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Sensitivity to Nondepolarizing Muscle Relaxants in Amyotrophic Lateral Sclerosis: Report of Two Cases
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Recent reports have documented massive hyperkalemia and cardiac arrest secondary to the administration of succinylcholine in patients with various neuromuscular disorders, including lower motor neuron disease.¹ ² Therefore, in the anesthetic management of a patient with amyotrophic lateral sclerosis (ALS), the use of succinylcholine was deliberately avoided.

ALS is characterized by pathologic degeneration of the lower motor neurons, motor nuclei of the caudal brainstem, and the descending pathways of the upper motor neurons.³ ⁴ Progressive muscular atrophy and progressive bulbar palsy are different manifestations of this disease.⁵ Spasticity due to pyramidal tract involvement may be prominent, and all muscles may eventually develop atrophy, weakness, and fasciculations secondary to neuronal degeneration.

The sensitivity of patients with myasthenia gravis to nondepolarizing muscle relaxants is well known. Less well appreciated is the marked relaxant effect small amounts of these drugs may have on patients with ALS ³-⁵ and possibly other diseases involving the lower motor neurons.⁶ ⁷ The following case reports, which, to our knowledge, are the first in the anesthesia literature, illustrate the marked sensitivity to nondepolarizing muscle relaxants which may occur in patients with ALS.

REPORT OF TWO CASES

Patient 1. A 53-year-old white man was seen because of a 20-month history of progressive weakness of the hands and arms. He also complained of more recent difficulty in swallowing and handling secretions, loss of memory, and impaired judgment. He had a history of hypertension, for which he was taking chlorothiazide, 500 mg, and reserpine, 0.125 mg, once daily. The patient denied smoking and all cardiorespiratory symptoms. He had lost 4.6 kg of body weight in the previous year and weighed 59.1 kg.

Physical examination revealed a blood pressure of 160/100 mm Hg, pulse rate 80 beats/min, and a normal respiratory pattern. No abnormalities were found on examination of the heart and lungs. The patient was oriented with respect to time, place, and person, but had some impairment of intellect (e.g., memory and calculations). Neurologic examination revealed weakness of the pharyngeal muscles and weakness and atrophy of the tongue. Fasciculations were present in the tongue, neck, arms, and legs. Marked atrophy of the hand muscles, moderate atrophy of the distal arms, and mild atrophy of the upper arms and legs were found. Weakness was present in proportion to the degree of atrophy. Sensory function and coordination were intact.

Laboratory studies revealed: serum sodium 144 mEq/l; serum potassium 3.8 mEq/l; serum chloride 103 mEq/l; CO₂ 34 mM/l. The following were normal: BUN, FBS, serum calcium, serum phosphate, hemoglobin, leukocyte count, total protein, SGPT, SGOT, LDH, alkaline phosphatase,
serum thyroxine level, Watson Schwartz test, serum bromide levels, urinary heavy metals, CSF pressure, CSF protein, CSF glucose, and chest x-ray. The electrocardiogram had a Q wave in leads II, III, and AVF, with decreased T-wave amplitude in these leads.

A pneumoencephalogram revealed moderately dilated ventricles with little air over the convexity of the brain. The radiologist believed that low-pressure hydrocephalus could not be excluded. The electromyogram (EMG) was consistent with lower motor neuron disease; unfortunately, EMG recordings during repetitive nerve stimulation or voluntary contraction designed to elicit fatigability were not made. Nerve conduction velocities in the median and peroneal nerves were normal. Skull x-rays, EEG, RISA cisternogram, and brain scan were normal.

The diagnostic impressions were either ALS with mild dementia, the latter possibly on the basis of low-pressure hydrocephalus, or Jakob-Creutzfeldt disease with anterior horn cell involvement. Histologic studies of a frontal lobe biopsy did not reveal the features of Jakob-Creutzfeldt disease; therefore, the patient was diagnosed as having ALS with mild dementia, a rare but reported condition.1

The patient was anesthetized for a brain biopsy and insertion of a ventriculojugular shunt to relieve any existing low-pressure hydrocephalus. He was premedicated one and a half hours before operation with morphine, 10 mg, secobarbital, 100 mg, and atropine, 0.4 mg, injected intramuscularly. He arrived in the operating room awake and cooperative. Anesthesia was induced with thiopental, 250 mg, injected intravenously, after which nitrous oxide (7 l/min) and oxygen (3 l/min) were administered by mask, using a circle system with CO₂ absorber. Respirations were regular, spontaneous, and deep. Needles were placed over the ulnar nerve at the wrist and elbow. Muscle twitch was observed using maximal stimulation by a Block-Aid Monitor. Twitch strength was somewhat subnormal due to muscle atrophy in the hand and forearm. Tetanus was well sustained.

