SAGE Open Medical Case Reports
Volume 11: 1–6

DOI: 10.1177/2050313X231211047
journals.sagepub.com/home/sco
Sage

Diagnostic dilemmas and challenges in the management of myasthenia in infants and toddlers: A case report

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Abstract

Myasthenia in the infancy and toddler age group is rare and often presents a challenge to treating pediatric neurologists. Our report addresses the challenges encountered when distinguishing myasthenia in infants and toddlers from similar illnesses, as well as the differentiation between congenital myasthenia, transient myasthenia, and autoimmune myasthenia. We present four cases of myasthenia between the ages of 10 and 30 months. The diagnosis and management of these cases were challenging due to the variability in clinical presentation. Four cases of myasthenia were diagnosed, with three having autoimmune myasthenia and one having congenital myasthenic syndrome. One patient initially tested negative for acetylcholine receptor antibodies, but later tested positive after 4 months and had a rare facial diplegia finding. The patient with congenital myasthenic syndrome had a novel genetic mutation, *DPAGT1* homozygous variants, and also had false positive acetylcholine receptor antibodies. These cases highlight the importance of genetic testing for all infants and toddlers suspected of having myasthenia.

Keywords

myasthenia, infants, toddlers, diagnostic challenge, management

Date received: 5 July 2023; accepted: 12 October 2023

Introduction

Myasthenia is a neuromuscular junction disorder, characterized by muscle weakness and fatigability.[1] In children, three types of myasthenia have pathophysiological distinct mechanisms: transient neonatal myasthenia, congenital myasthenic syndrome (CMS), and juvenile myasthenia gravis (JMG).[2,3] CMS is a group of genetic disorders resulting from mutations in genes that code for proteins at the neuromuscular junction. This leads to structural or functional abnormalities of the proteins involved in neuromuscular transmission.[2,4] Children with CMS usually present with fatigable weakness, having ocular or generalized symptoms. Genetic testing plays a crucial role in diagnosis and can guide therapeutic options, as certain drugs are more effective for certain gene mutations in CMS.[5]

JMG is an autoimmune disorder of neuromuscular transmission caused by the production of antibodies against components of the postsynaptic membrane of the neuromuscular junction.[3] These autoantibodies can target acetylcholine receptor (AChR), muscle-specific kinase (MuSK) as well as lipoprotein receptor-related membrane protein 4.[6–8] Childhood myasthenia comprises 10–15% of all myasthenia cases.[9] Autoimmune myasthenia in children usually presents after 5 years of age, but cases with onset at 2 years of age or earlier have been reported.[9] The exact data on the prevalence of autoimmune myasthenia in toddlers are still unknown. The youngest reported case was 10 months old, who presented with ptosis, ophthalmoplegia, and positive AchR antibodies.[10–12] AchR antibodies are often negative in young children with autoimmune myasthenia, which leads to difficulties in diagnosis.[1,10] The diagnosis is therefore either delayed or the patients are misdiagnosed. It is essential to distinguish between

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Table 1. Clinical summary of the cases.

Patient characteristics	Case 1	Case 2	Case 3	Case 4
Age	18 months	10 months	26 months	30 months
Gender	Male	Male	Female	Female
Clinical presentation	Bilateral ptosis, ophthalmoplegia, generalized muscle weakness	Ptosis since birth, developmental delay	Bilateral ptosis, ophthalmoplegia, dysphagia, facial diplegia, weak Gag, generalized muscle weakness	Bilateral ptosis, dysphagia, nasal speech, absent Gag, respiratory failure, generalized muscle weakness
Need of mechanical ventilation	No	No	No	Yes
Anti-AChR[a] antibodies (<0.4 nmol/L)	2.04 (Positive)	3.27 (Positive)	3.16 (Positive)	<0.25 (Negative)
Anti-MuSK[b] antibodies (<0.4 U/ml)	—	—	<0.18 (Negative)	0.21 (Negative)
Repetitive Nerve Stimulation (RNS) test	Significant decremental response	No decremental response	No decremental response	Significant decremental response
Next Generation Sequencing	—	Two variants identified in DPAGT1 (homozygous) in Neuromuscular genetic panel	Negative (whole exome sequencing)	Negative (neuropathy panel)
CT Scan Chest for Thymoma	—	Normal thymus	Normal thymus	Normal thymus
Use of IVIG[d]/ Plasmapheresis	—	—	intravenous immunoglobulin (IVIG)	IVIG followed by Plasmapheresis
Current medications	Pyridostigmine	Salbutamol	Pyridostigmine + Salbutamol	Pyridostigmine

a = acetylcholine receptor, b = muscle-specific kinase, c = not done, d = intravenous immunoglobulin; AChR = acetylcholine receptor; MuSK = muscle-specific kinase.

congenital and autoimmune myasthenia in young children due to the differing treatment options and prognosis.

