonia.

Groh et al. [54] highlighted that prolonged PR intervals (>240 ms), QRS durations > 120 ms, second- or third-degree AVB, and atrial tachyarrhythmias are independent predictors of SD via multivariate analysis. However, the positive predictive value of conduction defects on ECG for SD was only 12%, indicating limited predictive power and suggesting that electrophysiological study (EPS) may enhance diagnostic accuracy. Conversely, ECG can be valuable in predicting atrial fibrillation (AF) risk, particularly in patients with slowed intra-atrial conduction (p wave duration > 120 ms) [57].

7.3. Role of Electrophysiological Study

Lazarus et al. [58] suggested that an HV interval >70 ms, even in asymptomatic patients, is predictive of complete atrioventricular block (AVB). In DM1 patients with an HV interval >70 ms who received a pacemaker (PM), the incidence of cardiac sudden death (SD) was reported to be very low [59]. Similarly, Wahbi et al. [60], in a retrospective study of 914 DM1 patients, found that PM implantation in those with an HV interval >70 ms was associated with a 70% reduction in SD.

Considering that up to 50% of AVB cases may present with a normal ECG, Siméon et al. [61] recommended that an electrophysiological study (EPS) be performed in all adult DM1 patients, regardless of their baseline ECG findings, with PM implantation advised for those with an HV interval >70 ms. Conversely, the risk of AVB appears to be very low in patients with normal ECGs and HV intervals.

A multicenter observational study following 406 DM1 patients over ten years reported that 11.3% required PM implantation, primarily for first- or second-degree AVB or sinoatrial node dysfunction, and less frequently for fascicular blocks or third-degree AVB [62]. The 2021 ESC guidelines recommend PM implantation (Class I, level of evidence [LOE] B) in patients with second- or third-degree AVB or an HV interval >70 ms, with or without symptoms. PM implantation may also be considered (Class Iib, LOE C) for DM1 patients with only a PR interval > 240 ms, a QRS duration > 120 ms, or a fascicular block. (Class I, LOE B) [63,64].

7.4. Arrhythmic Risk and Indication for Defibrillator Implantation

Due to the high risk of ventricular tachycardia (VT), ventricular fibrillation (VF), and sudden death (SD) in patients with myotonic dystrophy type 1 (DM1) [65], careful consideration should be given to the use of an implantable cardioverter-defibrillator (ICD) instead of a pacemaker (PM) when PM indications arise. Guidelines also support ICD implantation in spontaneous or inducible ventricular arrhythmias, even in patients with preserved cardiac function (Class Iib, level of evidence [LOE] B). The indications for the primary prevention of ICD implantation in DM1 align with those for other forms of non-ischemic dilated cardiomyopathy [64]. Before deciding on any invasive therapy, including PM or ICD, it is crucial to consider that in patients with severe muscular involvement, the high risk of non-sudden death—primarily due to respiratory complications—may limit the benefit of device therapy.

8. Emery–Dreifuss Muscular Dystrophy

Emery–Dreifuss muscular dystrophy (EDMD), also known as humeroperoneal muscular dystrophy, is a slowly progressive disorder characterized by early joint contractures (elbows, neck, spine), the gradual onset of asthenia with humeroperoneal muscle atrophy, and cardiac involvement in adulthood. Mutations associated with EDMD primarily involve emerin (*EMD*, 8.5% of cases), *FHL1* (1.2% of cases), and *LMNA* (26.5% of cases), with the remaining cases attributed to unidentified genetic factors [66].

The diagnosis of EDMD is established through characteristic clinical features and genetic testing. Cardiac involvement may be absent in the first decades of life. Diagnosis requires a pathogenic variant, including homozygosity in *EMD* or *FHL1*, a heterozygous pathogenic variant of *LMNA*, or other variants identified by molecular testing.

Various forms of EDMD have been identified based on genetic mutations and inheritance patterns. The most common are Type 1 EDMD (*EDMD1*), associated with X-linked mutations in *EMD* or *FHL1*, and Type 2 EDMD (*EDMD2*), associated with autosomal dominant mutations in LMNA. An autosomal recessive form, *EDMD3*, also involves LMNA mutations. Notably, there is no clear correlation between the severity of muscle and cardiac involvement.

EDMD1 results from mutations in an X-linked gene encoding emerin, a protein that binds actin filaments in the cytoskeleton to the nuclear lamina and chromatin. In animal and experimental models, emerin is also localized at intercalated discs, which may explain conduction abnormalities in EDMD1 patients [67]. In EDMD1, emerin is absent from muscle and other cells (e.g., blood, skin). The myocardium gradually undergoes fibrofatty replacement, beginning in the atria and atrioventricular (AV) node and progressing to the ventricles [68]. Cardiac manifestations primarily involve bradyarrhythmias and atrial arrhythmias, particularly atrial fibrillation. *FHL1*, a protein in skeletal muscle and myocardium, plays a role in sarcomere synthesis, cellular integrity, and intracellular signaling, resulting in a phenotype similar to emerin mutations.

Muscular symptoms in EDMD1 often include flexor contractures, especially in the humeroperoneal muscles. Onset generally occurs in childhood, with symptoms such as an inability to fully extend the arms, tiptoe walking, equinus foot, and frequent falls. Diagnosis can be confirmed via muscle or skin biopsy, the immunohistochemical analysis of white blood cells, or the analysis of oral mucosal cells, procedures which reveal the absence of emerin in EDMD1 patients [69].

Due to a high affinity for atrial tissue and the conduction system, arrhythmias are the predominant cardiac manifestation in EDMD1. Ventricular involvement and arrhythmias are rare and generally occur later. Electrocardiographic abnormalities, including first-degree AVB, typically appear by the third decade, and P wave prolongation may occur without atrial enlargement. "Atrial electrical silence" can develop with junctional or ventricular escape beats. Conduction abnormalities are progressive, and pacemaker (PM) implantation is often necessary before age 40. Testing for emerin mutations is advised for young patients with idiopathic conduction disturbances [66–68] (Figure 5).

In a study by Boriani et al. [70] on EDMD1 arrhythmia incidence, four in ten subjects developed arrhythmias as the initial cardiac symptom. During follow-up, six patients (60%) developed both brady- and tachyarrhythmias, three (30%) had bradyarrhythmias only, and one (10%) had tachyarrhythmias only. Seven out of ten patients required PM implantation, all of whom later became PM-dependent. Atrial lead use was often limited by AF or atrial electrical silence, and four patients developed chronic AF.

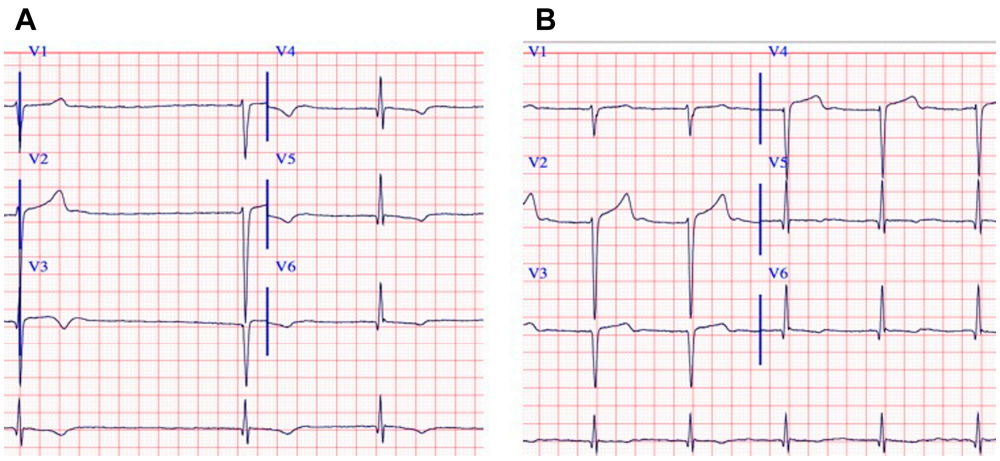

Figure 5. (**A**) Atrial fibrillation with slow ventricular response in a patient with Emery–Dreifuss muscular dystrophy. (**B**) Atrial fibrillation with complete heart block in a patient with Emery–Dreifuss muscular dystrophy [24].

