

inhibition of noradrenaline release during vagal stimulation in organs with dual antagonistic innervation.

Smith *et al.* suggested that patients with familial dysautonomia have a reduced release of sympathetic transmitters.<sup>10</sup> He discovered that these individuals display an exaggerated response to noradrenaline infusions, suggesting possible increased adrenergic receptor density or hypersensitivity as opposed to excessive catecholamine release.<sup>11</sup> Further investigations of three dysautonomic patients indicated significantly elevated catecholamine concentrations in adrenal gland tissue obtained less than 24 h *post mortem*.<sup>12</sup> It is possible that scopolamine administered to our dysautonomic patient may have blocked the parasympathetic modulation of noradrenaline release at the sympathetic nerve terminal, producing a greater than usual catecholamine release. The resulting hypertension and tachycardia may have been a consequence of either sympathetic denervation hypersensitivity, the liberation of excessively produced catecholamines, or a combination of both.

In conclusion, we describe a case of a patient with HSN type IV who developed an exaggerated hemodynamic response to intravenous scopolamine. We suggest that this agent as well as other belladonna alkaloids be administered with caution to patients with HSN type IV and possibly to patients with Riley-Day Syndrome.

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## Anesthesia for an Unsuspected Lambert-Eaton Myasthenic Syndrome with Autoantibodies and Occult Small Cell Lung Carcinoma

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Lambert-Eaton myasthenic syndrome (LES) is a disorder of neuromuscular transmission first recognized clinically in association with lung cancer. This report de-

scribes a patient with rectal adenocarcinoma presenting for low anterior resection who reacted to succinylcholine and/or *d*-tubocurarine with undue prolongation of neu-

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romuscular blockade. The diagnosis of LES was suspected postoperatively by simple bedside clinical testing and was later documented electromyographically and serologically. Six months later a diagnosis of small cell carcinoma of the lung was made following the appearance of brain metastasis. A new experimental assay to diagnose occult small cell cancer of the lung was used and substantiated. This case report introduces the immune model of pre-synaptic neuromuscular disease, which is equivalent to the elucidation of the mechanism of myasthenia gravis (MG) to the anesthesia literature.

### CASE REPORT

A 70-yr-old man, 175 cm tall and weighing 80 kg, presented with rectal adenocarcinoma for low anterior resection. The patient had received preoperative external beam radiation. Although the patient had smoked one pack of cigarettes a day for 50 yr, he denied cardiopulmonary symptoms or disease. He denied bulbar symptoms or muscle weakness. Although he had a dry mouth, he denied other symptoms of autonomic dysfunction such as impotence, anhidrosis, constipation, or orthostatic symptoms.

Preoperatively, routine hemogram, chemistry, chest x-ray, ECG, and metastatic work-up were unremarkable.

Anesthesia was induced with sodium thiopental 300 mg, fentanyl 100  $\mu$ g, and midazolam 2 mg. Succinylcholine 100 mg was administered to facilitate tracheal intubation. *d*-Tubocurarine was then slowly injected over 15 min in a total dose of 30 mg. Neuromuscular transmission was not monitored at this time. Anesthesia was maintained with 60% nitrous oxide in oxygen and intermittent enflurane inhalation at 0.5–1.25% inspired concentration with increments of morphine sulfate and midazolam. During the course of a 12-h surgical procedure, thumb adduction in response to supramaximal train-of-four ulnar nerve stimulation was tested several times. No response could be elicited. There was, however, at the end of the procedure, a very weak response to tetanic stimulation at 50 Hz for 5 s with no posttetanic potentiation. Oral temperature was maintained at 34.5–35° C intraoperatively and increased to 36° C in the postanesthesia care unit. Electrolytes, ionized calcium, magnesium, and blood gases were normal. No antibiotics known to cause neuromuscular blockade had been administered.

However, because the patient remained apneic and motionless and demonstrated no twitch response, he was transferred to the postanesthesia care unit for continued ventilatory support. Blood samples were drawn for measurement of dibucaine number and esterase activity. Ninety minutes later, after a weak posttetanic response, neostigmine 3.0 mg and glycopyrrolate 0.6 mg were administered. Spontaneous voluntary movement (eye-opening and weak respiratory efforts) could be elicited 30 min later. Respiratory mechanics measured 80 min after reversal were: inspiratory force –20 cmH<sub>2</sub>O, tidal volume 400–600 ml, and vital capacity 1,300 ml. In the next 3 h, the patient was separated from the ventilator, and the trachea was extubated when the inspiratory force was –32 cmH<sub>2</sub>O and the vital capacity 2000 ml and when the patient could sustain a head-lift for 5 s.

