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REVIEW ARTICLE

Italian recommendations for diagnosis and management of congenital myasthenic syndromes

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Abstract

Congenital myasthenic syndromes (CMS) are genetic disorders due to mutations in genes encoding proteins involved in the neuromuscular junction structure and function. CMS usually present in young children, but perinatal and adult onset has been reported. Clinical presentation is highly heterogeneous, ranging from mild symptoms to severe manifestations, sometimes with life-threatening respiratory episodes, especially in the first decade of life. Although considered rare, CMS are probably underestimated due to diagnostic difficulties. Because of the several therapeutic opportunities, CMS should be always considered in the differential diagnosis of neuromuscular disorders. The Italian Network on CMS proposes here recommendations for proper CMS diagnosis and management, aiming to guide clinicians in their practical approach to CMS patients.

Keywords Congenital myasthenic syndromes · Recommendations · Neuromuscular junction · Myasthenia gravis · Myopathy

Definition

Congenital myasthenic syndromes (CMS) are genetic disorders due to mutations in genes encoding proteins involved in the neuromuscular junction (NMJ) structure and function, causing skeletal muscle weakness and fatigability [1, 2].

Clinical presentation is highly variable, ranging from mild symptoms to severe manifestations, sometimes with life-threatening respiratory episodes, especially in the first decade of life. In recent years, many achievements have increased complexity in the CMS field, because a NMJ dysfunction suggestive of a myasthenic disorder has also been found in some genetic primary muscle disorders, mainly congenital myopathies, and some genes involved in CMS may be also causative of myopathy or skeletal muscle channelopathies, as *GMPPB* and *SCN4A*, respectively [3–9]. Hence, CMS should be always considered in the differential diagnosis of more common neuromuscular disorders, taking also into account

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that CMS are frequently well-responsive diseases to symptomatic treatments.

Herein, the Italian Network on CMS proposes expert recommendations for CMS diagnosis and proper management, which could be useful in clinical practice aiming to support clinicians in their approach to CMS patients. These recommendations are derived by accurate scrutiny of pertinent data available in literature and on diagnostic procedures and therapeutic approaches adopted in Italian tertiary referral neuromuscular centers.

Epidemiologic data

CMS are very rare diseases, considerably less frequent than autoimmune myasthenia gravis (MG). However, CMS represent the major cause of the myasthenic syndrome in the first years of life and are probably misdiagnosed among patients who have received a diagnosis of seronegative MG presenting within the second decade of life [10]. Recent studies showed a prevalence of genetically defined CMS of 1.8 cases per million total population in Spain, and 9.2 cases per million children in UK [11, 12], but complexity in the procedures to reach a firm diagnosis makes these numbers likely an underestimation. Specific populations, such as southeastern European Roma and North African from Maghreb, may be at higher risk for CMS, due to a possible founder effect and an increased rate of carriers of pathogenic variants in *CHRNE* gene, c.1327delG and c.1353dupG, respectively [13, 14].

Classification and pathogenic aspects

The landscape of the CMS is still partially unwritten. All CMS are characterized by an abnormal signal transmission between nerve and muscle caused by mutated proteins normally involved in the NMJ function and structure, but the list of associated genes is growing rapidly. CMS are recessively inherited diseases, except for slow-channel syndrome (SCS), due to mutations impairing the kinetic properties of the acetylcholine receptor (AChR) subunits, or other very rare CMS subtypes caused by *SYT2* or *SNAP25B* mutations, both of which are dominantly inherited. At present more than 30 genes are known to cause CMS, although fewer occur in single patient/kindred [15].

On the basis of the localization or the function of the mutated protein, CMS may be classified in presynaptic defects, synaptic space defects, AChR defects (AChR deficiency or, less frequently, AChR kinetic defect, divided into slow and fast-channel syndromes), endplate development and maintenance defects, congenital glycosylation defects and other uncommon forms [2]. About half of the CMS cases occur as a consequence of defects in the AChR, mainly due to epsilon subunit gene (*CHRNE*) mutations, followed by development and maintenance of the end plate defects (25%) and synaptic space defects (13%); remaining CMS forms are considerably less frequent [1, 2]. Considering the single genes, *CHRNE* is the most frequently involved in CMS, accounting for around 20–50% of the cases, according to different populations, followed by *RAPSN*, *DOK7*, and *COLQ* [1, 2, 12, 16, 17].