In a Polish study, atrial electrical activity was absent in 3 of 13 EDMD1 patients, preventing atrial catheter placement. Over time, 40% of patients had their device programming adjusted from DDD to VVI mode due to chronic AF progression, which was associated with increased thromboembolic risk [71].

Another possible cardiac manifestation of EDMD1 is a form of dilated cardiomyopathy that may develop post-device implantation. In female patients, skeletal muscle symptoms are absent, but cardiac and conduction abnormalities are common [72,73]. The risk of sudden death (SD) in EDMD1 appears to be primarily related to bradyarrhythmias and is low in PM-treated patients [74].

Type 2 EDMD (EDMD2) is an autosomal dominant form associated with mutations in the *LMNA* gene, which encodes lamins A/C. Lamins form an internal membrane network that interacts with emerin and the cytoskeleton. These proteins are essential for nuclear structural integrity, chromatin regulation, and nucleic acid replication.

Arrhythmias and Neuromuscular Diseases

In patients with *LMNA* deficiency, cardiac manifestations often include early intraventricular conduction abnormalities, supraventricular arrhythmias, and contractile dysfunction, which may occur even in the absence of overt myopathy. However, muscle involvement or elevated creatine phosphokinase (CPK) levels are expected in these patients [75]. The cardiomyopathic phenotype typically presents later than muscle symptoms, with a diagnosis of dilated cardiomyopathy being rare before age 20. An Italian multicenter study (Italian Network for Laminopathies, NIL), including 164 patients with LMNA deficiency, found that muscle alterations appeared at an average age of 25 years, while cardiac alterations appeared around age 36 and were more prevalent (90% vs. 67%) [76,77].

In a meta-analysis by van Berlo et al. [78], supraventricular or ventricular arrhythmias were found in 71% of *LMNA*-deficient patients, and 44% of those over 30 required pacemaker (PM) implantation. The average survival was 46 years, with mortality primarily occurring due to sudden death (SD) in 46% of cases.

Preventing SD in patients with EDMD2 and *LMNA* deficiency is a significant challenge, mainly because the risk profile differs from that seen in the X-linked form. *LMNA* mutations have been identified in at least 4% of dilated cardiomyopathy cases, up to 8% of familial cases, and as many as 30% of patients with familial dilated cardiomyopathy who exhibit atrioventricular conduction abnormalities, underscoring the importance of screening for *LMNA* mutations in these patients [79,80].

LMNA-related dilated cardiomyopathy generally carries a poorer prognosis than other genetic forms, including those involving desmosomal protein mutations. A multicenter study involving 269 patients identified predictors of SD risk, including moderate left ventricular dysfunction (ejection fraction < 45%), non-sustained ventricular tachycardia (VT), and male sex, supporting a Class IIa indication for implantable cardioverter-defibrillator (ICD) implantation if at least two of these factors are present [81,82]. The NIL study reinforced these findings, particularly highlighting the role of mild-to-moderate left ventricular dysfunction and non-sustained VT in risk stratification.

Arrhythmias are frequent in *LMNA* deficiency, even without contractility impairments. In a study by Boriani et al. [70], 50% of patients with EDMD2 developed both bradyarrhythmias and tachyarrhythmias (AF) during follow-up, while 13% developed bradyarrhythmias alone. Pacemakers were implanted in 37% of cases, and thromboembolic events occurred in three of eight patients before age 60. Patients with LMNA deficiency have an elevated thromboembolic risk, which is independent of heart disease or atrial arrhythmias [83].

Unlike patients with X-linked EDMD, arrhythmic risk in *LMNA* deficiency includes not only bradyarrhythmias and supraventricular arrhythmias but also a high risk of SD. In van Berlo et al.'s meta-analysis [78], the SD mortality was similar in PM carriers (50%) and other patients (43%), indicating that pacing alone does not adequately protect against SD. This was supported by a small case series in which patients with *LMNA* deficiency and PM indications for AV conduction abnormalities were treated with ICDs, even without other arrhythmic risk indicators or left ventricular dysfunction. In a study by Meune et al. [6], over a follow-up period of 33.9 $\pm$ 21 months, 8 of 19 patients (42%) received appropriate ventricular fibrillation (VF) or VT shocks. Another French study involving 21 patients with PM indications and ICDs reported appropriate device interventions in 52% of cases over a 62-month follow-up, with no SD episodes [84].

LMNA mutations have also been identified in approximately 4–5% of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) [85]. In these patients, the typical electrocardiographic features of right ventricular cardiomyopathy (such as epsilon waves and T-wave inversions) are less common, while intraventricular and atrioventricular conduction disturbances are more frequent [86].

9. Limb–Girdle Muscular Dystrophy

Limb–girdle muscular dystrophy (LGMD) encompasses a heterogeneous group of dystrophies characterized by proximal muscle weakness in the pelvic and shoulder girdles. LGMD can be classified into autosomal dominant (*LGMD1)* and autosomal recessive (*LGMD2*) forms, and only specific subtypes exhibit cardiac involvement. In general, LGMD2 has a later onset and follows a less severe course than autosomal dominant forms [24]. Various types of cardiomyopathy and rhythm disturbances may occur in LGMD, and guidelines for neurologists recommend cardiac evaluation in specific LGMD subgroups, including LGMDs 1A, 1B, 1D, 1E, and 2C-K, 2M-P [87].

Type 1B LGMD, associated with LMNA deficiency, is clinically similar to Emery–Dreifuss muscular dystrophy (EDMD), differing primarily in the distribution of limb weakness. Cardiac involvement in LGMD1B shares characteristics with EDMD, including a high risk of sudden death (SD), which can even occur in the early stages of the disease [24].

10. Friedreich's Ataxia

Friedreich's ataxia (FRDA) is the most common autosomal recessive spinocerebellar ataxia, with a prevalence of approximately 1 in 50,000 live births. It is caused by a *GAA* trinucleotide repeat expansion in the *FXN* gene, leading to reduced levels of frataxin, a mitochondrial protein crucial for oxidative phosphorylation and iron–sulfur cluster assembly [29,85]. While FRDA primarily manifests as a neurodegenerative disorder alongside ataxia, dysarthria, and diabetes, cardiac involvement, particularly hypertrophic cardiomyopathy, is a significant cause of morbidity and mortality [88]. The early identification of cardiac disease is critical, as nearly all patients develop some degree of cardiomyopathy during their lifetime [4].

10.1. Cardiac Involvement

Cardiac manifestations in FRDA stem from mitochondrial dysfunction and iron dysregulation, resulting in oxidative stress, mitochondrial proliferation, and myocardial fibrosis [28]. The most common phenotype is concentric or asymmetric left ventricular hypertrophy (LVH), but progression to dilated cardiomyopathy (DCM) may occur in advanced stages [89]. Cardiac MRI frequently reveals late gadolinium enhancement, indicative of subclinical fibrosis, even before hypertrophy is clinically evident [90]. The severity of cardiac involvement correlates strongly with the *GAA* repeat length and earlier disease onset rather than the duration of the disease or the severity of neurological symptoms [88]. Dilated cardiomyopathy is less frequent but associated with poorer outcomes, including heart failure and sudden cardiac death. Management focuses on early detection and routine screening through echocardiography and cardiac MRI to monitor disease progression [91].

10.2. Electrocardiographic (ECG) Findings and Arrhythmias

ECG abnormalities are common in FRDA (Figure 6), with repolarization changes, particularly T-wave inversions in inferior and lateral leads, seen in approximately 85% of patients (Payne and Wagner, 2012 [27]). Conduction abnormalities, including bundle branch blocks, are present in 15% of cases. While atrial arrhythmias such as atrial fibrillation and flutter are infrequent, they often reflect advanced myocardial involvement rather than a primary arrhythmic substrate [88]. Ventricular arrhythmias are rare, with preserved QT intervals and normal QRS complexes suggesting a lower risk of ventricular tachyarrhythmias than other cardiomyopathies. The pathogenesis of arrhythmias is primarily linked to myocardial fibrosis and scarring, which disrupt electrical conduction. In severe cases, implantable cardioverter defibrillators (ICDs) may be considered to prevent sudden cardiac death, particularly in patients with significant left ventricular dysfunction or frequent arrhythmic events [4,83].

