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COLQ-MUTANT CONGENITAL MYASTHENIC SYNDROME WITH MICROCEPHALY: A UNIQUE CASE WITH LITERATURE REVIEW

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Abstract

Congenital Myasthenic Syndrome (CMS) is a group of inherited neuromuscular junction disorders caused by defects in several genes. Clinical features include delayed motor milestones, recurrent respiratory illnesses and variable fatigable weakness. The central nervous system involvement is typically not part of the CMS. We report here a Saudi girl with genetically proven Collagen Like Tail Subunit Of Asymmetric Acetylcholinesterase (COLQ) mutation type CMS who has global developmental delay, microcephaly and respiratory failure. We have reviewed the literature regarding COLQ-type CMS and to the best of our knowledge this is the first ever reported association of congenital myasthenia syndrome with microcephaly.

Keywords

• COLQ mutant • congenital myasthenic syndrome • microcephaly • Saudi Arabia • pediatrics • Genetics

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Introduction/Literature review

CMS comprises a heterogeneous group of rare inherited diseases where neuromuscular transmission in the motor plate is compromised by one or more of the genetic pathophysiological specific mechanisms [1]. CMS is classified into three groups: postsynaptic, synaptic and presynaptic, depending on the localization of the defective molecules [2]. In CMS, the safety margin of neuromuscular transmission is compromised to an extent by which defines the severity and progression of the disease and its clinical manifestations. The disease manifestations differ according to the time of its onset and the underlying neuromuscular pathophysiology [3]. The most striking clinical presentations of CMS in neonates include feeding difficulties, poor suckling and crying, choking spells, ptosis, facial, bulbar and generalized weaknesses. On the other hand, the childhood onset subtypes show abnormal muscle fatigability, delayed motor milestones, a certain degree of ptosis, and fixed or fluctuating extraocular muscle weakness [4].

The diagnosis of CMS is based on a combination of clinical findings such as a decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation, a positive response to acetylcholinesterase (AChE) inhibitors, an absence of anti-acetylcholine receptor (AChR) and *anti*-muscle specific kinase (anti-MuSK) antibodies in the serum, and the lack of improvement of clinical symptoms with immunosuppressive therapy. Pathogenic variants found in the genes which encode proteins expressed at the neuromuscular junctions are currently known to be associated with CMS subtypes. The most commonly associated genes include: Choline acetyltransferase (ChAT), Acetylcholine receptor subunit epsilon (CHRNE), Acetylcholinesterase (COLQ), DOK-7, Glucosamine—fructose-6-phosphate aminotransferase (GFPT) and Receptor associated protein of the synapse (RAPSN) [5]. The COLQ gene is located at the chromosome 3p25 and encodes the collagenic tail of the acetylcholinesterase (AChE) which allows the molecule to anchor itself to the basal lamina of the neuromuscular junction endplate. Autosomal recessive missense mutation of the COLQ gene causes a synaptic form of CMS. This results in prolonged endplate currents which in turn leads to an overloading of cations at the synaptic space and eventually causing endplate myopathy with the loss of acetylcholine receptors [6].

We present here a unique case of COLQ-mutant congenital myasthenic syndrome associated with global developmental delay and microcephaly.

Case Report

AQ is an 8-year-old Saudi girl whose parents are first cousins. She is a product of full term, uneventful and normal spontaneous pregnancy with vaginal delivery, no Neonatal Intensive Care Unit (NICU) admission and she was discharged home in stable condition. Later on, she was found to be suffering from subglottic stenosis, severe gastroesophageal reflux, progressive scoliosis, hypotonia, developmental and speech delay, and a history of recurrent chest infections. During the course of evaluation she was found to have COLQ mutation.

At the age of 10 months old, she suffered from a bronchial asthma with intermittent upper airway stridor at the Security Forces

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Hospital. She was then referred to the Pediatric Cardiology unit at the King Faisal Specialist Hospital Research Center for potential vascular ring diagnosis. The cardiac Magnetic Resonance Imaging (MRI) and Echo ruled out vascular ring and other structural cardiac anomalies. The patient was then evaluated by the laryngology service and was found to have subglottic stenosis and underwent tracheostomy.

