Published in final edited form as:

Muscle Nerve. 2011 August ; 44(2): 289–291. doi:10.1002/mus.22153.

BENEFICIAL EFFECT OF ALBUTEROL IN CONGENITAL MYASTHENIC SYNDROME WITH EPSILON SUBUNIT MUTATIONS

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Abstract

Mutations in the epsilon subunit of the acetylcholine receptor (AChR) are a common cause for congenital myasthenic syndrome (CMS). Patients are usually treated with acetylcholine esterase inhibitors and 3,4-diaminopyridine with modest clinical benefit. We report two patients with CMS due to mutations in the AChR epsilon subunit. The first patient carries two heterozygous frameshift mutations, ϵ 127ins5 and ϵ 1293insG. The second patient is homozygous for ϵ C142Y mutation that curtails AChR expression to 22% of wild type in HEK cells. Treatment with pyridostigmine and 3,4 diaminopyridine had a limited beneficial effect in the first patient, and the second patient became wheelchair bound during therapy. The additional use of albuterol produced dramatic improvement in strength and in activities of daily living in both patients. The efficacy and safety of albuterol in patients who harbor identified low-expressor or null mutations in the epsilon or other subunits of AChR merits a well designed clinical trial.

Introduction

Mutations in the epsilon subunit of the acetylcholine receptor (AChR) are the commonest cause for congenital myasthenic syndrome (CMS)¹. The inheritance is recessive, except for mutations that cause slow-channel syndromes, and most patients are compound heterozygotes. Mutations in the epsilon subunit may change the kinetic properties of the AChR channel or decrease AChR expression. Changes in kinetic properties manifest as slow-channel or fast-channel syndromes. The slow-channel syndromes respond to treatment with long-lived open-channel blockers of the receptor, such as quinidine or fluoxetine. All other CMS patients with mutations in the AChE epsilon subunit are treated with acetylcholine esterase (AChE) inhibitors and 3,4-diaminopyridine (3,4-DAP) with variable results. We here describe an impressive beneficial response to treatment with the beta-2 adrenergic agonist albuterol in two patients with CMS due to epsilon subunit mutations.

Patient 1

This 56-year-old woman was born in Romania and came to Israel in 1959. She is a teacher, is married and has 4 children. Her parents are not related, and there is no family history of neurologic disease. At age of 3–4 months the patient had a weak cry and difficulties in sucking. At the age of 9 months she had bilateral ptosis. As a child, she had difficulty climbing stairs, lifting weights, or elevating her arms. During her pregnancies she felt well, but her weakness worsened after each delivery. Tests for antibodies against AChR were

negative. Repetitive nerve stimulation (RNS) at 3 Hz showed a decremental response. She was diagnosed as having CMS and was treated with pyridostigmine for many years with beneficial results. Seven years ago she had a severe attack of asthma. She was admitted to another hospital and was treated with high doses of prednisone. After 2 weeks, her weakness improved significantly so that she was able to climb stairs, which she could not do before, and the diagnosis was changed to probable autoimmune myasthenia gravis.

When seen at the Wolfson Medical Center in 2005 she had bilateral non-fatigable ptosis, limitation of gaze in all directions, and weakness of facial muscles. Limb muscle weakness was symmetrical, and strength was (MRC scale): Deltoid and triceps 4/5, biceps and infraspinatus 4+/5, iliopsoas 1/5. There was minimal weakness of the quadriceps and the adductors, and all other muscles were of normal strength. RNS of the trapezius and abductor digiti minimi muscles showed decremental responses of 25% and 11–16%, respectively. Treatment with prednisone and azathioprine was instituted. She improved markedly but also became hirsute, edematous and developed dermatophytosis. Prednisone treatment was gradually stopped, but therapy with 250 mg/day of azathioprine was continued. Within a period of 2–3 months the patient's condition deteriorated. High dose intravenous immunoglobulin was not beneficial. The failure of immunomodulatory treatment again pointed to a CMS, and mutation analysis revealed two heterozygous frameshift mutations in the epsilon subunit of AChR, $\epsilon 127\text{ins}5$ and $\epsilon 1293\text{ins}G$. Both have been reported previously.^{2,3}

Treatment was started with 3,4 diaminopyridine (DAP) at a dose that was gradually increased to 7.5 mg six times daily, and pyridostigmine, 60mg six times daily was continued. Under this treatment there was a modest improvement. If she took an extra 10 mg dose of 3,4-DAP she could take short walks at her home for over half an hour. On examination she had ophthalmoplegia with mild bilateral ptosis, mild to moderate weakness (4/5 on MRC scale) of facial and proximal arm muscle, and there was severe weakness of the iliopsoas muscles (1/5 on MRC scale).

Treatment with albuterol sulfate, 2mg three times daily, was added. Within a few weeks her strength improved dramatically. She rose easily from sitting and could walk 2 kilometers without becoming tired. Examination now only showed slight weakness of the deltoid muscles, and the iliopsoas muscles were 4/5 on the MRC scale. There was no change in the ophthalmoplegia or facial weakness. All other muscles had normal strength. There was no change in muscle strength during a year of follow-up.