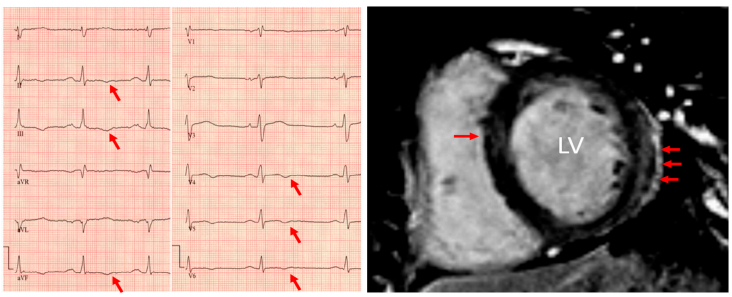

Figure 6. *Cont.*

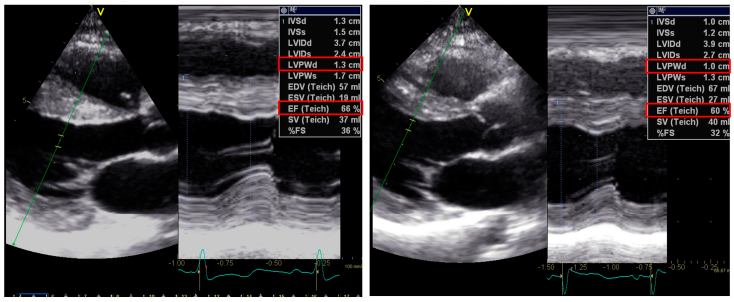

Figure 6. A typical example of a 26−year−old female Friedreich's ataxia patient with severe cardiomyopathy. **Left upper**: T−wave inversion observed on resting electrocardiography. **Right upper**: patchy late enhancement-positive regions in the left ventricle (LV), assessed by cardiac magnetic resonance imaging. **Left lower**: retrospective M-mode echocardiography showing LV hypertrophy with an end-diastolic wall thickness of 13 mm (ejection fraction = 66%). **Right lower**: M-mode echocardiography after 5 years of follow-up, showing a decrease in end-diastolic wall thickness to 10 mm (ejection fraction = 60%). In addition, hsTNT was elevated (16.5 ng/mL) in this patient [92].

11. Other Dystrophic Forms

In specific genetic mutations, skeletal muscle abnormalities are accompanied by cardiac complications, leading to an increased risk of arrhythmias. Examples include titin deficiency, which typically causes isolated dilated and hypertrophic cardiomyopathy; however, muscle alterations have also been reported in some African families. Desmin mutations are another example, often resulting in cardiomyopathy with diverse phenotypic expressions and, in some cases, associated muscle weakness [93].

12. Device Selection

Patients with neuromuscular diseases (NMDs) present a high risk of both bradyarrhythmias and tachyarrhythmias, although the arrhythmic profile varies across different conditions. Table 3 summarizes the most appropriate device type for each patient group. Dual-chamber devices are recommended to ensure atrial pacing in certain conditions, such as laminopathies and myotonic dystrophy. Conversely, in disorders like Emery–Dreifuss muscular dystrophy type 1 (EDMD1), 'electrical silence' may render the atrial lead unnecessary. In Duchenne and Becker muscular dystrophies, the use of a single- or dual-chamber device should be based on the individual patient's clinical presentation. Additionally, subcutaneous defibrillator implantation is generally contraindicated in NMD patients due to the potential need for pacing.

Table 3. Indications for a pacemaker and implantable defibrillator (ICD).

Disease	Indications for Pacemaker	Indications for Implantable Defibrillator (ICD)
Duchenne muscular dystrophy (DMD)	Second- or third-degree AV block [45,47]	LVEF < 35%, ventricular arrhythmias [32,43]
Becker muscular dystrophy (BMD)	Conduction disturbances e.g., AV block, right bundle branch block [34,38]	Ventricular arrhythmias, LVEF < 35% [38,94]
Myotonic dystrophy (DM1, DM2)	First-degree AV block with PR > 240 ms, bundle branch blocks [22,60]	ICD consideration for ventricular arrhythmias or heart failure [22,60]
Emery–Dreifuss muscular dystrophy (EDMD)	Severe bradycardia, second- or third-degree AV block [6,95]	Ventricular arrhythmias (especially in type 2), high incidence of sudden death [6,95]
Limb–girdle muscular dystrophy (LGMD)	AV block, atrioventricular conduction disturbances [7,55]	High risk of sudden death, need for monitoring for arrhythmias [7,55]
Friedreich's ataxia (FRDA)	Severe conduction defects, second- or third-degree AV block [4,27]	Ventricular arrhythmias, high risk of sudden cardiac death [4,28]

13. Role of Pharmacological Therapy, Gene Therapy, Heart Transplantation

Due to conduction disturbances, antiarrhythmic drugs must be carefully selected for patients with neuromuscular diseases (NMDs) [96]. Concerns have been raised about the safety of Vaughan–Williams class I antiarrhythmic drugs, particularly mexiletine, which is frequently used to treat myotonia in myotonic dystrophy type 1 (DM1). These drugs may exacerbate the loss of function in cardiac sodium channels, potentially increasing arrhythmia risk in DM1 patients. Specifically, the use of class IC drugs is discouraged due to their negative inotropic effects, as intravenous flecainide or ajmaline can trigger severe ventricular tachyarrhythmias or unmask a type 1 Brugada pattern in DM1 patients [97,98].

While data are limited, small studies showed mexiletine to be beneficial in treating myotonia without apparent arrhythmic complications or ECG changes, although the follow-up durations were short (7 weeks) [99,100]. Recent findings suggest that mexiletine (class IB) is safe in DM1 patients and does not increase the incidence of bradyarrhythmia. Class III drugs, such as amiodarone and ibutilide, appear safer, though further analysis is needed [101].

Reasonable safety monitoring strategies when initiating these drugs include inpatient telemetry or serial outpatient ECGs, especially for high-risk patients with baseline conduction disturbances (e.g., a prolonged PR interval or bundle branch block). The presence of a pacemaker (PM) or implantable cardioverter-defibrillator (ICD) may also affect monitoring needs. Inpatient monitoring may be preferred for those with conduction impairment, while outpatient monitoring may suffice for patients with normal baseline ECGs [102].

Clinical data on heart failure therapies in NMDs are limited. Antifibrotic therapies, including ACE inhibitors and angiotensin II receptor blockers, used either alone or in combination with beta-blockers or corticosteroids, have shown promise in slowing disease progression and improving cardiac function and survival in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) [103]. Selective aldosterone receptor antagonists also appear effective in providing cardiac protection in DMD [104]. Prospective studies are needed to determine the optimal timing and efficacy of standard and novel heart failure treatments for preventing or delaying myocardial impairment in NMDs [105].

Gene therapy represents a promising method of treating NMDs, correcting underlying genetic defects. Approaches include exon skipping, gene replacement, and RNA-targeted therapies. In DMD, adeno-associated virus (AAV) vectors, delivering microdystrophin, have shown potential in restoring muscle function and slowing disease progression [20]. Clinical trials, such as PF-06939926 (NCT03362502), SGT-001 (NCT03368742), and SRP-9001 (NCT03375164), are demonstrating improvements in muscle histology and function [106].

Antisense oligonucleotides (ASOs), such as eteplirsen, golodirsen, and viltolarsen, are approved for use against specific DMD mutations and have shown efficacy in promoting dystrophin production and clinical stability [6]. In DM1, ASOs target and neutralize toxic RNA, offering a new approach to the correction of abnormal RNA splicing associated with the disease [7].

Challenges remain, including delivering treatments effectively to skeletal and cardiac muscles, managing immune responses, and ensuring long-term safety. Ongoing research aims to optimize gene editing, improve vector design, and achieve sustained therapeutic benefits [107].

