Delayed diagnosis of DOK7 congenital myasthenic syndrome: Case report and literature review

Amber Johnson, BS, S.H. Subramony, MD, and Miguel Chuquilin, MD

Neurology: Clinical Practice December 2018 vol. 8 no. 6 e40-e42 doi:10.1212/CPJ.0000000000000530

Correspondence

Dr. Chuquilin
Miguel.chuquilin@
neurology.ufl.edu

Congenital myasthenic syndromes (CMSs) are genetic disorders characterized by a faulty neuromuscular junction causing muscle weakness with or without respiratory and oculomotor involvement. Congenital myopathies (CMs) can present similarly to CMS but are secondary to muscle protein defects. CMSs cause muscular weakness, hypotonia, and ptosis and can respond to treatment^{1,2}; CMs have no proven therapies. We present a patient with DOK7 CMS, previously diagnosed as CM for 25 years.

Case report

A 29-year-old man presented for evaluation of progressive muscle weakness that had made him nonambulatory for more than 10 years. He had delayed motor milestones, could not run, and had difficulty walking and getting up from the ground at age 2 years. He used a walker by age 6 years. He was diagnosed with Duane syndrome (congenital horizontal eye movement limitation) and congenital myopathy at age 4 years (muscle biopsy showed type 1 fiber predominance and mild type 2 fiber atrophy, without tubular aggregates in nicotinamide adenine dinucleotide [NADH] or electron microscopy). He had strabismus surgery at age 5 years. Medical, surgical, familial, and social histories were otherwise noncontributory.

He had mild bilateral ptosis and mild facial and 4/5 shoulder shrug weakness. On strength testing, the deltoids, biceps, triceps, and hip flexors were 3/5 bilaterally; finger/wrist flexors and extensors and hand intrinsics were 5/5 bilaterally; knee flexors and extensors, foot dorsiflexion, and plantar flexion were 4/5 bilaterally. Reflexes were absent. He could walk only a few steps. Mental status, language, and sensation were normal.

Given his progressive weakness, bilateral eyelid ptosis, and nonspecific muscle biopsy results, we re-evaluated him for a neuromuscular junction defect. Two-hertz repetitive nerve stimulation (RNS) of the right median and accessory nerves showed marked compound muscle action potential (CMAP) decremental responses, which worsened after 1 minute of exercise (figure). His acetylcholine receptor antibody was negative, and CK was 82. Genetic testing revealed 2 known pathogenic mutations, c.1124_1127dupTGCC (p.Ala378Serfs*30) and c.1623dupC (p.Ser422Leufs*97), in the *DOK7* gene. Before genetic test results were available, he took pyridostigmine 60 mg TID for 9 months, which worsened his weakness. Afterward, he started albuterol 5 mg PO TID, and 3 weeks later, he could walk up to 100 feet and had normal lower extremity muscle strength.

Discussion

Diagnosis of CMS requires clinical suspicion. Individuals with CMS or CM can have delayed motor development and limb-girdle muscle weakness. Patients with CMS can have bilateral

PRACTICAL IMPLICATIONS

Consider congenital myasthenic syndrome and perform repetitive nerve stimulation in patients with congenital myopathy or congenital muscular dystrophy and progressive weakness and extraocular movement abnormality or eyelid ptosis.

Department of Neurology, University of Florida, Gainesville.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Figure Right median nerve repetitive nerve stimulation (RNS)

Low-rate (2 Hz) RNS of the right median nerve showed 14.2% compound muscle action potential decrement at baseline (A) that worsened to 24% after 1 minute of exercise (B) consistent with a neuromuscular transmission defect.

eyelid ptosis, extraocular movement abnormality, and increasing weakness with exertion, but this is not always clear from history. Therefore, it is necessary to perform further testing such as muscle biopsy or RNS. In CM, muscle biopsy often shows features such as central cores, central nuclei, or nemaline rods, but many have nonspecific findings. Muscle biopsy in CMS will show a milder or nonspecific dystrophic pattern. RNS is the most helpful test, as it will show marked CMAP decremental response in CMS. Genetic testing identifies the underlying gene defect in up to 50% of cases,¹ and guides treatment, as some patients worsen with pyridostigmine (commonly used for neuromuscular junction disorders). If there is a suspicion of DOK7 CMS,

improvement with a trial of salbutamol (albuterol) usually supports the diagnosis.²

