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CONGENITAL MYASTHENIC SYNDROMES IN CHILDREN: CLINICAL SPECTRUM, MOLECULAR HETEROGENEITY AND THERAPEUTIC RESPONSE IN A PEDIATRIC NEUROLOGY CASE SERIES

Swetha Rampally MD DM, Department of Pediatric Neurology, SparkKids Children's Hospitals, Kurnool

Naveen Reddy MD DrNB, Department of Pediatric Critical Care, SparkKids Children's Hospitals, Kurnool

ABSTRACT

Background: Congenital myasthenic syndromes (CMS) are a heterogeneous group of inherited disorders of neuromuscular transmission characterized by impaired synaptic transmission and variable age at onset, clinical phenotype, and response to treatment. Recognition may be challenging because children can present with isolated ocular manifestations, fatigable limb weakness, hypotonia, respiratory or bulbar involvement, or developmental delay. Genetic diagnosis is particularly important because treatment response differs according to the molecular subtype.[1,6] **Objective:** To describe the clinical spectrum, neurophysiological findings, genetic abnormalities, and therapeutic response among children evaluated for suspected congenital myasthenic syndrome at a tertiary pediatric neurology center. **Methods:** We retrospectively reviewed five children evaluated for clinically suspected CMS. Clinical characteristics, age at presentation, distribution of weakness, ocular and bulbar manifestations, neurophysiological investigations, genetic testing, treatment, and clinical response were documented. Whole exome sequencing was performed in all patients, with variant interpretation according to laboratory-based molecular diagnostic criteria. The clinical phenotype was correlated with the identified genetic variants. **Results:** Five children with suspected CMS were identified. The predominant clinical manifestations included ptosis, fatigability, asthenia, hypotonia, gait difficulty, ophthalmoplegia, and bulbar symptoms. Pathogenic or likely pathogenic variants in CMS-associated genes were identified in three patients: CHRNE variants in two patients and a DPAGT1 variant in one. One child had a homozygous likely pathogenic CHRNE frameshift variant, c.168_178dup (p.Leu60Profs*2), associated with a phenotype of fluctuating ptosis, fatigable weakness, and gait difficulty. Another child had a homozygous pathogenic CHRNE c.1327del variant. A third child harbored a homozygous likely pathogenic DPAGT1 c.1139C>T (p.Thr380Ile) variant. One child with a compatible phenotype and decremental response on repetitive nerve stimulation had no pathogenic variant identified on whole exome sequencing. A further child had a heterozygous likely pathogenic CHRNE variant but an atypical neurological phenotype, emphasizing the importance of cautious genotype-phenotype correlation. Clinical improvement was observed with pyridostigmine, with salbutamol used in selected patients. **Conclusion:** CMS should be considered in children with fluctuating ptosis, fatigable weakness, unexplained hypotonia, gait difficulty, or bulbar symptoms. Molecular diagnosis can establish the subtype and facilitate treatment selection. Our series illustrates both the phenotypic and genetic heterogeneity of CMS and emphasizes that a strong clinical suspicion should not be discarded solely because genetic testing is nondiagnostic.[1,6,7]

KEYWORDS : congenital myasthenic syndrome; CHRNE; DPAGT1; ptosis; fatigability; pyridostigmine; salbutamol; pediatric neurology; neuromuscular junction.

INTRODUCTION

Congenital myasthenic syndromes are a heterogeneous group of inherited disorders caused by abnormalities affecting proteins involved in neuromuscular transmission. Depending on the affected component, CMS can be classified broadly into presynaptic, synaptic, and postsynaptic disorders.[1,6,8]

The clinical spectrum is broad. Children may present during infancy with hypotonia, feeding difficulty, respiratory compromise, or delayed motor development, whereas older children may develop fluctuating ptosis, ophthalmoplegia, limb weakness, exercise intolerance, gait difficulty, or bulbar dysfunction.[3,7] The variable phenotype can lead to diagnostic delay or misdiagnosis as cerebral palsy, congenital myopathy, mitochondrial disease, or autoimmune myasthenia gravis.

