Congenital myasthenic syndromes: an update

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The last 20 years has seen significant advances in our understanding and treatment of the congenital myasthenic syndromes. This article discusses individual syndromes, their management and how to distinguish the subtypes from each other as well as from other conditions that commonly mimic them.

BACKGROUND

What are congenital myasthenic syndromes?
Congenital myasthenic syndromes result from gene mutations affecting the neuromuscular junction structure and function. Unlike autoimmune myasthenia gravis, the immune system is not involved and there is no association with antibodies to the acetylcholine receptor (AChR) or muscle specific kinase. Although all congenital myasthenic syndromes share the feature of fatiguable muscle weakness, they are discrete syndromes each with their own, often distinct, phenotype. Significant advances in the last 20 years, mainly in molecular genetics, have enabled identification of at least 15 genes implicated in congenital myasthenic syndromes (table 1). About 80%–90% of patients with congenital myasthenia in the UK now have a confirmed genetic diagnosis. Thus, there are likely to be many unidentified associated genes.

The delineation of these different genetic syndromes has enabled the development of a range of effective symptomatic treatments. The choice of treatment is governed by the underlying pathogenic mechanism. Importantly, the treatments routinely used for some subtypes can cause significant deterioration in others. In addition, a range of conditions can mimic congenital myasthenic syndromes and these too require different therapy. Therefore, a definitive genetic diagnosis is important and guides treatment, prognosis and genetic counselling.

Most patients with congenital myasthenia present with symptoms at birth or early infancy, although in some subtypes, particularly those predominantly affecting proximal muscles such as downstream of kinase-7 (DOK7), onset is typically in childhood with walking difficulties. Patients with the slow channel syndrome may have symptom onset well into their second or third decades. While many patients are now identified in early life, many are diagnosed only well into adulthood. This is often because they are mildly affected or because they have been wrongly diagnosed, usually as a myopathic disorder. The syndromes often cause oculo-facial weakness—as in myasthenia gravis—as well as weakness of limb and axial muscles. Bulbar and respiratory involvement is common and can be life-threatening in some subtypes more than others. Starting treatment gives symptom benefit but it remains to be seen whether treating from an early age, as is now common, affects long-term disease severity. In subtypes with early life-threatening respiratory crises that are commonly associated with a family history of sibling deaths, recent improvements in diagnosis and treatment will probably improve survival.

Epidemiology
Congenital myasthenic syndromes are rare; the prevalence of genetically confirmed cases in the UK is at least 3.8 per million. Some subtypes are especially rare, such as agrin or muscle specific kinase congenital myasthenic syndromes, with only a handful of cases diagnosed worldwide. Figure 1 shows the proportion of each subtype in the British Isles, within which there is a large regional variation in prevalence. Although this is partly explained by familial clustering and racial population differences, the prevalence is greater near to some large neuromuscular centres, suggesting that these conditions are underdiagnosed.
**NEUROMUSCULAR JUNCTION STRUCTURE AND FUNCTION**

**Signal transmission**

A nerve impulse triggers release of the neurotransmitter acetylcholine from the presynaptic nerve terminal into the synaptic cleft (figure 2). Acetylcholine diffuses and binds to AChRs, which are clustered on the crests of the folded postsynaptic muscle membrane. Binding opens the central ion channel pore of the AChR, allowing flow of current through the channel, depolarising the muscle membrane.

If the degree of depolarisation exceeds a critical threshold, voltage-gated sodium channels (VGNa+) open, generating an action potential. This propagates along the muscle fibre, resulting in contraction.

**Safety factor and neuromuscular junction structure and function**

Usually the degree of depolarisation exceeds the threshold by a factor of threefold to fivefold. This is termed the ‘safety factor’ and means that under normal conditions neuromuscular transmission does not fail. Several features contribute to the efficiency of this process. Vesicles of acetylcholine are released from discrete areas, termed ‘active zones’, positioned opposite to the postsynaptic folds. The AChRs are themselves clustered in close proximity to the active zones. The postsynaptic membrane effectively acts as an amplifier of current because it is highly folded.

Mutations have been identified in genes encoding several key proteins involved in development and maintenance of the neuromuscular junction.

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**Table 1**  Congenital myasthenic syndrome subtypes, associated genes and main pathology

