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Atypical Cholinesterase in a Patient with Myasthenia Gravis

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Prolonged muscle paralysis with apnea is a well-recognized side-effect that follows administration of succinylcholine (SCh) to some patients.¹ Many of these patients have atypical plasma pseudocholinesterase resistant to inhibition by fluoride ion or the local anesthetic, dibucaine. There is evidence that in myasthenia gravis plasma cholinesterase activity is within normal limits.² With low doses of depolarizing neuromuscular blocking drugs, such as SCh or decamethonium, the myasthenic patient may show an initial resistance to the drug. Higher doses result in neuromuscular blockade of the nondepolarizing, desensitizing type (dual or phase II block).³

Recently, we were able to study a patient who had both myasthenia gravis and atypical cholinesterase. Because of the coincidence of these two rare disorders of neuromuscular transmission, the nature of the enzyme defect was studied. In addition, the effects of various neuromuscular blocking drugs on neuromuscular transmission were investigated.

REPORT OF A CASE

A 23-year-old woman who had well-documented myasthenia gravis was admitted to the hospital in early labor, with a term pregnancy. Because of cephalopelvic disproportion, cesarean section was done. Eight hours after the last dose of anticholinesterase medication (neostigmine, 15 mg; pyridostigmine, 30 mg) general anesthesia was induced with 175 mg thiopental and 30 mg SCh for tracheal intubation. Muscle fasciculations were not seen. A healthy female infant was delivered during nitrous oxide-oxygen anesthesia with narcotic supplementation. The patient made no respiratory effort during or following the 45-minute procedure. Edrophonium, 10 mg, iv, was given 65 minutes after induction of anesthesia, with no change. Subsequent administration of neostigmine and atropine produced no improvement, and mechanical ventilation was necessary for eight hours. A plasma sample

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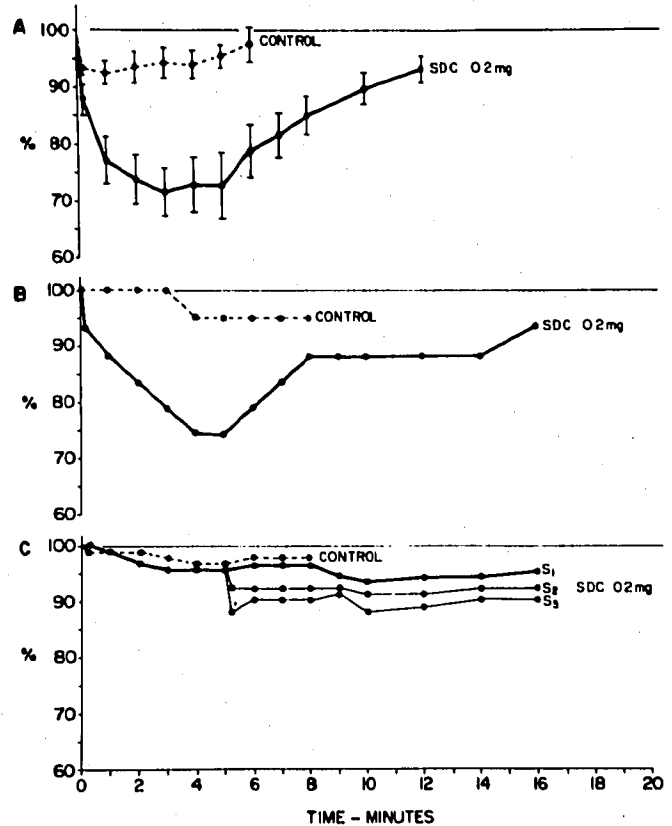


FIG. 1. Amplitudes of hypothenar compound muscle action potentials in response to ulnar-nerve stimulation following regional intravenous injection of physiologic saline solution and SCh, 0.2 mg. A, mean values and standard errors of the mean for six normal subjects. B, sibling 1. C, propositus. Horizontal axis: times following injection of saline solution or drug. The cuff was inflated prior to injection and released at 5 minutes. Vertical axis: amplitude of potential expressed as percentage of preinjection control. Each point represents response to a train of three stimuli at 2 Hz. When a decremental response occurred, amplitudes of individual responses are represented by S_1 , S_2 , and S_3 (panel C).