General clinical aspects

CMS clinical presentation is usually at birth, infancy, or in early childhood. When presenting at birth or perinatally, CMS are often characterized by hypotonia in association with ocular, facial, bulbar, or respiratory symptoms and followed by delayed motor milestones; after motor milestones acquisition, CMS may also present with walking difficulty and frequent falls. Later onset has been rarely reported in the second and third decade with difficulty in daily activities, such as running and climbing stairs, in particular in cases harboring mutations in *GMPPB*, *GFPT1*, and *MUSK* and in SCS [18–22]. Antenatal onset has been reported in Escobar syndrome, which is characterized by arthrogryposis multiplex congenital (AMC), multiple pterygium, and fetal akinesia (FA), due to mutations in *CHRNG*, coding for the gamma subunit of the fetal form of AChR [23]. No myasthenic symptoms are observed at birth or later in the Escobar syndrome because the adult AChR is normally expressed. AMC and FA have been reported also in association with mutations in *DOK7*, *RAPSN*, *CHRNA1*, and *CHRND*, characterized by the absence of adult AChR in the disease animal model [24–26].

As in MG, muscle fatigability and weakness may involve different muscular districts, including ocular, facial, bulbar, respiratory, axial, upper, and lower limb muscles, accounting for the great clinical variability and severity of CMS patients. Table 1 recapitulates clinical features according to genetic diagnosis.

Muscle weakness may worsen or, seldom, improve with exertion, depending on the localization of the NMJ defect, whether postsynaptic or presynaptic, respectively. Symptom fluctuations have been reported in CMS, although less frequent and pronounced than in MG.

Ocular presentation is common and characterized by eyelid ptosis and/or ophthalmoparesis, usually without double vision. Eyelid ptosis is most often bilateral, although sometimes asymmetrical. Isolated ocular symptoms without involvement of other districts during the disease course have been reported in a minority of CMS patients [16]. Conversely, ocular involvement, particularly ophthalmoparesis, is rare in specific CMS subtypes, such as *DOK7*, *RAPSN*, *CHAT*, and CMS due to defects of glycosylation, and it may be useful to differentiate the CMS subtypes [27–30].

Table 1 CMS clinical features according to genetic diagnosis

Gene and protein function/localization	Frequency[a]	Inheritance	Typical onset	Main clinical features	Treatment
Presynaptic					
CHAT	5%	AR	Birth, infancy, or childhood	Hypotonia and apnea at birth or sudden episodes of apnea in infancy and childhood, precipitated by infection, only mild symptoms between crises	PD
Synaptic space					
COLQ	13%	AR	Birth to 2nd decade	Predominant limb-girdle muscle weakness, ptosis (ophthalmoparesis less common), possible respiratory crises, delayed pupillary light reflexes	Sal, Eph
Defects in AChR					
Primary AChR deficiency (*CHRNE*, *CHRNA1*, *CHRNB1*, *CHRND*)	33%	AR	Birth, infancy, or childhood	Ptosis, ophthalmoparesis, facial, limb muscle weakness, possible bulbar weakness	PD, 3,4-DAP, Sal for refractory cases
AChR kinetic defect (*CHRNE*, *CHRNA1*, *CHRNB1*, *CHRND*)	18%	AD/AR			
Slow-channel syndromes	7%	AD	Birth to 3rd decade	Selective involvement of cervical, wrist, and finger extensor muscles, no ophthalmoparesis	Fluox or Quin
Fast-channel syndromes[b]	11%	AR	Birth	Severe acute respiratory crises, ptosis, ophthalmoparesis, facial, bulbar, axial, and limb muscle weakness	PD, 3,4-DAP
Defects in endplate development and maintenance					
RAPSN	14%	AR	Birth, infancy, or childhood	Worsening of weakness and respiratory crises triggered by infections or fever, congenital contractures, and/or dysmorphisms	PD, 3,4-DAP
DOK7	9%	AR	Birth to 2nd decade	Predominant limb-girdle weakness, possible ptosis, facial and bulbar weakness, uncommon ophthalmoparesis	Sal, Eph
Defects of glycosylation					
GFPT1	3%	AR	1st year to 2nd decade	Predominant limb-girdle weakness, mild facial weakness, no ocular involvement, tubular aggregates in muscle biopsy	PD
Uncommon CMS					
Musk, *LRP4*, *AGRN*, *SCN4A*, *GMPPB*, *DPAGT1*, *ALG2*, *ALG14*, *PREPL*, *COL13A1*, *MYO9A*, *SNAP25B*, *SLC25A1*, *SLC18A3*, *MUNC13-1*, *LAMA5*, *SLC5A7*, *SYT2*, *LAMB2*, *VAMP-1*, presynaptic high-affinity choline transporter defect, *PREPL*, *PLEC*	4%	AR/AD	Birth to 2nd decade	Very variable; of note, *DPAGT1*, *ALG14*, *SLC25A1*, *SNAP25B*, *MUNC13-1* may have central nervous system involvement	PD, DAP, Sal; *SCN4A* responsive to ACZ

AChR acetylcholine receptor, *PD* pyridostigmine, *Sal* salbutamol, *DAP* diaminopyridine, *Eph* ephedrine, *Fluox* fluoxetine, *Quin* quinidine, *ACZ* acetazolamide

[a] Data from Mayo clinic cohort of patients [2, 15]

