Congenital Myasthenic Syndromes: A paradigm shift.

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ABSTRACT

Very few areas of medical genetics have been so profoundly impacted by the advent of next-generation sequencing (NGS) as the field of congenital myasthenic syndromes (CMS). This is due to the formidable genetic heterogeneity of CMS, a dearth of diagnostic clinical clues of CMS types, and the imperative need to establish an accurate molecular diagnosis of CMS type before any medication is started. A molecular diagnosis of CMS is fundamental not only to provide an appropriate therapy, but more importantly, to avoid potential deleterious treatments. Thus, NGS has transformed the tedious and expensive task of searching for causative mutations in an ever-expanding list of genes linked to CMS into an effective, and relatively inexpensive process that can rapidly identify the variant of CMS in question. One of the consequences of this transformation is a paradigm shift in the clinical practice of CMS that no longer requires, with rare exceptions, the use of special muscle biopsies that enable the analysis of the function and ultrastructure of the neuromuscular junction to determine the type of CMS. Another technological advance of recent years is CRISPR/Cas9, which allows genome editing at the zygotic stage, thus greatly simplifying the generation of mouse models carrying the same human CMS mutations in orthologous mouse genes. This permits an in-depth analysis of the pathogenesis and treatments of CMS caused by specific gene mutations. In terms of therapy, in addition to the classical pharmacologic treatments of CMS, including pyridostigmine sulfate, albuterol and 3,4 dianinopyrindine, AAV-based gene therapies are now at the preclinical stage for several types of CMS. In this brief review, CMS are classified in six major groups: (1) presynaptic CMS, (2) synaptic CMS, (3) postsynaptic CMS; 4. CMS affecting the agrin-signal transduction pathway, (5) CMS linked to disorders of glycosylation, and (6) CMS associated with abnormalities of the cytoskeleton.

Keywords: Congenital myasthenic syndrome, neuromuscular junction, presynaptic, synaptic, postsynaptic

Introduction

Congenital myasthenic syndromes (CMS) continue being a topic of broad interest for clinicians and scientists alike because CMS are treatable disorders and because the understanding of these conditions provides fundamental knowledge about the function of the neuromuscular junction (NMJ).

Heterogeneity of CMS and patterns of genetic transmission:

The mechanisms of failure of neuromuscular transmission in CMS are quite heterogeneous, and all stem from defects of genes encoding proteins that participate directly or indirectly in neuromuscular transmission. Often, more than one mechanism contributes to the pathogenesis of a single disorder.

Mutations causing CMS usually involve single genes, except for large DNA deletions that affect more than one gene. The most common inheritance of CMS is Mendelian autosomal recessive, however mutations in several genes, including those encoding the adult subunits of the acetylcholine receptor (AChR), Synaptotagmin 2 (SYT2), and SNAP25 can also be dominantly inherited. De novo mutations, which are often seen in dominant forms of CMS, are the only type of mutations that have so far been described in CMS caused by defects of SNAP25. The X-linked pattern has not yet been associated with the pathogenesis of CMS.

CMS linked to proteins that are exclusive vs non-exclusive of the NMJ:

The first described variants of CMS were those caused by mutated proteins participating directly in the process of neuromuscular transmission and present only at the NMJ. Examples of these variants are CMS caused by mutations in the subunits of the adult AChR and rapsyn. Pathogenic mutations in these genes result only in CMS. By contrast, mutations of genes encoding proteins that participate indirectly in neuromuscular transmission and that are not present exclusively at the NMJ result in less consistent and more complex phenotypes in which CMS is only part of broader syndromes. An example of this is mutations in DPA1 that can result in a limb-girdle congenital myasthenic phenotype along with other features of glycosylation type Ij disease, including developmental delay, microcephalia and seizures. Another example is mutations in LAMB2 that can result in CMS along with other features of Pierson syndrome, including microcoria and congenital nephrotic syndrome.
Classification of CMS:

CMS are traditionally classified based on the location of the protein encoded by the gene causing the disease in three major groups: presynaptic, synaptic, and postsynaptic types (Figure 1). This classification is helpful to arrange CMS according to the primary site of pathology. However, in many types of CMS, such as those resulting from deficient proteins of the agrin signaling pathway and glycosylation disorders, there are both pre- and postsynaptic defects. Table 1 presents a proposed classification of CMS based on the primary site of the defect, while Table 2 lists the most important allelic variants of genes linked to CMS. Another approach to classify CMS is by sequential numbers in the order that they were discovered, and this is the way CMS variants are listed in the NCBI OMIM web site [https://www.ncbi.nlm.nih.gov/omim](https://www.ncbi.nlm.nih.gov/omim).

Table 1. Classification of CMS

<table>
<thead>
<tr>
<th>Presynaptic</th>
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<tbody>
<tr>
<td>a. Defects of the cholinergic pathway:</td>
</tr>
<tr>
<td>ChAT deficiency (CHAT)*</td>
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<tr>
<td>High-affinity presynaptic choline transporter deficiency (SLC5A7)</td>
</tr>
<tr>
<td>Vesicular ACh transporter deficiency (SLC18A3)</td>
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<tr>
<td>b. Defects of mitochondrial function with presumptive effect on the cholinergic pathway:</td>
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<tr>
<td>PREPL deficiency (PREPL)</td>
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<tr>
<td>Mitochondrial citrate carrier (SCL25A1)</td>
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<tr>
<td>c. Defects of SNAREs</td>
</tr>
<tr>
<td>SNAP25 deficiency (SNAP25B). DOMINANT*</td>
</tr>
<tr>
<td>VAMP1 deficiency (VAMP1)</td>
</tr>
<tr>
<td>d. Defects of Ca(^2+) sensors, active zone linkers, and kinetic proteins:</td>
</tr>
<tr>
<td>Synaptotagmin2 defect (SYT2). DOMINANT</td>
</tr>
</tbody>
</table>

Figure 1: Diagram showing the most important proteins linked to the pathogenesis of CMS in the postsynaptic (A), presynaptic (B) and synaptic (C) compartments. Abbreviations: AcCoA: acetyl coenzyme A, AChE: acetylcholinesterase catalytic subunits, BL: basal lamina, CHT: high-affinity choline transporter, ColQ: collagen-like tail subunit, mt: mitochondria, NaV1.4: sodium channel protein type 4 subunit alpha (SCN4A), VACHT: vesicular acetylcholine transporter, SV2A: synaptic vesicle protein 2A. 
Synaptotagmin2 recessive deficiency (SYT2)
Munc13-1 deficiency (UNC13A)
Rabphilin3a (RPH3A)
Myosin9a deficiency (MYO9A)

Synaptic
a. Defects of collagen proteins:
   - **ColQ deficiency (COLQ)**
     COL13A1 deficiency (COL13A1)
   b. Defects of laminins:
      Laminin beta2 deficiency (LAMB2)
      Laminin alpha5 deficiency (LAMA5)

Postsynaptic
a. Defects of the ACh receptor:
   - Without major kinetic changes:
     Receptor deficiency (CHRNA1/B1/D/E)
   - With major kinetic changes:
     Slow-channel syndrome (CHRNA1/B1/D/E) **DOMINANT**
     Fast-channel syndrome (CHRNA1/B1/D/E)
   b. Prenatal myasthenia (Escobar Syndrome) (CHRNG)
   c. Defects of rapsyn (RAPSN)
      Generalized
      With facial deformities
   d. Defect of the sodium channel
      Sodium channel myasthenic syndrome (SCN4A)

Defects of signaling pathways
Agrin deficiency (AGRN)
   Proximal
   Distal with presynaptic deficit
MuSK deficiency (MUSK)
LRP4 deficiency (LRP4)
DOK7 deficiency (DOK7)

Defects of glycosylation
GFPTI deficiency (GFPTI)
DPAGT1 deficiency (DPAGT1)
ALG2 deficiency (ALG2)
ALGI4 deficiency (ALGI4)
GMPPB deficiency (GMPPB)