We present a series of cases involving four patients from distinct families. All of the patients were infants or toddlers, which is an unusual age range for myasthenia. Of the four patients, three exhibited an atypical manifestation of myasthenia.

Methods

This case series includes four children diagnosed with myasthenia between the ages of 10 and 30 months. These children belonged to four different families and were treated at Aga Khan University Hospital in Karachi, Pakistan. The parents of these children have given written informed consent to publish their individual cases. We conducted a retrospective review of the medical records of all patients under the age of 3 years who were diagnosed with myasthenia and discharged from the hospital. Our review focused on their clinical presentation, age of onset of symptoms, speed of disease progression, difficulties encountered in reaching the final diagnosis, need for mechanical ventilation, treatment administered to each patient throughout the course of their illness, and the diagnostic tests that were conducted (including repetitive nerve stimulation (RNS), anti-AChR antibodies, anti-MUSK antibodies, CT chest for thymoma, genetic testing).

Results

Case 1

An 18-month-old previously healthy boy presented with complaints of drooping of eyelids for 6 months, which was progressively getting worse. He also developed difficulty in walking with frequent falls over the last few weeks. Parents did not report any diurnal variations in his symptoms. He had no history of respiratory distress or difficulty in swallowing. His past medical history, as well as his birth and family history, were unremarkable. He achieved all his milestones appropriately. On examination, the child showed drooping of the eyelids and bilateral external ophthalmoplegia. His lower limb tone and power were normal; however, his reflexes in all four limbs were +1. His RNS showed a decremental response (>10% decrement with 3 Hz stimulation) in bilateral facial and right axillary nerve, and AChR antibodies were positive 2.04 nmol/L (normal value <0.40 nmol/L) Table 1. As both these findings were suggestive of autoimmune myasthenia, he was started on pyridostigmine (2 mg/kg/day). He showed improvement as he was able to walk without falling and his ptosis was significantly better.

Case 2

A 10-month-old boy presented with complaints of ptosis since birth, with no diurnal variation. His past medical history included multiple hospital admissions due to respiratory tract infections. The patient was born to consanguineous parents and had a 6-year-old brother who was healthy. His mother had a history of getting tired easily, her AChR antibodies and TSH were normal. He experienced respiratory distress shortly after birth for which he required intensive care management. His immunizations were complete. Developmentally, all his milestones, including gross and fine motor skills, language, and speech, were delayed. On examination, he had bilateral ptosis, inverted V-shaped lips, high arched palate, generalized hypotonia with a power of 3/5, and reflexes 2+ in all four limbs. After the initial assessment, differential diagnoses of congenital myopathy, congenital muscular dystrophy, and congenital versus autoimmune myasthenia were considered.

His AChR antibodies were very high 3.27 nmol/L (normal value <0.40 nmol/L). Electromyography (EMG), nerve conduction study (NCS), and RNS were performed which showed no evidence of myopathy and absence of decremental response, see Table 1. A CT scan was done to rule out thymoma which was normal. The thyroid profile, vitamin D levels, creatine phosphokinase, and lactate levels were all normal. Based on clinical features and positive AChR antibodies, the diagnosis of myasthenia was made. The patient was started on oral pyridostigmine (1.5 mg/kg/day). He presented to the clinic shortly after a few days with lethargy, decreased activity, reduced power, and no improvement in ptosis. His parents were reluctant to continue the pyridostigmine due to the worsening of his clinical condition; hence, pyridostigmine was discontinued. Considering the possibility of CMS, we planned for the genetic testing with a comprehensive neuromuscular panel. According to the report, there was a homozygous deletion identified in the *DPAGT1* gene, specifically a variant of uncertain significance known as c.496+3A>G (intronic). This variant suggests the presence of glycosylation defects that may be related to CMS. Additionally, the patient's mother and sibling underwent screening, and their results showed a heterozygous mutation in the same *DPAGT1* gene, specifically C.496+3A>G. He was diagnosed with CMS caused by a DPAGT1 mutation, but his muscle biopsy was not taken to confirm tubular aggregates. Oral salbutamol did not improve his condition.

