Occasional Review

Progress in myasthenia gravis

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Myasthenia is a syndrome of increased fatigability in striated muscle. It may occur with lesions of the central nervous system or with lesions of muscle. The muscle weakness in these disorders is usually persistent and unrelenting. Myasthenia gravis, however, is a disorder of neuromuscular function due to a reduction of available acetylcholine (AC) receptors at the neuromuscular junction. 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. The muscle weakness has a characteristic distribution, 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 AC at the neuromuscular junctions, 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 psychiatric disease is commonly and erroneously diagnosed.

The incidence of myasthenia gravis is about 1 in 30 000. There is a 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. Patients with the purely ocular form of myasthenia gravis do not commonly develop generalised myasthenia if symptoms remain confined to the extraocular muscles for more than a year, and this may be a distinct variety of the disease.

Immune aspects of myasthenia gravis

The thymus gland is histologically abnormal in myasthenia gravis.¹ Its histological picture is similar to that of the thyroid in Hashimoto's disease, and this similarity first led Smithers² to suggest that myasthenia gravis was an autoimmune disease. Serum complement concentrations fall with disease activity.³ When myasthenia gravis is associated with a thymic tumour, and this occurs in 10% of cases, the tumour always has an epithelial component, arising in a type of cell that in its early development resembles striated muscle and hence has been called a myoid cell. Electron microscopy of the myoid cell has, however, shown them to have ultrastructural characteristics of epithelial cells rather than of striated muscle fibres, though they undoubtedly have AC receptors on their surface.⁴

Circulating antibodies to skeletal muscle and to myoid cells of the thymus are present in the sera of some patients.⁵ The

circulating antibody to skeletal muscle does not, however, attach itself to the motor end-plate and is not directly implicated in the production of muscle weakness.³ The presence of lymphorrhages in skeletal muscles suggests that lymphocyte-mediated immunological reactions take place in myasthenia, and peripheral and thymic lymphocytes from patients with myasthenia gravis have a cytotoxic effect on muscle cells grown in tissue culture.⁶⁻⁷ Lymphocytes from patients with myasthenia are stimulated when cultured in vitro with AC receptor.⁸ Myasthenia can be induced in animals by injecting purified AC receptor,⁹ and circulating antibodies to AC receptor occur in most patients with myasthenia gravis.¹⁰ Furthermore, the passive transfer of experimental myasthenia gravis with antireceptor antibodies suggests that these circulating antibodies are pathogenic.¹¹⁻¹²

Autoimmune diseases often appear together, and the clinical association of myasthenia gravis with immune disturbances such as agammaglobulinaemia, rheumatoid arthritis, pernicious anaemia, autoimmune haemolytic anaemia, systemic lupus erythematosus, and Sjögren's disease is well recognised. Myasthenic patients also have more circulating antibodies against thyroid, gastric, and other tissues than a control population.¹³⁻¹⁴

The genetic element is important. Histocompatibility typing has shown a high incidence of HLA-8 among the young patients who commonly have thymitis, in contrast with the high incidence of HLA-2 in the older patients and in those with thymoma.¹⁵ Furthermore, there is an increased prevalence of antibodies to skeletal muscles in first-degree relations of patients with myasthenia gravis.¹⁵

Pathogenesis

When I last reviewed this disorder¹⁶ it was not known whether the defect was presynaptic—that is, in the synthesis or storage of AC—or postsynaptic—that is, a defect in the AC receptor. It was known from studies of end-plate potential that the quanta of acetylcholine produced were only one-fifth of the normal size,¹⁷ but this did not distinguish a defect in the transmitter from one at the receptor. Searches over the years for a neuromuscular blocking agent in the blood of patients with myasthenia gravis had given inconclusive results.¹⁸ There is, however, now little doubt that the disorder in myasthenia gravis is due to a reduced number of functioning AC receptors and that this results from immunological damage provoked by circulating antibodies to the AC receptor. The story of the unfolding of the mysteries of the pathogenesis of myasthenia makes exciting reading and would not have occurred without the contributions of the cobra, the electric eel, and the rabbit.

OF COBRAS, EELS, AND RABBITS, AND ANTIGENS AND THINGS

Cobra venom is a small protein that binds to the AC receptor, thus preventing AC access and so leads to paralysis and death. It has now been isolated and named alphabungarotoxin.

