



Case Report: A Case Report of Congenital Myasthenia Gravis Presenting With Respiratory Distress



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Bullet Points:

- Congenital myasthenia should be considered in the differential diagnosis of episodic apnea and general weakness.

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ABSTRACT

Congenital Myasthenic Syndromes (CMS) are rare inherited disorders characterized by dysfunction of neuromuscular transmission at the neuromuscular junction. Most patients with congenital myasthenic syndromes present in the infancy. Major symptoms of affected individuals include weakness and fatigue during the first years of life. Patients may show hypotonia, facial weakness, swallowing difficulties, respiratory dysfunction, ptosis and ophthalmoparesis. Here we report a 6 month old boy congenital myasthenia gravis due to homozygous mutation in COLQ gene. The patient presented with several episodes of apnea and didn't have ptosis until 6 months of age, and even at this time it started as just left eye ptosis and after a few days became bilateral. He had been misdiagnosed with several other causes of episodic apnea. Later by using electrophysiology he was diagnosed as congenital myasthenia gravis and mutation analysis of the patient revealed the presence of mutation of COLQ gene and was treated successfully.

Keywords: Myasthenia gravis, Congenital, Apnea

Case Presentation

A 6 month of age boy was brought to the Children's Medical Center (CMC) clinic affiliated to Tehran University of Medical Sciences in Iran with the complaint

of "difficult breathing". He had respiratory distress and suprasternal retraction. Oxygen saturation from pulse oximetry was 85%, measured in ambient air and by introducing 6 liters per minute oxygen with head box, the saturation improved to 95%. As the respiration deteriorated rapidly and he started to have gasping, tracheal

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tube was placed for him immediately and transferred to Pediatric Intensive Care Unit (PICU).

The vital signs were as follows: pulse rate=160 beats per minute, respiratory rate=70 breathe per minute, temperature=37 centigrade degrees and blood pressure was 80.45 mmHg. Heart and lung auscultation, abdominal and extremities exams were normal. The patient looked lethargic, hypotonic and underweight. His current weight was 5500 grams. On the past medical history; the infant was born by cesarean section because of cephalopelvic disproportion at 38 weeks of gestational age to a primi-gravida mother and nonsanguine parents. His birth weight was 3370 grams and head circumference 35.5 centimeters (the current head circumference was 41 centimeters at the time of symptom presentation).

He had a history of episodic respiratory distress and apnea since the 10th day of age and had been admitted several times to the intensive care unit and intubated. Several times of pulmonary aspiration complicated the respiratory condition. In the previous admissions, the immunological profile regarding immunodeficiency conditions, metabolic diseases screening were assessed and reported normal. He had one uncertain episode of seizure in neonatal period, and brain Magnetic Resonance Imaging and Electroencephalogram (MRI and EEG), obtained and reported normal. Assessing the repeated pulmonary aspiration, upper gastrointestinal endoscopy and radiologic evaluation by upper gastrointestinal series performed and "esophagitis, gastroesophageal reflux disease and pharyngeal muscles incoordination", reported. His sucking was poor. Since the infant has

several episodes of pneumonia, apnea and respiratory distress, he was also evaluated for Cystic Fibrosis and the result was negative. Thyroid function and rheumatologic disease tests were normal.

Continuing the evaluations, the complete heart assessment and echocardiography was normal. A High Resolution Computerized scan (HRCT) of the thorax and a plain Chest Radiography (CXR) revealed hyperareation, bilateral parahilar opacities and a shrunken thymus, possibly because of frequent infections. The next CXR on the 2nd day of admission revealed airspace opacities consistent with aspiration pneumonia. The patient didn't have ptosis as the initial presentation and after a few days of admission left eye ptosis developed firstly and a few days after both eyes had ptosis. As the half open eyes condition were persistent, the neurologic consultant became suspicious to bilateral ptosis and ordered electro-diagnostic tests for evaluation of peripheral nervous system disorders as the cause of episodic apnea and respiratory distress in this patient.

The Electrodiagnostic (EDX) findings of the patient were as follows: 1. All recorded compound muscles action potential (CMAP) had normal amplitude; 2. All recorded sensory nerve action potentials (SNAP) were normal; 3. All recorded F-waves were normal; and 4. Repetitive Nerve Stimulation Test (RNST) performed with 3 HZ stimulation ([Table 1](#)) and recording from both abductor pollicis brevis muscles, showed greater than 10% decrement (35% in amplitude and 46% in area) of detected CMAPs. Because of possibility of apnea due to pain, high frequency stimulation not performed. These

Table 1. Repetitive Nerve Stimulation Test (RNST) performed with 3 HZ stimulation and recording from both left and right abductor pollicis brevis muscles

| Stim No. | Amp. | Decrement (%) | Area (mV. ms) | Decrement (%) |
|----------|---------|---------------|---------------|---------------|
| 1 | 2.50 mV | 0.0 | 9.01 | 0.0 |
| 2 | 2.11 mV | 15.6 | 6.08 | 32.6 |
| 3 | 1.70 mV | 32.0 | 4.86 | 46.1 |
| 4 | 1.61 mV | 35.6 | 4.85 | 46.2 |
| 5 | 1.65 mV | 34.0 | 4.87 | 46.0 |
| 6 | 1.68 mV | 32.8 | 4.90 | 45.6 |
| 7 | 1.71 mV | 31.6 | 6.91 | 23.4 |
| 8 | 1.72 mV | 31.2 | 4.90 | 45.7 |

The table shows more than 10% decrement, which indicates both synaptic and post synaptic disorders.

findings are compatible with neuromuscular junction transmission disorder.