Subsequently, she was also found to have a significant developmental delay. She only started walking at around 3 years of age and her speech is still not fully developed by the age of 8 years old. She uses her hand or shoulder as support during walking and falls frequently during running. She enjoys watching TV and there has been no diurnal variation in the weakness.

Her parents are first-degree cousins. She had one sibling who also suffered from recurrent chest infections and subglottic stenosis with tracheostomy performed but died at the age of 2 years old. Although AQ remains stable from the respiratory point of view, she is closely monitored by the Pediatric Pulmonary unit because she is oxygen-dependent mainly during night hours. Additionally, she has started to show evidence of scoliosis with disease progression and she is being monitored by the Pediatric Orthopedic Surgery with plans for scoliosis correction.

For developmental delay, she has been evaluated by the Pediatric Neurology and Medical Genetics units and her workup is as follows: Tandem *Mass Spectrometry* (TMS), urine Gas Chromatography–Mass Spectrometry (GC-MS), Microarray Comparative Genomic Hybridization (CGH), carbohydrate-deficient transferrin (CDT), lactic acid, and ammonia were all unremarkable. The chromosomal analysis was also unremarkable and the *Spinal Muscular Atrophy* (SMA) gene study was revealed to be negative. In addition, MRI of the brain has shown vermian hypoplasia with periventricular subcortical patchy T2 hyper-intensities. A whole exome sequence has shown homozygous pathogenic mutation in the COLQ gene associated with CMS.

On physical examination, the patient looked dysmorphic with upward slanting of the eyes and micrognathia. In addition to being cachectic with apparent scoliosis, she also had winging scapulae with poor and thin muscle bulk. The patient had mild ptosis with weak upward gaze but there was no ophthalmoplegia. There was weak neck muscle flexion and extension but normal extraocular movements. During motor examination, she was found to have decreased muscle bulk but normal tone, and the power was around 4+/5 for the upper and lower limbs. The deep tendon reflex was brisk in the upper and lower limbs, and the limbs elicited extensor plantar response. In the standing position, there was hyperextension with flex knee joint. The head circumference of the patient was 52 cm which was considered to be microcephalic and ranked below the 5th percentile.

In addition to the multidisciplinary care provided for various medical conditions, she has been prescribed with albuterol orally 2 mg three times a day (TID) with plan to change to intravenous (IV) ephedrine if necessary. Since starting the albuterol treatment, the patient has improved greatly. Even in the absence of IV ephedrine, there has been no relapse or the need for reintubation.

Discussion

This case report of congenital myasthenia syndrome is unique as no other cases of CMS have been reported so far to have microcephaly. The girl is 8 years old now, however she was presented with subglottic stenosis at the age of 10 months. Additionally, she was also suffering from severe gastroesophageal reflux, progressive scoliosis, hypotonia, developmental and speech delay, and a history of recurrent chest infections. During the course of evaluation, she was found to have COLQ gene mutation – a recognized cause for the synaptic form of CMS.

According to the most updated literature review, 10 mutant genes have been identified to cause CMS. They are ChAT, COLQ, Neuronal acetylcholine receptor subunit alpha-1 (CHRNA1), Acetylcholine receptor subunit beta (CHRNB1), Acetylcholine receptor subunit delta (CHRND), CHRNE, RAPSN, MUSK, DOK7, and Sodium Voltage-Gated Channel Alpha Subunit 4 (SCN4A) [7]. Depending on the localization of defective molecules at the neuromuscular junction, CMS is classified into pre-synaptic, synaptic basal lamina associated and post-synaptic. CMS can have two patterns of inheritance. For autosomal recessive CMS (AR-CMS), the parents of an affected child are obligate heterozygotes and therefore carry one mutant allele each. Heterozygotes (carriers) are asymptomatic. At conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier [8]. For autosomal dominant CMS (AD-CMS), some individuals have an affected parent while others have a *de novo* mutation. The proportion of cases caused by a *de novo* mutation is unknown. Each child of an individual with AD-CMS has a 50% chance of inheriting the mutant allele [9].