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Main pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presynaptic</strong></td>
<td><strong>Choline acetyltransferase (Chat) deficiency</strong></td>
<td><strong>CHAT</strong> Reduced acetylcholine synthesis</td>
</tr>
<tr>
<td><strong>Synaptic</strong></td>
<td><strong>Acetylcholinesterase (Ace) deficiency/COLQ</strong></td>
<td><strong>COLQ</strong> Paucity of Ace Increased lifetime of acetylcholine within synaptic cleft AChR desensitisation Excitotoxic end-plate myopathy</td>
</tr>
<tr>
<td><strong>Postsynaptic</strong></td>
<td>■ Receptor deficiencies, abnormalities of clustering or synaptogenesis</td>
<td><strong>AChR deficiency</strong> Reduced expression of AChR</td>
</tr>
<tr>
<td></td>
<td>■ ε subunit: <strong>CHRNE</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ α subunit: <strong>CHRNA</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ β subunit: <strong>CHRNB</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ δ subunit: <strong>CHRND</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The ε subunit is invariably affected (see text)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rapsyn</strong> <strong>RAPSIN</strong></td>
<td>Impaired clustering of AChR</td>
</tr>
<tr>
<td></td>
<td><strong>DOK7</strong> <strong>DOK7</strong></td>
<td>Synaptopathy; small and simplified presynaptic and postsynaptic structures</td>
</tr>
<tr>
<td></td>
<td><strong>GFPT1</strong> <strong>GFPT1</strong></td>
<td>Not ascertained</td>
</tr>
<tr>
<td></td>
<td><strong>DPAGT1</strong> <strong>DPAGT1</strong></td>
<td>Abnormal glycosylation of synaptic components AChR deficiency</td>
</tr>
<tr>
<td></td>
<td><strong>Escobar syndrome</strong></td>
<td>**AChR χ subunit: <strong>CHRNG</strong> Loss of fetal AChR</td>
</tr>
<tr>
<td></td>
<td>■ Kinetic abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Slow channel syndrome</strong></td>
<td><strong>CHRNE, CHRNA, CHRNB or CHRND</strong> Prolonged AChR channel opening Excitotoxic end-plate myopathy</td>
</tr>
<tr>
<td></td>
<td><strong>Fast channel syndrome</strong></td>
<td><strong>CHRNE, CHRNA or CHRND</strong> Abnormally brief AChR channel opening</td>
</tr>
<tr>
<td></td>
<td><strong>Rare subtypes</strong></td>
<td><strong>CHRNE</strong> Low conductance</td>
</tr>
<tr>
<td></td>
<td><strong>LAMB2</strong></td>
<td>Reduced β2-laminin, a basal lamina component that controls the alignment of nerve terminal with postsynaptic regions</td>
</tr>
<tr>
<td></td>
<td><strong>PLEC1</strong></td>
<td>Reduced plectin, a ubiquitous cytoskeletal linking protein concentrated at the postsynaptic membrane of the junctional folds</td>
</tr>
<tr>
<td></td>
<td><strong>MUSK</strong></td>
<td>Impaired MuSK, a protein involved in synapse formation and AChR clustering</td>
</tr>
<tr>
<td></td>
<td><strong>AGRN</strong></td>
<td>Impaired agrin, a neural peptide involved in synapse formation and the AChR clustering pathway</td>
</tr>
<tr>
<td></td>
<td><strong>SCN4A</strong></td>
<td>Altered postsynaptic voltage-gated sodium channel function</td>
</tr>
</tbody>
</table>

AChR, acetylcholine receptor; DOK7, downstream of kinase-7; MuSK, muscle specific kinase.
architecture, as well as directly with signal transmission. In each congenital myasthenic syndrome subtype, the safety factor is reduced by a different mechanism, depending upon the normal function of the affected protein.

Transmission also relies on the availability and control of acetylcholine at the synapse. The enzyme acetylcholinesterase (AChE) is anchored to the synaptic basal lamina by a collagen-like subunit tail encoded by COLQ. AChE cleaves acetylcholine to choline and acetyl-coenzyme A and thus affords temporal control of signal transmission. The choline and acetylcoenzyme A are then taken up into the nerve terminal where they are used to resynthesise acetylcholine in a process catalysed by choline acetyltransferase.

The AChR is central to neuromuscular transmission. The receptor is a pentamer comprising four different subunits (α, β, δ, ε in a ratio of 2:1:1:1), with each subunit encoded by a separate gene. These combine to form a transmembrane ligand-gated ion channel. Mutations in receptor subunit genes can cause either a reduced number of available receptors (receptor deficiency), abnormal kinetic properties of the channel (fast or slow channel syndromes) or reduced channel

**Figure 1** Proportions of genetically defined congenital myasthenic syndrome (CMS) subtypes in the British Isles, total n=255. AChR def ε: acetylcholine receptor deficiency due to ε subunit mutations; DOK7, downstream of kinase-7; AChE def (COLQ), acetylcholinesterase deficiency.

**Figure 2** The neuromuscular junction with proteins involved in neuromuscular transmission. Ach, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor; ChAT, choline acetyltransferase; DOK7, downstream of kinase-7; LRP4, low density lipoprotein receptor-related protein 4; MuSK, muscle specific kinase; VGNa⁺C, voltage-gated sodium channel.
conductance. These different effects give rise to different congenital myasthenic syndromes: which type occurs depends upon the structural effect of the individual mutations.

Localisation and clustering of AChRs on the crests of folds is critical for maintaining safety factor and is triggered by a number of proteins. These include the congenital myasthenia-associated proteins, DOK7 and rapsyn.