The molecular heterogeneity of CMS is considerable. Variants in CHRNE, encoding the epsilon subunit of the acetylcholine receptor, are an important cause of postsynaptic CMS, including fast-channel and acetylcholine-receptor deficiency phenotypes.[1,5,6] Other genes, including MUSK and DPAGT1, produce distinct clinical and pathological phenotypes.[2,8]

Correct molecular diagnosis has direct therapeutic implications. Acetylcholinesterase inhibitors such as pyridostigmine are useful in several CMS subtypes, whereas adrenergic agonists such as salbutamol may provide additional benefit in selected postsynaptic and other CMS phenotypes.[1,9] Conversely, some CMS subtypes may deteriorate with inappropriate use of acetylcholinesterase inhibitors, making accurate subtype recognition particularly important.[1,6]

Although genetic testing has substantially improved the diagnosis of CMS, access to testing and interpretation of variants remain challenging, particularly in resource-variable settings. Clinical recognition therefore remains fundamental. Pediatric cohorts have demonstrated substantial phenotypic diversity and variable long-term outcomes, reinforcing the importance of maintaining a high index of suspicion.[3,7]

We describe a pediatric series of clinically suspected CMS, focusing on clinical clues, molecular diagnosis, genotype-phenotype correlation, and response to targeted treatment.

METHODS

Study design and setting

This was a retrospective descriptive case series of children evaluated in a tertiary pediatric neurology practice for suspected congenital myasthenic syndrome.

Patient selection

Children were included when clinical features suggested a disorder of neuromuscular transmission, including one or more of the following:

- fluctuating or fatigable ptosis;
- ophthalmoplegia;
- fatigable limb weakness;
- exercise intolerance or asthenia;
- gait difficulty;
- hypotonia;
- bulbar or feeding difficulties;
- unexplained motor developmental delay; or
- supportive neurophysiological findings.

The diagnosis was considered based on the overall clinical phenotype, neurophysiology, genetic findings, and therapeutic response rather than on genetic testing alone.

Clinical assessment

Clinical records were reviewed for:

1. age at symptom onset;
2. presenting symptoms;
3. ocular involvement;
4. bulbar involvement;
5. limb weakness and fatigability;
6. developmental status;
7. respiratory involvement;
8. family history and consanguinity;
9. neuroimaging;

10. repetitive nerve stimulation (RNS), where performed; and
11. response to treatment.

Genetic investigations
Whole exome sequencing was performed in the patients using clinical diagnostic laboratories. Variants reported as pathogenic, likely pathogenic, or variants of uncertain significance were reviewed in relation to the phenotype and inheritance pattern.

Particular attention was given to variants in established CMS-associated genes.

Treatment assessment
Clinical response to pyridostigmine and, where used, salbutamol was assessed from documented follow-up. Improvement in ptosis, fatigability, endurance, gait, motor function, or bulbar symptoms was considered evidence of therapeutic response.

RESULTS

Five children were identified from the clinical series. Their clinical and molecular characteristics are summarized in Table 1.

Case 1: CHRNE variant with an atypical neurological phenotype
An 11-month-old girl was evaluated following infantile spasms beginning at approximately 8 months of age, with mild hypotonia and motor developmental delay. EEG demonstrated hypsarrhythmia. MRI brain was reported as normal. Whole exome sequencing identified a heterozygous CHRNE c.168_178dup variant, predicted to result in p.Leu60Profs*2, classified by the reporting laboratory as likely pathogenic.

Because CHRNE-related CMS is generally inherited in an autosomal-recessive manner, the finding of a single heterozygous variant requires cautious interpretation. In the absence of a second pathogenic allele, this result does not by itself establish CHRNE-related CMS. This patient therefore illustrates the importance of segregation analysis and complete genotype-phenotype correlation.

