Arthritis in myasthenia gravis

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SYNOPSIS Seven patients with myasthenia gravis developed clinical signs of arthropathy. In two patients, the symptoms were due to a deforming rheumatoid arthritis and the myasthenic symptoms appeared as a transitory phase during the course of the disease. Muscle antibodies of IgG class were demonstrated with sera from both patients. Autoreactivity between muscle antibodies and rheumatoid factor was detected in one patient. Both patients died from sudden cardiac failure. Necropsy was performed in one and revealed a spotty myocardial necrosis. One patient had juvenile rheumatoid arthritis. Two patients had mild articular symptoms with indices of multivisceral disease and serological findings indicating a systemic lupus erythematosus. One patient had classical ankylosing spondylitis, and one, unspecified arthropathy.

The concept of myasthenia gravis as a pure disorder of the neuromuscular transmission has probably been an obstacle to the full delineation of the clinical picture of this disease. Thus, careful clinical examination has revealed a series of signs and symptoms connected with myasthenia gravis which cannot be attributed to the defect of transmission of the neuromuscular junction (Simpson, 1960). Some patients with myasthenia gravis develop arthritis, even to a disabling degree. The occurrence of coincidental myasthenia gravis and rheumatoid arthritis may indicate a clinical overlap (Oosterhuis and de Haas, 1968). The aim of the present paper is a reappraisal of the relationship between myasthenia gravis and arthritis. Seven patients are described and the data compared with relevant literature.

METHODS

Patients were selected from among those treated at the Department of Neurology for myasthenia gravis (MG). The numerals refer to corresponding numerals in earlier publications (Aarli and Tønder, 1970; Aarli, 1970–1972b).

The diagnosis of MG was based mainly upon the criteria given by Schwab and Perlo (1966). Clinical data are presented in Table 1.

### TABLE 1

CLINICAL DATA IN SEVEN PATIENTS WITH MYASTHENIA GRAVIS (MG) AND ARTHROPATHY

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age at onset of MG (yr)</th>
<th>Type of MG*</th>
<th>Age when first arthropathy appeared (yr)</th>
<th>Type of arthropathy</th>
<th>Other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>♂</td>
<td>51</td>
<td>IIBA</td>
<td>60</td>
<td>Classical RA</td>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>2</td>
<td>♂</td>
<td>31</td>
<td>IIBA</td>
<td>17</td>
<td>Classical RA</td>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>3</td>
<td>♂</td>
<td>18</td>
<td>IIBA</td>
<td>17</td>
<td>Juvenile RA</td>
<td>Iridocyclitis</td>
</tr>
<tr>
<td>4</td>
<td>♂</td>
<td>17</td>
<td>IIBA</td>
<td>37</td>
<td>Probable SLE</td>
<td>Bell's palsy</td>
</tr>
<tr>
<td>5</td>
<td>♂</td>
<td>22</td>
<td>IIA</td>
<td>23</td>
<td>Probable SLE</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>♂</td>
<td>47</td>
<td>I</td>
<td>20</td>
<td>Ankylosing spondylitis</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>♂</td>
<td>34</td>
<td>IIA</td>
<td>36</td>
<td>Unspecified arthropathy</td>
<td>—</td>
</tr>
</tbody>
</table>

* Classification according to Oosterhuis (1964).
The diagnosis of rheumatoid arthritis (RA) and of systemic lupus erythematosus (SLE) followed criteria given by the American Rheumatism Association (1959).

**SEROLOGICAL TESTS**

The antiglobulin consumption test (AGCT) for muscle antibodies was performed as described earlier (Aarli and Tønder, 1970). When the tissue was treated with normal human serum, a small consumption of antiglobulin serum occurred (normal consumption). A consumption four or more times greater than normal was designated 'pathological consumption' (PC) (Aarli and Tønder, 1970).