Heart transplantation is a viable option for selected NMD patients with end-stage heart failure. Two large case series suggest that MD patients undergoing cardiac transplantation experience similar intraoperative and postoperative outcomes to non-MD patients [99,100]. Most transplant recipients achieved successful rehabilitation with no observed graft dysfunction during follow-up, maintaining good performance status [20]. However, patient

selection by a multidisciplinary team is essential, considering the severity of cardiac involvement and the prognosis related to skeletal muscle and respiratory symptoms.

Special perioperative considerations include anaesthesia adaptations to prevent malignant hyperthermia and rhabdomyolysis and careful postoperative management to limit disease progression. Dosage adjustments of immunosuppressants, such as cyclosporine, are necessary to avoid secondary myopathy or rhabdomyolysis, reduce iatrogenic effects, and promote recovery.

Transplantation offers significant benefits for patients with severe dilated cardiomyopathy and refractory heart failure. It remains the treatment of choice for patients with advanced DCM and mild-to-moderate muscle impairment. Overcoming hesitancy in accepting MD-related cardiomyopathy patients for transplantation is crucial, and establishing specialized neuromuscular cardiology teams (NMCTs) has proven effective in evaluating and managing these complex cases [20].

14. Future Perspectives

The future of neuromuscular disease research holds promise for advancing treatment and improving patient outcomes. Gene therapy is one of the most anticipated avenues through which to correct the underlying genetic mutations. Ongoing studies explore gene replacement, exon skipping, and RNA-targeted therapies, particularly for diseases like Duchenne muscular dystrophy (DMD). Technologies that use adeno-associated virus (AAV) vectors to deliver therapeutic genes (such as microdystrophin) have shown encouraging results in terms of restoring muscle function. Additionally, antisense oligonucleotides (ASOs) have emerged as promising treatments for specific mutations, as they target toxic RNA aggregates linked to disease mechanisms, notably in cases of myotonic dystrophy.

Efforts to refine these therapies include optimizing delivery to both skeletal and cardiac muscle tissues, enhancing vector design, and managing immune responses to ensure long-term safety. Furthermore, advancements in regenerative medicine are being studied to address muscle atrophy and cardiac fibrosis. Multidisciplinary care teams are also being promoted to integrate genetic counseling and personalized medicine into treatment strategies to provide comprehensive care for NMD patients.

Cell culture and animal models are critical in understanding NMD pathophysiology and testing therapeutic strategies. In vitro models, such as muscle cell cultures derived from patient cells, enable researchers to observe cellular dysfunctions like dystrophin deficiency in real time. These models also allow us to investigate genetic therapies and antisense oligonucleotides in order to correct or reduce the genetic anomalies driving muscle degeneration.

In vivo, animal models, particularly murine models, are extensively used to replicate human NMDs. For example, mdx mice lack functional dystrophin and have been instrumental in studying DMD. These models provide insights into disease progression, muscle weakness, and cardiac involvement. They are also invaluable for testing potential gene therapies, evaluating immune responses, and studying cardiac arrhythmias, common complications in human NMD patients. Combined with cell culture systems, animal models help bridge the gap between basic research and clinical application, providing a foundation for developing targeted treatments for neuromuscular disorders.

15. Conclusions

Neuromuscular diseases (NMDs) are a group of hereditary disorders, affecting motor neurons, peripheral nerves, the neuromuscular junction, or skeletal muscles. Cardiac involvement is frequently observed, manifesting as cardiomyopathies or arrhythmias, including tachyarrhythmias and conduction defects. The mechanisms underlying cardiac

manifestations in NMDs remain incompletely understood. Still, they may involve myocardial and conduction system fibrosis, altered membrane permeability, excessive sympathetic activation, or material deposition in the conduction system in certain storage diseases.

Early diagnosis is crucial, as electrocardiographic abnormalities, conduction defects, or arrhythmias—particularly in patients with a family history of cardiomyopathy or sudden death—may indicate early genetically determined cardiomyopathy. Genetic testing provides valuable prognostic information, particularly for arrhythmic risk stratification, and informs the selection of appropriate treatments, which may extend beyond standard indications. In cases of severe dilated cardiomyopathy with refractory heart failure associated with muscular dystrophies, heart transplantation may offer a viable therapeutic option. A proactive, multidisciplinary, and personalized approach is essential to improving the prognosis and quality of life for patients with these complex conditions.

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Abbreviations

NMD	neuromuscular disease
ECG	electrocardiogram
DMD	Duchenne muscular dystrophy
BMD	Becker muscular dystrophy
LGMD	limb–girdle muscular dystrophy
EDMD	Emery–Dreifuss muscular dystrophy
FRDA	Friedreich's ataxia
HTx	heart transplant
AVB	atrioventricular nlock
EP	electrophysiology
MFM	myofibrillar myopathy
RCM	restrictive cardiomyopathy
DES	(desmin) MIM #*125660*
CRYAB	(Alpha-B Crystallin) MIM #*123590*
FLNC	(filamin C) MIM #*123590*
DMPK	(myotonic dystrophy protein kinase): MIM #*605377*
CAPN3	(calpain-3): MIM #*114240*
DYSF	(dysferlin): MIM **603009*
FKRP	(fukutin-related protein): MIM #*606596*
MYOT	(myotilin): MIM **604103*
ZNF9	(Zinc Finger Protein 9, also known as CNBP): MIM #*116955*
EMD	(Emerin): MIM #*300384*

FHL1	(Four and a Half LIM Domains 1): MIM #*300163*
OMIM	Online Mendelian Inheritance in Man
QT interval	Interval on ECG representing ventricular depolarization and repolarization
CPK	creatine phosphokinase
MRI	magnetic resonance imaging
ICD	implantable cardioverter-defibrillator
VT	ventricular tachycardia
VF	ventricular fibrillation
DM1/DM2	myotonic dystrophy type 1/type 2
PM	pacemaker
AF	atrial fibrillation
EPS	electrophysiological study
LVEF	left ventricular ejection fraction
CACNA1C	calcium voltage-gated channel subunit alpha1 C
SCN5A	sodium voltage-gated channel alpha Subunit 5
GJA1	gap junction protein alpha 1
HRS	Heart Rhythm Society
LMNA	(lamin A/C gene) OMIM *150330*
SD	sudden death
PVCs	premature ventricular contractions
CK	creatine kinase
SCD	sudden cardiac death
IC	ischemic cardiomyopathy
GFR	glomerular filtration rate
NMCT	neuromuscular cardiology team

References

1. Zecchin, M.; Calvanese, R.; Pignalberi, C.; Mascioli, G.; Bardari, S.; China, P.; Sgarrito, G.; Nesti, M.; A Nome Dell'area Aritmie dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). Aritmie e morte improvvisa nelle malattie neuromuscolari. *G. Ital. Di Cardiol.* **2021**, *22*, 466–479.
2. Nigro, G.; Politano, L.; Nigro, V.; Petretta, V.R.; Comi, L.I. Mutation of dystrophin gene and cardiomyopathy. *Neuromuscul. Disord.* **1994**, *4*, 371–379. [CrossRef] [PubMed]
3. Finsterer, J.; Stöllberger, C.; Maeztu, C. Sudden cardiac death in neuromuscular disorders. *Int. J. Cardiol.* **2016**, *203*, 508–515. [CrossRef] [PubMed]
4. Hanson, E.; Sheldon, M.; Pacheco, B.; Alkubeysi, M.; Raizada, V. Heart disease in Friedreich's ataxia. *World J. Cardiol.* **2019**, *11*, 1–12. [CrossRef]
5. Bushby, K.; Finkel, R.; Birnkrant, D.J.; E Case, L.; Clemens, P.R.; Cripe, L.; Kaul, A.; Kinnett, K.; McDonald, C.; Pandya, S.; et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Implementation of multidisciplinary care. *Lancet Neurol.* **2010**, *9*, 177–189. [CrossRef]
6. Meune, C.; Van Berlo, J.H.; Anselme, F.; Bonne, G.; Pinto, Y.M.; Duboc, D. Primary prevention of sudden death in patients with lamin A/C gene mutations. *N. Engl. J. Med.* **2006**, *354*, 209–210. [CrossRef]
7. Mah, J.K.; Korngut, L.; Dykeman, J.; Day, L.; Pringsheim, T.; Jette, N. A systematic review and meta-analysis on the epidemiology of the muscular dystrophies. *Can. J. Neurol. Sci.* **2016**, *43*, 163–177.
8. Groh, W.J. Arrhythmias in the muscular dystrophies. *Heart Rhythm.* **2012**, *9*, 1890–1895. [CrossRef]
9. Brodehl, A.; Hedde, P.N.; Dieding, M.; Fatima, A.; Walhorn, V.; Gayd, S.; Saric', T.; Klauke, B.; Gummert, J.; Anselmetti, D.; et al. Dual Color Photoactivation Localization Microscopy of Cardiomyopathy-associated Desmin Mutants. *J. Biol. Chem.* **2012**, *287*, 16047–16057. [CrossRef]
10. Udd, B.; Krahe, R. The Myotonic Dystrophies: Molecular, Clinical, and Therapeutic Challenge. *Lancet Neurol.* **2012**, *11*, 891–905.
11. Brodehl, A.; Gaertner-Rommel, A.; Milting, H. Molecular insights into cardiomyopathies associated with desmin (DES) mutations. Andreas Brodehl, Anna Gaertner-Rommel, Hendrik Milting. *Biophys. Rev.* **2018**, *10*, 983–1006. [CrossRef] [PubMed]
12. Brodehl, A.; Hain, C.; Flottmann, F.; Ratnavadivel, S.; Gaertner, A.; Klauke, B.; Kalinowski, J.; Körperich, H.; Gummert, J.; Paluszkiewicz, L.; et al. The desmin mutation DES-c.735G>C causes severe restrictive cardiomyopathy by inducing in-frame skipping of exon-3. *Biomedicines* **2021**, *9*, 1400. [CrossRef] [PubMed]

