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Neuromuscular Disorders 22 (2012) 99–111

www.elsevier.com/locate/nmd

Review

Current status of the congenital myasthenic syndromes

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Received 11 September 2011; received in revised form 11 October 2011; accepted 13 October 2011

Abstract

Congenital myasthenic syndromes (CMS) are heterogeneous disorders in which the safety margin of neuromuscular transmission is compromised by one or more specific mechanisms. Clinical, electrophysiologic, and morphologic studies have paved the way for detecting CMS-related mutations in proteins residing in the nerve terminal, the synaptic basal lamina, and in the postsynaptic region of the motor endplate. The disease proteins identified to date include choline acetyltransferase (ChAT), the endplate species of acetylcholinesterase (AChE), β2-laminin, the acetylcholine receptor (AChR), rapsyn, plectin, $Na_v1.4$, the muscle specific protein kinase (MuSK), agrin, downstream of tyrosine kinase 7 (Dok-7), and glutamine–fructose-6-phosphate transaminase 1 (GFPT1). Myasthenic syndromes associated with centronuclear myopathies were recently recognized. Analysis of properties of expressed mutant proteins contributed to finding improved therapy for most CMS. Despite these advances, the molecular basis of some phenotypically characterized CMS remains elusive. Moreover, other types of CMS and disease genes likely exist and await discovery.

Keywords: Congenital myasthenic syndrome; Neuromuscular junction; EMG; Choline acetyltransferase; ColQ β2-laminin; Acetylcholine receptor; Rapsyn; Agrin; MuSK; Dok-7; GFPT1; Plectin; Fetal akinesia syndrome

1. Introduction

In each congenital myasthenic syndrome (CMS) the safety margin of neuromuscular transmission is compromised by one or more mechanisms. These mechanisms involve the synthesis or packaging of acetylcholine (ACh) quanta into synaptic vesicles, the Ca^{2+}-dependent evoked release of ACh from the nerve terminal, and the efficiency of released quanta in generating a postsynaptic depolarization. Quantal efficiency depends on the endplate (EP) geometry, the density and functional state of acetylcholinesterase (AChE) in the synaptic space, and the density, affinity for ACh, and kinetic properties of the acetylcholine receptor (AChR).

Table 1 presents a classification for CMS based on 321 unrelated index patients investigated at the Mayo Clinic. The genetic basis of the CMS was determined in 318 patients. In 220 other index patient the molecular basis of the CMS awaits identification.

Table 1 indicates that the purely presynaptic CMS are least frequent, accounting for only 6% of all cases. Of note, however, a defect in presynaptic quantal release is also present in EP AChE deficiency [1], Dok-7 myasthenia [2,3], β2-laminin deficiency [4], and in the CMS associated with centronuclear myopathy [5]. The purely postsynaptic CMS account for most patients in this group and mutations in AChR subunits account for more than one-half of all cases. Fig. 1 shows the distribution of the CMS disease proteins at the neuromuscular junction.

2. The investigation and diagnosis of the CMS

A full understanding of how the safety margin of neuromuscular transmission is compromised in a given CMS is based on clinical, morphologic, in vitro electrophysiologic, and molecular genetic studies. The clinical evaluation must include detailed electromyographic (EMG) studies

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doi:10.1016/j.nmd.2011.10.009

Table 1
Classification and relative frequency of congenital myasthenic syndromes based on index patients observed at the Mayo Clinic[a].

Defect site	Index cases	Relative frequency (%)
Presynaptic (5.9%)		
Choline acetyltransferase	17	5.3
Paucity of synaptic vesiclesb	1	0.3
Congenital Lambert–Eaton-like syndrome[b]	1	0.3
Synaptic Basal Lamina (13.7%)		
Endplate AChE deficiency	43	13.4
β-2 laminin deficiency	1	0.3
Postsynaptic (68%)		
Primary AChR deficiency with/without kinetic abnormality	109	34
Primary kinetic abnormality with/without AChR deficiency	58	18.1
Rapsyn deficiency	48	15
Plectin deficiency	2	0.6
Na-channel myasthenia	1	0.3
Defects in mechanisms governing endplate development and maintenance (12.5%)		
Dok-7 myasthenia	31	9.7
Glutamine–fructose-6-phosphate transaminase deficiency (GFPT1)	8	2.5
Myasthenic syndrome associated with centronuclear myopathy[b]	1	0.3
Total	321	100

[a] Mutations in MuSK [92,94,95] and agrin [88] have been identified in few kinships at other medical centers.
[b] No gene defect identified.