[b] Fast-channel syndrome diagnosis is possible only through in vitro microelectrode studies of the neuromuscular junction and single-channel patch-clamp studies

Facial weakness is common in CMS, including both orbicularis oculi and lower facial muscles, and may be associated with dysmorphic features. In the neonatal period, poor cry and suck are common. Masseter muscle weakness causes difficulty in chewing and when severe may lead to jaw drop. Bulbar symptoms include tongue weakness, dysphagia, and dysphonia. Difficulty in swallowing may result in significant nutritional problems and require feeding through a nasogastric tube or gastrostomy, mainly in the neonatal period. In addition, patients with dysphagia and weak cough reflex are at higher risk of developing aspiration pneumonia. Stridor due to laryngomalacia or vocal cord palsy in neonates may be another important clue to CMS and it is usually associated with *DOK7* mutations [31].

Predominantly, scapular or pelvic weakness, usually bilateral and symmetrical, has mainly been reported in *DOK7*, *COLQ*, and glycosylation defects, sometimes mimicking a limb-girdle muscular dystrophy and severely impairing walking ability [29, 30, 32].

Axial weakness is common in CMS and may manifest with neck flexor or extensor muscle involvement, causing dropped head syndrome in the latter, as in SCS-, *DOK7*-, *RAPSN*-, and *COLQ*-mutated patients [12, 19, 27, 29, 32]. Scoliosis may be also observed and may impair respiratory function.

Although distal involvement is present in CMS, predominantly distal weakness is rare, being mostly reported in patients with SCS and *AGRN* mutations [19, 33].

Respiratory involvement is common in CMS patients, usually manifesting as acute respiratory crises with cyanosis in the first years of life, including the neonatal period [31]. However, frequency of respiratory crises tends to decrease with age [34]. Respiratory crises may occur in association with global CMS worsening or, less frequently, may be isolated. In addition, respiratory crises may be recurrent and severe, sometimes with life-threatening episodes, more frequently in patients mutated in *CHRNE*, *RAPSN*, *CHAT*, *COLQ*, *SCN4A*, *SLC5A7*, and fast-channel syndromes [7, 27, 32, 34–36]. Some CMS subtypes, such as CMS due to mutations in *COLQ* and SCS may develop progressive respiratory muscle weakness requiring chronic ventilator support in childhood or adulthood [35].

Tendon contractures have been reported, mainly in patients mutated in *RAPSN* at birth [27]; if severe, contractures may compromise daily-life activities and walking abilities. Of note, CMS represent a main cause of arthrogryposis multiplex congenital and should be always suspected in case of multiple contractures in a newborn. The much rarer form of recurrent arthrogryposis in newborns from women with MG associated with AChR antibodies must however be taken into account in the differential diagnosis [37]. Joint laxity has been also reported in CMS, sometimes impairing significantly the motor function.

CMS usually have static or slowly progressive course over the years, although acute exacerbations may be triggered by infectious episodes, surgery, hot weather or stress, sometimes leading to acute respiratory failure, in particular in the first years of life. Although there are few information on natural history of the different forms, severe disease progression with impaired walking and loss of ambulation may be observed, for example, in patients having mutations in *GFPT1* and *DOK7* [12, 17].

Central nervous system involvement is rare in CMS, mainly owing to hypoxic-ischemic episodes secondary to respiratory insufficiency, as in *CHAT*, or in very rare cases, mainly showing intellectual disability, seizures, or brain malformations/atrophy [15].

Cardiac involvement has not been reported in CMS.

Diagnosis

CMS diagnosis includes two sequential steps: (1) diagnosis of a congenital NMJ disorder and (2) identification of the molecular defect, which may be guided by specific clinical, neurophysiological or histological clues.

CMS diagnosis requires a high clinical suspicion, because they are rare diseases and myopathic features are often more evident than myasthenic signs, in particular in SCS, glycosylation defect, and *COLQ*-mutated patients.

CMS should be always considered in the workup of patients with hypotonia at birth or recurrent respiratory crisis; ocular symptoms; such as eyelid drop and/or ophthalmoparesis, usually without double vision; and facial, bulbar, or limb fatigable weakness, particularly when presenting in the first decade of life. As a rule, CMS should always be considered in patients with clinically suspected myopathy, especially in case of normal or nonspecific muscle biopsy, but in the presence of severe muscle weakness. Of note, family history is negative in most of the patients.