**INDIVIDUAL SYNDROMES AND DIAGNOSTIC CLUES**

Several features help to distinguish between subtypes (table 2). Ophthalmoplegia is undoubtedly the most useful differentiating feature and forms the basis of the initial genetic screening strategy of the UK congenital myasthenia diagnostic genetics laboratory.

**Presynaptic**

Choline acetyltransferase deficiency

This is characterised by impaired acetylcholine synthesis within the nerve terminal. Patients classically experience sudden episodes of respiratory distress with apnoea and bulbar weakness, often precipitated by infection. They may be relatively strong in between such crises.

While symptoms are usually apparent from birth and continue episodically, affected children can also be normal at birth and develop episodic apnoeas later, during infancy or in childhood.

There may also be other myasthenic symptoms; although ptosis is usual, the extra-ocular muscles are spared.

AChE inhibitors help and 3, 4-diaminopyridine (3, 4-DAP) may also give symptomatic relief.

**Synaptic**

AChE deficiency/COLQ

COLQ mutations cause loss of AChE: this results in prolonged lifetime of acetylcholine in the synapse. Consequently, there is desensitisation of the AChR as well as prolonged end-plate potentials, leading to depolarisation blockade detectable on EMG. The prolonged end-plate potentials cause a secondary excito-toxic myopathy because of excessive cationic flow onto the muscle.

Patients classically present with severe and progressive weakness from birth or early infancy. However, there are also later onset and milder phenotypes. Respiratory involvement is common and patients can develop respiratory crises and/or chronic hypventilation.

Ophthalmoplegia and ptosis are common but variably present. In all, 18% of a large case series had neither of these.1 Within the same series, 25% showed abnormally slow pupillary dilation following constriction to light. In our experience, this is usually subtle and detected only after the genetic diagnosis has already been made. Treatment is with oral salbutamol or ephedrine. Typically symptoms worsen with pyridostigmine and this can be severe. 3, 4-DAP should also be avoided.

**Postsynaptic**

Postsynaptic gene mutations affecting the AChR, rapsyn and DOK7 comprise ~88% of UK cases of congenital myasthenic syndromes.

AChR deficiency (usually due to ε subunit mutation)

This is the most common form of congenital myasthenic syndrome in the UK (clinical vignette 1). Most patients present with feeding problems and ptosis at birth or infancy.

The ε subunit found in adult AChR replaces the γ subunit in fetal AChRs during late gestation. Maintained low level expression of fetal receptor type into and throughout adulthood explains why patients with ε subunit null mutations survive and why mutations of non-ε subunits in deficiency syndromes are rare and usually severe.

Ophthalmoplegia is invariably present and severe but usually not noticed at birth. It is likely that ophthalmoplegia develops within the first year.

Although patients’ weakness can worsen during intercurrent infection, they do not experience acute crises and the condition is usually stable in the long-term. Patients generally respond well to pyridostigmine with or without the addition of 3, 4-DAP.

Clinical vignette 1. A woman in her mid-sixties

A 64-year-old woman has had problems from birth with a weak suck and droopy eyes. She could never run properly and stairs have always been a problem. A myasthenic disorder was diagnosed at the age of 13 years following problems during a general anaesthetic. She has taken pyridostigmine since that time with benefit. Her main complaint is of limb weakness, which is variable and fatiguable. Chewing and swallowing were a problem before she started pyridostigmine. On examination, there is marked limitation of eye movements in all directions, without diplopia. Her eye movements have not improved despite pyridostigmine. Her condition has remained stable over the years.

Routine EMG shows mild myopathic change. Single-fibre EMG shows abnormal jitter and there is decrement on repetitive nerve stimulation. Genetic analysis identified mutations in the ε subunit of the AChR (CHRNE) known to cause AChR deficiency. This confirmed her congenital myasthenic syndrome.