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Bungarotoxin may be labelled with 125-I and is used as a specific molecular probe for the nicotinic AC receptor molecule. It interacts specifically and irreversibly with AC receptors and may thus be used to determine the number of AC receptor sites, the number of bungarotoxin-binding sites being proportional and perhaps equal to the number of AC receptor sites. Biopsy specimens of muscles from myasthenic patients disclose that these muscles have less than 30% of the AC receptors found in normal neuromuscular junctions.¹⁹ It might be argued that the reduction in AC receptors reflects an effect of anticholinesterase drugs on the receptors or be a secondary effect of the disease process rather than its primary cause. Identical end-plate changes, however, occur in untreated patients with myasthenia as in those who have received anticholinesterase drugs.²⁰ Furthermore, it was not long before it was shown that there is a factor located in the serum globulins of myasthenic patients that blocks the binding of bungarotoxin to AC receptors at the normal human neuromuscular junction.^{21 22} It was presumed that this factor in the serum of myasthenic patients had already bound to the AC receptor, thereby preventing bungarotoxin access. An autoimmune pathogenesis for myasthenia gravis seemed probable with the circulating antibody directed against the AC receptor. Further progress depended on isolating the antigen.

Interest in the AC receptor was intense, but the problem of purification seemed insoluble. Only minute amounts of AC exist at neuromuscular junctions, and a way to identify the receptor in extracts of homogenised muscle seemed difficult. Attempts had been made many years ago to produce an experimental myasthenia in animals using homologous muscle antigen, but the antigen contained so little AC protein that these efforts were not successful. The electric organs of electric fish are densely innervated to enable the amount of ions passing through AC receptors to generate several hundred volts. Despite the fact that some electric eels contain 40% of their body weight as electric organ, there are only a few milligrams of receptor. Purification presented formidable problems, particularly as it was not obvious how to identify a molecule responsible for regulating ion permeability of cell membranes in extracts of homogenised muscle. By coupling cobra toxin to agarose beads the minute amounts of solubilised receptor were bound and Lindstrom was able to isolate the AC receptor from the rest of the homogenised muscle.⁹

The few milligrams of receptor isolated by Lindstrom were used to raise antibodies in the rabbit. A few weeks after immunisation with AC receptor the rabbits became weak and died. They had developed antibodies to the electric eel AC receptor that cross-reacted with their own AC receptor. Furthermore, this muscle weakness could be transiently overcome with anticholinesterase drugs.⁹ This disease is now called experimental autoimmune myasthenia gravis. It has been induced in several different species, including the monkey, in which the clinical features of ptosis closely mimic human myasthenia gravis.²³ The disease has also been induced in rats by immunisation with syngeneic AC receptor and the ensuing myasthenia is associated with the formation of circulating antibodies to AC receptors that reduce the number of available receptors.²⁴ That the circulating antibodies are the cause of the disease is proved by the fact that the serum of rats immunised with AC receptor can cause the disease when injected into normal animals, and the histological changes at the neuromuscular junction are similar.¹¹

Experimental autoimmune myasthenia gravis has, however, been most closely studied in the rat in which it develops in two phases. About a week after immunisation with AC receptor there is an initial stage of acute severe muscle weakness from which they recover and about three weeks later they develop a more insidious persistent weakness that is fatal within a few weeks. Electron microscopic studies have shown that the first phase is associated with invasion of the neuromuscular junction by macrophages and a breakdown of the postsynaptic membrane at sites where AC receptor is most concentrated. In the later chronic phase the number of AC receptors is reduced. The area of the postsynaptic membrane is decreased and its folded structure is simplified.²⁵ It would seem that the circulating antibody to AC receptor damages the receptors and reduces their competence. Phagocytosis follows and the amount of AC receptor is reduced. Thus both a reduction in the total amount of AC receptor and the formation of antibody-AC receptor complexes both contribute to the impairment of neuromuscular transmission. It appears that some regeneration of AC receptor can take place and the ability to synthesise new receptor will have an important effect on the prognosis.²⁴