CMS diagnosis is primarily based on clinical findings, a decremental or incremental EMG response of the compound muscle action potential (CMAP) on low- (2–5 Hz) or high-(20–50 Hz) frequency repetitive nerve stimulation (RNS) and/or an increased jitter on single-fiber EMG (SF-EMG), a positive response to acetylcholinesterase inhibitors (AChE-Is). Similarly, CMS diagnosis has to be suspected in patients who have received a provisional diagnosis of MG, but with the absence of anti-AChR and anti-muscle-specific receptor tyrosine kinase (MuSK) antibodies in the serum, and/or lack of clinical improvement with immunosuppressive or

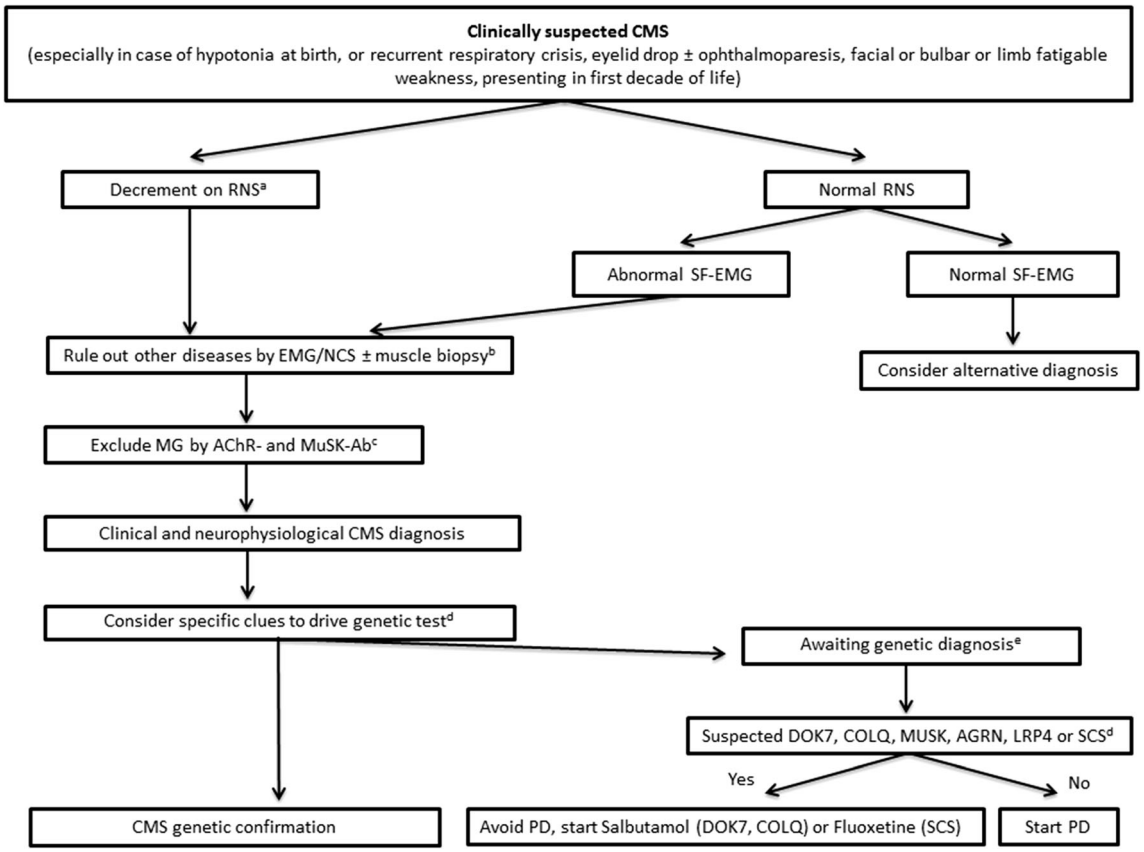

Fig. 1 Flow chart for CMS diagnosis. [a] In children SF-EMG should be performed in place of RNS. [b] Muscle biopsy to be performed in selected cases to rule out primary myopathies. [c] Lack of clinical improvement with immunosuppressive or immunomodulatory treatments, such as plasma exchange or intravenous immunoglobulins, should be also considered to distinguish CMS from MG. [d] See Fig. 2 for details. [e] More than 30 genes cause CMS and about half of CMS patients lacks genetic diagnosis; hence, genetic characterization may require a long time and treatment is usually needed in the meantime

immunomodulatory (plasma exchange or intravenous immunoglobulins) treatments. Flow chart for CMS diagnosis is shown in Fig. 1.