Defects of the cytoskeleton
Plectin deficiency (PLECI)

*The most frequent forms of each group are bolded.
† Linked gene is shown in parenthesis.
‡ Indicates dominant forms.
Table 2. Most important phenotypic and allelic variants of genes linked to CMS

**Presynaptic**
- \textit{SLC5A7} (choline transporter) hereditary motor neuropathy (dominant).
- \textit{VAMP1} spastic ataxia (dominant).
- \textit{SNAP25} epileptic encephalopathy, ataxia, and intellectual disability.
- \textit{SYT2} hereditary motor neuropathy (dominant).

**Synaptic**
- \textit{LAMB2} microcoria, congenital nephrotic syndrome (Pierson syndrome).
- \textit{LAMA5} congenital nephrotic syndrome, bent bone dysplasia, myopathy.

**Postsynaptic**
- \textit{CHRNA1, CHRNB1, CHRND} receptor deficiency and slow channel syndrome.
- \textit{CHRNE} receptor deficiency, slow channel syndrome and fast channel syndrome.
- \textit{RAPSN} proximal, focal with facial malformations in Jewish people from Iran and Iraq (E-box mutations).
- \textit{SCN4A} paramyotonia congenita, periodic paralysis (dominant).

**Defects of signaling pathways**
- \textit{AGRN} proximal variant and distal variant with LEMS-like features.
- \textit{LRP4} Cenani-Lenz syndactyly syndrome.

**Defects of glycosylation**
- \textit{DPAGT1} congenital disorder of glycosylation (developmental delay, seizures).
- \textit{ALG2} congenital disorder of glycosylation.
- \textit{ALG14} Myopathy, seizures, and progressive cerebral atrophy.
- \textit{GMPPB} Muscular dystrophy, intractable seizures.

**Defects of the cytoskeleton**
- \textit{PLEC1} myopathy, epidermolysis bullosa, pyloric atresia.

**Defects linked to mitochondrial metabolism**
- \textit{PREPL} hypotonia-cystinuria syndrome.
- \textit{SCL25A1} combined D-2- and L-2-hydroxyglutaric aciduria, agenesis of corpus callosum, developmental delay, seizures.

**PRESYNAPTIC DEFECTS**

CMS caused by presynaptic defects are rare, and with the exception of deficiency of choline acetyltransferase (ChAT) most are represented by single case reports or only by a few families.

Defects of the cholinergic pathway:

**ChAT deficiency (\textit{CHAT}):** The disorder was initially referred to as familial infantile myasthenia and later changed to CMS associated with episodic apnea.\textsuperscript{4,5} However, since not all cases of ChAT deficiency present with episodic apnea and not all the CMS associated with episodic apnea are due to \textit{CHAT} mutations, it is preferable to refer this condition simply as ChAT-CMS. The severity of this disease is extraordinary variable; it can range from mild forms that tend to improve after puberty to extremely severe forms resulting in wheelchair-bound status, continuous ventilatory support and gastric tube.\textsuperscript{7-9} This variant of CMS has several distinctive features including: (1) association with apneas, (2) fast-developing muscle fatigue (within minutes), (3) paradoxical impairment with cold temperatures such as weakness triggered by cold water of a swimming pool.\textsuperscript{10} (4) In mild cases no decrement to repetitive nerve stimulation (RNS), but decrement only after 5 minutes of nerve stimulation at 10 Hz.\textsuperscript{10} and (5) ptosis without ophthalmoparesis and unsatisfactory long-term response to pharmacologic treatments. Severe cases of ChAT-CMS present with psychomotor delay,\textsuperscript{12} but autonomic dysfunction is surprisingly absent. Mutations in \textit{CHAT} has been described in other species, including dogs,\textsuperscript{13} zebrafish,\textsuperscript{14} \textit{C elegans}\textsuperscript{15} and \textit{Drosophila}.\textsuperscript{16} Several molecular defects have been associated with ChAT-CMS, including missense, nonsense, frameshift, and microdeletions.\textsuperscript{7-11,17} Large deletions are peculiar because they also involve the VChT gene located in the first intron of \textit{CHAT}.\textsuperscript{19} This condition has been reported world-wide in North America,\textsuperscript{7,17} South America,\textsuperscript{9} Europe,\textsuperscript{19} the Middle East,\textsuperscript{20} Malaysia,\textsuperscript{21} and China.\textsuperscript{8}