Case 3

A 26-month-old girl was brought to the clinic with complaints of bilateral ptosis for 1 month, right-sided facial palsy for 1 week, and delayed milestones. She was born healthy to consanguineous parents and had one sibling, an elder brother aged four-and-a-half years. She started sitting without support at 1 year and walking at 2 years of age when she could speak two to five single words. On examination, she had bilateral ptosis. The results of her EMG/NCS tests were normal, and the RNS test showed no decrease in response for her facial nerve and right ulnar nerve. Her AChR and MuSK antibodies, plasma and CSF lactic acid levels were also found to be normal. She was started on pyridostigmine 2 mg/kg/day in three divided doses. Two days later, she visited the emergency department with symptoms including difficulty walking, shortness of breath, difficulty swallowing, choking, and regurgitation of liquids through the nose. On examination, she had a weak gag reflex, 4/5 power in all four limbs, and diminished deep tendon reflexes. As a result, we decided to discontinue Pyridostigmine. We suspected Bickerstaff encephalitis, limbic encephalitis, Miller Fisher syndrome, or autoimmune encephalitis due to progressive brainstem involvement. However, her CSF analysis was normal, and CSF autoimmune antibodies were negative. Nonetheless, her CSF antiganglioside antibodies (anti-GQ1b) were weakly positive. Her MRI brain with contrast and repeat EMG/NCS showed no significant findings. The patient received treatment for Miller Fisher syndrome and was given two doses of intravenous immunoglobulin (IVIG). She was discharged and kept on nasogastric tube feeding. However, her condition worsened during follow-up clinic visits, as she developed bilateral facial palsy and had difficulty walking and swallowing. On examination, she had bilateral ptosis, facial diplegia, bilateral ophthalmoplegia, and brisk deep tendon reflexes. A trial of Riboflavin was given for Brown Vialetto Van Laere syndrome (BVVL), but no improvement was observed. Additionally, her poliovirus PCR test came back negative, and whole exome sequencing yielded negative results. The parents showed a video where the patient's ptosis was improved in the morning. She was admitted again, and pyridostigmine challenge test was done to which she responded. She was then started on regular pyridostigmine 1 mg/kg/day in three divided doses. After 4 months of initial negative titers, her AChR antibodies were retested and came back positive 3.16 nmol/L (normal value <0.40 nmol/L). She was diagnosed with seronegative autoimmune myasthenia and continued taking pyridostigmine. Her ptosis, swallowing, facial weakness, and lower limb weakness all improved as a result. She currently receives regular follow-up care and is able to walk and develop normally for her age.

Case 4

This 30-month-old girl presented to the emergency with complaints of bilateral ptosis for 1 month associated with cough, difficulty walking, nasal speech, and progressive dysphagia for solids as well as liquids; all of which developed in the past week. Her past medical, family, and birth history were unremarkable. Developmentally, her milestones were age-appropriate. On examination, she was awake, with bilateral ptosis, normal tone, and diminished deep tendon reflexes. There was no neck holding or sitting. Her gag reflex was absent. On her

respiratory exam, there were coarse crepitations on the left side, tachypnea, and desaturation. After elective intubation, she was shifted to the pediatric intensive care unit (PICU). Her EMG/RNS was done along with CSF studies, and stool for poliovirus was sent. Table 1 The results of her RNS showed a decremental response in bilateral axillary and right accessory nerve, which was suggestive of myasthenia. She was started on pyridostigmine (2 mg/kg/day) and also given IVIG for 2 days, considering myasthenic crises. However, the IVIG did not show any improvement in her ptosis, cough, or gag reflex. Her AChR as well as MuSK antibodies were negative (Table 1), and so were the anti-GQ1b antibodies. Her CT mediastinum did not show thymoma. She failed an extubation attempt after 5 days of intubation. During this time, considering BVVL, she was started on Riboflavin. Genetic testing (Neuropathy Panel) was sent for BVVL, which was reported negative. As she did not improve after two doses of IVIG, plasmapheresis was started. A total of five cycles of plasmapheresis were done; after the fourth cycle, there was a marked improvement in her condition. She was awake and alert. Her ptosis and gag reflex were better. She was moving all four limbs and was able to sit and hold her neck. Her MRI brain was normal. Eventually, after 12 days of reintubation, she was extubated successfully. Her swallowing assessment was done, which was normal, and hence oral feed was allowed. She has been diagnosed with seronegative myasthenia and is currently taking pyridostigmine. She has been attending regular follow-up appointments at the clinic and has shown significant improvement in her symptoms.

