Published in final edited form as:
Exp Neurol. 2014 March ; 253: 28–30. doi:10.1016/j.expneurol.2013.12.005.

Nondystrophic Myotonia: Challenges and Future Directions

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Abstract

Non-dystrophic myotonias are rare diseases caused by mutations in skeletal muscle chloride and sodium ion channels with considerable phenotypic overlap between diseases. Common symptoms include muscle stiffness, transitory weakness, fatigue, and pain. Although seldom life-shortening, these myotonias cause life-time disability and affected individuals cannot perform many daily activities. A notable feature of the recessive form of chloride channelopathies is the presence of transient weakness. While there has been considerable progress in skeletal muscle channelopathies with regards to identifying biophysical abnormalities, the mechanism of transient weakness remains unclear. A recent study published in Experimental Neurology (Desaphy *et al.* , 2013) explored this question further by comparing the biophysical properties of 3 chloride channel mutations associated with recessive myotonia congenita, with varying susceptibility to transient weakness. The authors identified a variety of functional defects in channel behavior among the 3 mutations, suggesting that this variability contributes to (Jaya, just a suggested change. Even with this study, we are far from understanding the basis of transient weakness. That said, “explains” is probably too strong) the differing phenotypes among chloride channelopathies. This commentary discusses nondystrophic myotonias, the results of Desaphy et al., and the treatment challenges in this rare disease.

Keywords

non-dystrophic myotonia; SCN4A; CLCN1; myotonia; paramyotonia

Introduction

Skeletal muscle channelopathies, in particular non-dystrophic myotonias (NDM), represent one of the first known examples and best studied ion channelopathies of man (Fahlke, 2000). However, there is major genotypic and phenotypic heterogeneity of these disorders, the mechanism of which is not entirely clear. The differences in phenotypic expression are believed to be due to specific differences in the behavior of mutant channels. Functional characterization of the channels is important in not only distinguishing a benign polymorphism from a true mutation, but also in understanding the behavior of different

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mutations. Desaphy and colleagues have described the biophysical abnormalities of 3 recessively inherited chloride channel mutations from patients with different clinical and neurophysiologic phenotypes (G190S, F167L, and A531V) (Desaphy *et al.* , 2013; Fahlke, 2000). They performed expression studies in HEK293 cells and identified differences in chloride currents in all 3 mutations. They postulate that these varying abnormalities are responsible for the different phenotypes in recessive myotonic congenita. Their study adds to our understanding of disease mechanisms in this rare disease with ultimate goal being to identify better treatment strategies in this rare but remarkably interesting disease. In this paper, we review their findings in relevance to phenotypic variability in myotonia congenita.

Non-dystrophic Myotonias

Non-dystrophic Myotonias (NDM) are rare with a prevalence < 1:100,000 (Emery, 1991; Pinessi *et al.* , 1982). They are caused by mutations in the skeletal muscle sodium (SCN4A) and chloride (CLCN1) channels and include the classic diseases myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis with myotonia, and a diverse group of sodium channel myotonias (Cannon, 2006; Emery, 1991; Fialho *et al.* , 2007; Hoffman and Wang, 1993; Lehmann-Horn and Rudel, 1996; Pinessi *et al.* , 1982; Ptacek *et al.* , 1991; Sun *et al.* , 2001).The most characteristic symptom is muscle stiffness generated by voluntary movement. Other notable features include percussion myotonia elicited by mechanical stimulation of the thenar eminence or extensor digitorium communis.

Patients with MC have a muscular appearance, action myotonia, and percussion myotonia (Streib, 1987). Stiffness is worse after rest, and improves with repeated activity – the “warm up” phenomenon. The most common site of stiffness is the legs while the face is less commonly affected (Trivedi *et al.* , 2013). Inheritance is dominant (Thomsen's disease) or recessive (Becker's disease) with a more severe phenotype in the latter (Colding-Jorgensen, 2005; Fialho *et al.* , 2007; Raja Rayan and Hanna, 2010). Patients with recessive MC classically have transient weakness that improves with exercise. This transient weakness, mechanism of which is not clear, is unique to MC and is not seen in sodium channel mutations (Trip *et al.* , 2009).