The *DOK7* gene encodes the skeletal muscle adaptor protein DOK-7. This protein autophosphorylates MuSK and causes aggregation of acetylcholine receptors on the motor end plate. Without this protein, the receptors cannot properly aggregate, causing neuromuscular transmission failure and weakness.³ Patients usually present by age 5 years (some cases start in late adolescence and adulthood) with limb-girdle weakness without ophthalmoplegia.² Ptosis is commonly present. Progressive respiratory impairment typically occurs throughout life. Pyridostigmine does not help and can make symptoms

Table Cases of DOK7 CMS with delayed diagnosis

Initial diagnosis	Age at diagnosis of CMS	Age at onset of weakness	Symptoms	Biopsy findings	Treatment	References
Congenital muscular dystrophy	41–53	Birth	Proximal upper limb-girdle and trunk weakness	Mild and nonspecific dystrophic features	Salbutamol	2
Facioscapulohumeral dystrophy	26	Birth	Ptosis and muscle weakness in the face, proximal muscles, and trunk	NA	3,4-Diaminopyridine	5
Seronegative myasthenia gravis	39	39	Bilateral proximal upper limb weakness, dysphagia, and slight ptosis	NA	Fluoxetine and salbutamol	6
Myasthenia gravis	61	Childhood	Bilateral ptosis and proximal muscle weakness	Fiber size variability, angulated fibers, and internalized nuclei	Salbutamol	7
Myasthenia gravis	62	Childhood	Ptosis, muscle weakness, and respiratory difficulty	None	Salbutamol	7
None reported	68	12	Delayed motor milestones, upper extremity weakness, ptosis, drop-head, and loss of ambulation in 30 s	Myopathic without dystrophic changes	3,4-Diaminopyridine and salbutamol	8
Myasthenia gravis	31	29	Shoulder weakness, head drop, and fatigue	Normal	Albuterol	9
Congenital myopathy	29	4	Proximal muscle weakness, falls, and ptosis	Type 1 fiber atrophy	Salbutamol	This case

Abbreviation: CMS = congenital myasthenic syndrome; NA = not available.

worse. Unless treated, symptoms continue to progress with time. Our patient showed improvement with albuterol (salbutamol), which is the most effective treatment of DOK7 CMS. Salbutamol is a beta-2 agonist that works by bypassing the step in the receptor aggregation pathway that requires DOK-7 so that the acetylcholine receptors are still able to aggregate and function properly at the neuromuscular junction. Studies have demonstrated that oral salbutamol increased stamina and function in 1 month. It has even shown to make nonambulatory children walk again.⁴ Other DOK7 CMS cases with delayed diagnosis have been reported in the literature (table).

Conclusion

Consider CMS in patients with congenital or early-onset muscular weakness, eyelid ptosis, fluctuating symptoms, and/or improvement of weakness with salbutamol or “asthma medications.” RNS and genetic testing are paramount in achieving an early diagnosis and initiating treatment to prevent further muscle injury and disability.

Author contributions

A. Johnson: analyzed the data and drafted the manuscript for intellectual content. S.H. Subramony: designed and conceptualized the study, interpreted the data, and revised the manuscript for intellectual content. M. Chuquilin: designed and conceptualized the study, analyzed the data, drafted the manuscript for intellectual content, and revised the manuscript for intellectual content.

Study funding

No targeted funding reported.

Disclosure

A. Johnson reports no disclosures. S.H. Subramony was volume editor for the Handbook of Clinical Neurology (2011); performs clinical electrophysiology (20% effort) at the University of Florida Department of Neurology; and receives research support from Ionis Pharmaceuticals, Reata Pharmaceuticals, Horizon Pharma, Biohaven Pharmaceuticals, Pharnext Pharma, Acceleron Pharma, Medosome Biotech, NIH, STTR, Friedreich Ataxia Research Alliance, Muscular Dystrophy Association, Myotonic Dystrophy Wyck Foundation, and National Ataxia Foundation. M. Chuquilin reports no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received May 25, 2018. Accepted in final form July 26, 2018.

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