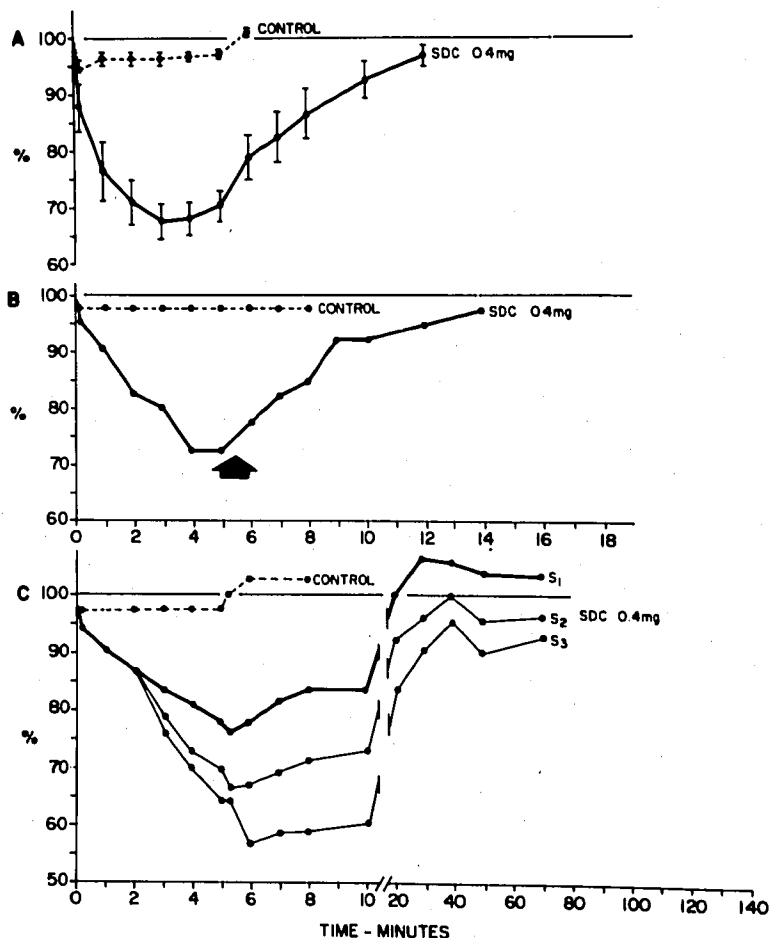
taken during the acute apneic episode had a cholinesterase activity of 9 units (normal 80-150) and a dibucaine number of 40 (normal > 70).

METHODS

Assessment of Cholinesterase Enzyme

Plasma cholinesterase activity, dibucaine and fluoride numbers were determined for the propo-

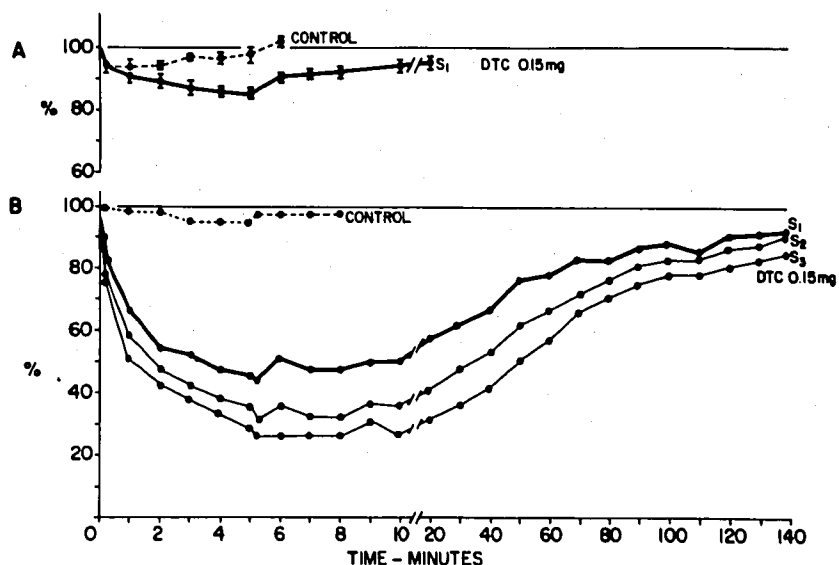
FIG. 2. Amplitudes of hypothenar muscle action potentials following regional iv injection of physiologic saline solution and SCh, 0.4 mg. A, three normal subjects. B, sibling 1. C, propositus. Arrow in panel B indicates point at which sibling 1 developed systemic symptoms (diplopia) following release of the cuff. Horizontal and vertical axis as in figure 1; note change in scale in C.



