Myasthenia gravis and its implications to anesthesia
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Myasthenia gravis—the rare disease characterized by impaired neuromuscular transmission—is a condition which merits special anesthetic consideration. The author details the history and treatment of the disease, the problems that it creates for the anesthetist, and the solutions to these problems.

Myasthenia gravis is said to be a rare disease characterized by the insidious onset of progressively severe fatigability and weakness of voluntary muscles.\(^1\) Although the abnormality is thought to involve the neuromuscular junction, the precise nature of the defect is still unknown.\(^2\) The term comes from the Greek words \textit{mys} (muscle) and \textit{asthenia} (weakness), and from the Latin word \textit{gravis} (heavy).\(^3\) The course of the disease is highly variable with an uncertain prognosis. Mortality is as high as 15 times that of the general population. The estimated incidence is one in 20,000 to one in 40,000.\(^4\)

As early as 1895, Jolly first used the name “myasthenia gravis pseudo paralytica” to describe the syndrome observed in two boys, ages 15 and 14. He showed that when their muscles were repeatedly stimulated with a current, a reaction of asthenia was demonstrated by recorded tracings. This has come to be known as the “myasthenia reaction” or “Jolly test”. He suggested, but never tried, physostigmine as a form of treatment.\(^5\)

The first American physician to report a fully studied case was Herman Hoppe in 1892. He summarized that the disease is primarily one of the motor system with only occasional pain or paresthesia. Chewing, swallowing, and eye movements are most affected at first, followed by involvement of the trunk and extremities. Stimulation results in rapid weakness. Twenty or thirty movements will bring a muscle response to zero. Daily remissions and relapses occur, but remissions may last as long as four years.\(^6\)

There is much discussion about whether the disease is due to a presynaptic failure of the transmitter release from the nerve terminals or to a postsynaptic failure of the motor endplate to respond to acetylcholine. Postsynaptic failure could be due to a circulating neuromuscular blocking agent or to a primary endplate disorder. A presynaptic impairment of the release of acetylcholine is the most suggestive cause at the present time.\(^7\)

Muscular activity is the result of a series of events which involve the nervous system. The neuromuscular junction is a synapse between the motor nerve ending and the muscle fiber. The side facing the muscle fiber is called the terminal (presynaptic) membrane. The subneural space is a gap separating the terminal membrane on one side from the sole plate. The postsynaptic membrane is the side of the sole plate facing the terminal membrane. Thus, the synapse consists of three parts: terminal
Depolarization of the endplate is said to be caused by acetylcholine release at the terminal membrane of the motor nerves. Acetylcholine diffuses through the subneural space to reach the postsynaptic membrane. The liberation and action of acetylcholine occurs as an intracellular process within the conducting membrane of the muscle. It leads to an increased ion permeability, with a change in the permeability of the muscle membrane. Potassium moves out and sodium moves into the muscle fiber. The transient change in permeability is produced by acetylcholine. It must be rapidly inactivated. Otherwise, a series of contractions could not occur. This inactivation is accomplished by the hydrolysis of acetylcholine through a specific enzyme, acetylcholinesterase. It may be contained within the nerve endings in synaptic vesicles and is discharged in an all-or-none fashion. The hydrolysis of acetylcholine into acetate and choline restores the membrane permeability to its resting state and repolarization is accomplished.

**Reversal agents**

The modern era in the study of myasthenia began about 1935 with the neurohumoral theory of Loewi and Dale. They realized that myasthenia, which clinically resembles curare poisoning, could be reversed by eserine and, later, by neostigmine (Prostigmine®). The fact that neostigmine is an anticholinesterase drug led to a frequent discussion of two possible abnormalities at the neuromuscular junction in myasthenia. These included either an increased choline activity or a diminished production of acetylcholine. Myasthenic terminals presumably contain a subnormal store of acetylcholine in the resting state. It becomes more actively depleted during exercise.

A final explanation of myasthenia recognizes the immunological features of this condition. Myasthenia tends to occur in conjunction with a number of "autoimmune" diseases including thyrotoxicosis, myxedema, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, and diabetes. About 40% of the patients with myasthenia have antibodies in their serum which react, not only against muscle, but also against the thymus in which striated muscle-like cells are normally present.

The antineuronal antibodies reported in the serum of myasthenia patients may be capable of the presynaptic failure. The high incidence of thymic hyperplasia, the increased number of germinal centers within the thymus, and the fact that a thymectomy often produces a remission of symptoms also supports the theory that the disease may be an autoimmune process. It is thought that the thymus, functioning through some endocrine-like mechanism, is the basic cause of the abnormality at the neuromuscular junction. The thymus gland may contain and release a blocking or depressing substance in myasthenia.

