Myasthenia gravis with hypergammaglobulinaemia and antibodies


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Myasthenia gravis is a disease characterized by fluctuating paresis of skeletal muscle, and often continuing weakness is present. The pathophysiology responsible for the fluctuating weakness is localized in the neuromuscular junction: most probably the basic disturbance is a defect in the (re) synthesis of acetylcholine (Desmedt, 1958, 1961). The permanent residual weakness may be due to a change in the receptor membrane of the muscle. Zacks, Bauer, and Blumberg (1962), using the electron microscope, reported some changes in the clefts of the second order. Certain electromyographic findings also point to a change in the functioning of the muscle itself. In addition to these local abnormalities, which elucidate the clinical findings, there is increasing evidence that in myasthenia gravis the immunological defence mechanism is functioning in an abnormal way. Nastuk, Plescic, and Osserman (1960) were the first to describe abnormal fluctuations in the serum complement level in myasthenic patients, and Strauss, Seegal, Hsu, Burkholder, Nastuk, and Osserman (1960), using the immunofluorescent technique with skeletal muscle, demonstrated that gamma globulin from sera of 13 of 30 patients with myasthenia was fixed to skeletal muscle.

White and Marshall (1962) found an antinuclear factor in six of 16 myasthenics. In three of these six patients the myasthenia gravis was connected with another disease which in itself could explain the presence of an antinuclear factor. Beutner, Witebsky, Ricken, and Adler (1962) found auto-antibodies against muscle in two out of 10 patients, both having a thymoma. Van der Geld and Oosterhuis (1963), van der Geld, Feltkamp, Loghem, Oosterhuis, and Biemond (1963), Feltkamp, van der Geld, and Oosterhuis (1963a) and Feltkamp, van der Geld, Kruijff, and Oosterhuis (1963b), using the sera of 118 myasthenics, demonstrated multiple antibodies in varying amounts. Antibodies against muscle tissue were present in 40% of the cases, against thyroglobulin in 35%, against thymus tissue in six of 22 cases investigated; in 10% an antinuclear factor was present, and the Rose-Waaler test was positive in 5%. These values are significantly higher than in controls matched for age and sex.

These investigations confirm Simpson's (1960) suggestion that in myasthenia gravis an autoimmune mechanism may be present. As the result of our investigations (van der Geld et al., 1963) we concluded that in myasthenia gravis there was a disturbed immunological tolerance with the production of large numbers of antibodies. Support for this view is found in several reports in the literature of cases of myasthenia gravis with hypergammaglobulinaemia. Lowenthal and van Sande (1956) reported an increase of gamma globulin in the sera of 12 of their 16 investigated myasthenics. Simpson (1960) mentions four cases of hypergammaglobulinaemia and six cases with a raised protein level in the spinal fluid in his series of 440 patients. The case of Castaigne, Lhermitte, Escourolle, Martin, and Binet (1961) had hypergammaglobulinaemia in addition to a thymoma and aplastic anaemia. De Haene and Roussel (1955) mentioned a patient with a high level of gamma globulin in the blood and spinal fluid.

We are now able to report the case histories of three patients with myasthenia gravis, who showed an increase in the gamma-globulin level in the blood serum, as detected by routine paper electrophoresis. This was an uncommon and at first unexplained finding. Later we found multiple antibodies which probably explain the abnormal level of gamma globulin in the serum. In cases 1 and 3 no other disease was present, and in case 2 any connexion with porphyrinuria is unlikely.

CASE HISTORIES

Case 1 A 57-year-old man, who had never been ill, except for attacks of malaria and a venereal disease, noticed during a period of excessive work (15 hours a day for many months), that his left arm became weak after

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a certain amount of work; three weeks later the same weakness was noted in his right arm. Moreover, after chewing one piece of bread, he could not chew any more; climbing stairs became very difficult. During that period he smoked 40 cigarettes and drank 20 cups of black coffee a day. During the first period of clinical observation his complaints diminished, but chewing remained impaired. After the injection of 1-5 mg. neostigmine intramuscularly and after oral mestinon chewing was improved. Besides the pareses of the muscles of mastication, of the deltoid, triceps, quadriceps and the long muscles of the trunk, there existed a Raynaud-like syndrome in both hands and slight hypertension (190-110 mm. Hg).

The family history showed that his father had suffered from dementia paralytica: the venereal infection had probably been acquired after the patient's birth. His sister had vague rheumatoid complaints. His two daughters had no complaints.

The laboratory investigations provided some data which were considered unusual for myasthenia gravis: high levels of gamma globulin were found in the serum and in the cerebrospinal fluid.