Cold-induced, prolonged, painful myotonia, and episodic weakness are the hallmarks of PMC (Cannon, 2006; Matthews *et al.* , 2010; Miller *et al.* , 2004; Ptacek *et al.* , 1993). Muscle activity often aggravates the myotonia associated with PMC (termed paradoxical myotonia). In contrast to myotonia congenita, facial stiffness and eye closure myotonia are more common in PMC; paradoxical eye closure myotonia is exclusively seen in PMC (Trivedi *et al.* , 2013). Muscle weakness in PMC can last from several hours to 2 days whereas it may last only seconds to minutes in MC (Fontaine, 1993).

The SCMs include acetazolamide-responsive myotonia, myotonia fluctuans, and myotonia permanens; common features include potassium aggravation and cold insensitivity - thus grouped as potassium-aggravated myotonias. Warm up phenomenon can be seen which often leads to confusion with myotonia congenita.

Pathophysiology

Bryant and colleagues demonstrated a greatly diminished sarcolemmal chloride conductance in affected muscle fibers from myotonic goats and this has been established as the basis for the enhanced muscle excitability in myotonia congenita (Bryant and Morales-Aguilera, 1971). In the absence of the chloride conductance, the repolarizing influence of the chloride current is lost and the length constant of the sarcolemma is significantly increased (Bryant and Morales-Aguilera, 1971). Therefore, elevations of the potassium concentration in the T-tubular lumen during electrical activity cause a greater depolarized shift in the resting potential of the sarcolemmal membrane, which leads to muscle hyperexcitability and myotonic discharges (Adrian and Bryant, 1974). Distinct allelic mutations in CLCN1 have been identified in a large number of autosomal dominant and autosomal recessive myotonia congenita cases (George *et al.* , 1993; Koch *et al.* , 1992). Several CLCN1 mutations have been reported to cause both autosomal dominant and autosomal recessive forms in different families (George *et al.* , 1994; Meyer-Kleine *et al.* , 1995; Papponen *et al.* , 1999; Sun *et al.* , 2001; Zhang *et al.* , 1996). Over 100 mutations in the CLCN1 gene have been identified thus far (Matthews *et al.* , 2010).

CLC-1 channel

The chloride channel ClC-1 exists as a homodimer with each individual subunit forming a gated pore. The channel has two main gating modes referred to as the fast gate, which can operate the two pores independently, and the slow gate, which regulates the open probability of both pores simultaneously (Saviane *et al.* , 1999). The dominant forms of MC occur due to effects of the mutated subunit when dimerized with the wild type (WT) subunit (dominant negative effect) whereas recessive MC occurs due to loss of function of the mutated subunit (Pusch *et al.* , 1995). Recessive mutations are more common than dominant mutations. Recessive mutations often result in a complete loss of the protein, impaired transport to the membrane, or inability to form dimers (Fialho *et al.* , 2007; Papponen *et al.* , 2008). ClC-1 subunits encoded by some recessively inherited CLCN1 mutations are able to form functional channels. Moreover, the biophysical properties for some of these mutant channels are indistinguishable from WT (e.g. F167L in the paper by Desaphy et al.).

Do differing chloride currents explain varying phenotypes in recessive MC?

The study by Desaphy and colleagues is an extension of their clinical electrophysiologic work showing a transient decrease in compound muscle action potential (CMAP) in most (66%) patients with recessive MC (Modoni *et al.* , 2011). Three ClC-1 mutations associated with recessive MC were selected for functional studies in the HEK cell expressions system. A comprehensive set of voltage-clamp studies was performed, which characterized the chloride current density, current-voltage behavior, and the voltage-dependent kinetics of channel gating. Importantly, these studies included recordings with physiological levels of internal chloride (4 mM) as well as the common practice of using high internal chloride (134 mM) to enhance current amplitudes. The G190S mutation, associated with pronounced CMAP depression (>50%), had a large positive shift in the voltage-dependence of activation, as has been reported for mutations in dominantly inherited MC (Pusch *et al.* , 1995). Conversely, no significant functional defect was identified for F167L mutant

channels, and patients did not have CMAP depression. The third mutation, A531V, was a mixed story with a reduction of current amplitude and variable CMAP depression. This work demonstrates that variations in the specific functional defects of a ClC-1 mutation are associated with variations in the clinical phenotype. Much remains to be done, however, with regard to establishing a mechanistic understanding. A large depolarized shift for the voltage-dependence of activation has been observed for several mutations (e.g. I290M or P480L in the Thompson family, G190S this study) and yet the clinical phenotype is variable with dominant (I290M, P480L) or recessive (G190S) inheritance and variability in susceptibility to transitory weakness and CMAP depression. Moreover, the F167L mutation had no identified functional defect in the HEK cell expression studies, and yet this is a common cause of recessive MC with variable effects on CMAP decrement. These variations illustrate the challenges that lie ahead in establishing a causal relationship between a particular class of functional defect in ClC-1 behavior and a specific clinical phenotype.

