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# Myasthenic Syndrome in Children

*Adel A. Kareem*

## Abstract

The myasthenic syndrome in children can be inherited or of acquired autoimmune origin. In the autoimmune syndrome, babies born to a myasthenic mother are floppy at birth with weak cry, ptosis, and impaired respiration. Fortunately, most of these cases are transient and complete recovery will take place after few weeks; however, good supportive measures are needed until recovery. On the other hand, the classical autoimmune myasthenia gravis (MG), which is known as juvenile myasthenia gravis, can occur in children of any age group. It is commonly divided into prepubertal and postpubertal, the latter usually follows adult criteria, is more common in females, generalized, and most of them are seropositive for neuromuscular antibodies. In contrast, in acquired myasthenia gravis that occurs in prepubertal children, there is no sex predilection and patients are less likely seropositive, and ocular myasthenia more likely to occur than postpubertal. An interesting group of childhood myasthenic syndromes is the congenital myasthenic syndrome; this is an uncommon, nonimmune-mediated heterogeneous syndrome with variable presentation, ranging from mild symptoms with little weakness to severe ones that may cause extreme weakness and respiratory failure. Congenital myasthenic syndrome is classified into presynaptic, synaptic, and postsynaptic, and each of them has subtypes, with the postsynaptic syndrome representing the most common type. Many patients with congenital myasthenic syndrome are misdiagnosed with seronegative acquired myasthenia or congenital myopathy; however, advances in disease investigation are showing promise in early and precise diagnosis.

**Keywords:** myasthenia gravis, congenital myasthenic syndrome, neonatal myasthenia

## 1. Introduction

Myasthenia gravis in children generally is not uncommon disease, either it is genetic type known as congenital myasthenia syndrome (CMS) that involve structural defect of neuromuscular junction [1]. It is significant that is included in the differential diagnosis of seronegative myasthenia gravis (MG), congenital myopathy, peripheral neuropathy, and childhood and adolescent motor neuron diseases.

The prevalence rates of acquired autoimmune myasthenia gravis on the other hand have been increasing in the last two decades, with approximately 20 cases per 100,000 in the US population. In this syndrome, autoantibodies act against the neuromuscular junction (NMJ) [2].

Furthermore, there is another type of syndrome called transient neonatal myasthenia in which there is a passive transfer of autoantibodies from a mother with myasthenia gravis (MG).

The primary manifestation is weakness typically with diurnal fluctuation; nevertheless, variant or atypical presentations must also be considered and appropriately recognized.

MG is suspected from clinical and neurological examinations, particularly fatigue test. Moreover, investigation tools like electromyography (EMG) with repetitive stimulation tests and special instances may need the use of single fibers.

In general, advances in intensive care, therapy, and the use of immunomodulatory agents are improving the quality of life of patients with MG.

## 2. Congenital myasthenic syndrome

Congenital myasthenic syndrome (CMS) is a genetic disease, inherited as autosomal recessive, nonimmunologic neuromuscular disorder, with a prevalence of about 1/200,000. Its onset occurs usually at infancy, although sometimes its presentation can be delayed to young adulthood. Weakness along with fatigue is major presentation of CMS, and repetitive nerve stimulations have revealed decremental response in CMS patients in the absence of antibodies against muscle or neuromuscular junction [1, 3].

## 3. Classification of congenital myasthenic syndrome

Usually classified according to the defective site of the neuromuscular junction, it is often divided into presynaptic, synaptic, and postsynaptic disorders (**Table 1**) [4].

Presynaptic CMS: the prototype is CMS with episodic apnea, which is genetically determined as mutations in the enzyme choline acetyltransferase (ChAT) [5, 6]. Moreover, other presynaptic disorders have been detected that have a paucity of synaptic vesicles release with features resembling the autoimmune Lambert-Eaton myasthenic syndrome [7].

Synaptic CMS: solely related to acetylcholinesterase (AChE) deficiency in which there are mutations in COLQ, it is the second most common cause of CMS (about 15%), coding for the collagen-like tail of the AChE molecule [8, 9].

Congenital myasthenic syndrome (CMS)	Presynaptic defects (5%)	Synaptic defect (basal lamina) (15%)	Postsynaptic defects (80%)
	Choline acetyltransferase deficiency	Endplate acetylcholinesterase deficiency	Reduced AChR expression
	Paucity of synaptic vesicles		AChR mutations
	Congenital Lambert-Eaton-like syndrome		Rapsyn mutations
	Other unclassified presynaptic defects		DOK-7 mutations
			AChR kinetic abnormality
			Slow-channel syndrome
			fast-channel syndrome
			Sodium-channel mutations

AChR, acetylcholine receptor.

