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## Neuromuscular Junction Acetylcholinesterase Deficiency Responsive to Albuterol

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### Abstract

A congenital myasthenic syndrome caused by endplate acetylcholinesterase deficiency is a rare autosomal recessive disease. We report a child who had early onset ptosis, complete ophthalmoplegia, facial and proximal muscle weakness, easy fatigability, a decremental electromyographic response, and a repetitive compound muscle action potential not improved by anti-acetylcholinesterase medication. Mutation analysis of collagenic tail of endplate acetylcholinesterase (*COLQ*) that encodes the collagenic structural subunit of acetylcholinesterase revealed two canonical splice-site mutations: a previously identified IVS15+1G > A mutation and a novel IVS2-1G > A mutation. Treatment with albuterol resulted in progressive improvement of muscle strength, exercise tolerance, and of the ophthalmoplegia. Further clinical studies are needed on the efficacy of albuterol in different types of congenital myasthenic syndrome and on the physiologic basis of its beneficial effects.

### Keywords

Congenital myasthenic syndrome; endplate acetylcholinesterase deficiency; *COLQ* mutation; Albuterol

### Introduction

Congenital myasthenia syndromes are a group of heterogeneous disorder caused by defects in proteins residing in the presynaptic, synaptic basal lamina, or postsynaptic regions of the motor endplate. The clinical, electromyographic and pathologic features of acetylcholinesterase deficiency were first described in 1977 in a patient presenting in the

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neonatal period with fatigable ptosis, generalized weakness increased by exertion, hyporeflexia, and refractoriness to anti-acetylcholinesterase drugs. Repetitive stimulation of motor nerves revealed a decremental response and single nerve stimuli evoked a repetitive compound muscle action potential. Acetylcholinesterase was absent from the motor endplates by histochemical and electron cytochemical criteria, and density gradient centrifugation studies of muscle extracts pointed to ColQ, the collagenic tail subunit of Acetylcholinesterase, as the disease protein [1]. In 1998, *COLQ* was mapped to chromosome 3p25 and the basis of endplate acetylcholinesterase deficiency was traced to mutations in *COLQ* [2, 3].

The endplate species of acetylcholinesterase is an asymmetric enzyme composed of globular forms of type T catalytic subunits ( $ACHE_T$ ) encoded by *ACHE\_T*, and a collagenic ColQ protein encoded by *COLQ*. The ColQ protein anchors the complex in the synaptic basal lamina and is composed of three identical strands. The N-terminal proline-rich domain of each strand binds a catalytic homotetramer. The collagenic central domain of ColQ confers rigidity on the molecule and binds the enzyme to the synaptic basal lamina by electrostatic bonds; the C-terminal globular domain is required for assembly of the triple-helical rod domain and contributes to binding the enzyme to the synaptic basal lamina by covalent bonds (reviewed in [2, 4]).

## Case report

The patient, now 8 years of age, is the only child of a Philippine mother and a Chinese father. He was born at full term after an uneventful pregnancy and had a normal delivery. The mother had a seizure at age 4 years; the father enjoyed good health. The patient had a generalized seizure on day 7 and again at age 2 months. In the first year of life, he was mildly hypotonic, had progressive bilateral ptosis and progressive limitation of his eye movements in both horizontal and vertical direction, but had no feeding or respiratory problems. Investigations included metabolic workup, spinal fluid studies, EEG, brain MRI, brainstem auditory and visual evoked potential and nerve conduction studies without repetitive stimulation gave normal results. He stood up at age 18 months, walked independently at age 2 years, and fatigued easily with these antigravity activities on mild exertion. At age 5 years, he had persistent bilateral ptosis, complete ophthalmoplegia, mild facial weakness, and Medical Research Council grade 4/5 weakness and abnormal fatigability of the proximal limb muscles. When tired he refused to walk, and could not be tested for the Gowers sign. The tendon reflexes were normal. The serum creatine kinase level was normal and tests for anti-acetylcholine receptor antibodies were negative. Edrophonium tests were repeatedly negative. Single stimuli applied to the median, ulnar, tibial and peroneal nerves evoked a repetitive compound muscle action potential (Figure 1) and stimulation at 3 and 20 Hz elicited a marked decremental response (Figure 2). Repeated edrophonium tests revealed no effect on the decremental repetitive motor nerve stimulation response. Needle electromyographic study of the left biceps muscle was interpreted as normal.