**High-affinity choline transporter (\textit{SLC5A7}):** Patients with mutations in this gene present many of
the symptoms described above for ChAT-CMS, thus representing an example of locus heterogeneity. However, the choline transporter CMS can present with antenatal forms resulting in arthrogryposis or stillbirths, and CMS involvement is more frequent than in ChAT-CMS.

**Vesicular ACh transporter deficiency (SLC18A3):** This is a rare condition that shares many clinical features with ChAT-CMS, including muscle fatigability, apneas and paradoxical worsening with low temperatures (swimming pool sign).²³

**PREP1 deficiency (PREPL):** This condition results from recessive deletions, involving the PREP1 gene and other contiguous genes on chromosome 2p21.²⁴ When the SLC3A1 gene is included in the deletion there is also cystinuria. The clinical manifestations include severe neonatal hypotonia, fluctuating ptosis, facial paresis, dysarthria, feeding difficulties and growth hormone deficiency. An anconeus biopsy in one patient showed severe reduction of MEPP amplitudes with normal AChR density strongly suggestive of an underlying abnormality of ACh synthesis. Beneficial response to pyridostigmine and albuterol is variable and often transient.

**Deficiency of mitochondrial citrate carrier (SCL25A1):** Biallelic mutations in this gene can result in mild proximal weakness and variable ocular and bulbar involvement.²⁵ Patients often show developmental delay and dysmorphic features. The mutation p.(Arg247Gln) is a recurrent mutation present in individuals of different ethnic groups.²⁶ As in the previous group an anconeus biopsy performed in a single patient showed normal MEPP amplitudes with normal AChR density, which points to a defect of ACh synthesis. Reported patients showed no consistent beneficial response to either anticholinesterase medication or albuterol.

**Defects of SNAREs:**

**SNAP25:** This severe and dominant form of CMS is associated with arthrogryposis, cortical excitability, ataxia, and developmental delay.²⁷

**VAMP1 (synaptobrevin 1):** VAMP-CMS is a recessive CMS characterized by hypotonia, impaired external ocular muscle function, developmental delay, joint contractures, and Lambert-Eaton myasthenic syndrome (LEMS)-like features on EMG testing.²⁷

**Defects of Ca²⁺ sensors, proteins of the active zone, and kinetic proteins:**

**Synaptotagmin 2 defect (SYT2) (dominant):** This is a relatively mild form of CMS with motor axonal neuropathy as an allelic variant. All mutations so far described are missense mutations altering calcium binding sites in the CB2 domain. There is frequent multigenerational involvement and LEMS-like features on electrophysiologic testing. The condition usually responds to treatment with 3,4 diaminopyridine (DAP).²⁸

**Synaptotagmin 2 defect (SYT2) (recessive):** This is a severe form of CMS with onset at birth or prenatally. Most of the reported cases involved consanguinity and nonsense or frameshift mutations resulting in protein truncation.²⁹,³¹ There is modest ocular involvement, but severe bulbar and generalized weakness with muscle atrophy. The EMG shows denervation and LEMS-like features in response to RNS. Patients show modest response to albuterol, pyridostigmine and 3,4 DAP.