Rapsyn

Mutations in the AChR clustering protein rapsyn also cause postsynaptic receptor deficiency, but rapsyn congenital myasthenia has a very different phenotype compared to AChR deficiency due to ε subunit mutation.” (clinical vignette 2)
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Typical age of onset</th>
<th>Typical presenting features</th>
<th>Ophthalmoplegia</th>
<th>Other ocular features</th>
<th>Respiratory crises</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline acetyltransferase</td>
<td>Birth and infancy</td>
<td>Episodic apnoeas</td>
<td>Absent</td>
<td></td>
<td>+</td>
<td>May be normal between episodes of apnoea</td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholinesterase deficiency</td>
<td>Birth &gt; infancy &gt;</td>
<td>Ptosis, falls, slower movement, poor feeding</td>
<td>Usually present</td>
<td>Slowed pupillary response following constriction to light</td>
<td>+</td>
<td>Chronic hypoventilation</td>
</tr>
<tr>
<td></td>
<td>childhood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine receptor deficiency</td>
<td>Birth and infancy</td>
<td>Ptosis, poor feeding</td>
<td>Severe</td>
<td></td>
<td></td>
<td>Generally stable course</td>
</tr>
<tr>
<td>Rapsyn</td>
<td>Birth and infancy</td>
<td>Crises, ptosis, poor feeding, contractures may require ventilation at birth</td>
<td>Absent</td>
<td>Strabismus: may be convergent or divergent and latent or manifest</td>
<td>+</td>
<td>Dysmorphic features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There is also a milder late onset phenotype with limb weakness ± ptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOK7</td>
<td>Early childhood, for example, 2–4 years</td>
<td>Deterioration in walking and falls in a child who has achieved normal milestones occasionally onset at birth with stridor and poor feeding</td>
<td>Absent</td>
<td></td>
<td></td>
<td>Limb girdle weakness, tongue wasting, stridor</td>
</tr>
<tr>
<td>Slow channel syndrome</td>
<td>Variable birth to</td>
<td>Hypotonia or weak neck muscles at birth/infancy limb weakness, especially distal upper limb,</td>
<td>Mild–moderate</td>
<td></td>
<td></td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>adulthood</td>
<td>ptosis, difficulty running</td>
<td>or absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast channel syndrome</td>
<td>Birth</td>
<td>Respiratory crises/apnoea, ptosis, weak cry, poor feeding/choking may require ventilation at birth</td>
<td>Severe</td>
<td></td>
<td>+</td>
<td>Usually profound weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abrupt</td>
<td></td>
</tr>
<tr>
<td>GFPT1, DPAGT1</td>
<td>Early childhood</td>
<td>Deterioration in walking, falls, limb weakness</td>
<td>Absent</td>
<td>Ptosis mild or absent</td>
<td></td>
<td>Little or no facial weakness, tubular aggregates on muscle biopsy</td>
</tr>
</tbody>
</table>

For ophthalmoplegia the typical findings are listed. DOK7, downstream of kinase-7; +, associated with.
Typical features of rapsyn congenital myasthenia are of onset at birth with respiratory weakness, feeding difficulties and generalised hypotonia. Mild arthrogryposis is common, and usually resolves with physiotherapy. Patients often have characteristic facial dysmorphism including a high-arched palate, resulting from fetal akinesia. Weakness is usually generalised. While most patients have ptosis and strabismus, ophthalmoplegia is very rare.

Acute life-threatening crises with respiratory failure are frequent in rapsyn congenital myasthenia particularly during infancy and early childhood. Crises usually, but not always, occur in the context of infection. The weakness responds well to pyridostigmine and, if needed, to 3, 4-DAP. The long-term prognosis of rapsyn congenital myasthenia is good, with the frequency and severity of life-threatening crises diminishing during childhood and usually resolving around the age of 7 years. Many adults can reduce or stop treatment.

There is also a late onset phenotype which can mimic autoimmune myasthenia gravis. Symptoms are usually milder although it is possible, in some cases, that early involvement has gone unnoticed.

Clinical vignette 2. A man in his early twenties
A 22-year-old man was born at term by emergency Caesarean section for fetal distress. His mother had reported reduced movement in utero. He was hypotonic at birth, with no voluntary movement and no respiratory effort. He was immediately intubated and ventilated for 12 days, though despite this he developed prolonged seizures secondary to anoxia.

He was always floppy as an infant but was late to sit and stand. Subsequently he had recurrent respiratory tract infections and was a poor feeder. During childhood, he developed respiratory failure during viral infections, requiring multiple admissions to the intensive care unit. These dramatic worsenings with infection lessened and he had no further infection-induced respiratory crises after the age of 7 years.

Congenital myasthenia was suspected at the age of 5 years. His single-fibre EMG was clearly abnormal but repetitive nerve stimulation was normal. Following this, he started to take pyridostigmine, with good response; 3, 4-DAP was added at the age of 12 years, with further benefit. He reports diurnal variation in symptoms though overall strength has improved.

On examination, there is mild bilateral ptosis but his eye movements are full apart from a mild latent squint. His facial muscle strength is normal and there is mild generalised limb weakness.

Genetic analysis has identified mutations in the RAPSN gene, confirming his congenital myasthenia.

DOK7
DOK7 congenital myasthenia usually presents with deterioration in walking in a child who has achieved normal motor milestones (clinical vignette 3). However, some patients present earlier with respiratory weakness, feeding difficulties and stridor in infancy.

Weakness is typically in a limb girdle distribution, often with facial muscles affected, with a ‘myasthenic snarl’ (figure 3). Similar to rapsyn congenital myasthenia, there is usually ptosis but eye movements are usually normal. About half of patients have tongue wasting: this can help to distinguish it from other subtypes (figure 4).