Case 2: Homozygous CHRNE-related CMS
A 9-year-old boy presented with progressive fatigability, gait difficulty, distal muscle weakness, lumbar lordosis, and external ophthalmoplegia. He had a history of one seizure episode. MRI brain demonstrated bilateral putaminal hyperintensity. Creatine kinase and nerve conduction studies were normal.

Whole exome sequencing demonstrated a homozygous CHRNE c.1327del variant (p.Glu443LysfsTer64), classified as pathogenic and consistent with autosomal-recessive acetylcholine receptor deficiency CMS.

The clinical phenotype and molecular diagnosis supported CHRNE-related CMS. Treatment with pyridostigmine, with adjunctive salbutamol where clinically indicated, resulted in symptomatic improvement.

Case 3: DPAGT1-related CMS
A 3-year-old girl born to consanguineous parents presented with global developmental delay, predominantly affecting motor and language domains. She had severe hypotonia, gait imbalance, early left-handedness, tongue protrusion, and behavioral abnormalities.

The family history was notable for an affected older brother with progressive involuntary movements and behavioral changes.

Whole exome sequencing identified a homozygous DPAGT1 c.1139 C>T (p.Thr380Ile) variant, classified as likely pathogenic. DPAGT1-related disease is associated with congenital myasthenic syndrome and may be accompanied by tubular aggregates and broader neuromuscular manifestations.[2,8]

The phenotype and molecular findings were considered consistent with DPAGT1-related CMS.

Case 4: Clinically suspected CMS with negative exome sequencing
A 1-year-old boy presented with bilateral ptosis and clinical features suggestive of congenital myasthenic syndrome. Autoimmune investigations, including acetylcholine receptor-related antibodies, were negative. MRI brain was normal.

Repetitive nerve stimulation demonstrated a decremental response, providing objective evidence of impaired neuromuscular transmission. Whole exome sequencing did not identify a pathogenic or likely pathogenic variant explaining the phenotype.

Despite the negative molecular result, the clinical and electrophysiological findings supported a diagnosis of clinically suspected CMS. The child demonstrated clinical improvement with pyridostigmine.

This case emphasizes that a negative exome does not exclude CMS, particularly when the phenotype and neurophysiology are strongly supportive.

Case 5: Homozygous CHRNE-related fast-channel CMS
A 7-year-old girl born to consanguineous parents presented with fluctuating ptosis that worsened toward evening, progressive weakness, difficulty walking, and reduced functional endurance. She also had difficulty with feeding/chewing and symptoms became more pronounced with fatigue. Neuroimaging did not reveal a structural explanation.

Acetylcholine receptor autoantibodies were within the reference range.

Whole exome sequencing identified a homozygous CHRNE c.168_178dup variant, predicted to cause p.Leu60Profs*2. The laboratory classified the variant as likely pathogenic. The variant produces a premature termination signal and is predicted to result in loss of normal CHRNE protein function, consistent with the established loss-of-function mechanism of CHRNE-related CMS.

The clinical phenotype, inheritance pattern, and molecular finding were strongly concordant with autosomal-recessive CHRNE-related CMS. The patient showed symptomatic improvement following pyridostigmine therapy. The additional MYH8 variant identified on sequencing was heterozygous and classified as a variant of uncertain significance; its contribution to the phenotype was considered unlikely in the context of the clearly pathogenic CHRNE finding.

Table 1. Clinical and Molecular Characteristics of the Series

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age	11 mo	9 y	3 y	1 y	7 y
Sex	F	M	F	M	F
Consanguinity	Not documented	Present	Present	—	Present
Major phenotype	Hypotonia, infantile spasms, motor delay	Ophthalmoplegia, gait difficulty, weakness	Hypotonia, developmental delay, gait imbalance	Ptosis, fatigability	Fluctuating ptosis, weakness, gait difficulty, bulbar symptoms
RNS	Not documented	Normal	Not documented	Decremental	Not clearly documented
Gene	CHRNE	CHRNE	DPAGT1	None identified	CHRNE
Variant	c.168_178dup	c.1327del	c.1139C>T	—	c.168_178dup
Zygosity	Heterozygous	Homozygous	Homozygous	—	Homozygous
Laboratory classification	Likely pathogenic	Pathogenic	Likely pathogenic	Negative WES	Likely pathogenic
Molecular diagnosis	Inconclusive alone	CHRNE-related CMS	DPAGT1-related CMS	Clinically suspected CMS	CHRNE-related CMS
Pyridostigmine response	—	Improved	Improved	Improved	Improved
Salbutamol	—	Used/considered	—	—	—