Neurophysiological studies must be performed by expert hands and are necessary for CMS diagnosis, although most of the studies investigating RNS and SF-EMG use in NMJ disorders focused on adult patients with MG and Lambert-Eaton myasthenic syndrome (LEMS) [38]. RNS should be performed on clinically affected muscles; however, this is not always possible; hence, the abductor digiti quinti and the upper trapezius muscles are generally recommended for RNS, being well tolerated and easy to study. Facial muscle studies may be less comfortable for the patient, but holds a higher diagnostic value in case of bulbar and perhaps ocular involvement [39, 40]. RNS should be considered abnormal if the fourth evoked CMAP has amplitude more than 10% smaller than the first evoked one. Decremental response on low-rate RNS is not completely specific for a myasthenic syndrome, being also present in other conditions impairing NMJ function (e.g., antibiotics, organophosphates), and seldom in different myopathies and neurogenic disorders such as X-linked bulbospinal muscular atrophy [40]. If the CMS is caused by a presynaptic defect in the acetylcholine (ACh) vesicle release, the decrementing CMAP response to low-frequency RNS is associated with a marked incremental CMAP response to high-frequency RNS or following maximum voluntary muscle contraction, as described in LEMS [41]. SF-EMG should be performed when RNS is negative or in children, being less uncomfortable than RNS. SF-EMG is more sensitive but less specific than RNS, because an increased jitter has been observed also in myopathies and neurogenic diseases. Contrary to RNS, SF-EMG is not able to discriminate between a pre- or postsynaptic NMJ disorder. Jitter may change among different muscles and also among different end-plates in the context of the same muscle; hence, at least 20 potential pairs should be always evaluated. SF-EMG should be initially tested on the forearm and, if negative, on a clinically affected muscle, usually in the facial region. If jitter is normal, a

NMJ disorder is unlikely, in particular if the tested muscle shows definite clinical weakness. AChE-Is should be withdrawn 48–72 h before testing with RNS or SF-EMG, to minimize the risk of masking an impairment of NMJ function. However, the interpretation of neurophysiological results in the pediatric myasthenic population is still difficult and debated due to the lack of normative data.

Repetitive CMAP evoked by single nerve stimuli, regardless the site of nerve stimulation, may be useful to drive molecular diagnosis, being observed in SCS- and *COLQ*-mutated patients [19, 32]. Repetitive CMAP, usually a double response, is caused by prolonged action of acetylcholine at NMJ and may be observed also in case of AChE-Is overdose.

Nerve conduction studies are normal in CMS, except in rare presynaptic subtypes due to a defect of ACh vesicle release, where a reduced CMAP may be observed. Needle EMG should always be performed to rule out neurogenic and myopathic disorders; however, a myopathic pattern does not exclude a CMS, being relatively common in these diseases.

As in MG, a positive response to AChE-Is may be used to support the diagnosis of CMS, although AChE-Is administration in a CMS patient without molecular characterization should be considered with caution as AChE-Is may worsen specific CMS subtypes. Although much less used than in the past, Tensilon test may be performed at bedside, administering edrophonium chloride, a short-acting AChE-Is, being aware of false-positive results [42]. It is safe to perform the test in ICU setting to minimize the risk of bradycardia and cardiac arrest.

Creatine kinase (CK) is usually normal or minimally elevated, apart from CMS due to *GFPT1* and *GMPPB*; the latter may have up to 10-fold increase of serum CK levels [21].

No specific clues have been reported on muscle biopsy taken from CMS patients. Although nonspecific, the predominance of type I fibers and the marked atrophy of type II fibers may be suggestive of CMS. Tubular aggregates may be detected in the muscle of some CMS subtypes, in particular those due to glycosylation defects (*GFPT1*, *DPAGT1*, *ALG2*), although not specific, being found also in periodic paralysis or myopathies due to *STIM1* or *ORA1* gene mutations [30]. To date, muscle biopsy is not required to entertain a diagnosis in CMS, but it may be useful to rule out different inherited myopathies in selected patients.

The use of muscle MRI has been poorly investigated in CMS; T1-weighted MRI at thigh and calf level usually displays normal or nonspecific findings, except for CMS due to glycosylation defects, being characterized by severe fatty changes [43]. Normal or mild imaging abnormalities in the context of severe weakness may suggest a possible CMS [43]; however, muscle MRI is not recommended in the CMS diagnostic workout, thus far, even if more data are warranted. Brain MRI should be limited only to cases with clinical evidence of central nervous system involvement.

Table 2 illustrates the main differential diagnosis in CMS.

Molecular analyses

Mutations in an increasing number of genes are known to cause CMS. In the past few years, whole exome sequencing has become a powerful tool for identifying CMS disease genes and mutations, yet a genetic characterization is still lacking in about half of CMS patients according to data from two wide cohorts in UK and France [16, 17].

Molecular analysis is routinely performed by Sanger sequencing. In recent years, next-generation sequencing (NGS) has been introduced in selected centers, for diagnostic purposes, aiming to improve and accelerate the genetic diagnosis.

The genetic diagnosis of CMS may be driven by clinical and neurophysiological findings, which may point to specific genes, as shown in Fig. 2.

Micro-electrophysiology studies may be performed to investigate the NMJ function on patient muscle tissue to establish the pathogenic meaning of genetic variants; however, these studies are research-based and available only in few specialized centers worldwide and not in Italy.

In the case of affected family members, genetic counseling is recommended to orient antenatal detection of the family mutation(s). Preimplantation genetic diagnosis is a possibility if the pathogenic variants have been identified in family members.