13. Brodehl, A.; Gaertner-Rommel, A.; Klauke, B.; Grewe, S.A.; Schirmer, I.; Peterschröder, A.; Faber, L.; Vorgerd, M.; Gummert, J.; Anselmetti, D.; et al. The novel αB-crystallin (CRYAB) mutation p.D109G causes restrictive cardiomyopathy. *HumanMutation* **2017**, *38*, 947–952.
14. Bermúdez-Jiménez, F.; Protonotarios, A.; García-Hernández, S.; Asensio, A.P.; Rampazzo, A.; Zorio, E.; Brodehl, A.; Arias, M.Á.; Macías-Ruiz, R.; Fernández-Armenta, J.; et al. Phenotype Clinical Outcomes in Desmin-Related Arrhythmogenic Cardiomyopathy Francisco. *Am. Coll. Cardiol. EP* **2024**, *10*, 1178–1190.
15. Vorgerd, M.; van der Ven Peter, F.M.; Bruchertseifer, V.; Löwe, T.; Kley, R.A.; Schröder, R.; Lochmüller, H.; Himmel, M.; Koehler, K.; Fürst, D.O.; et al. A mutation in the dimerization domain of filamin c causes a novel type of autosomal dominant myofibrillar myopathy. *Am. J. Hum. Genet.* **2005**, *77*, 297–304. [CrossRef]
16. Duff, R.M.; Tay, V.; Hackman, P.; Ravenscroft, G.; McLean, C.; Kennedy, P.; Steinbach, A.; Schöffler, W.; van der Ven, P.F.; Fürst, D.O.; et al. Mutations in the N-terminal actin-binding domain of filamin C cause a distal myopathy. *Am. J. Hum. Genet.* **2011**, *88*, 729–740. [CrossRef]
17. Valdés-Mas, R.; Gutiérrez-Fernández, A.; Gómez, J.; Coto, E.; Astudillo, A.; Puente, D.A.; Reguero, J.R.; Álvarez, V.; Morís, C.; León, D.; et al. Mutations in filamin C cause a new form of familial hypertrophic cardiomyopathy. *Nat. Commun.* **2014**, *5*, 5326. [CrossRef]
18. Golbus, J.R.; Puckelwartz, M.J.; Dellefave-Castillo, L.; Fahrenbach, J.P.; Nelakuditi, V.; Pesce, L.L.; Pytel, P.; McNally, E.M. Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy. *Circ. Cardiovasc. Genet.* **2014**, *7*, 751–759. [CrossRef]
19. Brodehl, A.; Ferrier, R.A.; Hamilton, S.J.; Greenway, S.C.; Brundler, M.A.; Yu, W.; Gibson, W.T.; McKinnon, M.L.; McGillivray, B.; Alvarez, N.; et al. Mutations in FLNC are Associated with Familial Restrictive Cardiomyopathy. *Hum. Mutat.* **2016**, *37*, 269–279. [CrossRef]
20. Politano, L. Is Cardiac Transplantation Still a Contraindication in Patients with Muscular Dystrophy-Related End-Stage Dilated Cardiomyopathy? A Systematic Review. *Int. J. Mol. Sci.* **2024**, *25*, 5289. [CrossRef]
21. Finsterer, J.; Stollberger, C.; Keller, H. Arrhythmia related work-up in hereditary myopathies. *J. Electrocardiol.* **2012**, *45*, 376. [CrossRef]
22. Groh, W.J.; Zipes, D.P. Neurologic disorders cardiovascular disease. In *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*; Mann, D.L., Zipes, D.P., Libby, P., Bonow, R.O., Eds.; Elsevier Saunders: Philadelphia, PA, USA, 2015; Volume 1890.
23. Finsterer, J.; Stöllberger, C. Primary myopathies and the heart. *Scand. Cardiovasc. J.* **2008**, *42*, 9–24. [CrossRef] [PubMed]
24. Ismail, H.; Raynor, E.; Zimetbaum, P. Neuromuscular disorders and the role of the clinical electrophysiologist. *JACC Clin. Electrophysiol.* **2017**, *3*, 1069–1079. [CrossRef]
25. Tracy, C.M.; Epstein, A.E.; Darbar, D.; Di Marco, J.P.; Dunbar, S.B.; Estes, N.A., 3rd; Ferguson, T.B., Jr.; Hammill, S.C.; Karasik, P.E.; Link, M.S.; et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am Coll. Cardiol.* **2012**, *60*, 1297. [CrossRef]
26. De Ambroggi, L.; Raisaro, A.; Marchiano, S.; Radice, S.; Meola, G. Cardiac involvement in patients with myotonic dystrophy: Characteristic features of magnetic resonance imaging. *Eur. Heart J.* **1995**, *16*, 1007. [CrossRef]
27. Payne, R.M.; Wagner, G.R. Cardiomyopathy in Friedreich ataxia: Clinical findings and research. *J. Child. Neurol.* **2012**, *27*, 1179–1186. [CrossRef]
28. Koeppen, A.H.; Ramirez, R.L.; Becker, A.B.; Bjork, S.T.; Levi, S.; Santambrogio, P.; Parsons, P.J.; Kruger, P.C.; Yang, K.X.; Feustel, P.J.; et al. The pathogenesis of cardiomyopathy in Friedreich ataxia. *PLoS ONE* **2015**, *10*, e0116396. [CrossRef]
29. Campuzano, V.; Montermini, L.; Lutz, Y.; Cova, L.; Hindelang, C.; Jiralerspong, S.; Trottier, Y.; Kish, S.J.; Faucheux, B.; Trouillas, P.; et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum. Mol. Genet.* **1997**, *6*, 1771–1780. [CrossRef]
30. Dent, K.M.; Dunn, D.M.; von Niederhausern, A.C.; Aoyagi, A.T.; Kerr, L.; Bromberg, M.B.; Hart, K.J.; Tuohy, T.; White, S.; den Dunnen, J.T.; et al. Improved molecular diagnosis of dystrophinopathies in an unselected clinical cohort. *Am. J. Med. Genet. A* **2005**, *134*, 295–298. [CrossRef]
31. Worton, R. Muscular dystrophies: Diseases of the dystrophin-glycoprotein complex. *Science* **1995**, *270*, 755–756. [CrossRef]
32. Kamdar, F.; Garry, D.J. Dystrophin-deficient cardiomyopathy. *J. Am. Coll. Cardiol.* **2016**, *67*, 2533–2546. [CrossRef] [PubMed]
33. Bushby, K.; Finkel, R.; Birnkrant, D.J.; Case, L.E.; Clemens, P.R.; Cripe, L.; Kaul, A.; Kinnett, K.; McDonald, C.; Pandya, S.; et al. Muscular dystrophy, part 1: Diagnosis and pharmacological and psychosocial management. *Lancet Neurol.* **2010**, *9*, 77–93. [CrossRef] [PubMed]
34. Romfh, A.; McNally, E.M. Cardiac assessment in Duchenne and Becker muscular dystrophies. *Curr. Heart Fail. Rep.* **2010**, *7*, 212–218. [CrossRef]
35. Florczyk-Soluch, U.; Polak, K.; Dulak, J. The multifaceted view of heart problem in Duchenne muscular dystrophy. *Cell. Mol. Life Sci.* **2021**, *78*, 5447–5468. [CrossRef]
36. Finsterer, J.; Stöllberger, C. Cardiac involvement in Becker muscular dystrophy. *Can. J. Cardiol.* **2008**, *24*, 786–792. [CrossRef]