**Table 1.**  
Classification of congenital myasthenic syndromes [7, 15].

Postsynaptic CMS: in which a variety of genes have been detected to encode the AChR subunits, resulting in defects in AChR function or AChR subunit deficiencies like congenital myasthenia associated with Dok-7 deficiency and sodium-channel myasthenia or their combinations. In general, AChR mutation represents the majority of CMSs, about 75–85% [1, 3, 10, 11]. Furthermore, mutations in the genes for rapsyn and muscle-specific receptor tyrosine kinase (MuSK) reduced AChR expression and are considered an important cause of postsynaptic CMS [12].

## **4. Clinical presentations of congenital myasthenic syndromes**

There are no constant clinical features for the diagnosis of CMS, and it is based on the age of presentation and type of neuromuscular defect; however, a nonspecific clue of the syndrome might be evident prenatally, which is reduced fetal movement. Neonates and infants with CMS experience generalized weakness, delayed motor milestone, and hypotonia with an evidence of wasted muscle bulk over time along with an evidence of exertional weakness and fluctuation of weakness, which gets worse with intercurrent infection. Various skeletal deformities are usually observed like high-arched palate, dysmorphic facial features, arthrogryposis, and scoliosis [4].

### **4.1 Presynaptic CMS**

#### *4.1.1 Congenital myasthenic syndrome with episodic apnea*

Congenital myasthenic syndrome with episodic apnea represents an exemplary standard of presynaptic CMS, an autosomal recessive disorder with mutations in the gene encoding choline acetyltransferase (ChAT) [4].

The baby is described at birth as floppy with irregular breathing and difficulty in feeding. Examinations show ptosis with mild extraocular muscle weakness; however, the baby experiences recurrent apneic episodes, which is considered as a hallmark of this disorder. Nonetheless, apneic episodes may occur with other types of CMSs also; so, CMS with episodic apnea may be a misnomer. Prolonged apnea may lead to brain damage due to hypoxia. The apnea is usually precipitated by stressful conditions like fever, infection, and exertion. Therefore, CMS must be considered in differential diagnosis in families with history of sudden infant death. The apnea in this type of CMS decreases with advancing of age and will respond to anticholinesterase medication such as pyridostigmine prophylaxis [4].

Although EMG remains the initial diagnostic procedure in suspected cases, it often shows normal repetitive nerve stimulation at low rate (3 Hz), and single-fiber EMG (SFEMG) is usually normal. But a decremental response is found at prolonged exertion or high-rate (10 Hz) repetitive nerve stimulation [4].

### **4.2 Synaptic CMS**

#### *4.2.1 Congenital acetylcholinesterase (AChE) deficiency*

Congenital acetylcholinesterase (AChE) deficiency is an autosomal recessive disorder that presents with hypotonia and weakness that is often significant and involves the face. There are also delayed motor milestones, feeding difficulties, and, sometimes, skeletal deformities like scoliosis. Moreover, the patient may have peculiar finding such as pupillary hyporeflexia and progressive myopathy. Unfortunately, the patient does not respond or may get worse with anticholinesterase or other medication that is used for other types of CMS; however, some cases respond to ephedrine [13].

EMG displays usual features of neuromuscular disorders with decremental compound muscle action potential (CMAP) with repeated nerve stimulation in addition to jitter with single-fiber electromyography (SFEMG). On the other hand, there is an interesting EMG finding, which occurs in AChE deficiency in addition to the slow-channel syndrome, and this is repeated CMAP in response to single nerve stimulation.

The pathophysiology behind that is prolonged exposure of acetylcholine (ACh) to its receptor due to defect in its destruction by absence or defect in AChE, in consequence there is muscle membrane depolarizing block [14, 15].

### **4.3 Postsynaptic CMS**

The postsynaptic CMS is considered the most common type of CMS and is caused by gene mutations that encode AChR subunits. In consequence, there is a defect in ion-channel gating and or a decrease in number of receptors resulting in slow-channel, fast-channel, or AChR deficiency syndrome; in addition, the mutation may be in the rapsyn, MuSK, or Dok-7, resulting in neuromuscular junction disorders [11, 16].

#### *4.3.1 AChR deficiency*

AChR deficiency is inherited as autosomal recessive with mutation in genes that encode AChR subunits in the postsynaptic neuromuscular junction. Clinically, the patient presents early in infancy with variable severity; the child experiences motor developmental delay, ptosis, limitation of extraocular movement, and impaired feeding. However, it is not progressive, and weakness improves to some extent when the child becomes older.

EMG displays typical myasthenic syndrome features that include decremental CMAPs at low-rate (3 Hz) stimulations and increasing jitters with block in single-fiber EMG [17].

#### *4.3.2 Kinetic abnormality of the AChR*

The functional character and kinetic properties of AChR may be impaired as a result of mutation in AChR deficiency gene, particularly when AChR is not significantly reduced. Slow-channel and fast-channel CMSs represent the main kinetic abnormalities of the AChR.

