MEDICAL PRACTICE

Occasional Survey

Progress in Myasthenia Gravis

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British Medical Journal, 1973, 3, 437-440

Myasthenia is a syndrome of increased fatigability in striated muscle. It may occur with lesions of the central nervous system, such as progressive muscular atrophy, or with lesions of muscle such as polymyositis. The muscle weakness in these disorders is usually persistent and unrelenting. Myasthenia gravis, however, is a disorder of neuromuscular function due to a defect in synthesis or storage of acetylcholine at the nerve ending. The muscle weakness is characteristically worse after effort and improved by rest. The patient starts to comb her hair and is unable to finish, or halfway through a meal finds that she can chew no longer. Myasthenia gravis occurs at all ages but the modal age of onset is about 20 years, with a secondary peak for males in the fifth decade. Below that age women outnumber men by over four to one but in later life men predominate.¹

Patients with thymic tumours tend to be 10 to 20 years older than those with thymitis. The incidence of myasthenia is about 1 in 20,000. There is tendency to early remission but complete remissions are not prolonged and are rarely repeated. They usually occur in those patients with the ocular forms of the disease and within two years of its onset.² Patients with the purely ocular form of myasthenia gravis do not commonly develop generalized myasthenia if symptoms remain confined to the extraocular muscles for more than a year, and there is evidence to suggest that this may be a distinct variety of the disease.³ The highest mortality for myasthenia gravis is in the first year, with a second danger period from four to seven years after the onset.⁴ The muscle weakness has a characteristic distribu-

tion, the extraocular, bulbar, neck, limb girdles, distal limbs, and trunk muscles being affected in that order. The myasthenia responds to cholinesterase inhibitors, which enhance the effects of the limited supply of acetylcholine at the neuromuscular junction, and the quick-acting anticholinesterase edrophonium (Tensilon) provides a useful diagnostic test for myasthenia gravis. The diagnosis is not difficult so long as the possibility is kept in mind. When the distribution of muscle weakness is atypical a diagnosis of psychiatric disease is commonly made, and the immobile frozen facies, with the inability of a myasthenic patient to smile when the facial muscles are weak, often leads to a misdiagnosis of depression. The relation between myasthenia gravis and the thymus has been recognized since Blalock *et al.*⁵ reported clinical improvement of myasthenia after removal of a thymic tumour.

Release of acetylcholine at the nerve ending occurs in discrete quanta, each of which gives rise to a miniature end-plate potential that can be measured with the aid of microelectrodes inserted into single neural end-plates in muscle.⁶ The size of the quanta remains stable whether release takes place spontaneously at intervals or in the momentary synchronous burst that accompanies the arrival of a nerve impulse. The only abnormality in the myasthenic neuromuscular junction is the size of the quanta of acetylcholine formed in the presynaptic vesicles. The quanta of chemical transmitter are normally formed continuously at a rate of one or two per second. When the nerve is stimulated there is a synchronous discharge of 100-200 of these quanta, and this creates the action potential which leads to contraction of the muscle fibre. In myasthenia gravis the quanta are only about one-fifth of the normal size, and despite their normal number the nerve impulse fails to generate enough potential for the muscle to contract.

There is evidence that the thymus gland secretes a hormone, thymin, which is involved in the regulation of neuromuscular transmission. It has been extracted from normal calf thymus⁷ and has been shown to reduce the size of

acetylcholine quanta when injected into rats.⁸ Furthermore, guinea-pigs immunized with calf thymus develop thymitis and a neuromuscular block which is cured by thymectomy,⁹ and a similar neuromuscular block has been reported after immunization of mice with thymus extract.¹⁰ The serum of myasthenic patients contains a substance that inhibits acetylcholine synthesis and this is due to a direct action on the enzyme choline acetylase.¹¹ Probably this circulating inhibitor of acetylcholine synthesis is identical with the inhibitor isolated from thymic extracts. Attempts to isolate thymin have so far suggested that it is a polypeptide of small size. This would correlate with the clinical observation that muscle strength in myasthenic patients is improved after haemodialysis.¹² Thymin does not simply produce a curare-like competitive inhibition of neuromuscular condition, since the block takes a week to develop and a week to resolve, but it does affect the production of acetylcholine at the nerve ending.