The negative edrophonium test and the repetitive compound muscle action potentials pointed to *COLQ* as the disease gene. Mutation analysis of *COLQ* by Sanger sequencing

revealed two splice-site mutations: a previously identified IVS15+1G > A mutation that predicts skipping of exon 15 and production of a stop codon after 64 missense codons [4], and a novel IVS2-1G > A in the intron of the exon coding for the N-terminal proline-rich domain that predicts skipping of 13 nucleotides followed by a threonine missense codon and a stop codon [5]. The father is heterozygous for IVS15+1G > A and the mother is heterozygous for IVS2-1G > A.

Albuterol therapy was initiated at 1 mg three times daily at age of 6 years and 1 month and was increased to 2 mg three times daily after 3 weeks. The patient's response was monitored by clinical examination, the Quantitative Myasthenia Gravis tests [6] and by monitoring his ptosis and ocular ductions. During the next 36 months, the Quantitative Myasthenic Gravis score improved continuously (Please see table) as did the patient's strength and exercise tolerance. Importantly, the patient also regained partial ability to move his eyes horizontally and downward but the bilateral ptosis did not improve, and repeated repetitive motor nerve stimulation studies revealed no improvement of the decremental response. Albuterol therapy had no major side effects. When not taking the medication during a holiday, the patient complained of increased weakness and fatigability.

Thirty months after the start of therapy, the dose of Albuterol was increased to 2.5 mg three times daily. On this regimen, the patient is now able to run around when playing and enjoys full participation with his peers in daily school activities. He has normal intelligence and performs well in school.

## Discussion

Since 1998, more than 30 different *COLQ* mutations have been identified. The mutations appear in all three domains of *COLQ* and include missense, nonsense, splice-site, frameshift, and in-frame deletions, with most producing a truncated and insertion incompetent ColQ protein. In a series of 22 patients, 11 had a slowly or subacutely progressive course [7]. As more patients harboring *COLQ* mutations were identified, the clinical spectrum of the ColQ-associated congenital myasthenic syndrome became wider [7–11]. Our patient who carries the two splice-site mutation that result in a truncated transcript became symptomatic during the first year of life with ptosis, progressive ophthalmoplegia, hypotonia, weakness of the facial, cervical and proximal limb muscles and poor exercise tolerance, but had no respiratory or feeding problems. Other patients harboring mutations in the C-terminal domain of the ColQ protein have had a milder course [3, 12]. Albuterol and ephedrine are both adrenergic agonist used for treatment of acute asthma for relieving bronchospasm. Albuterol is a  $\beta_2$ -adrenergic agonist, while ephedrine acts on both  $\alpha$ - and  $\beta$ -adrenergic receptors. The congenital myasthenic syndrome caused by defects in *DOK7* [13] and in *COLQ* have benefited from ephedrine but the reported number of patients is small [7, 12]. Recently, albuterol was also found to be beneficial in 15 patients with *DOK7* myasthenia, in 3 patients with ColQ deficiency [14], and in two patients with low-expressor mutations in the acetylcholine receptor epsilon subunit [15]. Most observed responses reflected increased muscle strength and endurance, but the weakness of the external ocular muscles, when present, did not improve. Patients exposed to ephedrine or albuterol often experience adrenergic side effects but our patient had no tremor, nervousness, hypertension, palpitation

or arrhythmia during 3 years of therapy. Further studies on a larger number of congenital myasthenic syndrome patients are required to determine the types of congenital myasthenic syndrome benefited by albuterol, and more basic science studies are needed to elucidate the physiologic basis of the beneficial response.