**Munc13-1 deficiency (UNC13A):** This is a severe form of CMS, which has been so far only described in a single patient. Munc13-1 has a C2A and C2B domains that interacts with SNARES and participates in calcium homeostasis. The reported patient had a homozygous nonsense mutation predicting a large truncation of the protein. The patient had microcephaly, developmental delay, cortical EEG irritability, joint contractures, and LEMS-like features on electrophysiologic testing. A muscle biopsy showed normal NMJ ultrastructure and LEMS-like electrophysiology.³²

**Rabphilin 3a deficiency (RPH3A):** Pathogenic mutations in the RPH3A gene have been found in two independent families of patients with a mild presynaptic CMS associated with hand incoordination and tremors.³³,³⁴ The muscle biopsies showed double membrane sacs encircling synaptic vesicles. The pathogenic mechanism of this condition is unclear, but rabphilin 3a, as Synaptotagmin 2 and Munc13-1, encompasses a C2A and C2B Ca²⁺ / phospholipid binding domains that when altered may affect synaptic vesicle homeostasis.

**Myosin 9a deficiency (MYO9A):** Two non-related patients affected with ptosis, ophthalmoparesis, global weakness, bulbar involvement, and respiratory crises were found to have deleterious mutations in MYO9A,³⁵ which encodes the unconventional myosin 9a. CNS symptoms, including learning difficulties and vertical nystagmus were also reported. Muscle biopsies were not available. Patients responded to pyridostigmine. The underlying pathogenic mechanism is unclear, but expression studies in cell lines and zebrafish indicated that myosin 9a is fundamental for neurite extension and axonal transport.³⁶

**SYNAPTIC DEFECTS**

Except for ColQ deficiency synaptic CMS are rare forms of CMS.

**Defects of collagen proteins:**

**ColQ deficiency (COLQ):** Deficiency of ColQ, is
a relatively common variant of CMS and is the first one that was completely characterized by microelectrode recordings and electron microscopy of the NMJ. The condition results from mutations in COLQ, the gene that encodes the triple-helix strands that assemble with three homotetramers of the AChE catalytic subunit and holds the enzyme at the endplate. The ultrastructure of the NMJ in CoQ-CMS shows a characteristic triad consisting of: (1) reduced size of nerve terminals, (2) encasement of nerve terminals by the Schwann cell, and (3) focal degeneration of the postsynaptic folds. In some cases, numerous endocytic vesicles in the subsynaptic region can be seen, a feature in common with slow-channel CMS (SCCMS). Because ACh cannot be hydrolyzed, once it is released from the nerve terminal it accumulates at the synaptic cleft re-exciting the AChR ion channel. This in turn results in endplate potentials (EPPs) of prolonged duration that remain above threshold level longer than the refractory period of the muscle fiber enabling them to trigger multiple muscle action potentials. This feature of CoQ-CMS is also shared with the SCCMS and can be clinically observed by EMG recordings showing repetitive compound muscle action potentials (CMAPs) in response to a single nerve stimulation. Failure of neuromuscular transmission in CoQ-CMS occurs as a result of multiple mechanisms, including presynaptic deficit, staircase summation of EPPs leading to depolarization of the endplate and AChR desensitization. Treatment is limited to sympathomimetic drugs, such as albuterol.

**COL13A1 deficiency (COL13A1):** This is a rare recessive CMS characterized by early onset in life and predominant involvement of bulbar and axial musculature without significant impairment of external ocular muscle function. The mechanism of failure of neuromuscular transmission is unknown, but studies in Col13a1 -/- mice indicate both pre- and post-synaptic involvement. Affected patients show a moderate response to albuterol and 3,4 DAP.

**Defects of laminin proteins:**

**Laminin beta2 deficiency (LAMB2):** This is a very rare form of CMS occurring in survivors of Pierson syndrome after a successful renal transplant. Only two cases reported in the literature, both showing ultrastructural changes of the NMJ reminiscent of CoQ-CMS. In one case there was a favorable response to 3,4 DAP, but pyridostigmine resulted in an adverse effect.

**Laminin alpha5 deficiency (LAMA5):** A rare recessive form of CMS with only one case formally reported. The described case showed LEMS-like features. The clinical manifestations of biallelic LAMA5 mutations are protein and include congenital nephrotic syndrome, bent bone dysplasia and myopathy. The reported case responded to 3,4 DAP, albuterol and pyridostigmine.