37. Manning, G.W.; Cropp, G.J. The electrocardiogram in progressive muscular dystrophy. *Br. Heart J.* **1958**, *20*, 416–420. [CrossRef]
38. Takami, Y.; Takeshima, Y.; Awano, H.; Okizuka, Y.; Yagi, M.; Matsuo, M. High incidence of electrocardiogram abnormalities in young patients with Duchenne muscular dystrophy. *Pediatr. Neurol.* **2008**, *39*, 399–403. [CrossRef]
39. Simonds, A.K.; Muntoni, F.; Heather, S.; Fielding, S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* **1998**, *53*, 949–952. [CrossRef]
40. Yoo, W.H.; Cho, M.J.; Chun, P.; Kim, K.H.; Lee, J.S.; Shin, Y.B. The evolution of electrocardiographic changes in patients with Duchenne muscular dystrophies. *Korean J. Pediatr.* **2017**, *60*, 196–201. [CrossRef]
41. Yilmaz, A.; Gdynia, H.J.; Baccouche, H.; Mahrholdt, H.; Meinhardt, G.; Basso, C.; Thiene, G.; Sperfeld, A.D.; Ludolph, A.C.; Sechtem, U. Cardiac involvement in patients with Becker muscular dystrophy: New diagnostic and pathophysiological insights by a CMR approach. *J. Cardiovasc. Magn. Reson.* **2008**, *10*, 50. [CrossRef]
42. Markham, L.W.; Michelfelder, E.C.; Border, W.L.; Khoury, P.R.; Spicer, R.L.; Wong, B.L.; Benson, D.W.; Cripe, L.H. Abnormalities of diastolic function precede dilated cardiomyopathy associated with Duchenne muscular dystrophy. *J. Am. Soc. Echocardiogr.* **2006**, *19*, 865–871. [CrossRef] [PubMed]
43. Silva, M.C.; Meira, Z.M.A.; Giannetti, J.G.; da Silva, M.M.; Campos, A.F.O.; Barbosa, M.d.M.; Filho, G.M.S.; Ferreira, R.d.A.; Zatz, M.; Rochitte, C.E. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. *J. Am. Coll. Cardiol.* **2007**, *49*, 1874–1879. [CrossRef] [PubMed]
44. Ho, R.; Nguyen, M.L.; Mather, P. Cardiomyopathy in Becker muscular dystrophy: Overview. *World J. Cardiol.* **2016**, *26*, 356–361. [CrossRef] [PubMed] [PubMed Central]
45. Frankel, K.A.; Rosser, R.J. The pathology of the heart in progressive muscular dystrophy: Epimyocardial fibrosis. *Human. Pathol.* **1976**, *7*, 375–386.45. [CrossRef]
46. Nomura, H.; Hizawa, K. Histopathological study of the conduction system of the heart in Duchenne progressive muscular dystrophy. *Acta Pathol. Jpn.* **1982**, *32*, 1027–1033. [CrossRef]
47. Thrush, P.T.; Allen, H.D.; Viollet, L.; Mendell, J.R. Re-examination of the electrocardiogram in boys with Duchenne muscular dystrophy and correlation with its dilated cardiomyopathy. *Am. J. Cardiol.* **2009**, *103*, 262–265. [CrossRef]
48. Brignole, M.; Auricchio, A.; Baron-Esquivias, G.; Bordachar, P.; Boriani, G.; Breithardt, O.-A.; Cleland, J.G.F.; Deharo, J.-C.; Delgado, V.; Elliott, P.M.; et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur. Heart. J.* **2013**, *34*, 2281–2329.
49. Stojanovic, V.R.; Peric, S.; Paunic, T.; Pavlovic, S.; Cvitan, E.; Basta, I.; Peric, M.; Milicev, M.; Lavrnic, D. Cardiologic predictors of sudden death in patients with myotonic dystrophy type 1. *J. Clin. Neurosci.* **2013**, *20*, 1002–1006. [CrossRef]
50. Benhayon, D.; Lugo, R.; Patel, R.; Carballeira, L.; Elman, L.; Cooper, J.M. Long-term arrhythmia follow-up of patients with myotonic dystrophy. *J. Cardiovasc. Electrophysiol.* **2015**, *26*, 305–310. [CrossRef]
51. Ha, A.H.; Tarnopolsky, M.A.; Bergstra, T.G.; Nair, G.M.; Al-Qubbany, A.; Healey, J.S. Predictors of atrioventricular conduction disease, long-term outcomes in patients with myotonic dystrophy types I and II. *Pacing Clin. Electrophysiol.* **2012**, *35*, 1262–1269. [CrossRef]
52. Nguyen, H.H.; Wolfe, J.T.; Holmes, D.R.; Edwards, W.D. Pathology of the cardiac conduction system in myotonic dystrophy: A study of 12 cases. *J. Am. Coll. Cardiol.* **1988**, *11*, 662–671. [CrossRef] [PubMed]
53. Petri, H.; Vissing, J.; Witting, N.; Bundgaard, H.; Køber, L. Cardiac manifestations of myotonic dystrophy type 1. *Int. J. Cardiol.* **2012**, *160*, 82–88. [CrossRef]
54. Groh, W.J.; Groh, M.R.; Saha, C.; Kincaid, J.C.; Simmons, Z.; Ciafaloni, E.; Pourmand, R.; Otten, R.F.; Bhakta, D.; Nair, G.V.; et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N. Engl. J. Med.* **2008**, *358*, 2688–2697. [CrossRef] [PubMed]
55. Wahbi, K.; Meune, C.; Bécane, H.M.; Laforêt, P.; Bassez, G.; Lazarus, A.; Radvanyi-Hoffman, H.; Eymard, B.; Duboc, D. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: A case-control study. *Neuromuscul. Disord.* **2009**, *19*, 468–472. [CrossRef] [PubMed]
56. Maury, P.; Audoubert, M.; Cintas, P.; Rollin, A.; Duparc, A.; Mondoly, P.; Chiriac, A.-M.; Acket, B.; Zhao, X.; Pasquié, J.L.; et al. Prevalence of type 1 Brugada ECG pattern after administration of Class 1C drugs in patients with type 1 myotonic dystrophy: Myotonic dystrophy as a part of the Brugada syndrome. *Heart Rhythm.* **2014**, *11*, 1721–1727. [CrossRef]
57. Russo, V.; Papa, A.A.; Rago, A.; Ciardiello, C.; Marano, M.; Proietti, R.; Politano, L.; Nigro, G. Interatrial block to predict atrial fibrillation in myotonic dystrophy type 1. *Neuromuscul. Disord.* **2018**, *28*, 327–333. [CrossRef]
58. Lazarus, A.; Varin, J.; Babuty, D.; Anselme, F.; Coste, J.; Duboc, D. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: A multicenter diagnostic pacemaker study. *J. Am. Coll. Cardiol.* **2002**, *40*, 1645–1652. [CrossRef]
59. Laurent, V.; Pellieux, S.; Corcia, P.; Magro, P.; Pierre, B.; Fauchier, L.; Raynaud, M.; Babuty, D. Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices. *Int. J. Cardiol.* **2011**, *150*, 54–58. [CrossRef]