Nevertheless, despite the increasing evidence that a circulating antibody damages the postsynaptic AC receptor experimental myasthenia is T-cell dependent for it will not develop in thymectomised animals and it can be passively transferred with cells.²⁶ Also, the acute lesion at the myoneural junction in the experimental disease shows

lymphocyte infiltration, characteristic of a cell-mediated immune response.²⁰ Recently a high concentration of cell-mediated immunity to purified AC receptor has been shown in human myasthenia gravis and an association noted between disease activity and the concentration of cell-mediated immunity to receptor. It does not seem likely that the cellular response is secondary to damage to the neuromuscular junction as it does not occur in amyotrophic lateral sclerosis in which breakdown of the neuromuscular junction regularly occurs.²⁷ Clinical experience in man also implicates the T cells in myasthenia. Both thymectomy and thoracic duct drainage deplete T cells and improve the disease. The answer probably lies in the immunological condition whereby B cell function is sustained by helper T cells.

THE HUMAN DISEASE

In 1974 it was shown that a circulating globulin in the serum of individuals with myasthenia blocked the binding of bungarotoxin to the AC receptor extracted from denervated rat skeletal muscle.²¹ Recently the passive transfer of human serum fractions from individuals with myasthenia gravis has induced the disease in mice.¹² The active serum fraction was identified as IgG. Furthermore, there was a rough correlation between the patient's clinical state and the potency of the serum factor in producing myasthenic features in the test animals, although disparities were seen in individual cases. Thoracic duct drainage is beneficial in myasthenia gravis, and reinfusion of the gammaglobulin fraction causes clinical deterioration.²⁸ Nevertheless, undoubtedly there is a myasthenia-producing IgG circulating in the blood of patients with myasthenia gravis. The action of this myasthenia-inducing IgG was influenced by the complement system for in the absence of C3 its effect was considerably lessened. Deficiency of C5 did not affect the results.

In about 90% of people with myasthenia gravis there are circulating antibodies to AC receptor. These antibodies have also been shown in babies with neonatal myasthenia. They do not occur in patients with other diseases of neuromuscular function, such as amyotrophic lateral sclerosis and the Eaton-Lambert syndrome. There is, however, no close correlation between antibody titre and the severity of the disease in myasthenia gravis.

The antibody titres fall after thymectomy, and indeed there is an inverse relationship between antibody titre and the interval after thymectomy.²⁹ A fall in antibody titre has also been reported after remissions induced by corticosteroids.³⁴ This suggests that clinical improvement is associated with a fall in antireceptor antibody titre that decreases over several years. It is, however, unlikely that thymectomy removes a major source of antibody as the titre should then fall more quickly. Thymectomy may therefore remove an antigenic stimulus or may cause a gradual decrease in T lymphocytes necessary for antibody formation by B lymphocytes. A fall in circulating T lymphocytes has recently been shown in myasthenic patients after thymectomy,³⁰ and this appears to be associated with an increase in the number of null cells, which are immature T cells needing thymic hormone to complete their development.

ROLE OF THE THYMUS

Undoubtedly great advances have been made in understanding the pathogenesis of myasthenia gravis. The immunological basis of the disease is beyond question but the role of the thymus, though fundamental to the disease, has not precisely been defined. Its importance is twofold.

Firstly, it is the primary immunological source of T cells and hence has a fundamental role in cell-mediated immunity. Secondly, it is a source of myogenic cells with demonstrable AC receptors on their cell surface.³¹ The recent work of Wekerle *et al* has shown the importance of this latter function. In long-term cultures of thymus reticulum cells from young adult rats and mice they detected skeletal muscle colonies in addition to the expected epithelial and mesenchymal reticular tissue types.³² These muscle cells were fully demonstrated

by all morphological and functional criteria and possessed demonstrable amounts of AC receptors on their cell membranes.³³ This finding is supported by the recent showing of bungarotoxin binding to epithelial cells of the thymus and an abundance of these cells in the thymuses of patients with myasthenia gravis.⁴

The fact that stem cells in the thymus can be induced to differentiate into striated muscle clones suggested the possibility that abnormal induction signals might occur in man in response to pathological changes in the thymus, and Wekerle and Ketelsen³⁴ have recently proposed a hypothesis for the pathogenesis of myasthenia gravis. They suggest that primitive intrathymic stem cells are induced by abnormal stimuli to differentiate into myogenic cells. Then immunologically competent T cells start an immune reaction against these newly differentiated myogenic cells. Sensitised T cells then leave the thymus and become killer T cells infiltrating the neuromuscular junction and destroying it or cooperate with B cells as helper cells to form antibodies to the AC receptor. The pathogenesis is under genetic control both at the differentiation of T cells to myogenic cells and at the stage of immune responsiveness of the lymphocytes to these atypical muscle cells.

