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Case Report

Congenital myasthenic syndromes a rare case of AGRN mutation

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Abstract: Background: Congenital myasthenic syndromes (CMS) are rare inherited disorders of neuromuscular transmission caused by mutations in presynaptic, synaptic, or postsynaptic components. They usually manifest in childhood with fatigability, ptosis, ophthalmoplegia, and generalized weakness, but late presentations also occur. Case Summary: We report a 20-year-old male presenting with heart failure and respiratory failure who was found to have a heterozygous AGRN gene mutation (c.4319>T; p. Pro1440Leu). Clinical features included muscle wasting, weakness, restricted gaze, and respiratory compromise requiring ICU care. Genetic sequencing confirmed AGRN-related CMS. Management included ICU support, pyridostigmine trial, heart failure therapy, salbutamol, and fluoxetine with improvement. Discussion: Diagnosis of CMS requires clinical suspicion, characteristic electrophysiology, and genetic confirmation. Treatment varies with subtype; AGRN-related CMS responds variably to salbutamol and ephedrine, while cholinesterase inhibitors may be ineffective. Prognosis depends on timely diagnosis and management.

Keywords: AGRN, congenital myasthenic syndrome, respiratory failure

Introduction

Diagnostic criteria for CMS include: characteristic clinical manifestations such as fatigability, ptosis, ophthalmoplegia, limb weakness, and respiratory involvement; laboratory findings such as normal CK levels; electrophysiological decremental response on repetitive nerve stimulation; and confirmatory genetic testing. Typical clinical subtypes are associated with mutations in AGRN, RAPSN, DOK7, COLQ, and others. Treatment options include acetylcholinesterase inhibitors, 3,4-diaminopyridine, salbutamol, fluoxetine, and ephedrine, with efficacy varying by subtype. Prognosis depends on early recognition, supportive care, and targeted therapy.

The congenital myasthenic syndromes (CMS) are uncommon causes of neuromuscular junction failure, generally seen in new-borns [1]. The etiology of these heterogeneous disorders are genetic defects in presynaptic, synaptic basal lamina, and postsynaptic components of the neuromuscular junction [2-6]. There is no involvement of the immune system [7]. The disorder generally presents in neonates and children with a median age of 5 years however it can present from birth to adult life. Many genetic mutations associated with congenital myasthenic syndromes have been identified and characterized. These mutations include Presynaptic CHAT, Synaptic COLQ, LAMB2 and Post synaptic CHRNA, CHRNB, CHRND, CHRNE, CHRNG, RAPSN, DOK7, MUSK, AGRN, SCN4A, GFPT1, or PLEC1 genes [21, 22]. These mutations are used to diagnose patients with congenital myasthenic syndromes [8-15, 18]. However, 30-50% of patients with congenital myasthenic syndromes do not carry any of these known mutations [8-11, 14, 18, 20, 25]. There are only a few cases reported about AGRN gene mutation so far [26-29] especially the heterozygous variant [30]. AGRN is a large proteoglycan that participates in the expression and aggregation of acetylcholine receptor at the neuromuscular junction [10, 18, 25]. A deficiency of this protein results in the failure of appropriate neuromuscular junction formation and maintenance [10, 25]. Electrophysiologic recordings demonstrating a decremental response are indicative of this rare form of congenital myas-

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thenic syndrome [22-25]. However, a morphologic study of muscle biopsy tissue and testing for AGRN gene mutations are needed to confirm the suspected diagnosis [25]. The treatment depends on type of CMS and is different for Presynaptic, Synaptic and Postsynaptic variants [26]. Because so few cases have been reported, no standard treatment protocol exists for congenital myasthenic syndrome associated with defects of AGRN. Cholinesterase inhibitors and 3,4-diaminopyridine are ineffective or provide only mild benefits in this form of congenital myasthenic syndrome [25]. Some patients exhibited initial improvement with oral ephedrine at a dose of 2 mg/kg/day each morning [25]. Albuterol/Salbutamol and Duloxetine have been used with some improvement. We report a case of heterozygous mutation of AGRN gene (Variant c.4319>T; p. Pro1440leu) first of its kind in a 20-year-old who presented with heart failures and respiratory failure.

Case

A 20-year male, reported to emergency medicine with one year history of easy fatigability one week history of swelling of legs especially on feet and puffiness of face with breathlessness on exertion and inability to move out of bed from 4 days.