Table 2. Genotype–phenotype Interpretation

Gene	Molecular finding	Mechanistic relevance	Clinical implication
CHRNE	Homozygous frameshift variants in Cases 2 and 5	Loss of functional AChR ε-subunit	Postsynaptic CMS; phenotype compatible with AChR deficiency/fast-channel CMS

DPAGT1	Homozygous missense variant in Case 3	Defective glycosylation affecting neuromuscular transmission	CMS with broader neuromuscular/developmental phenotype
CHRNE	Heterozygous frameshift variant in Case 1	Potential loss-of-function allele	Insufficient alone to establish AR CMS; segregation/second-allele assessment required
None	Case 4	Genetic cause unresolved	CMS remains clinically plausible because of phenotype and decremental RNS

DISCUSSION

This series demonstrates the broad clinical spectrum of congenital myasthenic syndromes and the complementary roles of clinical examination, electrophysiology, genetic testing, and therapeutic response.

The most important clinical message is that CMS should be considered whenever a child has fluctuating ptosis, fatigable weakness, ophthalmoplegia, unexplained gait difficulty, bulbar symptoms, or hypotonia, particularly when symptoms fluctuate during the day or worsen with exertion.[3,6,7]

CHRNE-related disease

Three patients in our series carried CHRNE variants, although only two had biallelic variants clearly supporting an autosomal-recessive molecular diagnosis. CHRNE encodes the epsilon subunit of the adult acetylcholine receptor. Loss-of-function variants can lead to reduced numbers or abnormal function of acetylcholine receptors and impaired neuromuscular transmission.[1,5]

The phenotype in Case 5 is particularly illustrative. The combination of evening-worsening ptosis, fatigable weakness, gait difficulty and bulbar symptoms, together with a homozygous loss-of-function CHRNE variant, provides a strong genotype-phenotype correlation.

Fast-channel CMS has been particularly well characterized clinically, with ocular manifestations and fatigable weakness being prominent features.[5] The clinical recognition of such phenotypes is important because patients may be misdiagnosed with autoimmune myasthenia gravis or other congenital neuromuscular disorders.

Therapeutic implications

A major clinical advantage of recognizing CMS is that it is potentially treatable. Pyridostigmine improves acetylcholine availability at the neuromuscular junction and is effective in several CMS subtypes.[1,6,9]

Adrenergic agonists, including salbutamol, have also demonstrated benefit in selected CMS phenotypes and can improve muscle strength and functional endurance.[9] The response observed in our patients reinforces the importance of considering a therapeutic trial when the clinical and electrophysiological phenotype is strongly suggestive.

However, treatment should ideally be guided by the underlying molecular subtype because CMS is not pharmacologically homogeneous. Some CMS subtypes respond poorly or may deteriorate with acetylcholinesterase inhibition.[1,6]

Importance of electrophysiology

The decremental response on repetitive nerve stimulation in Case 4 provided important objective evidence of neuromuscular transmission dysfunction. Neurophysiology remains particularly useful when genetic testing is negative or inconclusive.

A normal RNS does not necessarily exclude CMS, especially when testing is performed in young children, when appropriate muscles are not examined, or when the disorder produces subtle or intermittent transmission failure.[6]

Negative genetic testing does not exclude CMS

Case 4 highlights a clinically important issue. Whole exome sequen-cing may fail to identify the molecular cause despite a convincing clinical and electrophysiological phenotype. Possible explanations include variants outside routinely captured coding regions, structural variants, copy-number abnormalities, deep intronic variants, limitations of sequencing coverage, or currently unrecognized disease genes.[6,8]

Thus, genetic testing should complement rather than replace clinical and neurophysiological assessment.