Indirect haemagglutination test (IHA) for muscle antibodies was performed using tannic acid-treated red cells sensitized with citric acid extract (CA antigen) of skeletal muscle (Aarli, 1972b).

Waaler's test for rheumatoid factor (RF) and absorption of RF were performed as earlier (Aarli, 1971b).

**DIRECT IMMUNOFLUORESCENCE (IF)**

Quick frozen myocardial tissue was stained as described previously (Thunold et al., 1973) with monospecific FITC labelled rabbit antisera against human albumin, IgA, IgG, IgM, fibrinogen, and βc/1A-globulin (C3) obtained from Behringwerke AG, Marburg Lahn, West Germany and against Clq (Thunold et al., 1970).

**HISTOLOGY**

Myocardial tissue was fixed in 10% formalin and sections were stained with haematoxylin and eosin, Elastin van Gieson, periodic acid Schiff (PAS), and Mallory's phosphotungstic acid (PTAH).

**FIG. 1 Case 1. Male, aged 72 years. Anteroposterior radiograph of hands. There is narrowing with subluxations and ulnar deviation of the MCP joints. Erosive lesions in the metacarpal heads. Slight narrowing of the PIP joints and a few erosive lesions.**

**CASE REPORTS**

*Myasthenia gravis and classical rheumatoid arthritis*

**CASE 1 (MG-3)** A male patient, born in 1903, had no family history of neurological or rheumatic disease. He was previously of good health but, at the age of 51 years, noted intermittent but increasing painless fatiguability of both legs when walking. After a few months he also developed ptosis and diplopia. On admission to the Department of Neurology in 1957, bilateral ptosis was present which disappeared temporarily after injection of edrophonium. There was nasal regurgitation of fluid. The speech fatigued easily. There was symmetrical muscular weakness without wasting. Tendon reflexes were normal and there was no sensory loss. General examination and examination of the joints revealed nothing pathological. Except for a moderate elevation of ESR (21 mm in one hour), the routine laboratory investigations were normal. Tests for RF were not performed. There was no radiographic evidence of thymoma. He was treated with neostigmine and was able to work on a dose of 225–300 mg daily, but he was severely incapacitated for several years.

During 1964, he experienced a remarkable remission of myasthenic symptoms with only a slight left-sided ptosis on upwards gaze and a moderate reduction of motor power on repeated contractions of the muscles in the forearm and hand. From the same time, however, he started suffering from pains, swelling, and stiffness in metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints in both hands. Gradually his arthritis became worse, fulfilling the criteria of definite RA.
Radiographs showed typical rheumatic destruction of finger joints (Fig. 1). From the beginning of 1972, he also suffered from cardiac insufficiency with increasing dyspnoea, crural oedema, and tachycardia. Electroconversion was performed. In 1973 he was hospitalized for acute anteroseptal cardiac infarction. He died in his home, in January 1975, from sudden cardiac failure. Necropsy was not performed.

Serological findings IgG antibodies to striated muscle were demonstrated by the AGCT (PC = 128). Antibodies to the CA antigen of skeletal muscle were not detected by IHA test (Table 2). Accordingly, his serum contained antibodies of IgG class to some other component of striated muscle.

His RF titre of 1 280 remained constant until 1974, when a significant fall in titre occurred (titre 20-40). All sera were tested simultaneously.

When the patient's serum was absorbed with homogenized human skeletal muscle sensitized with his own serum after prior treatment with mercaptoethanol to destroy 19S RF, a significant reduction of RF titre occurred (Aarli, 1971b). This indicates autoreactivity between IgG muscle antibodies and RF.

Neither LE cells nor antinuclear factors (ANF) were detected.

Case 2 (MG-1) A female patient, born in 1921, had a mother with RA. The patient had polyarthritis from the age of 17 years with increasing and severe affection of multiple joints, fulfilling the criteria of classical RA.