Approximately four minutes after induction, a test dose of 20 mg of gallamine was injected intravenously. Within a minute after administration, both single twitch and tetanus were abolished and apnea occurred. The trachea was intubated without subsequent cough or movement. Respirations were controlled manually for 10 minutes, and no respiratory efforts were evident before the patient was mechanically ventilated. Anesthesia was maintained with 60 per cent nitrous oxide, oxygen, and halothane, 0.3 to 1.5 per cent. Approximately 45 minutes after induction of anesthesia, minimal muscle twitch was observed. Two hours after induction, twitch strength appeared to be near control levels, but fade was still evident when a tetanic stimulus was applied. Although spontaneous respirations appeared adequate, neostigmine, 1.5 mg, and atropine, 0.5 mg, were injected intravenously. After reversal, teta
nus was well sustained. The patient returned to his preoperative physical and mental condition.

Patient 2. A 50-year-old white woman weighing 50.5 kg was first seen with a three-month history of dysarthria and difficulty in swallowing and a 6.8-kg weight loss, believed to be secondary to decreased food intake. She denied other symptoms except a long history of nervousness, for which she was taking oxazepam, 30 mg t.i.d. Physical examination disclosed no abnormalities except weakness, atrophy, and fasciculations of the tongue, mild weakness of the sternocleido-mastoid muscles, and wide separation of the vocal cords in the paramedian position with possible bilateral posterior paralysis. The following were normal: hemoglobin, leukocyte count, serum electrolytes, serum calcium, serum electrophoresis, BUN, FBS, serum thyroxine, chest x-ray, and electrocardiogram. An EMG of the tongue was consistent with lower motor neuron disease; attempts to induce fatigue were not made. An EMG of the biceps muscle, which was normal on clinical examination, revealed mild changes consistent with lower motor neuron disease. The patient was diagnosed as having ALS.

A curare test was performed. A total of 0.9 mg of d-tubocurarine was administered intravenously in 0.1-mg increments (0.5-ml volume) given every two minutes. After this total dose the patient complained that her tongue felt thicker, but an increase in dysarthria was not impressive. Fifteen minutes after the termination of the initial curare test an additional 0.33 mg of d-tubocurarine was given intravenously, with no change. Two minutes later another 0.33 mg of d-tubocurarine was injected, which resulted in a marked decrease in the clarity of the patient’s speech such that ability to communicate was impaired. Protrusion of the tongue was diminished and increased difficulty in swallowing was noted. Thus, these symptoms appeared after a total dose of 1.5 mg of d-tubocurarine administered over approximately 30 minutes. No change in the strength of other muscles tested was evident. Without the patient’s knowledge, edrophonium, 10 mg, was given intravenously, and within approximately a minute speech and swallowing improved to pretest levels.

DISCUSSION

To our knowledge, only four cases of sensitivity to d-tubocurarine in ALS have been reported. Three of the patients were tested with d-tubocurarine, 0.3 mg/40 pounds of body weight, injected intravenously, and the fourth with twice this dose. All four patients had marked increases in muscle weakness which was completely reversible by anticholinesterase drugs. These four patients all showed fatigability on exertion and improve-
ment with rest, and had EMC's indicative of defects in neuromuscular transmission as well as positive curare tests.

An EMG abnormality indicative of a defect in neuromuscular transmission has been found in more than 50 per cent of patients with ALS; hence, the incidence of sensitivity to d-tubocurarine in this disease, although unknown, may approach 50 per cent. This EMG defect was shown in a study of 100 patients with ALS in whom the amplitudes of the motor unit action potentials during voluntary contraction either varied from moment to moment or declined progressively. ALS patients subjected to repetitive nerve stimulation had similar EMG recordings. These particular EMG characteristics of ALS are similar to those seen in myasthenia gravis. The patients with ALS were also similar to myasthenics in that small doses of d-tubocurarine aggravated the EMG phenomenon and anticholinesterase drugs alleviated it to some extent. High incidences of similar EMG findings have been reported for poliomyelitis and syringomyelia involving the lower motor neurons.