DOK7 congenital myasthenia is slowly progressive, probably because of a secondary myopathy. Muscle biopsy may show mild non-specific changes, for example, increased fibre size variability, type II fibre atrophy, central nuclei and, less commonly, fibre necrosis and regeneration. Mild bulbar weakness and respiratory weakness may develop later in life. About 25% of patients require regular non-invasive ventilation at some point.

Pyridostigmine typically worsens the symptoms and should be avoided. 3, 4-DAP can help but should be used with caution, as some patients show a significant deterioration. However, DOK7 responds well to oral salbutamol or ephedrine over months.

Clinical vignette 3. A woman in her late forties
A 48-year-old woman started to trip and fall at the age of 3 years. Her mother reports a normal birth and early milestones. At school she was unable to walk and was admitted to hospital with encephalopathy, presumed due to an autoimmune cause. He was started on pyridostigmine, with slow improvement over several years. As an adult he had occasional myasthenic attacks with colds.

A 48-year-old woman started to trip and fall at the age of 3 years. Her mother reports a normal birth and early milestones. At school she was unable to walk and was admitted to hospital with encephalopathy, presumed due to an autoimmune cause. He was started on pyridostigmine, with slow improvement over several years. As an adult he had occasional myasthenic attacks with colds.
participate in most sports. Her symptoms worsened at the age of 20 years, when she had to climb and descend stairs on her hands and knees. Fluctuations in her weakness could last for weeks or months at a time, without any obvious cause; she has slowly deteriorated over the years. Now, in her forties, she has developed nocturnal hypoventilation and requires nocturnal ventilatory support. There are occasional bouts of choking. She can walk up to 10 min with one stick. She has tried several treatments; pyridostigmine made her worse and 3, 4-DAP had no effect. She has one sister who is similarly affected.

On examination, there is mild fatiguable ptosis and moderate weakness of the limb girdle, neck and facial muscles.

A muscle biopsy at the age of 19 years showed non-specific myopathic features. Neurophysiology at the age of 26 years suggested a myasthenic disorder. In 2006, congenital myasthenia was confirmed when a mutation in \textit{DOK7} was identified.

Ephedrine treatment over the subsequent year gave her clear improvement in strength. She now walks unaided and manages stairs; her bulbar symptoms have also lessened.

\textbf{GFPT1 and DPAGT1 congenital myasthenic syndromes}

These recently discovered subtypes each result from mutation in genes encoding glycosylation pathway enzymes and share several features.\textsuperscript{5, 6}

Typically, there is insidious onset of limb girdle weakness in early childhood. Craniofacial muscles are usually only very minimally affected; ophthalmoplegia is not a feature. The clinical course is stable and acute crises do not occur. Overall these features, as well as the muscle biopsy findings—usually including tubular aggregates—make these subtypes often misidentified as myopathies.

AChE inhibitors and 3, 4-DAP are both usually beneficial; salbutamol and ephedrine may also help. \textit{DPAGT1} is also associated with congenital disorder of glycosylation type I\textsubscript{f}, which is sometimes associated with a severe multisystem disorder. It is likely that the spectrum of disease caused by \textit{DPAGT1} and \textit{GFPT1} mutation will widen. It is also likely that there are other glycosylation pathway genes responsible for congenital myasthenic syndromes.

\textbf{Slow channel syndrome}

This is the only dominantly inherited congenital myasthenic syndrome. The age of onset is widely variable, between birth and the fourth or fifth decade. Most patients present in childhood with neck flexion weakness and difficulty running, although within a single family the severity can vary. Examining asymptomatic family members may therefore be informative. When symptoms begin after childhood, upper limb weakness is a common presenting feature. Acute crises are unusual and early features seen in other forms of congenital myasthenia—such as feeding difficulty or apnoeas—are uncommon. There is often selective and asymmetrical involvement of cervical and distal upper limb muscles, notably wrist and finger extensors and thumb abductors. There may be ptosis and ophthalmoplegia though usually these are milder than in AChR deficiency.

The underlying pathology is prolonged AChR opening, which causes desensitisation blockade of the receptor; the EMG may show specific features (see below). Cationic overload of the muscle results in an excitotoxic end-plate myopathy with loss of structural integrity. This secondary damage explains the symptoms and the progressive deterioration. Predictably, pyridostigmine and 3, 4-DAP exacerbate the underlying pathology, usually cause deterioration and should be avoided. Treatment is with fluoxetine or quinidine since these act as open channel blockers.\textsuperscript{7}

\textbf{Fast channel syndrome}

Fast channel syndrome is usually the most severe form of congenital myasthenia. Patients typically experience life-threatening acute crises on a background of severe generalised weakness, even when treated. Many patients report a sibling death.\textsuperscript{8}

Patients are affected from birth with respiratory failure, feeding difficulties and generalised hypotonia. Ptosis and ophthalmoplegia are invariably and severe (figure 5), as in AChR deficiency due to \(\epsilon\) subunit mutation. Feeding difficulties persist into childhood and often necessitate nasogastric or percutaneous endoscopic gastrostomy feeding. Respiratory...
symptoms, including episodic apnoeas and chronic hypoventilation, require regular respiratory assessment and often non-invasive ventilation at home. Pyridostigmine and 3, 4-DAP help, though often the effect of pyridostigmine diminishes after an initial striking response.