At the age of 31 years, she noticed that her voice became nasal when talking. She also became progressively weaker in the facial and neck muscles. During a mild respiratory infection she developed left ptosis and deglutition difficulties. These symptoms persisted after the infection had subsided.

On admission to the Department of Neurology in 1953, there was a slight left ptosis in the basal state, but bilateral ptosis developed after looking upwards for less than two minutes. Tongue and facial muscles were weak.

The clinical condition was, however, dominated by the rheumatic disorder. There was swelling and symmetrical deformity of MCP and PIP joints, with typical ulnar deviation of the hands and rheumatoid affections of several other joints. Radiographs of her joints showed rheumatoid destruction.

Subcutaneous injection of neostigmine resulted in full but transitory improvement of muscle strength. She was treated with neostigmine, later pyridostigmine, with a satisfactory control of the myasthenic symptoms. She had intermittent diplopia but no other symptoms of muscular fatigue.

There was no radiological evidence of thymic enlargement in 1953 or at later examinations.

She received gold injections, was treated with chloroquine for six years (after manifestation of MG), but was never treated with ACTH or steroids.

She died from sudden cardiac failure at the age of 52 years. The heart was removed at a partial necropsy. It was enlarged (weight 440 g) but showed no signs of valvular defects or obstructing coronary atheromatosis or thrombosis. There were no signs of old or recent infarcts. However, microscopy revealed hypertrophic muscle fibres and small areas of fibrosis (Fig. 2a). In addition, multiple focal areas of muscle cell vacuolization and necrosis were seen, often accompanied by a slight infiltration of lymphocytes and histiocytes (Fig. 2b, c). In the pericardium, small perineural lymphocyte infiltrations were found (Fig. 2d). There were no signs of vasculitis or rheumatoid granulomas. Direct IF microscopy revealed no deposits of serum proteins or complement factors.

Serological findings In 1958, a positive Waaler's test for RF was found (titre 320). Serum was not stored. On all occasions from 1966, negative Waaler's tests were recorded. A positive latex RF test was found in 1969, but was negative in 1974.
FIG. 2 Case 2. Myocardium and pericardium stained with haematoxylin and eosin. (a) (×280). Fibrotic area surrounded by slightly hypertrophic muscle fibres. (b) (×280). Muscle fibres showing degenerative changes (arrows). (c) (×280). Muscle fibres with oedema, vacuolar degeneration (arrows), and hyperchromatic nuclei surrounded by mononuclear inflammatory cells. (d) (×70). Pericardium with a perineural lymphocyte infiltrate.
Muscle antibodies of IgG class were demonstrated by the AGCT. IHA test for muscle antibodies was negative (Table 2). Numerous LE cells were demonstrated in 1969 and 1972 but not in 1968. ANF, which was not detected in 1966, was demonstrated in 1968 by IF test (homogeneous fluorescence at 1:128).

Myasthenia gravis and juvenile rheumatoid arthritis

CASE 3 (MG-6) This patient was a woman of healthy family, born in 1941. At the age of 14 years she had juvenile RA, starting with acute arthritis in the neck. In the same year she had iridocyclitis. Three months later she had pain and swelling of the left knee and right first toe as well as restricted mobility and pains in the iliosacral joints. The ESR was elevated (78 mm) and there was a slight anaemia.

Her juvenile RA gradually subsided without treatment and went into a complete clinical remission until 1965. She had then a brief exacerbation, with painful swelling in the left ankle. Later observations have disclosed no rheumatic signs.

From the age of 18 years she noticed ptosis, increasing difficulty in swallowing, and generalized muscular weakness. She was admitted to the Department of Neurology and bilateral ptosis and facial weakness were found. There was a moderate weakness of both legs without muscular wasting. The muscular weakness was promptly but temporarily removed with injection of edrophonium. She was treated with anticholinesterase drugs with excellent effect. The course of the disease varied with remissions during the last two trimesters of two succeeding pregnancies and recurrence of symptoms during the puerperium. The symptoms of MG have gradually faded and she is at present (1975) almost free from muscular symptoms.