Importance of variant interpretation

Case 1 demonstrates another important diagnostic principle. A heterozygous likely pathogenic CHRNE variant in an autosomal-recessive disorder does not establish a molecular diagnosis by itself. The finding could represent carrier status, with a second pathogenic allele missed by testing, or an unrelated finding.

Segregation analysis and, where clinically indicated, additional genomic testing may therefore be necessary. This is particularly important in CMS because the increasing availability of exome sequencing has resulted in the detection of variants of uncertain significance and incidental findings.

DPAGT1-related CMS

The DPAGT1 case illustrates the broader phenotypic spectrum of CMS. DPAGT1 is involved in protein glycosylation, and biallelic variants have been associated with CMS with tubular aggregates and variable neuromuscular and developmental manifestations.[2,8]

The presence of developmental delay, hypotonia, gait dysfunction, and associated neurological features in our patient is consistent with the broader phenotype reported in DPAGT1-related disease.

Clinical relevance in pediatric practice

CMS can be mistaken for several more common pediatric neurological disorders. A child with ptosis and gait difficulty may be labelled as having cerebral palsy, while fluctuating weakness may be attributed to myopathy. Similarly, feeding difficulty and hypotonia in infancy may initially lead to investigations for central or metabolic disorders.

A simple clinical clue is fluctuation: weakness that becomes more prominent later in the day or after exertion and improves after rest should prompt consideration of a neuromuscular junction disorder.

The literature emphasizes substantial phenotypic heterogeneity and variable prognosis in CMS cohorts.[3,7]Recognition is particularly important because, unlike many inherited neuromuscular disorders, CMS may show a substantial response to pharmacological therapy.

LIMITATIONS

This study has several limitations.

- First, it is a small retrospective case series from a single center, limiting the generalizability of the findings.
- Second, clinical phenotyping and neurophysiological investigations were not uniform across all patients, reflecting the real-world nature of retrospective pediatric practice.
- Third, not all patients underwent comprehensive electrophysiological testing under identical conditions.
- Fourth, whole exome sequencing does not exclude all possible pathogenic variants, particularly deep intronic, regulatory, structural, or certain copy-number abnormalities.
- Finally, treatment response was assessed clinically rather than using standardized quantitative myasthenia or functional outcome scales.
- Importantly, the heterozygous CHRNE finding in Case 1 should be regarded as genetically inconclusive without identification of a second pathogenic allele or supportive segregation data.

Future Directions

A prospective pediatric CMS registry incorporating standardized clinical scoring, repetitive nerve stimulation, genetic testing, treatment protocols, and longitudinal outcome assessment would provide more robust genotype-phenotype correlations.

In genetically unresolved patients with a strong clinical phenotype, additional testing—including CNV analysis, genome sequencing, RNA studies, or targeted analysis of known CMS genes—may improve diagnostic yield.

Longitudinal assessment of treatment response may also help determine whether early molecular diagnosis leads to improved functional outcomes and reduced diagnostic delay.

CONCLUSION

Congenital myasthenic syndromes are rare but highly treatable pediatric neuromuscular junction disorders with considerable clinical and genetic heterogeneity. In this series, children presented with varying

combinations of ptosis, fatigability, hypotonia, gait impairment, ophthalmoplegia, bulbar symptoms, and developmental abnormalities.

Biallelic pathogenic or likely pathogenic variants in CHRNE and DPAGT1 established molecular diagnoses in several patients, while one child had a convincing clinical and electrophysiological phenotype despite negative exome sequencing.

The series emphasizes three practical messages:

1. Fluctuating ptosis and fatigable weakness should prompt consideration of CMS.
2. Genetic testing is crucial for molecular classification and treatment planning but does not replace clinical and electrophysiological assessment.
3. Early recognition matters because appropriate treatment with agents such as pyridostigmine and salbutamol can produce meaningful clinical improvement.

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