STUDENTS' CORNER
CASE REPORT

Salbutamol in the management of congenital myasthenic syndrome (CMS) and associated IgA and IgG Deficiency

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Abstract

A 13-month-old girl, diagnosed with congenital myasthenic syndrome due to CHRNE and GMPPB mutation, presented with involuntary movement of muscles and ptosis along with lethargy, having a poor response to Pyridostigmine and improved symptoms with Salbutamol. This case report highlights the significance of genetic testing and the clinical response to Salbutamol, emphasising its potential role in the continued treatment of CMS and providing a more economical and feasible therapeutic approach.

Keywords: Congenital myasthenia gravis, Pyridostigmine, Salbutamol, IgA, IgG.

DOI: https://doi.org/10.47391/JPMA.21352

Introduction

Congenital myasthenic syndrome (CMS) is a group of genetically inherited conditions that are present since birth or infancy affecting neuromuscular transmission leading to muscle weakness and fatigue, it is present at birth but may manifest later. CMS may result from a variety of genetic mutations. Depending on its location, CMS is categorised as pre-synaptic, synaptic, or post-synaptic. Pre-synaptic is caused by a defect in the synthesis and storage of acetylcholine (Ach) at nerve terminal caused by SLC5A7 mutations. Synaptic is caused by defects in the cleft involving COLQ mutation leading to endplate deficiency causing respiratory symptoms.[1] Fifty percent of all CMS are caused by post-synaptic CHRNE mutations, other mutations are GMPPB mutation, etc. CHRNE gene codes for the ε subunit of the muscle nicotinic AChR leading to AChR deficiency causing symptoms. Clinical manifestations of CHRNE mutations may differ in terms of type and severity.[2] Some people may just have ptosis, while others may have severe generalised myasthenia. The majority have ptosis or ophthalmoplegia along with mildly progressive bulbar, respiratory distress, or generalised limb weakness when they are born.[3]

Patients with AChR deficiency respond favourably to acetylcholinesterase inhibitors and 3,4-diaminopyridine (3,4-DAP) but they may have reduced or incomplete improvement in severe cases. Salbutamol and Ephedrine are b2-adrenergic receptor agonists used for benefit in CMS patients. This case report is presented to highlight the role of genetic testing in atypical myasthenic patients and to potentially present the successful use of Salbutamol in a patient with dual CHRNE and GMPPB mutations, especially in patients with IgA and IgG deficiency, a unique presentation seen.

Case Report

A 13-month-old girl presented to the Aga Khan University Hospital emergency room (ER) on February 23, 2023, with fever for the past 10 days along with unproductive cough and decreased oral intake. She also had involuntary muscle movements for the past day along with tiredness and lassitude.

Her past medical history was associated with recurrent hospitalisation for pneumonia but all baseline workup was negative. The mother had an uncomplicated antenatal period. After birth, the neonatal progress was normal with normal developmental milestones. Immunisations were up to date.

On physical examination, she was noted to be lethargic, tachypneic with partial ptosis with no pallor. On further respiratory examination, she had bilateral harsh vesicular breathing with bilateral equal air entry. Rest of the systemic examination was unremarkable. She was started on an IV infusion, antipyretics, antibiotic, and nebulisation to treat symptomatically.

The workup for cystic fibrosis was unremarkable. Subsequent testing of IgA and IgG levels was done in order to rule out immunodeficiency syndromes predisposing to infections exacerbating muscle weakness. Reports indicated IgA levels at 0.26 g/l (reference range: 0.4-3.5g/l)

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Submission completed: 19-07-2024 **1st Revision received:** 04-10-2024

Acceptance: 30-04-2025 **2nd Revision received:** 29-04-2025

and IgG levels at 5.23g/l (reference range: 6.5-16g/l). Additionally, an interferon-gamma release assay (IGRA) for latent tuberculosis was performed and returned negative results. Electromyography (EMG) with RNS was done in order to determine muscle health and confirm CMS diagnosis. It showed an electrodecremental pattern in three nerves consistent with a postsynaptic neuromuscular junction disorder. This was further confirmed by positive serum acetylcholine receptor antibody. Creatine kinase was elevated and Anti MuSk antibodies were negative. The patient was started on Pyridostigmine, 8mg/per-kg per day in divided doses; however, ptosis and fatigability did not improve. She was discharged after an initial response to therapy but deteriorated within 10 days and she was readmitted because of a myasthenic crisis, IVIG infusion and Ppyridostigmine dose were increased along with Ventolin nebulizers.