Almost 50% of patients with fast channel syndrome in the British Isles are aged 5 years or less, reflecting the severity of this syndrome.

GENETICS
All congenital myasthenic syndromes identified to date, apart from the slow channel syndrome, are autosomal recessive. Most patients have private missense mutations, although there are some common mutations (box 1).

NEUROPHYSIOLOGY
The neurophysiological findings in congenital myasthenic syndromes are similar to those in autoimmune myasthenia gravis. There is usually increased jitter on single-fibre EMG, although it can be normal in unaffected muscles. Depending upon the severity of neuromuscular junction transmission failure, there may be blocking of potentials on single-fibre EMG and compound muscle action potential amplitude decrement (>10%) on repetitive nerve stimulation. Single-fibre EMG is more sensitive but less specific than repetitive nerve stimulation; myopathic and neurogenic disorders may show increased jitter, although it is typically less abnormal than in myasthenia. As with autoimmune myasthenia gravis, mild myopathic potentials may be seen on standard EMG. Some syndrome specific features are detailed in box 2.

DIFFERENTIAL DIAGNOSES
Autoimmune myasthenia gravis
When the clinical features or neurophysiology results suggest a myasthenic condition but the AChR antibodies are negative, it is critical to distinguish the congenital from autoimmune myasthenia gravis. Doing so can avoid unnecessary thymectomy and immunosuppressive therapy. Recently, a cell-based assay was developed that can identify AChR antibodies in patients ‘seronegative’ in the standard radioimmunoprecipitation assay. However, some patients with autoimmune myasthenia gravis remain seronegative on both assays. Table 3 shows some helpful features.

Myopathy
Primary muscle disease is another major differential diagnosis. Many patients with congenital myasthenic syndromes, particularly those with DOK7, are initially diagnosed with myopathies such as muscular dystrophies and congenital myopathy. Myopathy can have a pattern of weakness similar to congenital myasthenia, and occasionally show mild improvement with AChE

Box 1 Common mutations
- **Acetylcholine receptor (AChR) deficiency (ɛ):** ɛ1267delG is common, present on one allele in ~20% patients. It arises from an ancient founder mutation, frequently occurs in families with origins in south-eastern Europe and usually confers a relatively mild phenotype.
- **Rapsyn:** Over 90% of UK patients have the N88K missense mutation on at least one allele. This mutation arises from a common ancient Indo-European ancestor.
- **DOK7:** The exon 7 frameshift duplication c.1124_1127dupTGCC is found in at least one allele in over half of all kinships.
- **Fast channel syndrome:** One allele bears the fast channel mutation that confers the kinetic abnormality. For the phenotype to express, the second allele must be abnormal and usually it bears a null or low-expressor mutation. In all, 90% of fast channel patients in the UK have the ɛP121L fast channel mutation.
- **Slow channel syndrome:** Mutations in any AChR subunit can cause slow channel syndrome. Around 70% of patients in the UK have the αG153S mutation, largely due to one very large kinship. Familial screening demonstrates variable penetrance.
inhibitors (particularly those with centronuclear core myopathies); also they can show jitter on single-fibre EMG (particularly mitochondrial myopathies). Often muscle biopsy helps to distinguish the two. In congenital myasthenia phenotypes with myopathic features muscle biopsy often shows variable fibre size and other mild non-specific myopathic features. MR imaging of muscle is increasingly used to evaluate myopathy and guide selection of appropriate genetic tests, but its value in evaluating congenital myasthenic syndromes is unclear.

Fatigue syndromes
A lack of objective muscle weakness and dramatic fluctuation in symptoms, for example, bedbound periods followed by quick recovery, might suggest chronic fatigue syndrome rather than congenital myasthenia. Myasthenia gravis causes fatigable muscle weakness rather than generalised energy fatigue.

Mitochondrial disease
Multisystem involvement is characteristic of mitochondrial disease rather than congenital myasthenia.

Congenital cranial dysinnervation disorders or acquired cranial nerve palsy
Some congenital cranial dysinnervation disorders cause bilateral ptosis and restricted eye movements and so can mimic myasthenia. Acquired cranial nerve palsies are usually unilateral and are therefore much less likely to be mistaken for congenital myasthenic syndromes (where marked asymmetry does not occur). Cranial nerve abnormality without weakness elsewhere is also atypical for congenital myasthenia, although this may be difficult to establish with certainty in very young patients.