**POSTSYNAPTIC DEFECTS**

More than half of CMS are caused by mutations in the genes encoding the adult subunits of the AChR or rapsyn.

**Deficiency of AChR expression (CHRNA1, CHRNBI, CHRND, CHRNE):** This is the most common variant of CMS and can result from mutations in any of the genes encoding the adult subunits of the AChR. There is an overwhelming majority of mutations in the gene encoding the epsilon subunit. The reason for this is unclear, but a possible explanation is that since the adult epsilon subunit can be compensated by re-expression of the fetal gamma subunit (encoded by CHRNA1), these patients tend to have milder forms of CMS. Thus, they are less vulnerable to natural selection pressure enabling them to pass their mutated genes to their offspring. Examples of this include CHRNE I267delG in Roma people and CHRNE 1293insG in Eastern Europeans.

Biallelic mutations in CHRNA1, which encodes the ACh binding alpha-subunit usually result in severe and potentially fatal CMS. By contrast mutations in CHRNA1 result in prenatal CMS and represent one of the multiple causes of the Escobar syndrome, which is characterized by arthrogryposis multiplex, joint contractures, pterygia, and respiratory distress.

Ocular involvement is usually prominent in patients with deficiency of AChRs. Patients respond well to pyridostigmine and surprisingly also to albuterol and 3,4 DAP, likely because the sizes of nerve terminals in these patients are normal allowing increased ACh output without depletion.

**Slow-channel CMS (CHRNA1, CHRNBI, CHRND, CHRNE):** SCCMS is the most common dominant form of CMS, and it can result from mutations affecting the AChR transmembrane domains M1 and M2, the M2–M3 linker, and the N-terminal. The most severe forms are those involving the M2 domain, while those affecting the N-terminal are milder. The SCS shares a number of similarities with CoQ deficiency even though they result from very different pathogenic mechanisms. The similarities include repetitive CMAPs to a single nerve stimulus, depolarization block from staircase summations of EPPs, subsynaptic degenerative changes and poor or adverse response to anticholinesterase medications. Treatment involves medications that shorten the channel open time, such as quinidine, quinine, and fluoxetine.
can cause low agonist affinity with shortened AChR ion channel kinetics and result in the fast-channel syndrome. However, as in the case of receptor deficiency, these mutations are most common in the epsilon subunit. The εP12L mutation is indeed the most common fast-channel mutations, and it results in a serious disease with a potentially fatal outcome.\textsuperscript{53,54} The treatment of this condition is similar to that of AChR deficiency.

**Rapsyn deficiency (RAPSN):** Mutations in the gene encoding rapsyn are another relative common cause of CMS. Rapsyn is a 43-kD postsynaptic protein intimately associated with the receptor and essential for clustering of AChRs.\textsuperscript{55,56} The severity of this disease is extraordinary variable, it can range from severe and potentially fatal neonatal forms to very mild forms with onset during childhood or adulthood. Often patients are born with arthrogryposis multiple indicating prenatal disease.\textsuperscript{57} Patients with severe forms suffer recurrent respiratory crises, which at variance with patients with ChAT mutations, do not occur spontaneously, but are usually triggered by intercurrent infections. A predominant bulbar involvement with facial malformations has been described in Jewish people from Iran and Iraq, who were found to possess pathogenic E-box mutations.\textsuperscript{58}

The mutation N88K, which derives from an old Indo-European founder is often found at least in one of the alleles of patients with Rapsyn-CMS.\textsuperscript{59,60} In contrast with patients with AChR ε subunit mutations, patients with RAPSN mutations seldom show involvement of extraocular muscles. Treatment is similar to that for patients with AChR deficiency.

**Defect of the skeletal muscle sodium channel (SCN4A):** This is a unique type of CMS characterized by recurrent episodes of generalized and bulbar weakness reminiscent of periodic paralysis. However, the clinical presentation also includes muscle fatigue, ptosis and ophthalmoparesis more consistent with CMS.\textsuperscript{61,62} Decrement of CMAP amplitudes in response to repetitive nerve stimulation at 2 Hz is modest but becomes obvious with nerve stimulations at higher rates. The management of this condition is based on a dual therapy with pyridostigmine and acetazolamide.