Serological findings  Muscle antibodies of IgG class were demonstrated by the AGCT but not by IHA (Table 2). RF and ANF were not detected.

Myasthenia gravis and probable systemic lupus erythematosus (SLE)

CASE 4 (MG-20) This female patient was born in 1934 of a healthy family. Her second child was born with neonatal myasthenia. At the age of 17 years, she had transient ptosis and diplopia. For several years she only had fluctuating ocular symptoms but from the age of 33 years she also suffered from facial weakness, deglutition, and speech difficulties and fatiguability when walking for a while. Radiography gave no evidence of thymoma. A diagnosis of MG was made in 1966 and treatment with pyridostigmine commenced. After a period with serious myasthenic symptoms, the weakness gradually faded and she became able to manage on a low dose of pyridostigmine.

In 1967 she had a left peripheral facial palsy of Bell's type with spontaneous recovery.

From the age of 37 years she had had migrating arthralgia with painful swelling and limitation of movements in various joints (PIP, shoulder, elbows). She also had periodic fever of unknown origin. On clinical examination, she presented synovitis in the second and fourth PIP of the left hand.
Arthritis in myasthenia gravis

22 years. She developed transient ptosis and diplopia. An edrophonium test was positive and she was treated with anticholinesterase drugs, at first with good response but with decreasing effect during the next months. A thymectomy was performed at age 23 years. Histology showed thymic hyperplasia but no thymoma. She had a short course of ACTH two months after the operation with moderate effect. Before she noticed the muscular weakness, she had periods with arthralgia. During improvement of myasthenic symptoms, she noticed swelling of both ankles, PIP and MCP joints of second and third fingers of both hands. She also had haematuria. There was a slight enlargement of the thyroid gland. Renal and thyroid functions were normal.

Serological findings Muscle antibodies of IgG class were detected by the AGCT but not by IHA. Numerous LE cells were detected on several occasions and ANF was demonstrated (titre 512). There was a false positive Wassermann reaction. RF and thyroid antibodies were not detected.

Myasthenia gravis and ankylosing spondylitis

Case 6 (MG-28) This man was born in 1922. From the age of 20 years he noticed the first symptoms of ankylosing spondylitis with increasing low back pain and progressive stiffness of the spine. Radiographs showed iliosacral arthritis (Fig. 3) and extensive ligamentous calcification (Fig. 4). He received x-ray treatment and later indomethacin. Nonetheless, the disease progressed.

From the age of 47 years he noticed diplopia and bilateral ptosis. The ocular symptoms fluctuated during the day and disappeared temporarily after injection of edrophonium. His myasthenic symptoms were confined to the extraocular muscles. No thymoma was demonstrated on radiological investigation. Renal and thyroid functions were normal.

Serological findings Muscle antibodies, RA and ANF were not detected.

Myasthenia gravis and unspecified arthralgia

Case 7 (MG-32) A female patient, born in 1937, noticed from the age of 34 years, intermittent diplopia and weakness of both shoulders and legs. An edrophonium test was positive and she received anticholinesterase medication with excellent effect. There was a total clinical remission during pregnancy but the disease recurred during the puerperium.

From the age of 36 years, she had migrating arthralgia and intermittent swelling of small joints of the hands and feet. Clinical examination, however, has on several occasions revealed no sign of

Serological findings Muscle antibodies were not detected by IHA or AGCT. LE cells, which were not found in 1967, were present in several specimens in 1974. ANF was demonstrated in 1974 but not in 1967. Serum values of C 3 and C 4 were depressed and there was a leucopenia with 1 800 cells/mm³. RF and thyroid antibodies were not detected.

