




A Case of Congenital Myasthenia Gravis due to ChAT Gene Mutation in a Term Neonate: A Case Report

Maya Soufan, MBBS¹  Haya Soufan, MBBS² Kushagra Chaudhari, MD³ Judith Klarr, MD⁴

¹Department of Pediatrics, Corewell Health East Royal Oak, Royal Oak, Michigan

²AlFaisal University College of Medicine, Riyadh, Saudi Arabia

³Department of Pediatrics, Corewell Health East Royal Oak, Royal Oak, Michigan

⁴Department of Neonatology, Corewell Health East Royal Oak, Royal Oak, Michigan

Address for correspondence Maya Soufan, MBBS, Department of Pediatrics, Corewell Health East Royal Oak, 3601 W 13 Mile Rd, Royal Oak, MI 48073 (e-mail: maya.soufan@gmail.com).

AJP Rep 2024;14:e193–e196.

Abstract

Congenital myasthenia gravis syndrome (CMS) is a rare genetic heterogeneous disorder due to abnormal neuromuscular transmission caused by several genes. CMS caused by choline acetyltransferase (ChAT) gene mutations have been reported in 53 cases since 2020, and only three of them have been identified as hemizygous mutations.

A 1-day-old term neonate was transferred from the nursery to the neonatal intensive care unit on 10 L of oxygen by face mask due to respiratory distress. Family history includes two ChAT gene variants in the elder brother and carrier genes in both parents. She was transitioned to continuous positive airway pressure +5, and chest X-ray showed poor chest expansion. Sepsis workup was negative. She was intubated due to worsening respiratory distress 3 days later. She was started on pyridostigmine, and genetic testing was done, which confirmed two ChAT gene mutations present. The patient had a tracheostomy placed on day 50 and was discharged on day 94 of life on tracheostomy and G-tube, given feeding intolerance.

This case illustrates the value of genetic testing in determining the type of CMS to guide management and the importance of obtaining family history to have such syndromes earlier in the differential diagnosis to initiate treatment promptly.

Keywords

- ▶ congenital myasthenia gravis
- ▶ neostigmine
- ▶ ChAT gene
- ▶ respiratory distress
- ▶ c.1669 G > A p. (A557T)
- ▶ c.938_939del p.(F313Cfs*7)

Introduction

Congenital myasthenia gravis syndrome (CMS) is a genetically rare heterogeneous neuromuscular transmission disorder caused by genes encoding neuromuscular junction proteins that cause abnormal signal transduction. CMS can be classified into presynaptic, synaptic, or postsynaptic, depending on the site of the mutation. The most common form of CMS is the postsynaptic form, which accounts for

75 to 80% of the patients, followed by synaptic CMS, which accounts for 14 to 15% of patients with the rarest being presynaptic form affecting 7 to 8% of patients.

Due to the overlapping clinical manifestations, family history, electrophysiological studies, and responses to acetylcholinesterase inhibitors in the different types of CMS, it is essential to identify specific mutations in the genes that cause the defect.^{1,2} Since 2011, due to the development

received

February 12, 2024

accepted after revision

July 26, 2024

accepted manuscript online

July 10, 2024

DOI <https://doi.org/>

10.1055/a-2363-6319.

ISSN 2157-6998.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

of whole-exon sequencing, more than 30 disease genes have been identified, such as CHAT, COLQ, LAMB2, CHRNA, CHRNB, CHRND, CHRNE, CHRNG, RAPSN, DOC7, MUSK, ARGN, SCN4A, GFPT1, or PLEC1.³ Identifying the genetic cause underlying CMS, the infant is presenting with is crucial, as each subtype entails a different treatment approach.

Choline acetyltransferase (CHAT) gene mutations, which account for 5% of CMS probands, fall under the presynaptic category. The CHAT gene is located on the long arm of chromosome 10 (10q11.23) and encodes for the biosynthetic enzyme of the neurotransmitter acetylcholine, CHAT.⁴ CHAT catalyzes the reversible synthesis of acetylcholine from acetyl coenzyme A (AcCoA) and choline at cholinergic synapses. In the form of the disease associated with the CHAT gene, studies of the neuromuscular junction show a stimulation-dependent abnormal decrease in miniature end plate potential amplitude but no deficiency in the acetylcholine receptors. This result suggests a defect in the resynthesis of acetylcholine or vesicular filling, which causes a decrease of acetylcholine at the neuromuscular junction, affecting appropriate neuromuscular transmission.⁵

CMS caused by CHAT gene mutations have been reported in 53 cases since 2020, and only three of them have been identified as hemizygous mutations.² This gene mutation can present as sudden episodes of apnea unprovoked or due to stress and can occur with few or no myasthenic symptoms. Some patients are apneic and hypotonic at birth, whereas other neonates are normal at birth and will start developing apneic episodes during infancy or childhood. In some children, an apneic attack is followed by respiratory failure and remaining ventilator dependent for weeks. Apnea resolves with the majority by 2.5 years of age. Few patients will ever be able to breathe spontaneously, and some develop cerebral atrophy secondary to hypoxemia.^{1,5}

We will report here a case of a CMS neonate with two pathogenic CHAT mutations (compound heterozygous) (c.1669 G > A p. (A557T), c.938_939del p.(F313Cfs*7)). This case also highlights the value of genetic testing to guide further management.