**DEFECTS OF SIGNALING PATHWAYS (AGRN, MUSK, LRP4, DOK7)**

This is an important group of CMS involving a signal transduction pathway that is fundamental for the development and maintenance of the NMJ.\textsuperscript{63-66} The clinical presentations of these disorders are very heterogeneous, but all share predominant proximal limb weakness, variable bulbar and ocular involvement and poor or adverse response to pyridostigmine. Stridor is also common, particularly in the DOK7-CMS.\textsuperscript{67} The disease can start anytime in life and weakness of neck muscles, sometimes presenting as a drop-head syndrome, is a distinctive characteristic of these conditions.\textsuperscript{68,69} From the pathophysiologic standpoint all these variants present presynaptic and postsynaptic involvement. Surprisingly, N-terminal mutations in the AGRN gene can result in distal limb involvement and a LEMS-like syndrome. The reason for this is unclear, but it may involve a disrupted interaction of agrin and the gamma subunit of laminin with the presynaptic voltage-gated calcium channel.\textsuperscript{70,71} The DOK7-CMS is the most common variant of this group, in part due to several recurrent mutations, including c.1124_1127dupTGCC and many other mutations affecting all the protein domains.\textsuperscript{72} Treatment is based on sympathomimetic drugs such as albuterol.

**DEFECTS OF GLYCOSYLATION (GFPT1, DPAGT1, ALG2, ALG14, GMPPB)**

The discovery of the association between limb-girdle myasthenia with tubular aggregates and the gene encoding the enzyme glutamine-fructose-6-phosphate-transaminase 1 (GFPT1) by linkage analysis was surprising but understandable given the heavy glycosylation of proteins of the NMJ.\textsuperscript{73} Patients in this group resemble patients with DOK7 mutations because of the proximal limb weakness. However, the muscle biopsies of these patients often reveal tubular aggregates and patients seldom show bulbar or ocular involvement.\textsuperscript{74} In addition, patients with DPAGT1 and ALG2 can present with more complex phenotypes that includes mental delay and seizures.\textsuperscript{75,76} Patients with mutations in GMPPB may present with myopathy, encephalopathy, and intractable seizures.\textsuperscript{77} The treatment of this group includes pyridostigmine and albuterol. 3,4 DAP should be avoided because of the possibility of seizures.

**DEFECTS OF THE CYTOSKELETON**

**Plectin deficiency (PLEC1):** Mutations in PLEC1 can cause epidermolysis bullosa simplex, which may associate with muscular dystrophy (EBS–MD) or pyloric atresia (EBS–PA).\textsuperscript{78,79} Rare cases may also show neuromuscular transmission failure.\textsuperscript{80} Treatment involves pyridostigmine and albuterol. 3,4 DAP should be avoided because of the possibility of seizures.

**Other genes with possible association with CMS:** Several other genes have been suspected to cause CMS, but the genetic mode of transmission and mechanism of failure of neuromuscular transmission have not been completely elucidated. These genes include,\textsuperscript{81-84} TOR1AIP1,\textsuperscript{85} PURA,\textsuperscript{86,87} CHD8,\textsuperscript{88} SCN8A,\textsuperscript{89} and many other genes linked to hereditary myopathies.\textsuperscript{86}

**Non-pharmacological treatments:** In children with
severe forms of CMS the protection of the respiratory function is of paramount importance. Therefore, tracheotomy, mechanical ventilation and gastric tube are all important measures that when indicated, need to be implemented early in the course of the disease to prevent respiratory insufficiency, anoxic brain injury and permanent neurologic damage. Surgical correction of scoliosis is also important to eliminate a potential mechanical impediment of proper respiratory function.

Finally, upcoming molecular therapies based on monoclonal antibodies, AAV-mediated gene therapy and many other target-therapies may expand in the near future the list of treatments available for CMS.

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CONFLICT OF INTEREST

None.

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