Serum immunoglobulin levels in myasthenia gravis, polymyositis, and dermatomyositis¹

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SYNOPSIS Analyses of serum immunoglobulin (Ig) levels were performed in patients with myasthenia gravis, polymyositis and dermatomyositis, and in normal subjects. The mean IgG levels were elevated in the disease groups and there was minimal depression of serum IgM levels in non-thymectomized myasthenic patients. There was no consistent pattern with regard to selective immunoglobulin class abnormalities, effect of thymectomy in serial studies, and no evidence of gross humoral immunological deficiency as manifested by consistent depression of serum IgA, IgG, or IgM in the disease groups.

Polymyositis, dermatomyositis, and myasthenia gravis are diseases affecting the neuromuscular system in which an autoimmune aetiology has been postulated (Simpson, 1960; McFarlin, 1971; Penn *et al.*, 1971; Bohan and Peters, 1975). Previous studies (Diessner *et al.*, 1966; Penn *et al.*, 1971; Bohan and Peters, 1975) employed electrophoresis to roughly quantitate serum globulins. We have seen no large scale study of the levels of the major immunoglobulins measured by the more quantitative radial immunodiffusion technique (Mancini *et al.*, 1965). We report such a comparative study in these three disorders.

METHODS

SERUM Serum was obtained from patients with unequivocal adult onset myasthenia gravis, adult onset polymyositis and dermatomyositis (confirmed by elevated enzymes, biopsy and/or electromyogram), as well as from normal volunteers. The serum was stored frozen at -20°C or -70°C until time of assay. No patients had a monoclonal gammopathy on cellulose acetate electrophoresis. Patients with myasthenia gravis were divided into pre- or non-

thymectomized and post-thymectomized groups. All patients studied after thymectomy had undergone this surgery at least six weeks (and frequently years) previously. No subjects were on corticosteroids or immunosuppressive therapy.

RADIAL IMMUNODIFFUSION Serum IgG, IgA, and IgM levels were determined by radial immunodiffusion (Mancini *et al.*, 1965) employing class-specific reagents purchased commercially (Mely Laboratories, Springfield, Virginia). All sera were tested with standard plates, sera giving a result below the lowest standards were then retested with low-level high sensitivity plates from the same supplier. Undiluted sera with levels above that of the highest standard were then diluted, as was the highest standard, and subsequently restudied using the routine level plates. Any sera with levels below 2SD of normal were also analysed by Ouchterlony double diffusion (Ouchterlony, 1968) employing heavy chain-specific anti-immunoglobulin sera.

RESULTS

MYASTHENIA GRAVIS The mean levels of IgA were 192 ± 17 mg/dl in non-thymectomized subjects and 203 ± 45 mg/dl in thymectomized subjects, both not significantly different from normal subjects (Table 1). Within the total disease group IgA levels were low in one (Table 2, subject 1) and elevated in four (subjects 2, 3, and 4). Subject 2 had a mildly elevated IgA level six

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TABLE 1

SERUM IMMUNOGLOBULIN LEVELS IN MYASTHENIA GRAVIS, POLYMYOSITIS, DERMATOMYOSITIS, AND NORMAL CONTROLS

	IgG*	IgA	IgM
Normal (n=24)	1 051 ± 61	168 ± 17	190 ± 21
PM-DM† (n=19)	1 496 ± 178	232 ± 45	237 ± 49
MG† non-thymectomized (n=39)	1 197 ± 56	192 ± 17	141 ± 14
Thymectomized (n=12)	1 085 ± 84	203 ± 45	216 ± 45

* IgG, IgM, and IgA as mg/dl ± SEM:

† PM-DM: polymyositis and dermatomyositis; MG: myasthenia gravis.

TABLE 2

ABNORMAL IMMUNOGLOBULIN LEVELS IN PATIENTS WITH MYASTHENIA GRAVIS, POLYMYOSITIS, AND DERMATOMYOSITIS

Subject	IgA (mg/dl)	IgM (mg/dl)	IgG (mg/dl)
Myasthenia gravis, non-thymectomized			
1	46	74	760
2	335	94	1 500
3	350	217	1 800
4	370	88	1 300
5	300	105	2 100
6	130	360	1 350
7	270	80	1 600
8	235	170	1 500
9	280	170	1 500
10	119	480	960
11	170	42	1 200
12	175	46	1 450
13	74	40	800
14	110	150	1 500
15	200	125	2 000
Myasthenia gravis post-thymectomy			
2	700	540	1 350
3	90	140	540
6	105	360	900
16	190	115	1 500
17	87	150	570
18	200	434	1 300
19	190	32	1 200
Polymyositis			
20	42	217	920
21	780	217	2 090
22	360	70	1 500
23	210	80	2 090
24	190	80	1 800
25	360	260	1 840
26	120	90	2 000
Dermatomyositis			
27	600	750	2 090
28	285	834	3 800
29	180	105	1 900
30	430	400	430

months before undergoing thymectomy for a thymoma and had a further increase after surgery. Three other subjects were studied before and after surgery. Two showed no change in IgA levels and the third showed a significant decrease in the IgA levels (subject 3).

A slight but significant depression of the group mean IgM level was found in non-thymectomized patients with myasthenia gravis when compared with controls ($P < 0.05$). Myasthenics after thymectomy had minimally elevated levels of IgM when compared with patients who had not undergone surgery ($P < 0.05$). Four myasthenics had minimally depressed IgM levels (subjects 11, 12, 13, and 19). Three subjects with myasthenia (subjects 2, 6, and 10) had increased IgM levels. In comparing pre- and post-thymectomy IgM serum levels in patients where serum was available before and after surgery, there was a significant increase in IgM in one patient with a thymoma (subject 2), no change in one with a thymoma (subject 6), and a minimal increase, but not to abnormal levels, in two others; one with and one without thymoma at surgery.