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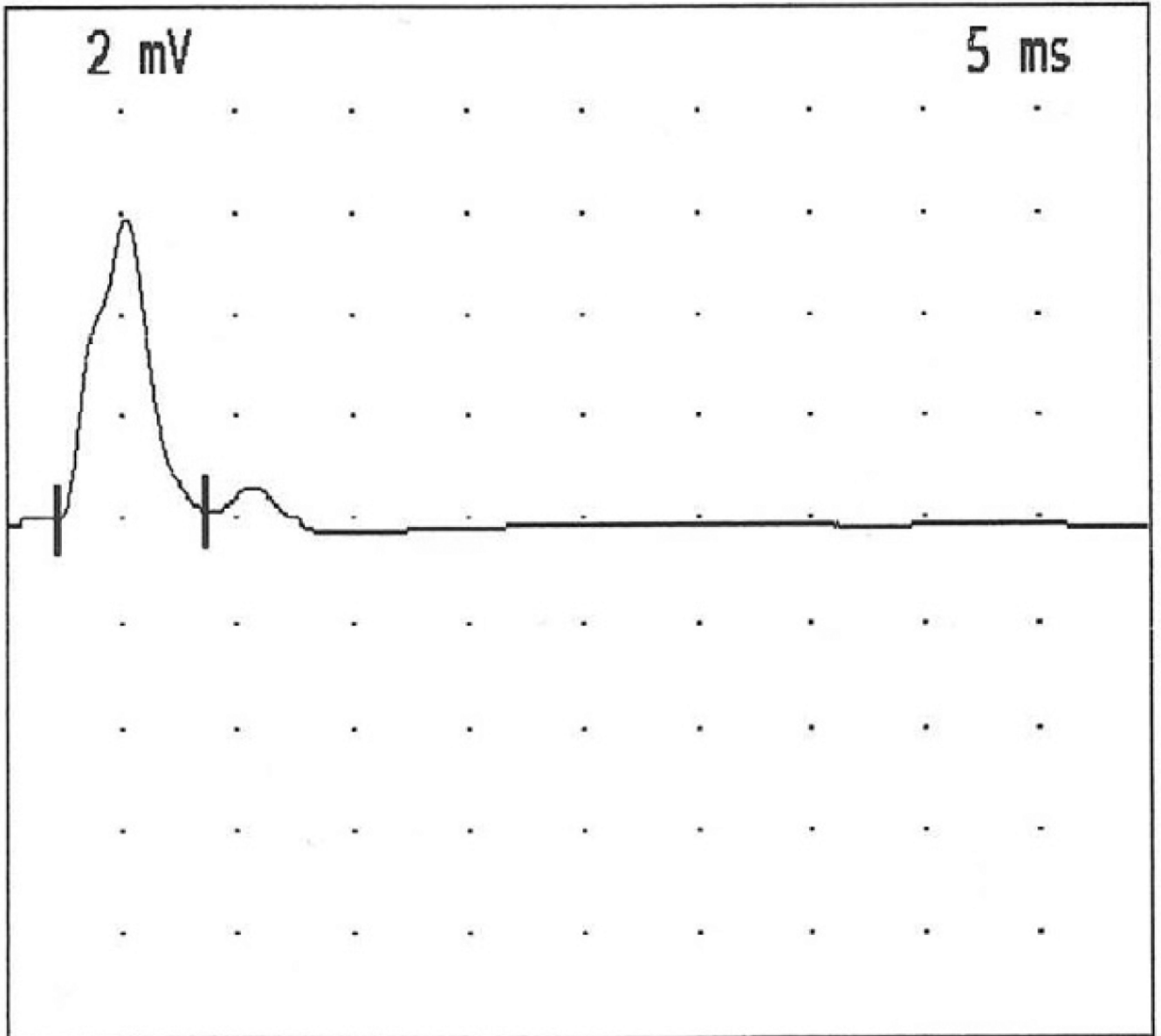
## Abbreviations

<b>ColQ</b>	collagenic tail of endplate acetylcholinesterase
<b>COLQ</b>	gene encoding ColQ
<b>DOK7</b>	gene encoding docking protein 7
<b>EEG</b>	electroencephalogram
<b>MRI</b>	magnetic resonance imaging