Myasthenic Syndrome

Myasthenia may be a feature of certain intrathoracic tumours, usually oatcell carcinomas, and this disorder must be distinguished from myasthenia gravis. This syndrome is known as pseudomyasthenia, the myasthenic syndrome, or the Eaton-Lambert syndrome. It is due to impaired release of acetylcholine from the nerve ending and it has distinct clinical and therapeutic features as well as producing characteristic electromyographic changes.¹³ The symptoms are muscle weakness and fatigability with a delay in developing the maximum strength of voluntary contraction. There is predominant involvement of the shoulder and pelvic girdle muscles, with sparing of the muscles supplied by cranial nerves. Peripheral neuropathy and myopathy are commonly associated and the edrophonium test gives an incomplete response. The electromyographic changes distinguish the syndrome unequivocally from myasthenia gravis. In myasthenia gravis a single nerve stimulus provokes an action potential of normal amplitude but repeated stimuli lead to a steady fall in amplitude. In the myasthenic syndrome a single stimulus causes a reduced action potential and repeated stimuli produce a temporary increase in amplitude. Patients with the myasthenic syndrome show an incomplete response to cholinesterase inhibitors but usually a good response to guanidine.

Immune Aspects of Myasthenia Gravis

The thymus gland is histologically abnormal in myasthenia gravis. It has a similar histological picture to that of the thyroid in Hashimoto's disease, and it was this similarity that first led Smithers¹⁴ to suggest that myasthenia gravis was an autoimmune disease. Serum complement levels fall with disease activity.¹⁵ Antibody reacting with skeletal muscle is present in the serum of over one-third of the patients with myasthenia and in almost every case in which a thymic tumour is present. The antibody to skeletal muscle also reacts with thymic epithelial or myoid cells and absorption with thymus abolishes its muscle reactivity.¹⁶ When myasthenia gravis is associated with a thymic tumour, and this occurs in 10% of cases, the tumour is always epithelial, arising in a type of cell which in its early development resembles striated muscle and hence has been called a myoid cell. The circulating antibody to skeletal muscle does not, however, attach itself to the motor end-plate and is not directly involved in the production of muscle weakness.¹⁷ Indeed, it would be difficult to envisage an antibody interfering directly with the action of a neurotransmitter as the space across the neuromuscular junction is smaller than the diameter of an IgG

molecule. Other circulating antibodies are found in the serum of patients with myasthenia. Antinuclear factor occurs in over a third of the cases¹⁸ and thyroid antibodies are significantly more common than in matched controls.¹⁹

Autoimmune diseases often appear together, and the clinical association of myasthenia gravis with immune disturbance such as agammaglobulinaemia, rheumatoid arthritis, pernicious anaemia, autoimmune haemolytic anaemia, systemic lupus erythematosus, and Sjögren's disease is well recognized.^{19, 20}

If myasthenia gravis is an autoimmune disease it should be possible to produce a similar reaction in animals by immunizing them against constituents of the myoid cell of the thymus or against skeletal muscle. This has, in fact, been done. By immunizing animals with as little as 5 µg of thymic extract in Freund adjuvant, Goldstein⁷ produced an experimental thymitis and a defect in neuromuscular transmission which mimicked that of myasthenia gravis. This was also confirmed by others.⁹ Development of this neuromuscular block is dependent on the presence of the thymus, and thymectomy restores neuromuscular function to normal within three or four days.⁹

Medical Treatment

Neostigmine and pyridostigmine are the basis of the medical treatment of myasthenia gravis. Physostigmine was an early cholinesterase inhibitor but it has been abandoned because it has the disadvantage of free passage across the blood-brain barrier with the production of toxicity by interfering with effects of acetylcholine on the central nervous system. These drugs act by inhibiting the action of cholinesterase, which normally destroys acetylcholine. When given at regular intervals during the day muscle strength can usually be restored to an adequate even if not normal level. It is important to establish the dose of anticholinesterase drugs which gives the maximum therapeutic response. This may not restore muscle strength to normal and the patient must often learn to live with some degree of disability. Most myasthenic patients can be improved only up to a certain level. Increasing the dose of drugs above the maximum response level in the forlorn hope of improving physical activity will produce the opposite effect, and progressive muscle weakness may finally end in a cholinergic crisis.²¹ Myasthenic patients like any other individuals are subject to the fatigue of mental and physical strain, and the temptation to increase the dose of medication to counter such physiological fatigue must be resisted. Intercurrent infection may also cause deterioration of myasthenia, but here the cautious and carefully supervised increase in dosage of the drugs is justified.²¹

Neostigmine is given in a dose of 15 mg four-hourly or more often if necessary. It is effective within 30 minutes. The optimum frequency of administration must be decided and then the precise dose determined. When given parenterally a dose of 1-2 mg is equivalent to 15 mg by mouth. The cholinesterase inhibitors enhance both the muscarine and the nicotinic effects of acetylcholine. Muscarine activity affects smooth muscle and exocrine glands and is manifested by abdominal colic, diarrhoea, nausea, salivation, and lachrymation. These side-effects can be reduced by the administration of atropine. These symptoms, however, usually indicate overdosage, and for this reason it is unwise to prescribe atropine routinely.