The non-thymectomized myasthenia gravis patients had an elevated mean IgG when compared with controls ($P < 0.05$) (Table 1). The post-thymectomy myasthenic group was intermediate between the normal subjects and non-thymectomized myasthenic group, but not statistically different from either. Eight non-thymectomized myasthenic subjects had elevated IgG levels (subject 2, 3, 5, 7, 8, 9, 14, and 15). In the post-thymectomy myasthenic group there was one subject with a mild elevation of serum IgG (subject 16). One myasthenic had a borderline IgG depression of 570 mg/dl (non-thymectomized) with normal levels of IgM and IgA. Pre- and post-thymectomy levels of IgG were not significantly different in the four subjects studied.

Although elevation of serum immunoglobulin levels of all three classes studied was found in myasthenics with associated putative autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis) and thymoma, elevations to the same degree were found in myasthenics without such associations. Moreover, there were several patients with myasthenia and thymoma who had normal immunoglobulin levels. Likewise, there was no consistent pattern among the

myasthenic subjects with regard to depression of Ig levels and associated disorders such as thymoma.

POLYMYOSITIS-DERMATOMYOSITIS The mean serum IgA levels (Table 1) in the patients with polymyositis and dermatomyositis were not significantly different from the normal subjects. One patient (subject 20) with polymyositis had a depressed IgA level but no other abnormalities of IgG or IgM. Five patients with polymyositis or dermatomyositis had elevated levels of IgA (subjects 21, 22, 25, 27, and 30). In all five cases, these increases were accompanied by increases in IgG and/or IgM. The mean serum IgM level of the patients with polymyositis and dermatomyositis was higher than that of normal controls, but not significantly so. No patients in this group had a depression of serum IgM levels and three subjects within this group had elevations of serum IgM (subjects 27, 28, and 30). In no case was this an isolated increase in the serum IgM level.

The patients with polymyositis-dermatomyositis had an elevated mean IgG level when compared with controls ($P < 0.01$). One subject had a decreased serum IgG level (subject 30). Nine patients in this group had elevated serum IgG levels ranging as high as 3 800 mg/dl. In five of the nine, the IgG was the only immunoglobulin class, of those studied, that was affected. In the other four subjects, either the IgA, IgM, or both were also elevated. Among this combined polymyositis-dermatomyositis group, elevations of IgM, IgA, and IgG occurred with equal frequency among subjects with dermatomyositis and polymyositis.

NORMAL SUBJECTS Two normal subjects showed mildly depressed levels of IgA (35 and 44 mg/dl). Neither of these control subjects showed significant increases or decreases in the levels of any other immunoglobulin classes. No normal subjects had a significantly elevated IgA level. There was a modest increase in the IgM levels in three normal subjects (320; 320; and 420 mg/dl). One of these normal subjects had a mild elevation of serum IgG level as well (1 500 mg/dl). One normal subject had a minimally depressed IgM level (48 mg/dl). No normal subjects had a depression of their serum IgG levels and two had

increased serum IgG levels (1 500 and 1 700 mg/dl). As previously noted one of these subjects had an increased serum IgM, whereas the serum IgM and IgA were normal in the other.

DISCUSSION

Isolated instances of monoclonal gammopathy have been described in myasthenia gravis (Rowland *et al.*, 1969) and polymyositis (Nishikai *et al.*, 1974) and hypogammaglobulinaemia has been described in two subjects with thymoma and myasthenia (TeVelde *et al.*, 1966; Cohen and Waxman, 1967). Simpson *et al.* (1975) have recently reported depressed serum IgA levels in many patients with myasthenia gravis. Among subjects with myasthenia, patients with congenital myasthenia seemed to have the highest incidence of depressed IgA levels. Depressed IgA levels have been reported in juvenile onset myasthenia gravis by others (Bundey *et al.*, 1972). An increase in total serum gammaglobulins measured by serum protein electrophoresis has been reported in a third of patients with dermatomyositis (Diessner *et al.*, 1966; Penn *et al.*, 1971), but analysis of levels of individual classes of immunoglobulins have not been reported in polymyositis, dermatomyositis, or myasthenia gravis.

Our analysis reveals an increase in the mean IgG level in patients with myasthenia gravis and polymyositis-dermatomyositis when compared with controls. Such elevations did not seem to correlate in the myasthenic group with the presence or absence of associated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, or thymoma. The patterns of increased Ig levels were similar in patients with dermatomyositis and polymyositis. IgM levels were significantly lower in non-thymectomized myasthenics when compared with normal subjects or post-thymectomy myasthenics but the differences were minimal. The IgA levels did not differ in any of the disease groups when compared with controls. The reason for the difference between our results and that of Simpson and his co-workers (1975) may well relate to the lack of any congenital juvenile myasthenics in our patient population. In those myasthenics who were studied before and up to several years after thymectomy, no consistent pattern of change was

seen in any of the immunoglobulin classes studied. As noted previously, none of our patients had monoclonal gammopathy by cellulose acetate electrophoresis.

The pathogenic significance of elevated levels of immunoglobulin classes in these diseases is not clear. Such elevated levels are compatible with the hypothesis of autoimmune aetiology postulated by others (Simpson, 1960; McFarlin, 1971; Penn *et al.*, 1971; Bohan and Peters, 1975), but could be explained by other factors leading to the chronic inflammatory responses commonly seen in these disorders. On the other hand, there have been isolated reports of hypogammaglobulinaemia (Gotoff *et al.*, 1972; Guilliano, 1974) and a deficiency of a complement component (Leddy *et al.*, 1975) associated with polymyositis.

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