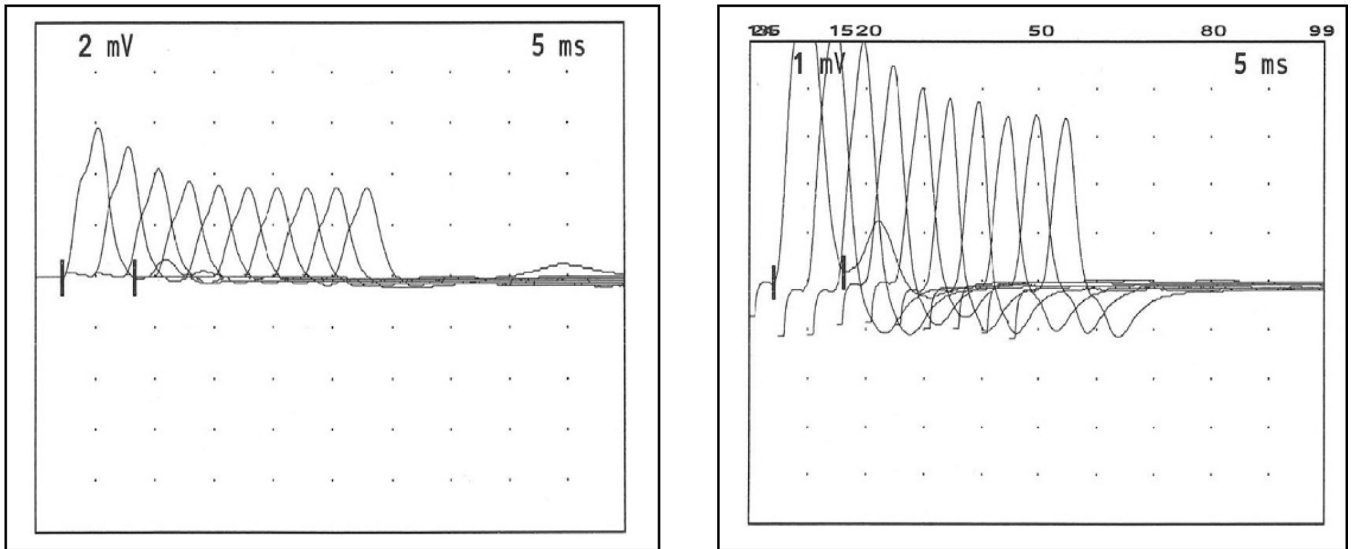
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**Figure 1.** Repetitive CMAP evoked from left abductor digiti minimi by a single supramaximal stimulus applied to the left ulnar nerve.



**Figure 2.**

Decremental EMG responses on stimulating the left ulnar nerve and recording from left abductor digiti minimi muscle. Three Hz stimulation elicits a 41% decrement (left panel) and 20 Hz stimulation elicits a 59% decrement (right panel) of the amplitude of the fourth CMAP compared to that of the first CMAP.

Serial monitoring using Quantitative Myasthenia Gravis (QMG) test. Performance at pre-salbutamol was compared to 4 months, 16 months, 29 months, 40 months post salbutamol, showing definite improvement post treatment and also progressive improvement over 3 years of treatment.

**Table**

TEST ITEMS <u>WEAKNESS</u>	<u>NONE</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>	DATE	DATE	DATE	DATE	DATE
					17-4-08 Pre- albuterol	17-11-08 4 months albuterol	13-11-09 16 months albuterol	23-12-10 29 months albuterol	11-11-11 40 months albuterol
<b>GRADE</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	SCORE	SCORE	SCORE	SCORE	SCORE
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	2 (10s)	0	0	0	0
Prosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous	1 (15s)	1 (40s)	1 (32s)	1 (60s)	1 (60s)
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	1	0	0	0	0
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing, choking or nasal regurgitation	Cannot swallow (test not attempted)	0	0	0	0	0
Speech following counting aloud from 1-50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	0	0	0	0	0
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	3 (5s)	2 (17s)	2 (50s)	2 (75s)	1 (128s)
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	3 (5s)	2 (17s)	2 (50s)	1 (95s)	1 (128s)
Forced vital capacity	≥80%	65-79%	50-64%	<50%	0	0	0	0	0
Rt hand grip: male (Kg): female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4	3 (1-2kg)	3 (3kg)	2 (8 kg)	2 (11 kg)	2 (7 kg)
Left hand grip: male (Kg): female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4	3 (1-2kg)	3 (2.5 kg)	2 (7 kg)	2 (9 kg)	2 (8 kg)
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	3 (0s)	2 (5s)	2 (7s)	2 (15s)	1 (41s)
Right leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	2 (13s)	2 (20s)	2 (27s)	1 (60s)	1 (60s)
Left leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	2 (13s)	2 (19s)	2 (27s)	1 (60s)	1 (58s)
<b>Total MG Score</b>					23	17	15	12	10