Medical treatment

Neostigmine and pyridostigmine are the basis of the medical treatment of myasthenia gravis. Ambenonium is occasionally used. Edrophonium has no place in treatment as its action is so short. These drugs are water-soluble and hence do not cross lipid barriers readily. They are thus distributed in the extracellular space and do not enter the central nervous system. Anticholinesterase drugs are, however, in no sense a cure and have no influence on the primary cause of the disease. They act by inhibiting the action of cholinesterase, which normally destroys AC: they are active by mouth but may if necessary be given parenterally.

When given at regular intervals during the day muscle strength can usually be restored to an adequate even if not normal level.

The dose of anticholinesterase drugs that gives the maximum therapeutic response must be established. 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. The dose-response curve for anticholinesterase compounds has a rapid fall-off once the peak is reached. This may be because to some extent these agents may occupy the AC receptors and if present in excess prevent the normal action of AC. Overdosage thus not only increases the quantity of AC at the neuromuscular junction but also reduces the number of free receptors available for its effect. 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 is justified.

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 0.5 mg equals 15 mg by mouth. There are two varieties of peripheral cholinergic activity. Muscarine activity affects smooth muscle and glandular tissue while nicotinic activity affects autonomic ganglia and neuromuscular junctions. The cholinesterase inhibitors enhance both the muscarine and the nicotinic effects of AC. As muscarine activity affects smooth muscle and exocrine glands it is manifest by abdominal colic, diarrhoea, nausea, salivation, and lachrymation. Atropine may reduce these side effects. These symptoms, however, usually indicate overdosage, and for this reason it is unwise to prescribe atrophine routinely.

Pyridostigmine (Mestinon) has the advantage of more prolonged action, and it is rarely necessary to give it more often

than four-hourly. It does, however, take longer to act. A dose of 60 mg equals 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. Patients with myasthenia gravis tend to develop anxiety over the disease. Everyday activities depend on taking tablets. The patient is thus inclined to increase the 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.

NON-CHOLINESTERASE INHIBITORS

Drugs other than cholinesterase inhibitors have a place in treating myasthenia gravis. The beneficial effect of ephedrine has long been recognised, though the response is rarely striking. A dose of 30 mg, however, thrice daily should be tried if the response to anticholinesterase agents is inadequate. Hypokalaemia aggravates muscle weakness so that potassium supplements may be useful.

The response to corticosteroids is often dramatic.³⁵⁻³⁶ A good response can be expected in about half the patients. In some series patients with a longer history of myasthenia have shown the best response, while in other series patients who have not been ill so long have fared better. Transient exacerbation of myasthenia commonly precedes the improvement. Deterioration tends to occur between the first and sixth day and is usually maximal by the 10th day. Patients should therefore not be treated with corticosteroids unless there are facilities for assisted respiration. Neither deterioration nor benefit has been associated with any change in serum electrolyte concentrations. The usual dose of steroids has been about 30-60 mg of prednisolone daily. Continuous corticosteroid treatment is sometimes needed and alternate-day treatment has been advocated to avoid some of the complications of prolonged steroid treatment.³⁷ Prednisolone may be effective when ACTH has failed. By starting treatment with a small dose of prednisolone, such as 25 mg on alternate days, and gradually increasing the dose, the initial, though transient, deterioration that characterises steroid treatment in this disease may be prevented. The results reported by different observers vary, and it is not possible to make any final assessment on the various regimens that have been recommended.

We do not know why steroids are beneficial. It is unlikely to be due to their thymolytic effect as patients benefit after thymectomy. Improvement may occur after a 10-day course has been completed or during treatment. Patients on alternate day treatment report reduced strength when prednisolone is not given and this suggests that steroids facilitate the effect of AC at the neuromuscular junction in the myasthenic patient. The cause of the initial deterioration so commonly seen is difficult to explain but could be the result of enhanced effects of the cholinesterase inhibitors provoking a cholinergic crisis. Good results may occur in patients on steroids when the cholinesterase inhibitors are discontinued. It is not possible to withdraw anticholinesterases in most patients as this would result in a dangerous increase in the myasthenia. The effects of corticosteroids are often most beneficial and allow a reduction in dose of anticholinesterase drugs, and this beneficial effect may continue for many weeks after steroids have been discontinued. Complete remissions have also been recorded. Nevertheless, prolonged corticosteroid treatment should be given only to patients who have been offered thymectomy as there is increasing evidence that this operation offers the best chance of remission.