Examination revealed generalised muscle wasting with furrowing in lumbricals raised jugular venous pressure, pedal oedema, facial muscle weakness and gaze restriction. Neck flexor muscle power was 3 fingers and grade 4 power in upper limbs, grade 3 in lower limbs and hand grip 75%. There was hypotonia all over limbs with deep tendon reflexes 1+. Respiratory examination revealed chest expansion of 3 cm with bilateral infrascapular area crepts, cardiovascular examination was normal.

Baseline investigations revealed only Mild Respiratory acidosis in ABG (PH 7.32) with hypercarbia (PCO2 53) and hyponatremia, serum Na of 123 mg/dl. (Likely dilutional hyponatremia). Patient sensorium worsened within twelve hours of hospital admission with fresh ABG suggestive of severe Type 2 respiratory failure (PH 7.20, PCO2 -137, HCO3 - 53.5) and patient developed altered sensorium. Patient was intubated and mechanically ventilated in ICU. In view of above clinical context neuromuscular junction disorder (Myasthenia) was suspected and patient was put on pyridostigmine 60 mg three times a day however Acetylcholine receptors antibody (Ach R antibody) levels came negative and patient didn't show any response to pyridostigmine.

Patients respiratory and metabolic profile improved on mechanical ventilation and an unsuccessful extubation was tried once but had to be reintubated again as patient again landed in respiratory failure. In view of difficulty in weaning off the patient from ventilator tracheostomy was performed. A preliminary diagnosis of congenital myasthenic syndrome was made and patient was started on heart failure treatment along with Fluoxetine and latter salbutamol was added once patients heart failure settled. Gene Sequencing showed heterozygous carrier variant of AGRN gene on chromosome 1 (Variant c.4319>T; p.Pro1440leu) causing Congenital Myasthenic Syndrome confirmed the diagnosis of CMS. Patient responded to the treatment was gradually weaned off from the ventilator and discharged from hospital after five weeks of hospital stay on NIV.

Salbutamol 2 mg three times, Fluoxetine 30 mg twice daily, tab. Ramipril 2.5 mg once daily. Follow up. After 2 months of discharge from hospital, patient is doing well without any supplement oxygen support and is ambulatory.

There are currently no guidelines for treatment of CMS specifically AGRN mutation because of rarity of this disorder however clinical trials need to investigate the efficacy of treatment protocols in CMS.

Discussion

This case demonstrates the diagnostic and therapeutic challenges in AGRN-related CMS. Our patient presented unusually with cardiac and respiratory failure, emphasizing the need for considering CMS in young individuals with unexplained weakness and crises. Genetic testing was pivotal in confirming the diagnosis. Treatment with salbutamol and fluoxetine showed clinical benefit, consistent with recent reports [16, 17, 19]. However, unlike some cases, our patient showed minimal response to pyridostigmine. Compared with other published AGRN mutation cases, our findings highlight phenotypic variability and the need for individualized therapy [4-6]. Clinicians should maintain a high index of suspicion and promptly initiate

supportive care, as prognosis improves significantly with early intervention.

AGRN was originally identified as an essential neural regulator that induces the aggregation of acetylcholine receptors (AChRs) and other postsynaptic proteins on muscle fibers and is crucial for the formation and maintenance of the neuromuscular junction [27, 28]. In 2009 first report of two siblings from a consanguineous family carrying a homozygous missense mutation (G1709R) and presented with ptosis, mild facial and limb-girdle muscles weakness, however our patient had a heterozygous mutation and had no parent or sibling with similar illness in family [32]. The other report described as severe CMS in a patient who required continuous respiratory support caused by two compound heterozygous mutations (V1727F, Q353X) [28, 31], our patient although developed respiratory failure was successfully weaned off and is ambulatory. Five patients from three unrelated families who shared different phenotypes of distal muscle weakness and atrophy [29]. A 17-month-old boy harbouring a homozygous mutation (G1765S) who presented with dropped head in addition to proximal muscle weakness, ptosis, and ophthalmoplegia [30]. Our case highlights the acute deterioration that can occur in patients with CMS where they need ICU support and sometimes mechanical ventilation however the aetiology of such deterioration needs to be investigated.

Conclusion

The case reflects the need for investigating the factors that can cause acute worsening in patients with congenital myasthenic syndromes, in addition needs focussed research how such and patients can be managed.

Disclosure of conflict of interest

None.

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