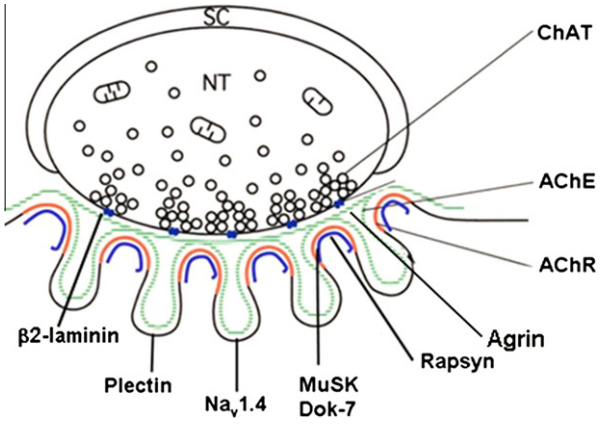

Fig. 1. Schematic diagram of an EP with locations of presynaptic, synaptic and postsynaptic CMS disease proteins. Green line, synaptic basal lamina; red line, AChR on crests of the junctional folds; blue line, MuSK and Dok-7 closely associated with AChR. GFPT1, present in all tissues and potentially affecting multiple proteins, is not represented.

to demonstrate a defect in neuromuscular transmission, tests for anti-AChR and anti-MuSK antibodies in sporadic patients presenting after the age of 1 year and in infants born with contractures, even if the mother has no symptoms to suggest an autoimmune myasthenia. The morphologic evaluation of the EP includes localization of AChR and AChE and ultrastructural analysis. In vitro electrophysiologic studies must be sufficiently complete so they provide information on parameters of quantal release and the factors affecting the efficiency of the released quanta. A surprising number of CMS stem from a kinetic abnormalities of the AChR. These can be recognized by examination of the decay phase of the miniature EP current (MEPC), and analyzed by patch-clamp recordings of currents flowing through single AChR channels. Because only few medical centers are able to perform all or some of the above studies, and mutations analysis of DNA isolated from blood or other tissues has been increasingly used to identify CMS disease genes and mutations. Indeed, automated sequencing methods of currently identified CMS genes are widely available and morphologic and functional studies are only indicated when mutation analysis of known CMS genes yields negative results.

3. Genetic analysis

This is greatly facilitated when clinical, physiologic, or morphologic studies point to a candidate protein or gene. For example, a kinetic abnormality of AChR detected at the single channel level [6], or severe EP AChR deficiency revealed by α-bungarotoxin binding studies [7], predicts mutations in an AChR subunit gene. Table 2 lists generic and specific clinical clues that facilitate targeted mutation analysis.

When no candidate genes are apparent, mutation analysis can be based on frequencies of the heretofore identified mutations in different EP proteins, as shown in Table 1. This approach is more expensive and time intensive than the candidate gene approach.

In patients with strong phenotypic clues for a given recessive CMS but only one or no identified mutations in the open reading frame, cDNA isolated from muscle can reveal an intronic mutation. This was the case for some patients with Dok-7 myasthenia [3]. cDNA analysis was also useful in deciphering the consequences of a frameshifting mutation in *COLQ* [8].

Genetic testing for CMS is now commercially available and facilitates diagnosis and management by neuromuscular specialists. It is best used in a targeted manner based on specific clinical features, as listed in Table 2, or beginning with the most frequently mutated genes, as shown in Table 1. However, this approach has a number of drawbacks: (1) it is expensive, especially if used in a shotgun manner; (2) it does not establish that recessive mutations are heteroallelic unless they are homozygous; therefore DNA from both parents also must be analyzed; (3) it will miss intronic mutations not close to exons; (4) evaluation of pathogenicity is based on software programs whose reliability is still debated; (5) it does not inform on kinetic consequences of mutations in AChR or ChAT, or on pathogenicity of mutations that render the disease protein structurally unstable; and (6) negative results do not exclude the diagnosis of a CMS because only previously identified disease genes are sequenced.