IMMUNOSUPPRESSIVE AGENTS

The increasing evidence of the immunological pathogenesis of myasthenia gravis has led to renewed interest in immuno-

suppressive agents. Thoracic duct drainage has a beneficial effect in myasthenia and improvement is maintained as long as drainage is continued.³⁸ Plasma exchange improves muscle strength in patients with severe myasthenia who have failed to respond to anticholinesterases, thymectomy, and corticosteroids,³⁹ and it seems that the beneficial effect can be maintained with subsequent immunosuppressive treatment. Probably the beneficial effects of corticosteroid treatment are partly due to immunosuppression. Certainly before prednisolone treatment there is a high cellular immunity to AC receptor while after it there is diminished cellular immunity to AC receptor.⁴⁰ Moreover, in patients who had an exacerbation after starting prednisolone treatment there was an increase in cellular immunity to the receptor. Azathioprine is an effective immunosuppressive agent but reports of its use in myasthenia are few. Swedish workers have found the drug useful.⁴¹ This beneficial effect does not appear for 6-12 weeks and reaches its zenith at 6-15 months. A favourable response was recorded in 20 of 26 patients but there were severe complications in three patients and one death.

DRUGS TO BE AVOIDED

It is important to remember that there are drugs that aggravate myasthenia. Myasthenic patients are obviously much more sensitive to the neuromuscular blocking drugs. Antiarrhythmic drugs reduce the excitability of muscle membrane and probably also inhibit neuromuscular transmission so that quinine, quinidine, procainamide, lignocaine, and propranolol should be avoided. Tonic water contains quinine, and this may be enough to upset someone with myasthenia. Antibiotics of the aminoglycoside group impair neuromuscular conduction by inhibiting the release of AC so that streptomycin, gentamicin, kanamycin, neomycin, and polymyxin should be avoided. Patients with myasthenia are sensitive to the central nervous system depressants so that drugs such as morphine and barbiturates must be used with caution.

MYASTHENIC AND CHOLINERGIC CRISES

A myasthenic crisis may result from a natural deterioration of the disease or it may be precipitated by infection or surgery. The symptoms are due to a relative deficiency of AC and may usually be corrected by 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 10 mg edrophonium intravenously will usually enable the correct diagnosis to be made. If the crisis is cholinergic no such improvement occurs, and indeed the position may deteriorate. The action of the drug is so short that any deterioration due to increased anticholinesterase activity is unlikely to have any serious consequence. One of the difficulties that may arise after edrophonium is that one muscle group may become stronger and another weaker. It is therefore important that emphasis should be placed on the essential bulbar and respiratory muscles rather than the less essential ocular and limb muscles.

VALUE OF THYMECTOMY

Thymectomy is increasingly important in managing 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. The incidence of remission increases with the number of years after thymectomy. Complete remission or substantial improvement may be expected in 80% of patients without a tumour of the thymus, though it may take three to five years before the benefits of operation are apparent.⁴² Older

patients are less likely to benefit from thymectomy but respond well to corticosteroids.⁴³ In patients with a tumour early operation is also indicated but the prognosis is worse. With the exception of those with the purely ocular form of the disease, most patients with myasthenia should be offered thymectomy. The earlier the operation is undertaken in the course of the disease the better the results.⁴⁴

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WORDS Of the four humours, believed in former times to be responsible for one's state of health, phlegm is the one most obvious to the layman, at least in its manifestation as mucus in the respiratory tract. Nasal phlegm (mucus) was thought to be a secretion of the PITUITARY gland, supposedly flowing by way of the sphenoidal air sinus into the back of the nasal cavities. *Pituita* is Latin for phlegm; hence the phlegm (producing) or pituitary gland. The pre-Harveian mind, which could postulate invisible pores in the interventricular septum through which blood flowed from right to left ventricle, would scarcely have regarded as an impenetrable barrier the thin plate of bone separating the sella turcica from the sphenoidal sinus.