Further neuromuscular genetic panels were sent which utilised sequence analysis and deletion/duplication testing of 230 genes associated with neuromuscular disorders, as listed in the Genes Analysed section of the Invitae Comprehensive Neuromuscular Disorders Panel.[4] Genomic DNA from the submitted sample was enriched for targetted regions using a hybridisation-based protocol and sequenced with Illumina technology, achieving a coverage depth of ≥50x for most regions. The analysis focussed on coding sequences, flanking intronic regions (20bp), and other specific genomic areas implicated in disease causation. Alignment was performed against the GRCh37 reference genome, and variants were interpreted using a clinically relevant transcript for each gene. For some genes, only targetted loci were analysed. Exonic deletions and duplications were identified through an in-house algorithm comparing read depth from the sample to a clinical reference set. Variants were reported according to Human Genome Variation Society (HGVS) guidelines and confirmed using orthogonal methods where necessary.[5] Additional analyses, such as RNA sequencing, were employed when relevant to the gene panel, providing insights into abnormal exon junction usage. Specific protocols, such as long-range PCR and PacBio sequencing, were applied for genes like PMS2 to distinguish between closely related sequences.

The results identified two pathogenic variants in the CHRNE gene, associated with autosomal recessive and dominant congenital myasthenic syndrome, and one pathogenic variant in the GMPPB gene, linked to autosomal recessive muscular dystrophy-dystroglycanopathy and congenital myasthenic syndrome.

Per oral Salbutamol 2 mg, three times a day was added, and her fatigability and ptosis began to improve, (Figure-1 and

Figure-1: Pre-Salbutamol.

Figure-2: Post-Salbutamol; Figures shows the physical difference before and after using Salbutamol. Pre-Salbutamol the patient had bilateral ptosis with a stiff expression. Whereas post- Salbutamol showed no signs of stiffness and ptosis appearing unremarkable on sight.

Figure-2). Now she is able to walk and run and there are no more episodes of recurrent pneumonia and hospitalisation.

Discussion

Many gene mutations, each quite different, can lead to congenital myasthenic syndrome. Mutations in CHRNE gene are the most common cause of congenital myasthenia gravis, but in this patient genetic testing showed mutations in both CHRNE and GMPPB genes.

Mutations in the CHRNE and GMPPB genes both contribute to congenital myasthenic syndrome (CMS), but their clinical

presentations and underlying mechanisms differ significantly, influencing diagnosis and management. CHRNE mutations, such as the identified homozygous variant c.1327del (p.Glu443Lysfs*64), are associated with autosomal recessive and dominant CMS, typically presenting in infancy or early childhood. Symptoms include fatigable skeletal muscle weakness, eyelid ptosis, feeding difficulties, choking spells, apnoea, and respiratory insufficiency.[1] Weakness in CHRNE mutations often involves facial, ocular, bulbar, and limb muscles, fluctuating with activity and rest. Additional features such as hypotonia, congenital arthrogryposis multiplex, and foetal akinesia deformation sequence may also occur.[1]

Conversely, GMPPB mutations, such as the pathogenic variant c.1000G>A (p.Asp334Asn), are associated with a broader spectrum of autosomal recessive disorders, including muscular dystrophy-dystroglycanopathy and CMS.[6] Symptoms can range widely, often presenting later in adolescence or adulthood. Common features include proximal muscle weakness in the upper and lower limbs, elevated serum creatine kinase levels, and less pronounced involvement of facial and ocular muscles. Other manifestations include hypotonia, delayed motor milestones, exercise intolerance, and, occasionally, intellectual disability. Severe forms, particularly those associated with dystroglycanopathies, may include brain anomalies, such as cobblestone lissencephaly, cerebellar malformations, retinal abnormalities, and congenital muscular dystrophy.[7]