Treatment and long-term management

At present, there is no causative cure for CMS and only symptomatic pharmacological therapies are available. Furthermore, CMS treatment includes management of possible complications, such as contractures and respiratory failure. Indications on CMS treatment and management are mainly based on clinical experience and retrospective analyses on small cohort of patients. Of note, drugs with positive effects on specific CMS may worsen other CMS forms. Hence, definite genetic diagnosis is highly recommended to optimize pharmacologic treatment.

The aim of symptomatic treatment is to provide some relief to the patient, reducing to minimum the expected risks and side effects. To this purpose, therapies should be, as far as possible, tailored on the single patient.

Different drugs are available as symptomatic therapies: cholinergic agonists [pyridostigmine, 3,4-diaminopyridine

Table 2 Main differential diagnosis of congenital myasthenic syndromes

Disease	Distinctive features
MG	• MG is by far more common than CMS.
	• MG has not been reported in the first year of life.
	• CMS may have positive family history or ophthalmoparesis without double vision.
	• CMS have no benefit from IMMS, no thymoma or thymus gland involvement, no AChR- and MuSK-Ab.
Neonatal MG	• Presenting in the first weeks of life in children of MG female patients (MG not always known in the mother).
	• Self-limiting course.
Primary myopathies*	• If neurophysiological studies (RNS and SF-EMG) are inconclusive, muscle biopsy should be performed.
	• Muscle MRI pattern may help.
Mitochondrial myopathy	• Multisystem involvement is typical of mitochondrial diseases.
	• Muscle biopsy with respiratory chain enzymes analysis and southern-blot for detection of mtDNA deletions on muscle tissue may help the differential diagnosis.
Motor neuron diseases (ALS, SMA type I–III)	• Presence of muscle cramps/fasciculations, atrophy, or upper motor neuron signs in motoneuron diseases.
	• Neurophysiological studies and gene analysis usually allows differential diagnosis.
Botulism	• Rapid descending pattern of progression and pupillary, autonomic involvement in botulism.
Cranial nerve palsy, brain stem diseases	• Possible presence of coordination, pyramidal and sensory involvement in brain stem diseases and in some cranial nerve paralyzes.
	• Neurophysiological studies and/or brain MRI usually allow differential diagnosis.

MG myasthenia gravis, *Ab* antibodies, *IMMS* immunosuppressive and immunomodulatory treatments, *RNS* repetitive nerve stimulation, *SF-EMG* single-fiber electromyography

*Of note, some myopathies, in particular congenital myopathies, have NMJ impairment and show improvement by acetylcholinesterase inhibitors or salbutamol

(3,4-DAP)], adrenergic agonists (salbutamol/albuterol and ephedrine), and long-lived open-channel blockers of acetylcholine receptor ion channel (fluoxetine and quinidine) [2]. Cholinergic agonists have a fast effect, providing symptomatic relief as they are absorbed; on the contrary, adrenergic agonists and blockers of AChR channel act more slowly, usually needing days to months to show their benefit. Details and dosage of the aforementioned drugs are included in Table 3. To date, data on efficacy of these drugs have been obtained from single case reports or small series of patients reported in literature, due to the rarity of the disease.

Pyridostigmine (PD) is the most commonly used cholinergic agonists and symptomatic treatment for CMS. PD is an AChE-Is and acts by slowing the degradation of ACh at the NMJ, prolonging the interaction of ACh with its receptor and enhancing neuromuscular transmission. Common adverse reactions of PD are usually mild; however, individual tolerance varies greatly. AChE-Is may be stopped during acute respiratory failure due to the exaggerated bronchial and salivary secretions, which could interfere with management of mechanical ventilation. AChE-Is are particularly indicated in CMS associated with AChR defect, whereas are ineffective or most often determine worsening of symptoms in SCS, *COLQ*, *DOK7*, and *MUSK* CMS [2].

3,4-DAP is a potassium channel blocker, increasing the release of ACh quanta from the presynaptic membrane into the synaptic cleft. 3,4-DAP is usually well tolerated and its main side effect is tingling in the perioral area and in extremities, usually mild and not causing drug withdrawal. Seizures have been rarely reported in LEMS patients treated with 3,4-DAP; the risk seems to be dose dependent [44]. Electroencephalography is not recommended before starting the treatment, although may be useful in children, considering the higher risk of seizures. Cholinergic agonists are often used in combination; in particular 3,4-DAP may be used as add-on therapy for patients with unsatisfactory benefit from PD.