The COLQ gene is located at the short arm of chromosome 3 and is responsible for the transcription of triple-stranded collagenic tail of the acetylcholinesterase (AChE) which anchors itself to the basal lamina of the neuromuscular endplates. Autosomal recessive mutation of the COLQ gene causes a synaptic form of CMS. This results in prolonged endplate currents which in turn leads to an overloading of cations at the synaptic space and eventually causes endplate myopathy with the loss of acetylcholine receptors [6]. An electron microscopy study of the endplate of patients with COLQ mutation has revealed degeneration of the junctional folds and the presence of abnormally small nerve terminals encased by Schwann cells [10].

There have only been a few case reports of COLQ-mutant CMS. Wargon et al. has studied 15 cases of *COLQ* mutation with a ten-year follow-up [11]. In their case series, the age of their subjects was ranged from 3 to 48 years old. They have reported that COLQ-mutant CMS can show relapses for a short or long period of time which is characterized by the worsening of muscle weakness and this is sometimes associated with respiratory issues. All the relapses were reported to have ended spontaneously or with 3,4-diaminopyridine (3,4-DAP) or ephedrine treatment with no residual impairment. The triggering factors identified were esterase inhibitors, effort,

puberty or pregnancy, thus highlighting the importance of hormonal factors. There was no genotype-phenotype correlation. At the end of the follow-up, 80% of the patients were ambulant and 87% of the patients did not have any respiratory difficulties in spite of severe relapses.

Additionally, Guven et al. has reported four cases of COLQ mutation in Turkish patients with CMS [12]. In all of their cases, symptoms started to appear at birth with subsequent severity ranging from independent ambulation to wheelchair use during childhood. Treatment was partially effective with one patient being asymptomatic after 3,4-DAP treatment. On the other hand, Matlik et al. has reported COLQ-mutant CMS in two Syrian siblings [13]. One of them has mild symptoms including difficulties in gait and feeding with mild respiratory insufficiency while the other died within the first month of life because of severe respiratory failure. The deceased patient had severe symptoms from birth and required mechanical ventilation. On top of that, DNA sequencing has revealed a novel homozygous single nucleotide substitution mutation in the COLQ gene in both patients. More recently, Al-Shahoumi has presented 2 cases of COLQ-mutant CMS with vocal cord paralysis as a major sign [14].

Millichap has reported COLQ-mutant CMS in 22 patients from 14 centers located mainly in Europe [15]. In 11 of the patients, the disease was presented at birth with hypotonia, ptosis, ophthalmoparesis, facial weakness, weak cry and suckle, and respiratory insufficiency. In four of the patients, the initial symptoms of muscle weakness and fatigability were delayed until 2 to 7 years of age. Respiratory crises occurred in 10 patients and were precipitated by infections in 5 of them. None had arthrogryposis; one had congenital clubfeet. Diurnal fluctuation of the symptoms was noted in 8 patients and disease progression was observed in 9 of them (41%). Repetitive nerve stimulation caused a decremental response in all but 2 of them. Myopathic potentials were recorded on EMG in 15 of the patients and a characteristic double CMAP was observed in more than half of the patients. None of the 8 patients tested showed AChR antibodies while the serum CK level was normal. In 11 of the patients, muscle biopsy was observed to be unremarkable in 4 of them and myopathic changes were observed in other 4 patients. AChE inhibitor treatment (pyridostigmine) is generally ineffective on a long-term basis and may worsen the symptoms. A surprising short-term beneficial effect was observed in 4 patients. Tensilon test was performed in 4 patients and was observed to be positive in 2 of them. Ephedrine has been reported to be beneficial in 5 of the treated cases. Genetic analysis of their family members has revealed a recessive inheritance where nine of them belong to a consanguineous marriage.

Finlayson et al. has reported *DPAGT1*-mutant CMS in 5 patients [16]. Patients have prominent limb girdle weakness and minimal craniobulbar symptoms. Tubular aggregates on muscle biopsy are characteristic but may not be apparent in early biopsies. Typical myasthenic features such as pyridostigmine and 3,4-DAP responsiveness, and a decrement on repetitive nerve stimulation are present. As a result, patients with DPAGT1-CMS share similar clinical features with patients who have CMS caused by mutations in *GFPT1*, another recently identified CMS subtype.