tus and immediate relatives, utilizing previously described techniques.⁴ True (erythrocyte) cholinesterase activity was also determined, utilizing an adaptation of an automatic pH-stat titrimetric

method.⁵ The propositus was admitted to the hospital and had all medication withdrawn for 72 hours prior to assessment of cholinesterase activity and neuromuscular function.

FIG. 3. Amplitudes of hypothenar muscle action potentials following regional iv injection of physiologic saline solution (control) and dTc, 0.15 mg. A, four normal subjects. B, propositus. Horizontal and vertical axis as in figure 1. S₁, S₂, and S₃ represents amplitudes of the first three responses to a train of three repetitive stimuli at 2 Hz.



Assessment of Neuromuscular Transmission

Because of the risks associated with systemic administration of SCh and *d*-tubocurarine (*d*Tc) to patients with myasthenia gravis and/or atypical plasma cholinesterase, a regional intravenous perfusion technique was utilized.⁶ A 21-gauge needle was inserted into a vein on the dorsum of the hand close to the hypothenar muscles, and a cuff was placed around the forearm to occlude arterial blood flow. Following inflation of the cuff to 200 torr, the drug, diluted in 0.9 per cent NaCl to 15 ml and warmed to 37 C was injected iv over 10 seconds.

Trains of three supramaximal stimuli at 2 Hz were delivered to the ulnar nerve by means of surface electrodes applied over the nerve just above the wrist. Stimulation was carried out just prior to injection and at one-minute intervals following injection. Compound muscle action potentials were recorded with surface electrodes and were displayed on an electromyograph. After 5 minutes, the cuff was released, but measurements were continued at one-minute intervals until all apparent drug effects had terminated.

To provide control data for each subject, the procedure was first performed in the same limb with an injection of 0.9 per cent NaCl, without drug. Identical studies were performed on nine normal volunteers, as well as on one sibling (sibling 1) of the propositus, who was presumed to be homozygous for atypical cholinesterase. Student's *t* test for paired data was used to compare the subject's responses to the drug and to saline solution, at the end of the 5-min test period.

RESULTS

Assessment of Cholinesterase Enzyme

Assessment of the family pedigree indicated that the common phenotypic pattern of atypical cholinesterase (dibucaine- and fluoride-resistant) was present, with the propositus and one other sibling (sibling 1) being presumed homozygotes for atypical cholinesterase (cholinesterase activities of 68 and 42 units, respectively [normal 143–263 units]; dibucaine numbers of 29 and 17, respectively; fluoride numbers of 27 and 14, respectively). Two other siblings were assessed as heterozygotes for atypical cholinesterase, while the remaining four siblings were normal. All family members were found to have normal true (erythrocyte) cholinesterase.

Assessment of Neuromuscular Transmission

In all subjects, injection of saline solution produced slight decreases in amplitudes of the evoked muscle action potentials, which returned to normal pre-injection values following release of the cuff

(figs. 1–3). In all normal volunteers, SCh, 0.2 mg, and SCh, 0.4 mg, produced depolarizing neuromuscular blocks, with depression of evoked action potentials significantly different ($P < .025$) from the saline-solution control values. *d*-Tubocurarine, 0.15 mg, produced competitive neuromuscular blocks in four of six normal volunteers, significantly different from the saline-solution responses ($P < .05$). The two volunteers who did not initially respond to *d*Tc did so at a higher dose of 0.3 mg, suggesting that the lower dose was below the threshold of neuromuscular blockade for those individuals.