Pyridostigmine (Mestinon) has the advantage of more-prolonged action and it is rarely necessary to give it more than four-hourly. It does, however, take longer to act. A dose of 60 mg is equivalent to 15 mg neostigmine. A dose of pyridostigmine of 60 mg four times daily should be used initially and the size of the dose increased until the maximum benefit is obtained. Patients who tend to be weak on

awakening benefit from a dose of the quicker-acting neostigmine with the first dose of pyridostigmine. There is an inevitable tendency for a patient with myasthenia gravis to develop anxiety over her disease. Her everyday activities are dependent on taking tablets. There is thus an inclination for the patient to increase her dose even when the fatigue is of emotional origin. Not only does emotional distress commonly aggravate myasthenia gravis but increasing the dose of anticholinergic drugs above the maximum response level may aggravate the muscle weakness and even provoke a cholinergic crisis.

Drugs other than anticholinesterases have a place in the treatment of myasthenia gravis. Striking benefit may be obtained from the administration of corticosteroids, but there is often an initial deterioration, so that these drugs should not be first introduced outside hospital. Unusual neuromuscular blocking activity has been shown in the serum of myasthenic patients on receiving corticosteroids, and this is possibly provoked by the sudden release resulting from the known lympholytic effects of corticosteroids.³ Ephedrine has been recommended for many years as enhancing the effects of anticholinesterase preparations but the results are rarely striking.

Myasthenic and Cholinergic Crises

A myasthenic crisis may result from a natural deterioration of the disease or it may be precipitated by infection or by surgery. The symptoms are due to a relative deficiency of acetylcholine and can usually be corrected by the administration of increasing doses of an anticholinesterase. A cholinergic crisis, on the other hand, is the result of excessive doses of cholinesterase inhibitors, and the treatment demands withholding these drugs. Both these crises present with severe weakness leading to paralysis. The differential diagnosis may be difficult but the administration of 10 mg edrophonium intravenously will usually enable the correct diagnosis to be made. If the crisis is myasthenic temporary improvement will follow, but if the crisis is cholinergic no such improvement occurs, and indeed the situation may deteriorate. The duration of action of the drug is so short that any deterioration due to increased anticholinesterase activity is unlikely to have any serious consequence.

Value of Thymectomy

Thymectomy has an increasingly important role in the management of patients with myasthenia gravis. The risks of thymectomy are now small provided the operation is undertaken in a centre with good facilities for intensive care and in a unit with experience of the operation.

It was undoubtedly due to the energy and conviction of Keynes²²⁻²⁵ that thymectomy ever became recognized as an important treatment of myasthenia gravis. In 1958 Simpson,⁴ in a study of 404 patients with myasthenia gravis, showed convincingly that thymectomy offered a great saving of life even when the hazards of operation were included, and furthermore he found that a greater proportion of remissions occurred in those patients treated surgically. He was able to show that the poor results of thymectomy in some of the early American reports were due to a failure to separate patients with thymic tumours, who have a notoriously bad prognosis, from those with thymitis. The prognosis of patients with thymic tumours and myasthenia gravis is such that if no therapy is directed towards the tumour 85% are dead within a year.²⁶

The risks of thymectomy in myasthenia gravis have been drastically reduced over recent years. The tremendous advances in the management of ventilatory failure with assis-

ted respiration and the better recognition of the differences between myasthenic and cholinergic crises have contributed to this improvement. Simpson in 1968¹ reported no post-operative deaths over the previous 12 years, and Kreel *et al.*²⁶ reported no deaths in the last 54 patients operated on between 1959 and 1967. In a smaller series from Liverpool²⁷ no postoperative deaths had occurred in 14 patients undergoing thymectomy since 1966. Papatestas *et al.*²⁸ recorded a post-operative mortality of 2.9% in 69 patients without thymoma operated on between 1960 and 1969, compared with 20% before 1960. At New End Hospital, London, there have been two deaths in the last 70 thymectomies.