Therapeutic Options and Challenges in NDM

There is no FDA-approved treatment for NDM at this time. NDM patients experience constant, life-long symptoms and their impact on quality of life is comparable to that of some muscular dystrophies (Rose *et al.* , 2012; Sansone *et al.* , 2012). Physicians rely on off-label use of anti-epileptic, anesthetic, and anti-arrhythmic drugs to treat myotonia. Anecdotal data support the use of quinine (Leyburn and Walton, 1959), procainamide (Griggs *et al.* , 1975; Leyburn and Walton, 1959), and phenytoin (Griggs *et al.* , 1975) in patients with myotonia. There is also evidence for class 1B antiarrhythmics, tocainide and mexiletine, which may be more effective than quinine, procainamide, or phenytoin for autosomal recessive myotonia and paramyotonia congenita (Kwiecinski *et al.* , 1992; Streib, 1987). In a prospective multinational NDM study, about 40% patients were not on any anti-myotonic treatment (Trivedi *et al.* , 2013). A Cochrane review concluded that there was insufficient data to consider any treatment safe and effective in NDM (Trip *et al.* , 2006). However, challenges in performing randomized controlled trials in NDM include the rarity of this disorder and the genetic heterogeneity.The NIH-funded Rare Disease Clinical Research Network (CINCH) offered an unprecedented opportunity to study this rare disease using a common infrastructure, data elements, and centralized training. Through this mechanism, a therapeutic trial demonstrated that mexiletine significantly reduced stiffness, in addition to improving severity of graded myotonia on electromyography and quality of life measures in NDM (Statland *et al.* , 2012). However, 15% subjects experienced GI side effects and a third of the subjects had suboptimal or no response. Use of mexiletine is further limited by a black box warning about increased mortality in asymptomatic non life-threatening ventricular arrhythmias in patients who had a myocardial infarction more than six days but less than two years previously.

Other potential anti-myotonic drugs include lacosamide and ranolazine. Lacosamide, approved for use in partial epilepsy, has a distinct mechanism of action in that it enhances slow inactivation of sodium channels in contrast to other anti-myotonic agents which affect fast inactivation (Errington *et al.* , 2008). Preliminary (unpublished) data suggest lacosamide has anti-myotonic properties and there are anecdotal observations of its use in NDM (communication among neuromuscular experts through a website founded by Richard

Barohn, MD; Ricks Real Neuromuscular Friends; www.rrnmf.com). Ranolazine, approved for use in angina (Kahlig *et al.* , 2010; Rajamani *et al.* , 2009; Rajamani *et al.* , 2008; Wang *et al.* , 2008), has demonstrated anti-myotonic properties through in-vitro studies on HEK293 cells expressing wild type $Na_v1.4$ and mutations related to PMC. However, these drugs need to be tested in clinical trials to assess safety and efficacy in NDM.

An ideal treatment strategy would target mutation-specific biophysical abnormalities, with goal being better control of myotonia and transient muscle weakness with minimal side effects. This requires better understanding of the mutant channel behavior, which can be done through functional expression studies. The work performed by Despahy et al. is important as they have tried to explore disease mechanisms in MC with goal being to identify better treatments for this rare disease.

Despite advances in understanding NDM, the diverse genetic and phenotypic manifestations remain a challenge in diagnosis, therapeutics, genetic counseling, and research planning. These limitations are compounded by the rarity of this disorder. However, research networks now facilitate development of randomized clinical trials in NDM (Hoffman and Kaminski, 2012).

Abbreviations

NDM	non-dystrophic myotonia
CLCN1	skeletal muscle voltage gated chloride channel gene
SCN4A	skeletal muscle voltage gated sodium channel gene

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