Sibling (1), who was presumed to be homozygous for atypical cholinesterase, showed responses to SCh, 0.2 mg, and SCh, 0.4 mg, that were very similar to those seen in normal volunteers (figs. 1B and 2B). However, with SCh, 0.4 mg, transient diplopia and blurring of vision occurred following release of the cuff. Similar systemic effects were not seen in any of the normal volunteers.

The responses of the propositus to both SCh and *d*Tc were markedly different from those of volunteers and sibling 1. Succinylcholine, 0.2 mg (fig. 1C), produced only a minimal decrease in the amplitude of the evoked muscle action potential. However, after release of the cuff, there was a progressive decrease in the amplitudes of the evoked responses to repetitive stimuli at 2 Hz, similar to that seen with a desensitizing neuromuscular block. At the higher dose of SCh, a desensitizing neuromuscular block developed, with decremental responses to the train of three stimuli, and to tetanic stimulation at 30 Hz given 9 minutes following drug injection. The propositus also experienced transient diplopia and blurring of vision following release of the cuff after SCh, 0.4 mg. The propositus responded to *d*Tc, 0.15 mg, with a profound competitive neuromuscular block (fig. 3B).

DISCUSSION

Although both pregnancy⁷ and long-term treatment with anticholinesterases⁸ may contribute to low plasma cholinesterase activity, the enzyme determinations for the propositus were done when she was not taking medication and not pregnant. The results suggest the presence of the common phenotypic pattern of atypical cholinesterase in the propositus and sibling 1. It seems likely that the presence of these two disorders in the propositus represents a coincidence. The incidence of myasthenia gravis has been estimated to be 1/20,000 population,⁹ while 1/3,200 of the general population is believed to be homozygous for atypical cholinesterase.¹ Therefore, the probability that these two disorders would occur in the same individual is extremely low.

The initial effects of SCh, 0.2 mg, on the propositus represent the initial resistance to low doses of depolarizing neuromuscular drugs seen in myasthenic patients.¹⁰ Following cuff release, a progressive decrement in amplitudes of evoked responses to a train of stimuli occurred. There is at present no obvious explanation why the initial facilitatory effects of the low dose of SCh would change upon cuff release to an effect resembling neuromuscular desensitization and neuromuscular transmission failure.

With SCh, 0.4 mg, a desensitizing neuromuscular block became evident while the cuff was still inflated, becoming more apparent following cuff release and persisting for approximately 80 minutes. Since this desensitizing effect of SCh was not seen in sibling 1, it would again appear that it is related to the myasthenic defect and not to the presence of an atypical cholinesterase.

The response of sibling 1, presumably homozygous for atypical cholinesterase, was very similar to that observed in normal controls. The desensitizing of SCh due to the enzyme defect was not seen in the peripheral hand muscles. It is possible that an inadequate amount of SCh was present, or that insufficient time elapsed before release of the cuff to allow development of the desensitizing neuromuscular block. The enzyme defect was manifest upon release of the cuff after SCh, 0.4 mg. The blurring of vision and transient diplopia reflect the increased numbers of acetylcholine receptors in small fine ocular muscles and demonstrate the inability of the atypical cholinesterase to metabolize systematically even the small amount of SCh released from the forearm.

The small dose of *d*Tc, which produced only minimal competitive neuromuscular blockade in normal volunteers, caused a profound prolonged block in the propositus. This type of response is what one would expect to see in myasthenia gravis, and is not likely to be affected by the presence of the atypical cholinesterase. The fact that sibling 1, who was also homozygous for the atypical enzyme, did not show abnormal sensitivity to *d*Tc supports this observation.

The use of the regional intravenous perfusion technique provided a safe opportunity to evaluate responsiveness to muscle relaxants in a patient with the rare combination of myasthenia gravis and atypical plasma cholinesterase. It was possible to demonstrate in the same patient both the response of a myasthenic to muscle relaxants and the systemic sensitivity to SCh that arises from an atypical plasma cholinesterase.

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