60. Wahbi, K.; Babuty, D.; Probst, V.; Wissocque, L.; Labombarda, F.; Porcher, R.; Bécane, H.M.; Lazarus, A.; Béhin, A.; Laforêt, P.; et al. Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. *Eur. Heart J.* **2017**, *38*, 751–758. [CrossRef]
61. Siméon, E.; Patier-Dussauge, A.; Bernard-Brunet, A.; Clémenty, N.; Gouraud, J.-B.; Guyomarch, B.; Magot, A.; Probst, V.; Babuty, D. Insufficiency of electrocardiogram alone in predicting infrahisian abnormalities in patients with type 1 myotonic dystrophy. *Int. J. Cardiol.* **2014**, *172*, 625–627. [CrossRef]
62. Bhakta, D.; Shen, C.; Kron, J.; Epstein, A.E.; Pascuzzi, R.M.; Groh, W.J. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. *J. Cardiovasc. Electrophysiol.* **2011**, *22*, 1369–1375. [CrossRef] [PubMed]
63. Glikson, M.; Nielsen, J.C.; Kronborg, M.B.; Michowitz, Y.; Auricchio, A.; Barbash, I.M.; Barrabés, J.A.; Boriani, G.; Braunschweig, F.; Brignole, M.; et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur. Heart J.* **2021**, *42*, 3427–3520. [CrossRef] [PubMed]
64. Priori, S.G.; Blomström-Lundqvist, C. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur. Heart J.* **2015**, *36*, 2757–2759. [CrossRef] [PubMed]
65. Nikhanj, A.; Sivakumaran, S.; Miskew-Nichols, B.; Siddiqi, Z.A.; Oudit, G.Y. Ventricular tachycardia in patients with type 1 myotonic dystrophy: A case series. *Eur. Heart J. Case Rep.* **2019**, *3*, 2. [CrossRef]
66. Bonne, G.; France, L.; Rabah, B.Y. *Emery-Dreifuss Muscular Dystrophy*; Adam, M.P., Feldman, J., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 2004.
67. Cartegni, L.; di Barletta, M.R.; Barresi, R.; Squarzoni, S.; Sabatelli, P.; Maraldi, N.; Mora, M.; Di Blasi, C.; Cornelio, F.; Merlini, L.; et al. Heart-specific localization of Emerin: New insights into Emery-Dreifuss muscular dystrophy. *Hum. Mol. Genet.* **1997**, *6*, 2257–2264. [CrossRef]
68. Buckley, A.E.; Dean, J.; Mahy, I.R. Cardiac involvement in Emery Dreifuss muscular dystrophy: A case series. *Heart* **1999**, *82*, 105–108. [CrossRef]
69. Sabatelli, P.; Squarzoni, S.; Petrini, S.; Capanni, C.; Ognibene, A.; Cartegni, L.; Cobianchi, F.; Merlini, L.; Toniolo, D.; Maraldi, N.M. Oral exfoliative cytology for the non-invasive diagnosis in X-linked Emery-Dreifuss muscular dystrophy patients and carriers. *Neuromuscul. Disord.* **1998**, *8*, 67–71. [CrossRef]
70. Boriani, G.; Gallina, M.; Merlini, L.; Bonne, G.; Toniolo, D.; Amati, S.; Biffi, M.; Martignani, C.; Frabetti, L.; Bonvicini, M.; et al. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: A long-term longitudinal study. *Stroke* **2003**, *34*, 901–908. [CrossRef]
71. Steckiewicz, R.; Stolarz, P.; Świętoń, E.; Madej-Pilarczyk, A.; Grabowski, M.; Marchel, M.; Pieniak, M.; Filipiak, K.J.; Hausmanowa-Petrusewicz, I.; Opolski, G. Cardiac pacing in 21 patients with Emery-Dreifuss muscular dystrophy: A single-centre study with a 39-year follow-up. *Kardiol. Pol.* **2016**, *74*, 576–583. [CrossRef]
72. Finsterer, J.; Stöllberger, C.; Sehnal, E.; Rehder, H.; Laccone, F. Dilated, arrhythmogenic cardiomyopathy in Emery-Dreifuss muscular dystrophy due to the Emerin splice-site mutation c.449 + 1G>A. *Cardiology* **2015**, *130*, 48–51. [CrossRef]
73. Emery, A.E. Emery-Dreifuss muscular dystrophy—A 40 year retrospective. *Neuromuscul. Disord.* **2000**, *10*, 228–232. [CrossRef] [PubMed]
74. Wang, S.; Peng, D. Cardiac involvement in Emery-Dreifuss muscular dystrophy and related management strategies. *Int. Heart J.* **2019**, *60*, 12–18. [CrossRef] [PubMed]
75. Taylor, M.R.; Fain, P.R.; Sinagra, G.; Robinson, M.L.; Robertson, A.D.; Carniel, E.; Di Lenarda, A.; Bohlmeyer, T.J.; A Ferguson, D.; Brodsky, G.L.; et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. *J. Am. Coll. Cardiol.* **2003**, *41*, 771–780. [CrossRef]
76. Pasotti, M.; Klersy, C.; Pilotto, A.; Marziliano, N.; Rapezzi, C.; Serio, A.; Mannarino, S.; Gambarin, F.; Favalli, V.; Grasso, M.; et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. *J. Am. Coll. Cardiol.* **2008**, *52*, 1250–1260. [CrossRef]
77. Peretto, G.; Di Resta, C.; Perversi, J.; Forleo, C.; Maggi, L.; Politano, L.; Barison, A.; Previtali, S.C.; Carboni, N.; Brun, F.; et al. Cardiac and neuromuscular features of patients with LMNA-related cardiomyopathy. *Ann. Intern. Med.* **2019**, *171*, 458–463. [CrossRef]
78. Van Berlo, J.H.; de Voogt, W.G.; van der Kooi, A.J.; van Tintelen, J.P.; Bonne, G.; Yaou, R.B.; Duboc, D.; Rossenbacker, T.; Heidbüchel, H.; de Visser, M.; et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: Do lamin A/C mutations portend a high risk of sudden death? *J. Mol. Med.* **2005**, *83*, 79–83. [CrossRef]
79. Gigli, M.; Merlo, M.; Graw, S.L.; Barbati, G.; Rowland, T.J.; Slavov, D.B.; Stolfo, D.; Haywood, M.E.; Ferro, M.D.; Altinier, A.; et al. Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J. Am. Coll. Cardiol.* **2019**, *74*, 1480–1490. [CrossRef]
80. Van Tintelen, J.P.; Hofstra, R.M.W.; Katerberg, H.; Rossenbacker, T.; Wiesfeld, A.C.P.; du Marchie Sarvaas, G.J.; Wilde, A.A.M.; van Langen, I.M.; Nannenberg, E.A.; van der Kooi, A.J.; et al. High yield of LMNA mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. *Am. Heart J.* **2007**, *154*, 1130–1139. [CrossRef]