Paper electrophoresis of the serum (Fig. 1) showed that the gamma globulin fraction was considerably elevated (total protein 8.0 g. %), and of the cerebrospinal fluid, that the total protein level was raised (80 mg. %) with a relative increase in the gamma globulin fraction. The colloidal reactions were positive; the cell count was normal.

Immu-no-electrophoresis (Fig. 3) by the method of Peetoom (1963) showed a diffuse increase of the immuno-globulins but no paraproteins in the precipitation picture. An ultracentrifuged specimen showed diffuse increase of the immuno-globulins but no abnormal macro-globulins. Tests for cryoglobulins were positive.

The Wassermann reaction was anticomplementary in serum, but negative in cerebrospinal fluid.

The anti-globulin consumption test (A.G.C.T.) on skeletal muscle and thymus tissue (Van der Geld and Oosterhuis, 1963) demonstrated antibodies, and their presence was confirmed by a positive immunofluorescence test with skeletal muscle (Feltkamp, et al., 1963a) and with thymus tissue (Van der Geld, Feltkamp, Oosterhuis, 1964). Immunofluorescence tests with thyroid tissue and smears of leucocytes to demonstrate an antinuclear factor (A.N.F.) were negative.

Tests for L.E. cells and the Rose-Waaler test were negative. In tests for the specificity of the consumption test, extracts of heart muscle, pancreas, kidney, and liver were used with negative results. In the unconcentrated spinal fluid no antibodies could be demonstrated.

This extended analysis of the abnormal protein fractions in the blood did not lead to the diagnosis of a known disease. The conclusion was to infer the presence of an increased number of immuno-globulins and of antibodies reacting with muscle and thymus tissue.

X-ray examination of the skeleton did not show any abnormalities. The bone marrow was normal both by smear and crestal puncture. A carcinoma in the digestive tract could not be demonstrated. The first series of tomographs of the anterior mediastinum were negative. Temperature, blood cell picture, and urine analysis were
normal; creatinuria was not present. The E.S.R. was 30 mm. The values for Na, K, P, Ca, cholesterol, Mg, aldolase, phosphatases, S.G.O.T., S.G.P.T. were normal. The sputum contained no tumour cells. Renal function, a glucose tolerance test, and thyroid function were normal; the basal metabolic rate + 24% but the uptake of I131 was normal. Except for the changes in the blood proteins no arguments for liver damage were present. In a muscle biopsy from the triceps and quadriceps discrete but unmistakable infiltrations of lymphocytes were found (Fig. 4).

Although some doubt was thrown on the diagnosis of myasthenia gravis as the only disease, this diagnosis as such seemed to be probable from the clinical picture, the reactions to anticholinesterases, the typical exhaustion after exercise in the electromyogram, the increase after quinidine, and the picture in muscle biopsies. After an initial improvement the illness became gradually worse in about a year from its beginning. Ocular and bulbar muscles became further involved: the patient complained of 'a pressure on his breast' and of short attacks of dyspnoea. One night, when his wife left him alone for a short time, he went into a myasthenic crisis, in which he nearly died. In hospital his main difficulties were the sudden attacks of dyspnoea, frequently provoked by emotion. As the progressive course of the myasthenia with respiratory paralysis made it likely that a thymoma was present, tomographs of the anterior mediastinum were done after insufflation of air. Retrosternally a suspect mass was found. Although the prognosis was supposed to be poor, operation seemed to offer a last chance.

At operation a slightly lobulated tumour (weight 100 g., \(6 \times 7 \times 2\frac{1}{2} \text{ cm.}\)) was found invading the pericardium and the artery anoma. The tumour was removed whole and appeared to contain calcifications and necrosis. The microscopic picture was that of a thymoma: alternating fields of lymphocytes and reticulum cells were seen.

The post-operative course was complicated by sudden respiratory failure (a tracheotomy was done following the operation), dilatation of the stomach and haemorrhage from the digestive tract, circulatory shock with atrial fibrillation, and renal insufficiency with uraemia.

The patient died on the sixth post-operative day. Necropsy showed a post-thymomectomy condition without local haemorrhage, hypertrophy of the heart, dry pericarditis, erosion of the gastric mucosa, melaena; zonal necrosis of the liver; no occult carcinoma was present. The microscopic picture of the bone marrow, kidney, thyroid, and spleen did not reveal abnormalities. Eighteen muscles were studied microscopically and in nine of them infiltrations of lymphocytes were seen. The muscle fibres were normal. The cerebrum, brain-stem, spinal cord, and peripheral nerves were extensively studied. Several annular haemorrhages were seen, localized especially parieto-occipitally, which were interpreted as terminal.

The period of observation from the onset of the disease was two years. Antibodies against muscle and thymus tissue were present in several blood samples during the last year of the disease.