The patient's condition was reassessed the next morning. He had a weak response to single-twitch stimulation and a strong response to 50-Hz tetanic stimulation with posttetanic potentiation. Repeated hand-grip strength evaluation revealed a stronger grip as hand-squeeze continued. This simple bedside testing suggested the diagnostic possibility of LES. Two days later, with the knowledge that the dibucaine number was 80% (normal 77–83%) and serum cholinesterase activity was 2.0 IU/ml (normal 2.5–7.1 IU/ml), electromyogram studies were re-

quested. The initial compound muscle action potential amplitude during repetitive ulnar nerve stimulation at 0.5 Hz in rested abductor digiti minimi was 0.18 mV. After 10 s of maximal isometric contraction of the right abductor digiti minimi, there was a 12-fold increase in amplitude of the compound muscle action potential (2.2 mV). These findings were consistent with the diagnosis of LES. In addition, the patient had electrophysiologic evidence of mild peripheral sensorimotor neuropathy. The patient was informed of the diagnosis of LES and its implications during his hospitalization, but he refused further testing.

Immunologic testing revealed seronegativity for acetylcholine receptor antibodies. However, antibodies reactive with neuronal voltage-gated calcium channels (VGCC)<sup>1</sup> were detected at 771 pmol/l (normal range  $\leq$  31 pmol/l). These antibodies are currently found in > 80% of LES patients with lung cancer and in 36% of LES patients without cancer; they have not yet been found in association with cancers other than lung.<sup>††</sup> We therefore gave this information to the patient's surgeon and suggested that a computed tomography scan of the chest and other studies should be performed. Further care was organized by the patient's primary care physician. Four months after discharge, the patient became weak and later was admitted to a regional community hospital. He was obtunded with new neurologic findings. A computed tomography scan revealed brain metastases and probable cancer of the left lung. The patient received x-ray treatment to the brain and later a tissue diagnosis of a small cell lung cancer was made.

### DISCUSSION

Both LES and MG involve an autoimmune defect at the neuromuscular junction that is caused by antibodies directed against cationic channels—one (LES), VGCC at the motor nerve terminal, and the other (MG) nicotinic acetylcholine receptors at the postjunctional membrane.

LES is a rare disorder of neuromuscular transmission. Its pathophysiology was elucidated by Lambert *et al.*<sup>2</sup>, and Lambert and Elmquist.<sup>3</sup> The characteristic electromyographic finding is an abnormally low amplitude of the compound muscle action potential evoked by a single nerve stimulus in rested muscle and a progressive increase during high-frequency stimulation (> 10 Hz) or immediately after brief maximal voluntary contraction of the muscle.<sup>4</sup> The abnormality was identified as presynaptic because of the decreased number of acetylcholine quanta released from motor nerve terminals by each nerve impulse.<sup>3</sup> This is the basic cause of the muscle weakness. The clinical features described by Rooke *et al.*<sup>5</sup> and O'Neill *et al.*<sup>6</sup> are proximal weakness, especially in the lower limbs, with diminished tendon reflexes and post-tetanic potentiation. The weakness is worse in hot weather or after a hot bath.<sup>6,7</sup> Muscle ache and stiffness aggravated by exercise is a common complaint, as are dry mouth, impotence, impaired lacrimation, and impaired sweating. This may imply a selective cholinergic dysautonomia.

Apart from dry mouth, our patient denied any of the above symptoms. Numerous reports have associated LES with intrathoracic tumors, most notably small cell lung

†† Lennon VA: Unpublished data.

cancer (SCLC). Our patient had clinical evidence of SCLC 6 months after the diagnosis of LES. MG is usually diagnosed on the basis of history and physical examination. Diplopia and other bulbar symptoms are often primary complaints in MG but also can occur in LES, as can ptosis.<sup>‡‡</sup> Muscle weakness in MG is usually distal as well as proximal and is painless. Resistance to succinylcholine is seen in MG, in contrast to LES, and the electromyogram in MG shows normal to slightly reduced evoked compound muscle action potential and fade rather than facilitation in response to repetitive stimuli.

An autoimmune pathogenesis has been substantiated both in carcinomatous LES and in noncarcinomatous LES, where plasma exchange, chemotherapy or radiation therapy have produced improvement and remission of the neurologic syndrome.<sup>8</sup> The immunoglobulin-G fraction of LES plasma injected systemically into mice can transfer the physiologic abnormalities.<sup>9,10</sup> The characteristic morphologic changes (reduction in the number of presynaptic active zones and active-zone particles that are believed to represent VGCCs) were revealed by freeze-fracture electron microscopy of LES neuromuscular synapses.<sup>11</sup> The microelectrophysiologic abnormalities found in patients with LES<sup>3</sup> and induced in mice by LES immunoglobulin-G<sup>10,12</sup> are consistent with a loss of functional VGCCs, which would result in reduced calcium entry during nerve terminal depolarization and thus a decrease in transmitter release.