Table 3 Differentiating congenital myasthenic syndromes from autoimmune myasthenia gravis

<table>
<thead>
<tr>
<th>Suggestive of autoimmune myasthenia gravis</th>
<th>Suggestive of congenital myasthenic syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitous onset from normal although mild previous abnormalities may have been missed</td>
<td>Onset at birth or infancy</td>
</tr>
<tr>
<td>Marked asymmetry of ptosis and fluctuation in ophthalmoplegia with diplopia</td>
<td>Ankle dorsiflexion weakness common in congenital myasthenic syndromes but almost never a feature of myasthenia gravis</td>
</tr>
<tr>
<td>Response to immunotherapies</td>
<td>Ophthalmoplegia not responsive to treatment</td>
</tr>
<tr>
<td>Spontaneous resolution especially in children</td>
<td>Family history or consanguinity in parents</td>
</tr>
<tr>
<td></td>
<td>Dystrophic features due to early in utero weakness</td>
</tr>
</tbody>
</table>

Figure 6 Repetitive compound muscle action potential to single stimuli. Reproduced from^{1} by permission of Oxford University Press.
Paediatric hypermobility (joint laxity) and dyspraxia
In children, these symptoms commonly occur together but can occur in isolation. Although generally considered to be benign, they can cause significant functional compromise.

The mechanical disadvantage of joint laxity makes a movement less efficient than if the joint was stable. Joint laxity is fairly common in congenital myasthenic syndromes, especially in children. Dyspraxia in children occurs usually in the context of developmental coordination disorder. In these children, congenital myasthenia is sometimes considered because of motor delay or difficulty. Lack of fattiguing over the course of a day, a lack of craniobulbar or respiratory symptoms and normal neurophysiology all suggest a non-congenital myasthenia cause.

The neonate or infant with hypotonia, respiratory and bulbar problems
Hypotonia, respiratory and bulbar symptoms are non-specific features in neonates and infants in whom congenital myasthenia is only one of many causes. Evaluating these children can be challenging and the problem is further confounded by the difficulty assessing muscle strength at this age. Neurophysiological studies are the best way to determine whether neuromuscular junction transmission is abnormal.

DRUG TREATMENTS
The choice of treatment varies with the subtype (figure 7). All treatments in congenital myasthenia are used out of licence.

Cholinesterase inhibitors and 3, 4-DAP
Both these treatments reduce myasthenic weakness by causing an increase in end-plate potential amplitude and therefore an increase in safety factor. However, they each achieve this by different mechanisms.
- Cholinesterase inhibitors prolong the lifetime of acetylcholine at the end-plate giving more opportunity for each molecule to bind to a receptor.
- 3, 4-DAP is a potassium channel blocker whose action on the presynaptic nerve terminal results in increased release of acetylcholine into the synaptic cleft.

The two drugs are often used together to provide symptom relief.
Pyridostigmine is the most commonly used AChE inhibitor; the dose is similar to that used in myasthenia gravis. The dose is titrated according to response and in children is calculated by weight: a typical high dose is 7 mg/kg/day. Higher doses (eg, 10 mg/kg/day) are sometimes needed during episodes of acute deterioration, particularly in children, though this increases the risk of muscarinic side effects and cholinergic crises. Propantheline or glycopyrrolate may help to reduce muscarinic side effects.

Like pyridostigmine, 3, 4-DAP has a short duration of action and so is usually taken three or four times per day. At peak dose, patients often report short-lived tingling sensations in the extremities and periorally. This is not a cause for concern unless protracted and uncomfortable, but rather indicates that the patient is on an adequate dose. The dose required varies by severity and size, but a typical starting dose for an adult would be 10 mg three times daily. The total daily dose should not exceed 80 mg per day, largely because of the risk of seizures. The actual risk of

Figure 7 Treatment algorithm. 3, 4-DAP, 3, 4-diaminopyridine; AChR, acetylcholine receptor; ChAT, choline acetyltransferase; DOK7, downstream of kinase-7.
seizures is not known but in our experience of using 80 mg/day or less, they are uncommon. We use 3, 4-DAP more cautiously in children, usually starting it under observation in hospital and at a low dose (e.g., 0.25 mg/kg/day).

**Ephedrine and oral salbutamol**

Both agents stimulate muscle β2-adrenergic receptors and improve signal transmission by stabilising the postsynaptic architecture.

They form the mainstay of treatment of DOK7 and COLQ CMS. The response can be dramatic, even when therapy is started in adulthood. A few patients with other subtypes—including AChR deficiency, slow channel syndrome, GFPT1 and DPAGT1—have also found some benefit.

A typical adult starting dose of salbutamol is 4 mg twice or three times daily, depending upon size; the dose can increase gradually to a maximum total daily dose of 16 mg, depending on response. In adults, ephedrine is usually started at 15–30 mg twice daily and increased as necessary to a maximum of 30 mg three times daily. A low dose often works well and increasing it does not help further but gives side effects.