81. Van Rijsingen, I.A.; Arbustini, E.; Elliott, P.M.; Mogensen, J.; Hermans-van Ast, J.F.; van der Kooi, A.J.; van Tintelen, J.P.; van den Berg, M.P.; Pilotto, A.; Pasotti, M.; et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: A European cohort study. *J. Am. Coll. Cardiol.* **2012**, *59*, 493–500. [CrossRef]
82. Al-Khatib, S.M.; Stevenson, W.G.; Ackerman, M.J.; Gillis, A.M.; Bryant, W.J.; Hlatky, M.A.; Callans, D.J.; Granger, C.B.; Curtis, A.B.; Hammill, S.C.; et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* **2017**, *138*, e272–e391.
83. Van Rijsingen, I.A.; Bakker, A.; Azim, D.; Ast, J.F.H.-V.; van der Kooi, A.J.; van Tintelen, J.P.; Berg, M.P.v.D.; Christiaans, I.; Deprez, R.H.L.D.; Wilde, A.A.; et al. Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. *Int. J. Cardiol.* **2013**, *168*, 472–477. [CrossRef] [PubMed]
84. Anselme, F.; Moubarak, G.; Savouré, A.; Godin, B.; Borz, B.; Drouin-Garraud, V.; Gay, A. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. *Heart Rhythm.* **2013**, *10*, 1492–1498. [CrossRef]
85. Pandolfo, M.; Pastore, A. The pathogenesis of Friedreich ataxia and the structure and function of frataxin. *J. Neurol.* **2009**, *256* (Suppl. S1), 9–17. [CrossRef] [PubMed]
86. Kato, K.; Takahashi, N.; Fujii, Y.; Umehara, A.; Nishiuchi, S.; Makiyama, T.; Ohno, S.; Horie, M. LMNA cardiomyopathy detected in Japanese arrhythmogenic right ventricular cardiomyopathy cohort. *J. Cardiol.* **2016**, *68*, 346–351. [CrossRef]
87. Narayanaswami, P.; Weiss, M.; Selcen, D.; David, W.; Raynor, E.; Carter, G.; Wicklund, M.; Barohn, R.J.; Ensrud, E.; Griggs, R.C.; et al. Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology* **2014**, *83*, 1453–1463.
88. Pousset, F.; Legrand, L.; Monin, M.L.; Ewenczyk, C.; Charles, P.; Komajda, M.; Brice, A.; Pandolfo, M.; Isnard, R.; Tezenas du Montcel, S.; et al. A 22-Year Follow-up Study of Long-term Cardiac Outcome and Predictors of Survival in Friedreich Ataxia. *JAMA Neurol.* **2015**, *72*, 1334–1341. [CrossRef]
89. Weidemann, F.; Scholz, F.; Florescu, C.; Liu, D.; Hu, K.; Herrmann, S.; Ertl, G.; Störk, S. Heart involvement in Friedreich's ataxia. *Herz* **2015**, *40* (Suppl. S1), 85–90. [CrossRef]
90. Raman, S.V.; Dickerson, J.A.; Al-Dahhak, R. Myocardial ischemia in the absence of epicardial coronary artery disease in Friedreich's ataxia. *J. Cardiovasc. Magn. Reson.* **2008**, *10*, 15. [CrossRef]
91. Corben, L.A.; Lynch, D.; Pandolfo, M.; Schulz, J.B.; Delatycki, M.B.; Clinical Management Guidelines Writing Group. Consensus clinical management guidelines for Friedreich ataxia. *Orphanet J. Rare Dis.* **2014**, *9*, 184. [CrossRef]
92. Weidemann, F.; Liu, D.; Hu, K.; Florescu, C.; Niemann, M.; Herrmann, S.; Kramer, B.; Klebe, S.; Doppler, K.; Üçeyler, N.; et al. The cardiomyopathy in Friedreich's ataxia—new biomarker for staging cardiac involvement. *Int. J. Cardiol.* **2015**, *194*, 50–57. [CrossRef]
93. Sinagra, G.; Camerini, F.; Fabris, E. Cardiomyopathies and skeletal muscle involvement. In *Genetic Cardiomyopathies. A Clinical Approach*; Sinagra, G., Mestroni, L., Camerini, F., Eds.; Springer: Milano, Italy, 2013; pp. 25–42.
94. Hoogerwaard, E.M.; de Voogt, W.G.; Wilde, A.A.; van der Wouw, P.A.; Bakker, E.; van Ommen, G.J.B.; de Visser, M. Evolution of cardiac abnormalities in Becker muscular dystrophy over a 13-year period. *J. Neurol.* **1997**, *244*, 657–663. [CrossRef] [PubMed]
95. Boriani, G.; Gasparini, M.; Landolina, M.; Lunati, M.; Proclemer, A.; Lonardi, G.; Iacopino, S.; Rahue, W.; Biffi, M.; DiStefano, P.; et al. Incidence and clinical relevance of uncontrolled ventricular rate during atrial fibrillation in heart failure patients treated with cardiac resynchronization therapy. *Eur. J. Heart Fail.* **2011**, *13*, 868–876. [CrossRef] [PubMed]
96. Merino, J.L.; Peinado, R. Arrhythmias associated with neuromuscular disorders. *Card. Electrophysiol. Rev.* **2002**, *6*, 132–135. [CrossRef] [PubMed]
97. Otten, R.F.; Scherschel, J.A.; Lopshire, J.C.; Bhakta, D.; Pascuzzi, R.M.; Groh, W.J. Arrhythmia exacerbation after sodium channel blockade in myotonic dystrophy type 1. *Muscle Nerve.* **2009**, *40*, 901–902. [CrossRef]
98. Wahbi, K.; Algalarrondo, V.; Bécane, H.M.; Fressart, V.; Beldjord, C.; Azibi, K.; Lazarus, A.; Berber, N.; Radvanyi-Hoffman, H.; Stojkovic, T.; et al. Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. *Arch. Cardiovasc. Dis.* **2013**, *106*, 635–643. [CrossRef]
99. Kwiecinski, H.; Ryniewicz, B.; Ostrzycki, A. Treatment of myotonia with antiarrhythmic drugs. *Acta Neurol. Scand.* **1992**, *86*, 371–375. [CrossRef]
100. Logigian, E.; Martens, W.; Moxley, R.; McDermott, M.; Dilek, N.; Wiegner, A.; Pearson, A.; Barbieri, C.; Annis, C.; Thornton, C. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology* **2010**, *74*, 1441–1448. [CrossRef]
101. Heatwole, C.; Luebbe, E.; Rosero, S.; Eichinger, K.; Martens, W.; Hilbert, J.; Dekdebrun, J.; Dilek, N.; Zizzi, C.; Johnson, N.; et al. Mexiletine in Myotonic Dystrophy Type 1: A Randomized, Double-Blind, Placebo-Controlled Trial. *Neurology* **2021**, *96*, e228–e240, Erratum in *Neurology* **2024**, *102*, e207915. [CrossRef]

102. Vio, R.; Zorzi, A.; Bello, L.; Bozzoni, V.; Botta, A.; Rivezzi, F.; Leoni, L.; Migliore, F.; Bertaglia, E.; Iliceto, S.; et al. Evaluation of mexiletine effect on conduction delay and bradyarrhythmic complications in patients with myotonic dystrophy type 1 over long-term follow-up. *Heart Rhythm.* **2020**, *17*, 1944–1950. [CrossRef]
103. Russo, V.; Papa, A.A.; Williams, E.A.; Rago, A.; Palladino, A.; Politano, L.; Nigro, G. ACE inhibition to slow progression of myocardial fibrosis in muscular dystrophies. *Trends Cardiovasc. Med.* **2018**, *28*, 330–337. [CrossRef]
104. Raman, S.V.; Hor, K.N.; Mazur, W.; He, X.; Kissel, J.T.; Smart, S.; McCarthy, B.; Roble, S.L.; Cripe, L.H. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: Results of a two-year open-label extension trial. *Orphanet J. Rare Dis.* **2017**, *12*, 39. [CrossRef] [PubMed]
105. Russo, V.; Sperlongano, S.; Gallinoro, E.; Rago, A.; Papa, A.A.; Golino, P.; Politano, L.; Nazarian, S.; Nigro, G. Prevalence of left ventricular systolic dysfunction in myotonic dystrophy type 1: A systematic review. *J. Card. Fail.* **2020**, *26*, 849–856. [CrossRef] [PubMed]
106. Laugel, V.; De Lucia, S.; Davion, J.; Daniele, N.; Cao, F.; Sanz, M.; Buscara, L.; Blaie, S.; Thibaut, L.; Sagot, M.; et al. 410P GNT0004, Genethon's AAV8 vector-delivered microdystrophin gene therapy of Duchenne muscular dystrophy, first data of the phase I/II part of the GNT-016-MDYF all-in-one clinical trial in ambulant boys. *Neuromuscul. Disord.* **2024**, *43* (Suppl. S1), 104441.281. [CrossRef]
107. Xu, L.; Yao, S.; Ding, Y.E.; Xie, M.; Feng, D.; Sha, P.; Tan, L.; Bei, F.; Yao, Y. Designing and optimizing AAV-mediated gene therapy for neurodegenerative diseases: From bench to bedside. *J. Transl. Med.* **2024**, *22*, 866. [CrossRef] [PubMed]

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