In the serum of the 56-year-old sister of the patient essentially the same abnormalities were found. In the immune electrophoresis a diffuse increase of the immune globulins was observed; the tests for antibodies reacting with muscle tissue were positive. These findings explain the increased E.S.R. of 40 mm. in one hour, which was constantly found after 1953 whenever she was seen for vague rheumatoid pains in the hands and feet, paraesthesias in the fingers, and in 1957 at the time of a radiological castration because of excessive bleeding.

The case histories of the other two patients are briefly as follows:

**Case 2** A 18-year-old young woman, working as a nurse, experienced ptosis and diplopia, followed six months later by generalized myasthenia gravis. At first the disease reacted well to neostigmine and mestinon but gradually the effect became worse. She was observed in the neurological clinic when it was clear that a generalized myasthenia gravis existed. Moreover tuberculosis of the lung was detected which responded well to chemotherapy. Only the E.S.R. was never normal and fluctuated from 30 to 90 mm. in the first hour: the fibrinogen and gamma globulin were both elevated. The myasthenia gravis underwent a partial remission but recurred when she was aged 22 years. In addition to the symptoms of a generalized myasthenia, elevation of the gamma globulin in the serum was constant: the Rose-Waaler test was positive (1:1,024) without signs of rheumatoid arthritis.

No reason for these findings could be found. The cerebrospinal fluid was not investigated. As the diagnosis of myasthenia gravis was not in doubt, thymectomy was performed four years after the onset. At operation a thymus weighing 30 g. was found, with typical reaction centres. The effect was excellent, and two months later the patient began nursing again, taking two tablets of Mestinon (60 mg.) a day. Only when she was fatigued did she complain of diplopia. In her 24th year she was readmitted because of attacks of pain in the abdomen, fever, dermatitis, and an acute hysteriform reaction.
Porphyrin was present in the urine, which appeared to be familial. In the acute stage liver function was disturbed, but soon returned to normal. Normal liver tissue was obtained by means of a liver biopsy. Afterwards she suffered from a highly resistant pyoderma with Staphylococcus aureus, finally reacting to lodermycin. The myasthenia gravis was restricted to slight ptosis and diplopia at night. At present, two years later, she is again in good health. Nevertheless the E.S.R. remains moderately elevated, probably due to the constant rise in gamma globulins in the serum, present during the eight years during which she has been under observation and remains unexplained by the pathology. In repeated blood samples during the last two years antibodies reacting with muscle, thymus, and thyroid were found (Table I). The Rose-Waaler test was positive, the titres fluctuating from 1:1,024 to 1:16.

CASE 3 A 63-year-old woman was admitted to the Wilhelmina Gasthuis on account of a tumour in the anterior mediastinum of which she had no complaints. Five years previously she had sought medical help for double vision and ptosis of the eyelids: at that time she had also noted a weakness in both arms. There was a family history of gouty arthritis and glycogen storage disease (von Gierke—van Creveld). At 50 years of age she had been treated for syphilis without clinical symptoms. While she was in hospital only a slight bilateral ptosis was observed. Physical investigations showed no abnormalities. The x-ray picture with tomography revealed a large round tumour in the anterior mediastinum, reaching the anterior chest wall. Direct puncture of the tumour gave epithelial cells. The provoked electromyogram from the m. abductor dig. V showed an abnormal decrease of the action potentials; the curare tolerance was lowered (total ptosis after 1½ mg., reacting to prostigmine).

A blood count gave 11,000 white cells/cm. with a relative lymphocytosis; liver and renal function tests were normal; mild diabetes; increased gamma globulin in the serum; lues reactions were positive (Wassermann 1:32, V.D.R.L. + Reiter +), S.L.E. tests were mildly positive (Loose body test +, S.L.E. cell test: group IV, nuclear agglutination inhibitory test: doubtful).

The diagnosis was thymoma associated with mild myasthenia gravis. Antibodies reacting with muscle and thymus tissue and an increase of the immuno-globulins were present in the serum (Table I).

### DISCUSSION

Increased gamma globulin in the serum of a patient with myasthenia gravis seems to be an uncommon finding. It has been reported several times in cases histories as an unexplained (de Haene and Roussel, 1955) or unemphasized (Castaigne, Lhermitte, Escurrolle, Martin, and Binet, 1961) feature. The significance of the four cases in Simpson’s (1960) large series is not clear. Lowenthal and Van Sande (1956) did not give clinical particulars of their 16 patients, of whom 12 showed a moderately raised gamma globulin in the blood sera.

We have to consider three possible explanations: (1) the patient had two diseases, myasthenia gravis and another disease responsible for the increase of the gamma globulin; (2) the patient had a myasthenic syndrome secondary to an underlying disease; (3) the abnormal findings in the serum belong to the myasthenia gravis and are perhaps not uncommon if adequate investigations are made.