Several authors suggested that VGCC of SCLC cells might be the autoimmunizing stimulus in patients with LES.<sup>13,14</sup> Omega conotoxin, a potent and selective antagonist for certain neuronal VGCC (Yoshikami *et al.*<sup>15</sup>), antagonizes VGCC activity in SCLC lines.<sup>16</sup> A soluble omega conotoxin binding component of VGCC complex, extracted from small cell lung carcinoma, bound to antibodies found in the serum of these patients.<sup>16</sup> Based on this observation, Lennon and Lambert demonstrated that autoantibodies in the serum of 52% of LES patients bind specifically to this detergent-soluble omega conotoxin binding component of SCLC.<sup>1</sup> This finding provided a clinically useful diagnostic aid for LES, because these antibodies were not found in control subjects without SCLC, including patients with neuromuscular immunity (MG) and endocrine autoimmunity (insulin-dependent diabetes mellitus). Antibodies reactive with these solubilized binding components of SCLC are more frequent in patients with LES who have clinical evidence of primary lung cancer (76% positive) than in those with cancer other than the lung (none of 5) or those without evidence of any cancer (30% positive).<sup>1</sup> The finding in our patient (with

a long history of smoking) of VGCC antibodies at a serum level of 771 pmol/l (normal  $\leq$  31 pmol/l) was therefore strongly suggestive of an underlying lung cancer, although chest x-ray did not reveal a tumor at the time of LES diagnosis.

Sensitivity of LES patients to depolarizing and nondepolarizing muscle relaxants (succinylcholine and tubocurarine) has been reported.<sup>4,6,17-20</sup> In a recent case report,<sup>21</sup> an extreme sensitivity to vecuronium (3 mg) was found in a patient with LES in remission who was being treated with 3,4-diaminopyridine 20 mg every 6 h. The latter selectively blocks potassium channels, thus preventing potassium efflux and prolonging the action potential. The prolonged activation of VGCC will increase intracellular calcium in the nerve terminal and increase acetylcholine release. Reversal with neostigmine 5 mg was incomplete. Dramatic improvement followed oral administration of 3,4-diaminopyridine. Our patient, who was not known preoperatively to have LES, presented with extreme sensitivity to succinylcholine and/or *d*-tubocurarine even though he had normal dibucaine number and a low normal esterase activity with no apparent cause to account for this extreme sensitivity.

*Summary.* We have described a patient with LES who first presented with an unduly prolonged response to succinylcholine and/or *d*-tubocurarine. The patient had undergone low anterior resection for rectal adenocarcinoma. The diagnosis of LES was first suspected and provisionally made by the anesthesiologist by simple bedside testing in the first postoperative day and later documented electromyographically. The postoperative finding of seropositivity in a new assay for autoantibodies to VGCC was diagnostic for LES and highly suggestive of a primary lung cancer. SCLC was diagnosed 6 months after rectal surgery.

Major advances have been made in understanding the pathogenesis and treatment of LES. These have led to the development of an immunologic assay that should be helpful in delineating the natural history of the disease and the possible diagnosis of an occult small cell carcinoma of the lung, while possibly still curable, in suspected cases of LES. Monitoring neuromuscular function in the operative period is essential for 1) careful titration of relaxant requirement, 2) identification of unsuspected cases of LES, and 3) evaluation of the differential diagnosis of inadequate recovery from neuromuscular blockade. Therapy with a combination of anticholinesterases and 3,4-diaminopyridine would assist in managing these patients when nondepolarizing relaxants are clinically required.

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## Detection of Occult Hemopericardium Using Intraoperative Transesophageal Echocardiography

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### CASE REPORT

Transesophageal echocardiography (TEE) has been shown to be useful for intraoperative evaluation and monitoring of patients who have suffered major trauma.<sup>1,2</sup> The following is a report of a case in which intraoperative TEE detected an otherwise occult hemopericardium.

A 35-yr-old otherwise healthy man presented with a stab wound in the left upper quadrant of the abdomen. He was alert and hemodynamically stable and had no other injuries. Supine chest x-ray showed no pneumothorax, hemothorax, or widening of the mediastinum. Transthoracic echocardiography (TTE) was not available in the trauma resuscitation area. He was brought on an emergency basis to the operating room for diagnostic peritoneal lavage and exploration of the wound. Anesthesia was induced with thiopental and the trachea intubated after administration of succinylcholine. Upon inspection of the pharynx and passage of an oral-gastric tube, no blood was found, and trauma to the stomach and esophagus was assessed as unlikely. In addition, no blood was found by peritoneal lavage, and it was decided that exploratory laparotomy was not indicated.

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There was still some concern about the possibility of intrathoracic injury because of the location of the wound, but the patient remained