Case Report

Initial Case Presentation

We present a case of an unusual congenital myasthenia gravis mutation in a nonconsanguineous family. Patient was born at 39 weeks 1 day via spontaneous vaginal delivery to a G3P3 mother whose pregnancy was complicated by gestational diabetes managed with metformin and elevated blood pressure and Procardia, respectively. Apgar scores were 9 and 9 at 1 and 5 minutes at the infant's birth. Cord clamping was delayed for 45 seconds, and no resuscitation was required. Shortly after birth, her skin was dusky, and transient shallow breathing was noted, responsive to tactile stimulation. The neonatal intensive care unit (NICU) team was called to evaluate. She was not in respiratory distress, and physical examination showed equal and good air entry bilaterally on all lung fields. Physical examination was only

remarkable for nevus simplex on the nape and a tongue tie. Pertinently, there was no evidence of muscle or tone abnormalities, i.e., arthrogryposis. She was stable and stayed in her mother's room.

On day 1 of life, she developed respiratory distress, grunting, retractions, and cyanosis. Oxygen saturation was 77%, and glucose level was 105 mg/dL. The infant was then placed on 10 L of oxygen via a face mask, which improved her oxygen saturation. At this time, she was also noted to have rhythmic upper body movements. She was then transferred to the NICU. In the NICU, she was started on continuous positive airway pressure (CPAP) with a peak end expiratory pressure of 5 cm H₂O, transcutaneous carbon dioxide monitoring was placed and was made nothing by mouth and was started on 10% dextrose and 0.2% normal saline of fluids. Chest X-ray showed poor chest expansion. Differential diagnoses at that time included congenital myasthenia gravis, sepsis, and less likely seizure, given that her abnormal movements improved after oxygen supplementation. Sepsis workup was initiated, and she was empirically treated with ampicillin and cefepime. Pediatric genetics and pediatric neurology were consulted. Antibiotics were discontinued 2 days later after blood cultures were negative. Genetics testing was done on day 3 of life.

Family History

Further history revealed an elder brother with a diagnosis of myasthenia gravis. The brother was born with shoulder dystocia and was in the NICU for 6 weeks with seizures, trouble breathing, and difficulty being weaned off the ventilator. Parents also reported that he required 2 hours to feed after discharge from the NICU. He also had ptosis. These findings prompted genetic testing and revealed congenital myasthenia gravis with two CHAT gene variants (CHAT mutations c.1669G > A/p. Ala557Thr, c.938_939delTT/p. Phe313Cysfs*7). The nonconsanguineous parents being carrier for one CHAT gene. Currently, he is 11 years of age and is being treated with neostigmine. He now only has muscle weakness on the left side. They have another younger sibling who is healthy.

Infant's Genetic Testing

Genetic testing returned 3 weeks later and was positive for the carrier of two pathogenic CHAT mutations (compound heterozygous) (c.1669 G > A p. (A557T), c.938_939del p. (F313Cfs*7)).

Case Progression

On day 4 of life, she demonstrated increased respiratory distress and increased values on transcutaneous monitor, which warranted intubation. Per neurology consult, she was started on neostigmine on day 8 of life and was gradually titrated during her stay to a maximum dose of 6.8 mg/kg/d divided every 4 hours. She did not demonstrate adverse effects of the medication during her stay. Her feeds consisted of maternal breast milk through gavage feedings during her intubation period. During her 3-month hospital stay, she was intubated a total of four times after three

failed extubation attempts. She self-extubated on day 29 of life and was transitioned to noninvasive ventilation followed by CPAP.

A multidisciplinary team discussion was done, and the decision was made to place her on tracheostomy after also discussing with the infant's parents. The pediatric otolaryngology team placed a tracheostomy on day 47 of life.

She was transitioned to a home ventilator, pressure-controlled synchronized intermittent mandatory ventilation (PC-SIMV) mode on day 50 of life. The ventilator settings were adjusted during her NICU stay based on her clinical exam and capillary blood gas. However, after her tracheostomy placement, the infant had persistent emesis with weight loss. Abdominal X-rays and upper gastrointestinal studies were done to rule out malrotation and volvulus, which were negative. The feeding regimen was changed to continuous feeds through gavage at night and bolus feeds during the day with some oral intake. Due to persistent nasogastric tube dependence, a gastrostomy tube was placed on day 87 of life. Enteral feeds were advanced, and she tolerated her gastrostomy tube feeds. Her percentage oral intake was around 5 to 10% after its placement. The first dose of respiratory syncytial virus prophylaxis was administered a day before her discharge. Her ventilator settings on the day of discharge were PC-SIMV, respiratory rate (RR) of 12, pressure control (PC) of 13, positive end-expiratory pressure (PEEP) of 5, pressure support (PS) of 7, inspiratory time (I-time) of 0.5, and fraction of inspired oxygen (FiO₂) of 21. She was discharged on day 94 of life with skilled nursing care. She is closely following up with pediatric pulmonology and pediatric neurology for neostigmine dosing adjustments. It was discussed with the infant's family to do a brain magnetic resonance imaging on an outpatient basis, given that there were no concerns for hypoxic-ischemic insult in her course, apart from apneic episodes.