The diagnosis of myasthenia gravis is not to be doubted in the three patients described. In the first patient extensive clinical and laboratory investigations and necropsy did not reveal a second disease except a thymoma, mild hypertension, and acrocyanosis. A systemic disease was not present; the analysis of the raised globulin fractions did not lead to a known disease. In particular M. Kahler, M. Waldenström, and systemic lupus erythematosus were excluded. The lymphorrhages in nine of the muscles are compatible with myasthenia gravis.

Neither was this the case in the third patient except for the syphilitic infection which was not considered the cause of the immunological abnormalities. In both cases 1 and 3 a thymoma was present. In combination with a thymoma acquired hypogammaglobulinaemia in adults is reported (Lambie, Burrows, and Sommers, 1957). Nevertheless, the direct relation between the thymoma and the abnormal normal gamma globulin levels of the serum remains unexplained. The second patient has demonstrated a constant elevation of the gamma globulin fraction of the serum during the eight years of observation.

### TABLE I

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<th>Muscle Antibodies</th>
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<td>Thyroid Antibodies</td>
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<td>Thymus Antibodies</td>
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This finding was independent of the associated diseases, tuberculosis and porphyrinuria. Moreover the presence of these diseases in itself is no explanation of the elevation of the gamma globulin.

The concept of the myasthenic syndrome or symptomatic myasthenia is frequently encountered in the current literature. Our opinion (Oosterhuis, 1963) is that this concept has a far more limited value than is suggested in the literature, because most cases reported as such are true myasthenia gravis associated with another (or no other) disease, or are not myasthenia gravis at all. This problem will be elaborated elsewhere.

Myasthenia gravis is a well-defined neurological illness; its nosological entity is not threatened by the very few syndromes which have some features in common with myasthenia gravis. In our first and third patient no internal or other neurological disease could be demonstrated. The occurrence of hypergammaglobulinaemia in myasthenia gravis has not been systematically investigated. Oscellman (1958) did not find abnormalities in 12 patients. In our series of 175 patients only 15 had been investigated, of whom the three described had an increased gamma globulin detected by paper electrophoresis. However, with the aid of immuno-electrophoresis in 100 patients of this series, an increased activity of the immuno-globulins was detected in 60%. Consistent with these findings multiple antibodies were demonstrated in our series (van der Geld et al., 1963).

The three patients reported here all had multiple antibodies in the sera. In the first patient a constant increase of the total protein and the gamma globulin in the cerebrospinal fluid was demonstrated: in the unconcentrated cerebrospinal fluid no antibodies were present. This finding remains unexplained, but the case of de Haene and Roussel (1955) was similar to ours in this respect. As no abnormal exogenous antigenic stimulation, for instance infection, had occurred, the constant diffuse increase of the immuno-globulins may be assumed to correspond with the synthesis of antibodies against various tissues. This phenomenon of chronic hyper-immuno-globulinaemia is also observed in several other auto-immune diseases. Important for the understanding of the relation between the serological abnormalities and the disease is the existence of the same abnormalities in the serum of the sister of the first patient who did not show signs of myasthenia gravis. Serological abnormalities in relatives are also reported in cases of systemic lupus erythematosus and other auto-immune diseases.

That these antibodies reacting with constituents of the patient's own body have no direct relation with the myasthenic lesion appears from the fact that in the second patient antibodies were found after a nearly complete remission by thymectomy; in some severely ill patients in our series no antibodies could be demonstrated. It should be noticed that the presence of circulating antibodies is probably only one aspect of the immunological disturbance. The cellular component, responsible for phenomena such as the delayed hypersensitivity, seems to be important but is difficult to investigate. Possibly the ultimate pathogenetic causes partly separated the myasthenic and the immunological lesion. The occurrence of multiple antibodies and certain clinical data fit in with the phenomena of an auto-immune disease. Further, the existence of a permanent increased immunoglobulin level of the serum supports our concept that in myasthenia gravis a dysfunction of the antibody-producing apparatus exists.

SUMMARY

Three patients are described with myasthenia gravis and hypergammaglobulinaemia; two of them also had a thymoma. No other disorder could be held responsible for this increased level of gammaglobulins. All patients had multiple antibodies, which are supposed to cause this abnormality. These findings support our concept that in myasthenia gravis a dysfunction of the antibody-producing apparatus exists.

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The thymic operations were performed by Professor I. Boerema. Radiographs of the mediastinum were taken by Dr. D. Westra. The biopsy from the first patient was taken by Dr. L. H. T. Kwee, and the neuropathology was studied by Dr. J. Bethlem; electromyography was performed by Dr. W. Hootsmans.

REFERENCES

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