Not only has the risk of thymectomy been greatly reduced but the benefits of the operation are now becoming more apparent, for the incidence of remission increases with the number of years after thymectomy. Perlo *et al.*²⁹ in Boston and New York found complete remission or substantial improvement after thymectomy in 84% of 45 female patients with severe myasthenia, and Edwards and Wilson²⁷ reported improvement in 80%. A recent series of 111 patients with myasthenia associated with thymitis²⁸ showed that of patients who achieved remission 50% did so after a delay of two or more years and that five years after thymectomy 90% of patients were in remission or had shown improvement. It seems that clinical remissions after thymectomy appear to be of two types. A rapid response may occur as a result of removal of the major source of neuromuscular damage, and a more delayed response takes place when depletion of T cells prevents the abnormal response in other tissues. Papatestas and his colleagues concluded that their observations were consistent with the hypothesis that myasthenia gravis is due to abnormal clones of immunocompetent lymphocytes proliferating in the thymic germinal centres and that thymectomy produces stable remission by eliminating these centres. Its effect is often delayed because of the long life span of the existing pool of small immunocompetent lymphocytes. This suggestion receives support from Japan with the recent finding that in experimental myasthenia in mice the passive administration of sensitized lymphocytes to normal animals produces neuromuscular block.¹⁰

There are, of course, other reasons why thymectomy may not be followed by clinical remission of myasthenia gravis. Irreversible damage may be done to the neuromuscular junction by prolonged disease.⁴ Furthermore, the thymectomy may not be complete, for ectopic tissue occurs in 20% of the patients.³⁰ In patients with thymoma failure to remove the residual thymus in addition to the tumour may result in reappearance of myasthenia after operation. Recurrence of the tumour itself is also common and may be the cause of persistent disease or of reappearance of myasthenia after thymectomy.

Indications for Thymectomy

An important aspect in the management of patients with myasthenia gravis is the decision to recommend thymectomy. If the patient has a thymic tumour it should be irradiation or removed, or removed after irradiation. For patients with thymitis the indications for thymectomy are less easily defined. At the Mount Sinai Hospital, New York, with experience of 185 patients with myasthenia gravis, the indications for operation in patients without a tumour are an increasing need for anticholinesterase drugs or a poor response to medication.²⁸ With the decreasing risk of operation over recent years there has been an increasing tendency at Mount Sinai Hospital to recommend surgery earlier in the disease.³¹ Prolonged duration of symptoms was not considered to be a contraindication to surgery. All patients with thymoma irrespective of the severity of the myasthenia gravis were subjected to surgery.

The indications prompting thymectomy in Liverpool²⁷ are severe weakness and incapacity despite anticholinesterase therapy, recurring respiratory infections leading to one or more incidents of myasthenic or cholinergic crisis, and recently married women with hopes of having children.

At New End Hospital over 260 patients with myasthenia gravis have been treated. We offer thymectomy to most patients, as the sooner operation is performed the better the prognosis.³² The exceptions are: patients with the purely ocular form of myasthenia, as this seems to be a distinct form of the disease³ and the response to thymectomy is disappointing; major contraindication to surgery or anaesthesia such as severe pulmonary or heart disease; elderly patients with mild myasthenia who respond well to drugs; and tumours of the thymus that have not been irradiated.

Preparing Patients for Thymectomy

The first decision to make is whether a thymic tumour is present or not. Many believe that a tumour should be irradiated before surgery as this improves the already grim prognosis for myasthenic patients with thymic tumours.³² Others are unconvinced of the necessity for irradiation before surgery.²⁸ Secondly, by trial and error the dose of anticholinergic drugs that will produce the maximum therapeutic response must be determined. Thirdly, pulmonary function studies should be undertaken, and if the vital capacity is seriously reduced a tracheostomy should be performed at the time of thymectomy so that assisted respiration can be provided in the immediate postoperative period. Postoperatively cholinesterase inhibitors are withheld until clinical evidence of their need is apparent, and in this way the serious complication of cholinergic crisis may be averted.³³ The patient is allowed up by the fifth day and discharged at the end of the second or third week. During the convalescent period the amount of medication, if any, is suitably adjusted.

I am grateful to my surgical colleague M. J. Lange for the benefit of his counsel and experience.

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Outside Europe

Delayed Attacks of Malaria in Visitors to the Tropics

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British Medical Journal, 1973, 3, 440-442

Summary

Out of 80 Danish college students and their teachers visiting the Middle East, West Pakistan, and India by bus in two four-month journeys during the summer and autumn of 1971, six individuals developed an apparently first attack of vivax malaria within seven to nine months

after their return to Denmark. No cases of malaria were seen in the group during the journeys. Prophylaxis with chloroquine (Resochin) was strictly observed when visiting the areas in which malaria is endemic.

All cases responded rapidly and completely to a full course of treatment with chloroquine. The most probable cause of the delay of the clinical manifestations is drug prophylaxis, which can prevent a clinical attack but not always eradicate the parasite.

Introduction

In North Western Europe malaria is probably one of the most

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