The question whether muscles in which involvement with ALS is not clinically apparent will show sensitivity to nondepolarizing muscle relaxants has not been finally answered. Muscles which do not show involvement clinically may evidence the characteristics of ALS on the EMG. Mulder and Lambert reported a patient with ALS in whom involvement of the left hand was not demonstrable clinically; weakness of the left hand did not develop with curare testing, although muscles clinically demonstrated to be involved became weak. Our unanesthetized female patient also developed increased weakness only in those muscles clinically demonstrated to be involved with the disease. However, our anesthetized male patient developed total respiratory paralysis after 20 mg of gallamine. Weakness of respiratory muscles may not be obvious, since significant respiratory reserve can be lost without evidence of clinical symptoms unless the patient undergoes exertional stress. This patient did not have dyspnea during his limited daily activities. Unfortunately, pulmonary function tests, which might have revealed compromised pulmonary mechanics, were not performed.

Although our anesthetized patient was not given a formal curare test, there is considerable evidence that total respiratory paralysis and peripheral paralysis, as shown by the Block-Aid Monitor, are definitely abnormal responses to 20 mg of gallamine. Marbury et al. found that gallamine, 0.5 mg/kg, produced only modest changes in respiratory minute volume in patients anesthetized with cyclopropane or ether. No change in blood gas values was found by Tobias and Beswick when gallamine, 40 mg, was administered to patients anesthetized with nitrous oxide, oxygen, and trichlorethylene.

Our anesthetized patient was taking a thiazide diuretic which has been reported to potentiate muscle relaxants on the basis of inducing hypokalemia. Although case reports have implicated hypokalemia as responsible for some occurrences of neostigmine-resistant curarization, the exact degree and consistency of muscle relaxant potentiation in man remain to be defined. It seems unlikely that a serum potassium concentration of 3.8 mEq/l would be responsible for such a profound effect of 20 mg of gallamine. To confirm this impression, two patients on chronic thiazide diuretic therapy for hypertension with serum potassium values of 3.1 and 3.2 mEq/l, respectively, were studied with a nerve stimulator and force transducer before and after the administration of 20 mg of gallamine during thiopental, nitrous oxide, and oxygen anesthesia. Muscle twitch heights were reduced to only 95 and 83 per cent, respectively, compared with control values. The elevated total CO₂ content of 34 mM/l in our patient probably represents the increased serum bicarbonate ion concentration which has been reported to follow administration of thiazide diuretics.

A possible mechanism for the defect in neuromuscular transmission in ALS and other diseases affecting the lower motor neurons is suggested by the observation of collateral branching or sprouting by residual nerve fibers to muscles denervated by the disease. It is suggested that these newly formed branches and their corresponding motor endplates have defective neuromuscular transmission. Rabbit limb muscle reinnervated 42 days after a nerve-crushing injury had greater sensitivity to curare than the same contralateral muscle not previously denervated. Similarly, the greater
sensitivity of newborn infants to \(d\)-tubocurarine\(^{18}\) may be the result of their immature neuromuscular junctions. Anesthetists should be aware of the sensitivity to nondepolarizing muscle relaxants in some patients with ALS, and possibly those with other diseases of the lower motor neurons. A normal dose of relaxant may represent a gross overdose in ALS, and thus lead to problems with reversal. However, in view of the hyperkalemia and cardiac arrest that may follow administration of succinylcholine in patients with lesions of the lower motor neurons\(^{2}\) and pyramidal tracts (cord transactions\(^{1}\)), the judicious use of nondepolarizing relaxants in patients with ALS would seem preferable.

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Hematoma Following Epidural Anesthesia: Report of a Case

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Butler and Green recently reported a case of hemorrhage into the spinal epidural space associated with epidural catheterization and anticoagulation.\(^{1}\) We have had a similar case, a report of which follows.

REPORT OF A CASE

The patient, a 76-year-old man, was admitted with a three-day history of intermittent claudication in the right calf and a cold right foot. About two weeks prior to admission, he had had atrial