##### *4.3.2.1 Slow-channel congenital myasthenic syndrome (SCCMS)*

SCCMS is considered the most common type of CMS [1]. The primary pathogenesis is increased duration of channel opening resulting from kinetic impairment of AChR. In consequence, there is slowing of the rate of channel closure with an increase in the rate of channel opening; moreover, sometime increase receptor-AChE affinity resulting in depolarizing neuromuscular block and weakness with exertion. It is an autosomal dominant inheritance with variable penetrance and expression in most cases; however, autosomal recessive inheritance has also been reported [18, 19]. Its presentation had variable severity and variable age of onset from early infancy, which could be delayed to teenage. Clinical manifestation is characterized by muscular weakness and wasting involving neck and scapular and extensor muscles of finger. Ptosis and extraocular muscle involvement mild or spared. The circumstances have been different from other types of CMS, this type usually progressive although its slowly, furthermore respiratory muscle and other

muscles particularly upper limb, intrinsic and fingers extensor muscles in addition to bulbar muscles are regularly involved [19].

EMG must be done to the involved muscle for sensitive results; and usually, it shows decremental CMAP in low-rate (3 Hz) stimulations. Interestingly, like endplate AChE deficiency, single-nerve stimulation usually but not always shows unique repetitive CMAP response [20].

SCCMS must be considered in the differential diagnosis of congenital muscular dystrophy, congenital myopathy, autoimmune-type MG, and metabolic and mitochondrial myopathy.

Patients with SCCMS like AChE deficiency get worse with the use of cholinesterase inhibitors due to enhanced desensitization of receptors via prolonged endplate current, which gives clue to differentiate this syndrome from autoimmune MG; however, if the patient does not receive treatment, the symptoms get worse in consequent years. Quinidine and fluoxetine are considered the medication of choice, their action on decrease opening of AChR channel [21, 22]. The dose of quinidine is 200 mg; when given twice or three times per day, it leads to improvement in short- and long-term weakness and even improved nerve conductivity as detected by EMG follow-up. In practice, fluoxetine with a dose of 80–160 mg per day is preferable as it has less side effects with same effectiveness as quinidine [15].

#### *4.3.2.2 Fast-channel congenital myasthenic syndrome*

Fast-channel congenital myasthenic syndrome is an autosomal recessive inheritance and has common features with AChR deficiency syndromes; however, it is more severe. The pathophysiology disparity to SCCMS in which Ach., when bound to Ach receptor, the time of channel opening is short, in consequence the activation become short resulting in decrease transmission of signals [11, 23, 24]. Clinically, it is like other CMSs presenting with delayed motor milestones, ptosis, limitation of extraocular movement with difficulties in feeding and chewing, and also fatigue and generalized weakness triggered by exertion [25]. Nonetheless, mild cases may be missed clinically and even via EMG procedures and erroneously diagnosed as congenital myopathy. In contrast, the severe cases experience respiratory distress, facial involvement or even arthrogryposis multiplex features [1]. Of note, fast-channel CMS must be considered in differential diagnosis of patients with seronegative myasthenic syndrome.

EMG findings show typical symptoms of postsynaptic neuromuscular disorders that include decremental CMAPs at repetitive low-rate stimulations (3 Hz), increased jitter with block in single-fiber EMG, and no observation of repetitive CMAPs.

Fortunately, the patient benefits from the use of cholinesterase inhibitors and 3,4-diaminopyridine or both [26] and if left without treatment may experience slowly progressive disease or remain stationary.

#### *4.3.3 Mutations affecting acetylcholine receptor (AChR) clustering and synaptic structure*

To achieve effective synaptic transmission, there must be functional and structural integrity of all involved neuromuscular postsynaptic parts [27].

##### *4.3.3.1 AChR deficiency due to receptor-associated protein of the synapse (RAPSN) mutations*

AChR deficiency due to receptor-associated protein of the synapse (RAPSN) mutations may occur at any age; nevertheless, neonates are the most commonly affected and might need nasogastric tubes for feeding and mechanical ventilation

due to severe hypotonia and significant bulbar involvement. Sometimes, the baby is born with arthrogryposis multiplex, but the condition improves with advancing age with less probability of apnea. It is sometimes misdiagnosed as seronegative acquired autoimmune myasthenia gravis. Ankle dorsiflexion weakness is considered a characteristic feature of this syndrome and might give hint for the diagnosis [28].

EMG; as other myasthenic syndrome show decremental CMAP and jitter in single fiber. Nevertheless, sometimes, there is difficulty in detection of these typical features in EMG.

Fortunately, those patients respond to anticholinesterase agents and may get additional improvement from 3,4-diaminopyridine [28].