**Clinical implications**

Despite the uncertainty over the etiology, the clinical implications of the existing knowledge are relatively clear. Neuromuscular transmission is impaired. Drugs that inhibit acetylcholinesterase, introduced first by Mary Walker in 1934, are required and are the only symptomatic therapy. Anticholinesterase drugs are given to enhance effective synaptic levels of acetylcholine. They improve transmission by the "saving of the transmitter whether the lack is due to insufficient release or to an abnormally low endplate sensitivity to the normal transmitter release."

In 1953, it was pointed out that a patient with myasthenia may develop weakness either as a part of the disease itself or from an overdosage with anticholinesterase drugs. A crisis may be precipitated or contributed to by an overdosage with neostigmine. Neostigmine can produce directly opposite results in the patient from those which maintain life. In the presence of a crisis, anticholinesterase drugs do not over-
come the block at the neuromuscular junction. Continued administration of anticholinesterase drugs to the point of toxicity produces too much acetylcholine. This results in a neuromuscular depolarizing block causing increased weakness and, ultimately, paralysis of muscles or, better stated, a cholinergic crisis.

The action of acetylcholine is twofold: a muscarinic-like action on smooth muscles and glands and a nicotinic-like action on ganglia and striated muscle. Muscarinic effects include anorexia, nausea, sweating, epigastric and substernal tightness, and heartburn. These are followed by abdominal cramps, increased peristalsis, vomiting, profuse sweating, dyspnea with a decrease in vital capacity and maximum breathing capacity. The nicotinic-like effects are increased muscular fatigability, mild generalized weakness, involuntary muscle twitchings and scattered fasciculations. If these cholinergic symptoms are allowed to progress, hypotension and bradycardia with resultant cardiac arrest can occur.¹

When a myasthenic is presented for surgery, one should remember that there is extreme sensitivity to non-depolarizing relaxants as curare and gallamine. Dosages of 1-4 mg, or about 1/20 the usual clinical dose, will produce complete and long lasting paralysis of all voluntary muscles. One should proceed very cautiously if a patient has any history of muscle weakness or fatigability because myasthenia may not have been diagnosed. Muscle relaxants are best avoided and are seldom necessary. If needed, it would be best to use small doses of curare (0.5-2.0 mg) or gallamine (2.5-10 mg). The course of neuromuscular blockade after the administration of these small doses is similar to that found after the administration of usual doses in normal persons.¹

The response to depolarizing relaxants is also abnormal. The myasthenic patient may be resistant to these drugs, although uninvolved muscles may be abnormally sensitive. Anticholinesterase therapy will inhibit the effect of pseudocholinesterase which is responsible for the breakdown of succinylcholine. Therefore, the duration and intensity of its action may be prolonged.¹

If a non-depolarizing relaxant has been used, Prostigmine® may be used at the end of the procedure, reverting to oral therapy once the patient is fully awake. In the postoperative period, caution should be exerted not to over-treat the patient, especially, if a thymectomy has been done. These patients often experience a temporary but remarkable remission. Signs of mild respiratory distress may well be due to wound pain or anxiety rather than indicative of a myasthenic crisis.⁷

Myasthenics are abnormally sensitive to drugs not usually thought of as blocking agents. Among such drugs are central nervous system depressants, such as morphine; narcotic analgesics; barbiturates; and tranquilizers. Antiarrhythmic and local anesthetic agents as quinine, quinidine, propranolol, and lidocaine have been shown to inhibit neuromuscular transmission. Antibiotics such as streptomycin, dihydrostreptomycin, gentamicin, kanamycin, neomycin, paromomycin, and polymyxin A and B have a postsynaptic effect.⁴

Conclusion

In conclusion, although much has been learned about myasthenia, its cause is still a debated subject. Two of the most acceptable theories are concerned with whether there is an impairment of the release of acetylcholine, or whether nerve terminals contain subnormal stores of acetylcholine. Anticholinesterase drugs offer a means of treatment but not a cure.

A myasthenic crisis may well represent undermedication and a cholinergic crisis overmedication. It is important to recognize which crisis is present because the treatment is opposite in each one. The important anesthetic consideration is an awareness of the neuromuscular junction problem which is present. These
patients are sensitive to muscle relaxants, and, if needed, dosages must be reduced.

REFERENCES

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