Based on clinical and EDX findings, neuromuscular junction transmission disorders should be considered, so genetic test performed and reported a homozygous COLQ mutation in the patient. The neurologic consultant diagnosed the patient as "Congenital Myasthenia" and recommended to administer Pyridostigmin (Mestinon) **Table 1** milligram per kilogram per dose every 6 hours, and in case of apnea crisis, intramuscular Neostigmin 0.04 milligram per kilogram should be immediately injected.

By prescribing Mestinon, the patient's respiratory drive improved gradually and started breathing normally without the aid of mechanical ventilation. Physical therapy for helping the sucking activity besides Mestinon, improved his swallowing activity. After about one week of treatment the anti-cholinesterase inhibitors didn't have the previous effect and Ephedrine 0.5 mg/kg every 6 hours started and the patient's condition started to improve again.

Discussion

Myasthenia gravis is a chronic autoimmune neuromuscular disorder caused by neuromuscular blockade and quick fatigability of the striated muscles especially extra ocular, swallowing and eyelid muscles. In myasthenia gravis, Acetylcholine (Ach) releases normally, but the post-synaptic muscle membrane is not normally responsive. Rarely, increasing anti-Ach antibodies causes familial myasthenia gravis which is an autosomal recessive trait. Myasthenic mothers may give birth to infants with transient neonatal myasthenic syndrome which is caused by anti-Ach receptor antibodies that are transferred from placenta [1].

The first signs of juvenile autoimmune myasthenia gravis are unilateral or bilateral ptosis (which is often asymmetric). Other presentations are diplopia, dysphagia, weakness of facial muscles, feeding difficulties and aspiration. Electromyography (EMG) shows a specific decremental response in repetitive stimulation of nerve. The conduction velocity of motor nerves is normal in myasthenia gravis. This specific pattern can be reversed by administration of cholinesterase inhibitors and may be reported normal in muscles that are not involved [1]. With a single stimulus on routine motor nerve conduction assessment, multiple motor action potential discharges may appear which is a nonspecific finding in slow channel syndrome [2].

Congenital Myastenic Syndromes (CMS) manifest at birth or early infancy and present with ptosis, external

ophthalmoplegia, difficulty in swallowing, hypotonia, weak cry, respiratory failure (that may be caused by minor respiratory infections), facial weakness and episodic apnea [1]. The origin of hypotonia in CMS is in the neuromuscular junction [3]. CMS has also been reported as a cause of Apparent Life Threatening Events (ALTE) [4]. Infantile botulism should also be considered in any infant who sustains inactivity, weak cry, sucking and swallowing, ptosis and constipation [5].

Children afflicted by CMS mostly present the illness during the first 2 years of life and many of them have the symptoms since neonatal period or early infancy. Sometimes the clinical presentation may not appear until adolescence or adulthood. The patients may have episodic symptoms or get worse by fever and emotional stress [2].

Congenital myastenic syndromes can be categorized as presynaptic, synaptic, and post synaptic. Mutations in AchE gene do not cause end-plate AchE deficiency, but mutations in COLQ gene cause esterase deficiency that mostly described in synaptic CMS, in which involvement of axial muscles can lead to scoliosis and restrictive respiratory disease [6]. AchE deficiency was first described in 1977 by Engel et al. [2]. Mutations of COLQ gene lead to lack of AchE in the synaptic end plate [7].

These syndromes are almost always permanent disorders, do not improve spontaneously, and most of them are transmitted as recessive traits, however the slow channel syndrome is transmitted as autosomal dominant trait. Most of them respond favorably to cholinesterase inhibitors, but in some forms of congenital forms of congenital myasthenic syndromes, the signs and symptoms become worse [1].

In less than half of patients with CMS, the genetic mutations are known. Mutations of COLQ gene have been responsible for 10% of CMS with known genetic mutations. In 85% of these patients, mutations of DOK7, and in 5% of cases mutations of ChAT have been identified [1].

Unlike the autoimmune form of myasthenia gravis, in CMS, anti-Ach Receptor (anti-AchR) and anti-Muscle-Specific-Tyrosine Kinase (anti-MuSK) antibodies usually (but not always) are not detected. Assessment of anti-DOK7, anti-rapsyn, COLQ, and ChAT antibodies are performed in a few specific centers. Muscle biopsy is not required in most of the cases. Administering edrophonium hydrochloride which improves ophthalmoplegia and ptosis in a few seconds and reduces muscle fatigability is also a clinical test [1].

Recurrent apnea in infancy and childhood which usually triggered by infection or stress, is a distinctive presentation of the presynaptic CMS (due to mutations in CHAT) and postsynaptic CMS (caused by mutations in RAPSN). Synaptic CMS (due to mutations in COLQ) and the slow channel syndromes (caused by mutations in acetylcholine receptor subunits) lead to end plate myopathy, which cause progressive respiratory muscle weakness and respiratory failure [8].

In COLQ mutant CMS patients (esterase deficiency), treatment with AchE inhibitors have no effect and it may block the residual AchE activity and also may block butyryl cholinesterase, that compensates part of the AchE deficiency. However AchE inhibitors may initially improve the muscle strength [9]. Ephedrine can be effective in the treatment of these patients [1].

Congenital myasthenia should be considered in the differential diagnosis list of Apparent Life Threatening Events (ALTE), episodic apnea and general weakness, especially when other more common causes have ruled out.

Conclusion

Congenital myasthenia should be considered in the differential diagnosis of apnea and general muscle weakness.

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Conflict of Interest

The authors have no conflicts of interest.

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