In this case, the patient's early-onset symptoms, including fatigable weakness and involvement of ocular and bulbar muscles, align more closely with CHRNE mutations, though the GMPPB variant may contribute to the phenotype. CMS associated with CHRNE mutations often responds to cholinesterase inhibitors or adrenergic agonists, while treatment for GMPPB-related conditions may require a more tailored approach, particularly in cases involving dystroglycanopathy. The patient in this case had a combination of these symptoms.

Medications like acetylcholinesterase inhibitors, for example Pyridostigmine, increase the availability of acetylcholine at the neuromuscular junction, improving muscle strength. In this case report, the patient with CMS had responded to treatment with Salbutamol which is a short-acting beta-2 adrenergic agonist. The precise mechanisms by which Salbutamol exerts its therapeutic effects are not fully understood but several studies provide insights into its potential modes of action, i.e. Salbutamol has shown to enhance both the functionality and structural integrity of the neuromuscular junction (NMJ). In a mouse model of DOK7-congenital myasthenic syndrome (CMS), treatment with Salbutamol led to an increase in the number of active NMJs and acetylcholine receptor-positive NMJs, essential for efficient neuromuscular transmission. These findings suggest that Salbutamol may play a role in improving synaptic architecture and facilitating neurotransmission at the NMJ.[8]

Literature search has demonstrated that CHRNE mutation patients may respond poorly to AChE inhibitors.[9] The patient was initially given Pyridostigmine but responded poorly, whereas she responded well to Salbutamol.[10]

Salbutamol may be more effective in improving muscular strength if the patient has a severe form of CMS, along with improving stamina in mild cases. This patient showed reduced ptosis and was able to walk. Salbutamol had less side effects compared to Pyridostigmine as the patient was already diagnosed with IgA and IgG deficiency, making her more susceptible to the side effects of Pyridostigmine.[11] In this case, the evaluation of IgA and IgG levels was undertaken to rule out immunodeficiency in a patient with recurrent pneumonias and multiple hospitalisations, despite initial findings being deemed insignificant for long-term outcomes.

Serum creatine kinase concentration is used as a marker for diagnosis, with it being elevated in GMPPB-related CMS as with this patient's elevated values. In 70% of the cases of congenital myasthenic syndrome, patients have positive serum anti MuSK antibodies differentiating from myasthenia gravis. Some patients may not have antibodies as in this case and the condition is called seronegative CMS. The reason suspected is acetylcholine receptors being susceptible to attack by other antibodies.[12]

The child is on regular follow-up in the outpatient clinic at Aga Khan University with no ptosis and no recurrent hospitalisation since the past one year.

Conclusion

In conclusion, this case report emphasises the importance of genetic testing in facilitating the diagnosis of myasthenia gravis (MG). The inclusion of Salbutamol in a patient with mutations in the CHRNE and GMPPB genes, along with deficiency of IgA and IgG, as a management strategy not only alleviated the patient's symptoms but also played a pivotal role in preventing recurrent pneumonia, reducing hospitalisations, and ultimately improving the quality of life.

Disclaimer: The views expressed in the submitted article are our own and not an official position of the institution.

Competing interests: All authors have completed the ICMJE uniform disclosure form and declare no support

from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding Sources: None.

Patient consents: Obtained.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

Ethical approval: Data and clinical images were collected by the responsible clinical team and anonymised at the point of extraction. Written informed consent was given for the use of all clinical images and details of disease progression.

Data availability statement: Anonymised data is available on reasonable request.

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Author Contribution:
AA & SA: Writing, revision, drafting and final approval.
PC: Concept, revision and final approval.