After Discharge from the Neonatal Intensive Care Unit

She has currently total of four brief pediatric intensive care unit admissions at the ages of 4, 6, 11, and 13 months where the first three of them were due to acute or chronic respiratory failure secondary to viral upper respiratory tract infection and the latest one was for concern for aspiration due to choking event and was observed for a day prior to discharge. She did not require increase in ventilatory support in any of her admission or periods of illnesses.

At 11 months of age, she has been off ventilator support during the day and only uses it at nighttime or nap time on PC-SIMV with passive adult circuit with RR of 10, PEEP of 5, PC of 12, I-time of 0.5 seconds, PS of 6, FiO₂ of 21%. Her neostigmine dose has been weaned to 4.6 mg/kg/d divided every 4 hours. Oral feedings are being increased gradually where she eats small amounts of crackers, pureed meals, vegetables, and meat and is working with occupational therapy for her feeds. In addition, she exhibits no gross motor delay.

Discussion

Our infant here presented with apnea, difficulty feeding requiring gastrostomy tube placement, and required mechanical ventilation. She showed clinical improvement on pyridostigmine, which made her wean off the home ventilator at 11 months of age for most of the day. Based on her clinical presentation and genetic study, her presentation is consistent with CHAT gene CMS.

Our patient had a heterozygous missense mutation in c.1669 G > A p. (A557T), which is found on exon 12 of the CHAT gene. The A557T mutant variant disturbs the conformation of the active site of CHAT; hence, this creates very low affinity with AcCoA and choline and low catalytic rate. A557T mutant variant has higher incidence of apnea and respiratory failure, more so than bulbar dysfunction, and frequently results in tracheostomy/ventilator dependency per the infant's genetics report. The mutant variant was found to be less severe than other variant mutations of CHAT and responds well to pyridostigmine.^{3,6}

The second heterozygote variant found in our patient was c.938_939del p.(F313Cfs*7). Per GeneDx genetic report, this is a loss of function frameshift variant mutation found on exon 7 of the CHAT gene that is predicted to cause protein truncation and nonsense-mediated decay. This variant has not been reported in gnomAD; however, it was observed in trans with a pathogenic variant on the opposite allele, which manifested with failure to thrive, neonatal seizures, gross motor delay, hypotonia, dystonia, ptosis, and learning disability. There has been no previous report on the variant whether it is benign or pathogenic but it was reported as pathogenic in the genetics report. In our case, the mutant variant was found in her elder brother.

It is imperative to perform genetic testing to determine the type of CMS the patient has as medications may be beneficial in certain mutations but can be contraindicated subtypes of the disease. For example, using cholinesterase inhibitors is one of the mainstays of treatment for CMS caused by CHAT mutation. Still, it can lead to deterioration in CMS caused by collagen-like tail subunit of acetylcholinesterase mutation.²

This case emphasizes the importance of obtaining family history earlier during prenatal visits to prepare for the delivery of the baby and assess if there is a need for further observation and to have such rare disease earlier in the differential diagnosis to initial prompt treatment to prevent clinical deterioration.

Conflict of Interest

None declared.

References

- Lorenzoni PJ, Scola RH, Kay CSK, Werneck LC. Congenital myasthenic syndrome: a brief review. *Pediatr Neurol* 2012;46(03):141–148
- Zhang Y, Cheng X, Luo C, et al. Congenital myasthenic syndrome caused by a novel hemizygous CHAT mutation. *Front Pediatr* 2020; 8:185

- 3 Shen XM, Crawford TO, Brengman J, et al. Functional consequences and structural interpretation of mutations of human choline acetyltransferase. *Hum Mutat* 2011;32(11):1259–1267
- 4 National Center for Biotechnology Information. ClinVar. [VCV000461452.12]. Accessed August 27, 2023 at: <https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000461452.12>
- 5 McMacken G, Whittaker RG, Evangelista T, Abicht A, Dusl M, Lochmüller H. Congenital myasthenic syndrome with episodic apnoea: clinical, neurophysiological and genetic features in the long-term follow-up of 19 patients. *J Neurol* 2018;265(01):194–203
- 6 Mallory LA, Shaw JG, Burgess SL, et al. Congenital myasthenic syndrome with episodic apnea. *Pediatr Neurol* 2009;41(01):42–45