- **Episodic apneas**→ *CHAT, RAPSN, COLQ, SCN4A, SLC5A7,* Fast channel syndromes;
- **Onset since 2nd decade**→ especially slow-channel syndromes, *GFPT1, MUSK* and *GMPPB*;
- **Delayed pupillary light reflexes**→ *COLQ*;
- **Selective involvement of cervical, wrist and finger extensors**→ Slow-channel syndromes and elder COLQ patients;
- **Neonatal stridor**→ *DOK7,* fast channel syndromes;
- **Arthrogryposis multiplex congenita**→ *RAPSN, CHRNG, CHRND, CHRNA1, CHAT, SNAP25B, SYT2*;
- **Contractures**→ *RAPSN*;
- **Limb-girdle weakness** → *DOK7, GFPT1, DPAGT1, ALG2, ALG14, COLQ*;
- **Distal involvement**→ *AGRN, RAPSN*;
- **Weekly fluctuations of symptoms**→ *DOK7*;
- **Nephrotic syndrome and ocular malformations**→ *LAMB2*;
- **Seizures, brain malformations/atrophy or intellectual disability**→ *DPAGT1, ALG14, GMPPB, SNAP25B, SLC25A1, MUNC13-1*;
- **Epidermolysis bullosa simplex and muscular dystrophy**→ Plectin deficiency;
- **Repetitive CMAP evoked by single nerve stimuli** → *COLQ*, slow-channel syndromes.
- **Tubular aggregates** → *GFPT1, DPAGT1, ALG2*;
- **Increased CK** → *GMPPB* (more than 10X upper limit normal), *GFPT1* (less than 10X upper limit normal);
- **Worsening by PD**→ *COLQ*, slow-channel syndromes, *DOK7, MUSK, AGRN, LRP4.*

Fig. 2 Clinical, laboratory, histological, and neurophysiological clues pointing to specific CMS genes. CMAP, compound motor action potential; CK, creatine phosphokinase; PD, pyridostigmine

Salbutamol (or albuterol in the US market) and ephedrine act as stimulating β2-adrenergic receptors improving NMJ function. Both are the treatment of choice for CMS due to mutations in *COLQ* and *DOK7* [45–47]; in addition, salbutamol and ephedrine may be used in patients with CMS due to AChR defect not responsive to AChE-Is and 3,4-DAP [48]. Although to date there is no indication on superiority of salbutamol on ephedrine, salbutamol tends to be more frequently used for lack of α-adrenergic side effects and a higher accessibility. Before starting adrenergic agonists and during the treatment, blood pressure control and 12-lead ECG are recommended.

Fluoxetine and quinidine are long-lived open-channel blockers of the AChR ion channel; they shorten the duration of the prolonged synaptic currents, preventing a depolarization block and desensitization of AChR at physiological rates of stimulation and mitigating the cationic overloading. Fluoxetine and quinidine are indicated only in SCS [19]; due to a better safety profile, although less effective as long-lived open-channel blocker of the AChR channel, fluoxetine should be preferred to quinidine, which can cause more frequently QT interval prolongation, interferes with drugs metabolized by the cytochrome P450IIDA pathway, and needs serum level monitoring [1, 49]. Salbutamol may represent an add-in therapy in SCS [50], but its psychotropic effects in children and adolescents recommend caution in the first two decades of life [31]. In addition, fluoxetine may be associated with significant side effects, such as serotonergic crisis and symptomatic hypotension [19].

For any other myasthenic syndrome, some drugs should be avoided, e.g., ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta-blockers, procainamide, quinidine, and benzodiapezine. In addition, around a half of CMS women report symptoms worsening at the end of each menstrual period and may have benefit from hormonal contraception [51].

To prevent CMS worsening due to infections, in addition to routine vaccinations, children and adults patients should have flu vaccination every year and pneumococcal vaccine, if not performed before as part of routine immunization schedule [52].

Joint contractures and scoliosis should be always considered in the follow-up of CMS patients and if present, managed by neuromuscular specialists together with physical therapists, rehabilitation physicians and orthopedic surgeons. Surgery