Discussion

In our report, the most characteristic feature was the age at diagnosis of myasthenia. Ages ranged from 10 to 30 months. The youngest child was 10 months old with CMS, and the youngest one with autoimmune myasthenia was 18 months old. Autoimmune MG is rare in this age group with few cases reported under 2 years. The youngest reported ages for autoimmune myasthenia are 10, 17, and 18 months, respectively.[12–14] In a retrospective cohort study of congenital myasthenia, the age of onset reported was from neonatal age to 96 months.[15]

Facial diplegia is an important finding in myasthenia and was present in one of our patient. Felice et al reported a 4-year-old child who presented with facial diplegia and nasal speech and was diagnosed with myasthenia on the basis of a positive edrophonium test and response to pyridostigmine.[16] The other report of facial diplegia was from an adult who presented only with this complaint for 1 year without ocular or limb muscle weakness.[17] Our child with facial diplegia (Case 3) presented with miller Fischer syndrome-like illness initially and had negative AChR antibodies as well as negative RNS. It was only later that her symptoms evolved, and she was diagnosed as myasthenia, with positive AChR antibodies subsequently on repeat testing after a gap of 4 months. We could not find any previous report of false negative AchR antibodies in myasthenia. Our case would be the first case to report this finding.

AChR antibodies are present in 70–80%, whereas MuSK antibodies account for 5–8% of cases of autoimmune myasthenia. However, purely ocular cases have a higher chance of being seronegative.[18] Three of our four patients had positive AChR antibodies, whereas none was positive for MuSK antibody. Interestingly, our two-and-a-half-year-old child (Case 4), arrived in the emergency department with respiratory crises, and had a prolonged PICU stay; she did not respond to IVIG but showed a dramatic response to plasmapheresis. She was found to be double seronegative. Double-seronegative myasthenia gravis (dSNMG) is a new entity, which includes patients negative for both AChR as well as MuSK antibodies. In a retrospective study of 250 adult subjects with myasthenia gravis, 38 (15.2%) of them were double seronegative; 9 out of 38 of them were positive for cortactin antibodies.[19]

To date, mutations in at least 35 genes are known to cause CMS.[20] The most commonly identified genes are *CHAT, COLQ, RAPSN, CHRNE, DOK7*, and *GFPT1*.[21] Mutations in *DPAGT1* have been found to impair AChR glycosylation and export to the plasma membrane. It has also been hypothesized that deficient glycosylation impairs neuromuscular transmission by altering function of endplate glycoproteins such as MuSK, agrin, and dystroglycans.[22] *DPAGT1*-related CMS affects multiple parameters of neuromuscular transmission, causes fibre-type disproportion and an autophagic myopathy, and can be associated with intellectual disability. In addition, tubular aggregates are a common histological feature observed in the muscle of patients with CMS caused by glycosylation defects.[23] We could not do a muscle biopsy of our CMS patient for tubular aggregates; however, the EMG/NCV was not suggestive of a myopathy.

In Case 2, CMS-related glycosylation defects have been inherited through autosomal recessive pattern. The patient was homozygous for *DPAGT1*, whereas mother and brother were carriers. However, the patient's clinical presentation is unique, with an early onset and typical symptoms of ptosis and motor delay. Additionally, the patient tested positive for AChR antibodies twice before undergoing genetic testing. Although AChR antibodies are generally considered highly specific for myasthenia, there have been reports of false positives in a large group of patients who were not clinically diagnosed with the condition. It is possible that in these cases, the AChR antibodies detected by the radio immunoprecipitation assay were non-pathogenic and directed towards intracellular epitopes of the AChR, as reported by Maddison et al.[24]

It has been reported that CMS caused by a *DPAGT1* mutation can be effectively treated with pyridostigmine.[25] However, our patient with CMS did not respond to pyridostigmine, which is an unusual observation. We only followed up with Case 1 for 8 months after diagnosis, but there

was an improvement in symptoms during the last clinic visit. Case 2 did not respond to pyridostigmine and salbutamol, and his parents did not want to pursue further pharmacological treatment. Cases 3 and 4 are regularly monitored and have responded well to pyridostigmine.

Conclusion

In infants and toddlers, myasthenia can display a variety of clinical and laboratory characteristics. In young children, it may take some time for AchR antibodies to show up and if there is a strong suspicion, the test should be repeated 3–6 months later. Our cases indicate that genetic testing may be considered when there is a high clinical suspicion of CMS, and the response to treatment is not as expected. We also suggest conducting more research on the common features of congenital and autoimmune myasthenia in this age group.

Acknowledgements

We acknowledge our patients and their parents for giving consent for this publication.

Author contributions

K.M. and M.R. came up with the concept for this write-up. K.M., M.R., I.T., and F.A. drafted the manuscript and contributed to acquisition and analysis of data. S.I. contributed to interpretation of patient data and critically revised the manuscript for important intellectual content. All authors gave final approval of the manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not needed for reporting individual cases or case series, as per the policy of the Ethical Review Committee of Aga Khan University, Karachi.

Informed consent

Written informed consent was obtained from the parents for anonymized patient information to be published in this article.

Submission declaration and verification

This manuscript was neither published before nor it is under consideration for publication elsewhere. All authors have agreed and approved the publication of this manuscript. If accepted, it will not be published elsewhere.

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