Improvement usually begins within a month of starting treatment and continues for 6–9 months before plateauing. It is therefore worth persisting with treatment to determine whether it is helpful. It is not clear if either ephedrine or salbutamol is superior; some patients respond better to one or other. The main side effects are insomnia and cardiac effects such as tachycardia, palpitations and hypertension. We routinely perform initial and follow-up blood pressure and 12-lead ECG. Muscle cramps commonly develop when salbutamol is used in DOK7.

**Fluoxetine and quinidine in slow channel syndrome**

Slow channel syndrome needs entirely different treatments from those used in other forms of congenital myasthenia. The primary pathogenic mechanism is of an abnormally prolonged opening of the central ion channel pore of the AChR. Both fluoxetine and quinidine are open channel blockers and bind the channel in its open state, thereby reducing channel opening time. Although it is not known whether either treatment is more effective, fluoxetine is the usual drug of choice. It has a better safety profile than quinidine, which can cause QT interval prolongation and requires an ECG and serum level monitoring. A caveat to this is the potential risk of suicidality in children and adolescents taking fluoxetine. The effective dose of fluoxetine varies with some patients responding to low doses (20 mg) and others requiring large doses of 120 mg per day.

**Ophthalmoplegia is resistant to treatment**

The ophthalmoplegia of congenital myasthenia seldom improves with drug treatment, even when there is a substantial generalised improvement. This contrasts with autoimmune myasthenia gravis where ophthalmoplegia can fully resolve with treatment. Ptosis, however, responds to treatment and 3, 4-DAP is more effective than pyridostigmine at this.

**OTHER ASPECTS OF MANAGEMENT**

**Respiratory care**

Hypoventilation can occur in any subtype and some patients require regular non-invasive ventilation at home. Nocturnal sleep studies may be normal between episodes in patients who experience acute crises. Often these patients have a non-invasive ventilation machine at home for emergencies before transfer to hospital. When there are respiratory problems, parents and carers must be trained in basic life support. It is good practice for the local hospital to be aware of the patient’s condition and to make prior arrangements for fast-track access to hospitals or directly to the ward teams.

**Genetic counselling**

Prenatal diagnosis or fast-turnaround diagnosis on umbilical cord blood from unaffected siblings is possible when the abnormal gene is known. Genetic counselling is particularly important in families where there is consanguinity.

**Anaesthetic considerations**

Anaesthetic considerations for the congenital myasthenic syndromes are the same as for myasthenia gravis. It is important to avoid depolarising neuromuscular blocking drugs. Where possible, local, regional or spinal anaesthesia is preferred to general anaesthesia. It is important to avoid depolarising neuromuscular blocking drugs. Where possible, local, regional or spinal anaesthesia is preferred to general anaesthesia. It is important that the anaesthetist is aware of the condition and that regular medication (e.g., pyridostigmine) is not withheld preoperatively or postoperatively.

**Ptosis surgery**

Because congenital myasthenia is rare, the long-term success of ptosis surgery is not known. However, some patients develop recurrence of symptoms following ptosis surgery.

**Patient support groups**

The Myasthenia Gravis Association is a source of support for patients and carers. Their website (http://www.mga-charity.org) has an information booklet on congenital myasthenic syndromes and will soon have a patient information DVD.

**UK National Commissioning Group Service**

The UK Congenital Myasthenia Service is a Nationally Commissioned Specialised Service based at the John Radcliffe Hospital in Oxford, UK, and provides a national clinical and genetic service. Further information about the service and a prereferral form are
available at the website (http://www.ouh.nhs.uk/services/referrals/neurosciences/myasthenia.aspx).

Key points

- Congenital myasthenic syndromes are rare but underdiagnosed.
- There is no immune abnormality and so they do not respond to immunotherapies.
- Although typically presenting in infancy, they can present later in adulthood.
- Patients with congenital myasthenia often carry a long-standing incorrect diagnosis, such as an undefined (on muscle biopsy) congenital myopathy.
- It is worth pursuing a definite genetic diagnosis since this guides prognosis, genetic counselling and, most importantly, treatment choice.
- The presence or absence of ophthalmoplegia is the most important differentiating feature guiding genetic screening.
- All treatments used for congenital myasthenia are out of licence.
- Some subtypes (slow channel syndrome, COLQ and downstream of kinase-7) can worsen with pyridostigmine or 3,4-diaminopyridine.

Acknowledgements We thank the patients attending the National Commissioning Group Congenital Myasthenic Syndromes service and their referring clinicians for allowing continued increasing understanding of these rare conditions. We also acknowledge the help of the late Professor John Newsom-Davis, Dr Robin Kennett, Dr Sandeep Jayawant, Dr Stephanie Robb and previous CMS Fellows. We also acknowledge Roddy Easson for producing figure 2.

Contributors All authors contributed to the drafting and writing of this article. SF takes responsibility for the overall content.

Funding No specific funding was received for this paper, though we acknowledge the work was made possible by funding of the CMS service by the National Commissioning Group.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Commissioned. Externally peer reviewed. This paper was reviewed by Georgina Burke, Southampton, UK.

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