#### *4.3.3.2 Congenital myasthenic syndrome with proximal weakness due to mutations in DOK7*

This syndrome is sometimes called limb girdle CMS as proximal muscle weakness is more than that of the distal one [29]. Although the patient initially attained milestones on time, but the patient might have ptosis since early infancy and could be progressive on the other hand in childhood age experience progressive weakness with predominant proximal muscle weakness and may lead to nonambulation state. Fifty percent of patients display tongue atrophy and ptosis which might be progressive, but often still no ophthalmoplegia and the fluctuation of symptoms are predominant nevertheless a lot of patients misdiagnosed as myopathies [30, 31].

#### *4.3.3.3 Mutations in CHRNG neuromuscular transmission*

Mutations in CHRNG neuromuscular transmission is caused by prenatal inherited myasthenia, which in consequence might result in fetal developmental abnormalities [32].

Escobar's syndrome (multiple pterygium syndrome) is the most well-known type of CMS attributed to CHRNG mutation. It is inherited as autosomal recessive with cranial deformities including ptosis, low-set ear, high-arched palate, receded chin, and orthopedic deformities including arthrogryposis multiplex and cervical pterygia; in addition, many of them die in the uterus [33].

#### *4.3.3.4 MuSK mutations postsynaptic CMS*

The mutation impairs postsynaptic voltage-gated sodium channel (SCN4A) and might cause severe respiratory distress with fluctuation of disease severity. Unfortunately, patients do not respond to anticholinesterases but might respond well to combined therapy with diaminopyridine [34, 35].

## **5. Childhood autoimmune myasthenia gravis**

Generally, there is no significant difference in myasthenia gravis between patients younger than 18 years and adults in terms of pathophysiology, clinical presentation, and diagnosis [36, 37]. CMS must be considered in seronegative MG, but low incidence of seropositive cases in acquired MG makes the diagnosis challenging. There is no female predominance with higher rate of spontaneous remission in prepubertal children. On other hand, there is evidence of higher prevalence of ocular MG in prepubertal children [38].

Although the treatment line is the same as that of adults, there is concern of stunted growth with steroid treatment, as well as the drawback of accumulative

effect of immunosuppressive drugs [39, 40]. Thymectomy is usually postponed as there is a possibility of spontaneous remission to happen and attempt to avoid such invasive procedure. Therefore, the treatment should be individualized, and generally, the treatment is often less aggressive, particularly in the prepubertal age group.

Although respiratory failure might occur in some cases, the general prognosis is often satisfactory.

## **6. Neonatal myasthenia caused by maternal MG**

Maternal MG can cause transient neonatal myasthenia in about 20% of cases, the pathophysiology behind is AChR autoantibodies cross the placenta from the mother to the fetus. The neonate may have born with severe weakness to mother with mild MG and the invers is true, therefore, the severity of disease in neonate is not related to mother MG. Moreover, it is not related to the duration of maternal MG and can occur even in those with seronegative MG [41–44]. Nevertheless, the effect may have decreased with proper maternal treatment, while subsequent pregnancy may cause more affected neonates [45–47].

The condition is usually transient, and it presents clinically soon after birth with generalized weakness, difficulty in sucking and swallowing, weak cry, respiratory distress, which may get worse with inability to clear pharynx that may cause airway obstruction and cyanosis, in addition to ptosis and strabismus, but it is less common in older children.

The diagnosis is suspected by history of maternal MG, detection of AChR antibody in the infant and mother, and EMG—older children show decremental response with low rate of repetitive stimulation but not for high rates as decremental response occurs in high-rate stimulations in normal neonates. Furthermore, responding to cholinesterase inhibitors make diagnosis most likely [48].

Treatment involves cholinesterase inhibitors, in addition to supportive measures. Plasma exchange may be needed for severe, life-threatening conditions.

The prognosis fortunately is good as the syndrome is transient and improvement is complete in most infants with the duration of recovery ranging from 1 week to 8 weeks without recurrence, which is most probably related to the clearance of causative autoantibodies. However, about 10% of patients may die because of inadequate respiratory support and delayed or improper treatment [49].

## **7. Conclusion**

Myasthenia syndrome in children not uncommon but the unique in children is the inherited congenital myasthenia syndrome which is not follow autoimmune and no antibodies determined. Therefore, a precise diagnosis is important for treatment. The challenge is to differentiate this syndrome from seronegative acquired myasthenia gravis and one may need, in addition to conventional investigation, specialized microelectrode analysis of neuromuscular transmission with or without genetic test.

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### **Author details**

Adel A. Kareem  
Welfare Teaching Hospital, Baghdad, Iraq

\*Address all correspondence to: [adelkareemlh@gmail.com](mailto:adelkareemlh@gmail.com)

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