Table 3 Drugs used for the treatment of the congenital myasthenic syndromes

Drug	Doses	Main side effects	Indications	Note
Pyridostigmine	Adults, 240–480 mg/day in 4–6 divided doses (starting with 120 mg/day in 4 divided doses); children, 4–-6 mg/kg/day (starting with 1 mg/kg/day)	Muscarinic: abdominal cramps, diarrhea, increased sweating and bronchial secretions, hypotension and bradycardia; Nicotinic muscle fasciculation and cramps	AChR subunit deficiency, *RAPSN* (also if pt is asymptomatic), *CHAT* (also if pt is asymptomatic), *GFPT1*, *DPAGT1*, *ALG2*, and *ALG14*	To avoid in *COLQ*, slow-channel syndromes, *DOK7*, *MUSK*, *AGRN*, *LRP4*; caution in case of bronchial asthma, bradyarrhythmias or recent coronary occlusion
3,4-Diamonipyridine	Adults, 10 mg 3–4 times daily, not exceed 1 mg/kg/day; children, 1 mg/kg/day in 3–4 divided doses (start under medical observation with 0.25–0.50 mg/kg/day)	Tingling; seizures (rare if total daily dose ≤ 80 mg)	AChR subunit deficiency, *RAPSN*, *DOK7*	To avoid in *COLQ* and slow-channel syndromes; to avoid in case of seizures or long-QT interval
Salbutamol	Adults, 4–12 mg/day in 2–3 divided doses; < 12 years, 4–6 mg/day; 2–6 years, 0.1 mg/kg/day	Insomnia, tremor, muscle cramps, tachycardia, and hypertension	*COLQ*, slow-channel syndromes, *DOK7*, *MUSK*, *AGRN*, refractory primary AChR deficiency	Blood pressure and ECG before starting and during treatment
Ephedrine	Adults, 45–90 mg/day in 2–3 divided doses; children, 3 mg/kg/day in 3 divided doses. Usually started with 0.5–1 mg/kg/day and increased with caution	Insomnia, epistaxis, anxiety, tremor, confusion, tachycardia and hypertension, muscle cramps	*DOK7*, *COLQ*	Blood pressure and ECG before starting and during treatment
Fluoxetine	Adults, 80–100 mg daily; maximal dose not established in children	Serotonergic crisis, nausea, hyponatremia in the elderly, sexual dysfunction, hypotension, insomnia, QT interval prolongation, suicidal ideation in children and adolescents	Slow-channel syndromes	Caution in children and adolescents due to the risk of suicidal ideation (not be used in those with signs of depression). ECG before starting treatment
Quinidine	Adults, 600 mg/day in 3 divided doses, then titrated according to serum level (1–2.5 μg/mL or 3–7.5 μM/L); children, 15–60 mg/kg/day in 4–6 divided doses.	Cardiac conduction defect, including QT interval prolongation, blood cell abnormalities, diarrhea, impaired liver function tests, inhibition of cytochrome P450IIDA	Slow-channel syndromes	ECG and serum level monitoring are recommended

pt patients

option should be limited to selected cases. Stretching for prevention of joint contractures is recommended.

Surgery for eyelid drop is not recommended and should be proposed in selected cases. Ptosis crutch glasses may be useful to overcome psychological problems in children and adults.

Respiratory follow-up with spirometry and nocturnal saturimetry is recommended in the first years of age and in case of frequent chest infections or symptoms, such as dyspnea, orthopnea, or waking-up headache or daily sleepiness [35]. Period pneumological evaluation is recommended in CMS. Parents or caregivers of CMS patients with known respiratory problems should be instructed on emergency procedures such as the intramuscular injection of neostigmine, which is an AChE-Is, basic life-saving techniques, management of noninvasive ventilation (NIV) and AMBU bag use, and physiotherapy for airway clearance. In case of respiratory crisis, patients should be hospitalized and close monitoring of respiratory parameters and arterial blood gases is required. Patients with diurnal hypercapnia or nocturnal hypoventilation should start chronic NIV. Tracheostomy may be required for management of stridor in children [31]. Expert recommendations for respiratory management of CMS in childhood have been published [35].

Swallowing and feeding difficulties should always be investigated in CMS patients, in particular in the neonatal period when they may be subtle. Weight and height should be regularly followed up in pediatric patients and eventual failure to thrive managed with adequate dietetic input. Gastrostomy should be considered in cases not resolved by medical treatment.

As in MG, in case of anesthesia, depolarizing neuromuscular blocking drugs must be avoided. The anesthetist should be informed of the condition and therapies for CMS should not discontinue in pre- or postoperative period.

Hence, multidisciplinary approach is strongly recommended for management of possible complications in CMS patients and requires the involvement of orthopedics, pediatrician, infantile and adult neurologists, pneumologists, gastroenterologists, and rehabilitation physician.

Pregnancy

CMS may frequently worsen during pregnancy; hence, pregnant CMS women should have close neurological and gynecological follow-up [51]. However, most of the patients recover the clinical status preexisting their pregnancy [51]. Vaginal delivery and peridural anesthesia are safe in CMS patients and should be considered as first-line choice [51]. Pyridostigmine may be continued during pregnancy and is allowed during breastfeeding. Salbutamol is not clearly contraindicated; however, few data on its safety during pregnancy are available and a teratogenic effect has been shown in animal studies at high doses [49, 51]. Postpartum period represents a further risky period. The outcome for children is usually good [51].

Prognosis

CMS has a highly variable course in terms of severity and progression, ranging from minor symptoms to progressive disabling weakness and this makes difficult to assess a reliable prognosis, also because identification of gene etiology is not sufficient to anticipate progression lacking natural history data on the single forms. A favorable outcome is possible in the cases of CMS initially thought to be severe because of respiratory or bulbar involvement. In contrast, motor and respiratory degradation occurring late in adulthood has been reported in patients initially only slightly affected [53]. However, static or slowly progressive course over the years is usually reported after first stages of the disease, which may be more frequently associated with acute exacerbations [12]. To this purpose, CMS subtypes with severe and recurrent respiratory crises have usually a worse prognosis. Furthermore, the response to treatments known to ameliorate neuromuscular transmission is a significant prognostic factor.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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