Judith et al. has identified apoptosis linked *gene*-14 (ALG14) and ALG2 as novel genes in which their mutations could cause a congenital myasthenic syndrome [17]. Using yeast as a model of study, ALG14 was thought to form a multi-glycosyltransferase complex with ALG13 and DPAGT1 which catalyzes the first two committed steps of asparagine-linked protein glycosylation. It has been shown that ALG14 is concentrated at the muscle motor endplates and silencing of ALG14 with small interfering RNA results in reduced cell-surface expression of muscle acetylcholine receptor in human embryonic kidney 293 cells. ALG2 is an alpha-1,3-mannosyltransferase which also catalyzes the early steps of the asparagine-linked glycosylation pathway. Mutations were identified in two kinships of which the mutant form ALG2p.Val68Gly was found to severely reduce the ALG2 expression both in patient muscle and cell cultures. The identification of DPAGT1, ALG14 and ALG2 mutations as a cause for congenital myasthenic syndrome underscores the importance of asparagine-linked protein glycosylation for proper functioning of the neuromuscular junction. These syndromes form part of the wider spectrum for congenital disorders of glycosylation caused by impaired asparagine-linked glycosylation. It is likely that further gene-encoding components of this pathway are associated with congenital myasthenic syndrome or impaired neuromuscular transmission as part of the more severe multi-system disorder. Their findings suggest that treatment with cholinesterase inhibitors may improve muscle functions in many of the congenital disorders of glycosylation [17].

Violeta et al. has presented a clinical and molecular genetic finding based on 22 *COLQ*-mutant CMS patients who carry a total of 20 different *COLQ* mutations of which 11 of them have not been reported previously [18]. Typically, patients with esterase deficiency suffer from a severe and progressive muscle weakness with onset at birth or in early infancy. In addition, patients with late onset show a mild course of the disease. Although the AChE inhibitor therapy is beneficial for other forms of CMS, it has no effect in cases with esterase deficiency. The large cohort of *COLQ* patients reported in this study has enabled them to define additional clinical presentations associated with *COLQ* mutations that differ from the 'classic' phenotypes. For example, several patients with disease onset at birth or in early infancy were presented with an unexpected and mild disease course without a significant progression of muscle weakness. Moreover, many of these patients have clinical features resemble limb-girdle CMS with mutation in the recently discovered *DOK7* gene, such as sparing of eye movement and a predominantly proximal muscle weakness. There has been no long-term objective benefit reported from esterase inhibitor treatment in *COLQ* patients. Surprisingly, a short-term beneficial effect was observed in four patients and a Tensilon test was positive in two of them. Treatment with ephedrine was efficient in all five cases where the drug was administered [18].

According to most recent published review, no cases have been reported for CMS with cognitive impairment [19]. Most individuals with CMS benefit from acetylcholinesterase (AChE) inhibitors and/or potassium channel

blocker 3,4-DAP. However, caution must be used in giving 3,4-DAP to young children and individuals with fast-channel CMS (FCCMS). Individuals with COLQ and DOK7 mutations usually do not respond to long-term AChE inhibitor treatment [20]. Some individuals with slow-channel CMS (SCCMS) have been treated with quinidine which can have some major side effects and may be detrimental to individuals with acetylcholine receptor deficiency [21]. Fluoxetine has been reported to be beneficial for SCCMS [22], while ephedrine and albuterol have been beneficial to a few individuals, especially those with DOK7 or COLQ mutations [23]. Prophylactic anti-cholinesterase therapy has been recommended to prevent sudden respiratory insufficiency or apneic attacks provoked by fever or infections in those with mutations in ChAT or RAPSN. [9] Parents of an affected infant must be advised to use apnea monitors and should be given basic life support training to counter cardiopulmonary arrest. It is extremely important to investigate if the disease-causing mutation (mostly autosomal recessive and less commonly autosomal dominant) is also found in asymptomatic family members especially newborns and young children, who could be benefited from early treatment to prevent sudden respiratory failure [8].

Regarding the distinctiveness of this CMS case with COLQ gene mutation followed by a prescription of oral albuterol with a plan to change to intravenous ephedrine if necessary, the co-occurrence of microcephaly is baffling. This is our main reason for reporting this unique case in the literature with the intention to receive insight and feedback from experts in the field.

Conclusion

This is the first reported case of congenital myasthenia syndrome with microcephaly. We recommend that care providers should consider microcephaly as one of the clinical presentations for CMS and should start oral albuterol as a trial to roll in with the disease.

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