Patient 2

This 35-year-old woman had generalized weakness from the age of 3 months. She wept silently and had bilateral ptosis; however, she gained motor mile-stones on time. Her parents are first cousins. A son of her mother's brother is similarly affected. As a child she had difficulty walking, episodes of shortness of breath and required hospitalization repeatedly for recurrent pneumonia. She was examined in another hospital, underwent electrophysiological studies, and was diagnosed to have seronegative myasthenia gravis. Therapy with prednisone 60 mg daily for 4 months was of no benefit and was gradually tapered. At the age of 16 years she underwent thymectomy. Her condition worsened, and the diagnosis was reconsidered at the age of 26 years. A muscle biopsy to rule out myopathy only revealed scattered small muscle fibers, some angulated. She had surgery for correction of ptosis. She could barely rise from sitting and could walk only a few steps unaided. She was wheelchair bound by the age of 28 years. Because of severe upper arm weakness she could not dress or wash herself or shower.

On examination, she had complete ophthalmoplegia with mild ptosis and moderate weakness of the facial muscles. Neck flexors and extensors were weak (4/5 on MRC score). She had severe weakness of proximal limb muscles: deltoids 3/5, biceps and triceps 4/5, iliopsoas 2/5, quadriceps, adductors and glutei 3/5. There was only very mild distal muscle weakness. She could not rise from sitting without help.

Three Hz stimulation of the trapezius muscle showed a decremental response of 25% without a double response to single stimuli. AChR antibodies were not detected. Sequencing of the AChR subunits revealed a homozygous ϵ C142Y mutation. This mutation involves the cysteine of the signature cys-loop. Expression of genetically engineered ϵ C142Y-AChR in HEK cells by established methods² revealed its expression was reduced to 22% compared to wild-type. Subsequently, the patient was treated with pyridostigmine and 3,4-DAP with only mild beneficial effects. She was repeatedly hospitalized because of recurrent pneumonias. In 2010, treatment with albuterol, 2mg three times a day, was instituted and resulted in marked improvement within several weeks. The patient now raised her arms well, rose from sitting unaided, and walked unsupported. Examination revealed ophthalmoplegia with mild ptosis, only mild weakness of facial muscles, and 4/5 strength of the deltoid and iliopsoas muscles. All other muscles were of normal strength. Her strength remained stable, and she did not have recurrence of pneumonia during 6 months of follow-up.

Discussion

Albuterol is an essentially exclusive beta-2 adrenergic agonist. Its main use is in treating bronchospasm by relaxing airway smooth muscles and is used mostly with inhalers. Ephedrine, another sympathomimetic agent acting on both alpha and beta adrenergic receptors, is also used for treating bronchospasm.

Ephedrine previously was also used for the symptomatic treatment of myasthenia gravis⁴, but its use was abandoned because it was not sufficiently effective.⁵ In the past decade, ephedrine was found beneficial in CMS due to AChE deficiency⁶ and in DOK7 myasthenia.⁷ A favorable response to ephedrine was also observed in a case of Lambert-Eaton syndrome⁸. The mechanism of action of ephedrine on the neuromuscular junction is not fully understood. *In vitro* studies⁹ revealed that it increases quantal release and reduces the conductance of the AChR channel, but only in doses that cannot be attained in clinical practice. A subsequent single-channel patch-clamp study¹⁰ revealed that ephedrine as well as albuterol increased the number of brief intraburst closures causing an open-channel blockade of AChR but again in doses that cannot be used in clinical practice. In an alpha-bungarotoxin-induced model of myasthenia gravis in rats, ephedrine caused some improvement, but this was attributed to a difference in susceptibility to arousal¹¹. The mechanism by which ephedrine improves the CMS caused by AChE deficiency and Dok-7 myasthenia remains unknown.

We preferred to use albuterol instead of ephedrine in our patients, because it has fewer adverse effects and is readily available. The possible adverse effects of albuterol include tremor, nervousness, arrhythmias, hypertension and myocardial ischemia. Therefore, as long as patients are taking albuterol they must be carefully monitored for adverse effects. Our two patients reported no adverse effects over periods of 12 and 6 months, respectively.

Albuterol has been added to treatment with pyridostigmine and 3,4 DAP. It may be less effective as a sole medication. However, our observations indicate that CMS with epsilon subunit mutations respond to albuterol therapy. This information should prompt a larger clinical trial to determine its efficacy and safety in patients who harbor low-expressor

mutations in the epsilon or other subunits of AChR. The use of albuterol as a substitute for ephedrine in AChE deficiency and Dok-7 CMS awaits investigation.

Acknowledgments

Supported in part by NIH Grant N26277 and a Research Grant from the Muscular Dystrophy Association (to Dr. Engel).

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