Case 5 (MG-25) A female patient, born in 1947, noticed weakness in arms and legs from the age of

FIG. 4 Case 6. Lateral radiograph of lumbar spine, showing moderately advanced ossification deep to the anterior longitudinal ligament. Advanced osteoporosis.
synovitis. Radiographs revealed no signs of thymoma. Renal and thyroid function were normal.

**Serological findings** Muscle and thyroid antibodies, RF and ANF have not been detected.

**DISCUSSION**

Seven patients with myasthenia gravis (MG) developed clinical signs of arthropathy. One of these had ankylosing spondylitis and one arthralgia without objective signs of arthritis. The other five patients all showed clinical signs of polyarthritis.

The degree of polyarthritis varied from a slight, non-deforming articular affection to a manifest and deforming rheumatoid arthritis (RA) in two of the patients (case 1 and 2). The course of the rheumatoid disease was, from the start, progressively destructive, advancing to an incapacitating stage with ankylosis and severe deformation of several joints. With both patients, the diagnosis was a definite RA, with the modification that high concentrations of LE cells were demonstrated in the serum of case 2.

In these two patients, the myasthenic symptoms were a transitory clinical phase during the development of rheumatoid disease. As the articular symptoms progressed, the myasthenic weakness became less prominent. Similar amelioration of myasthenic symptoms in connection with the appearance of RA has been reported by Oosterhuis and Haas (1968). Another case of regression of myasthenic symptoms during the development of RA is reported by Storm-Mathisen (1961).

Serum from case 1 contained both IgG muscle antibodies and RF. In an earlier study, evidence for autoreactivity between the muscle antibodies and RF was presented. Furthermore, RF was also demonstrated in eluates prepared from muscle tissue sensitized with autologous serum (Aarli, 1971b). These results indicate *in vitro* autoreactivity. The titre reduction of RF observed in case 1 during 1974 may therefore represent *in vivo* binding of RF to skeletal muscle tissue.

The muscle antibodies in sera from cases 1 and 2 reacted with skeletal as well as heart muscle. Such cross-reactivity was first described by Beutner et al. (1962). A recent theory postulates that muscle antibodies may be indicators of autoimmune muscle disease (Dawkins and Zilk, 1975). Case 2 died from sudden cardiac failure and necropsy revealed an enlargement of the heart. There were no signs of rheumatoid myocarditis. The histological findings were a spotty myocardial necrosis accompanied by a mild inflammatory reaction—a common lesion in myasthenia gravis (Russell, 1953; Jenkins et al., 1961). However, IF did not reveal antibody protein or complement factors within the myocardial lesions.

The relationship between muscle pathology and muscle antibodies is not clarified. Beutner et al. (1965) have described *in vivo*—binding of gamma-globulin only to the sarcolemmal–subsarcolemmal region of skeletal muscle fibres from patients with MG. The concomitant histological lesion was abnormally large numbers of subsarcolemmal nuclei. But this phenomenon was observed only when the IHA test for muscle antibodies was positive. Antibodies of this type are probably directed towards antigens in the sarcolemmal/subsarcolemmal region (Aarli, 1972a). Such antibodies were not demonstrated in sera from case 1 and 2.

Several patients with concomitant MG and RA are reported in the literature. Sera from a number of these patients are reported to give negative reactions in IF or IHA tests for muscle antibodies (Downes et al., 1966; Szobor et al., 1969; Durance, 1971). Recent reports have shown that the AGCT also detects antibodies to other muscle antigens (Aarli and Tønder, 1970; Aarli, 1972b). Therefore, the specificity of the muscle antibodies in MG patients who develop RA seem to differ from that described in other MG patients.

It has been discussed whether the arthritis occurring in MG represents RA or a different form of polyarthritis (Simpson, 1960, 1964). The results of the present study clearly show that both definite RA and juvenile RA (case 3) may develop during myasthenia. There are, however, forms of arthropathy, seen in MG (case 7) which are probably not of rheumatoid nature.

In the two patients with SLE (cases 4 and 5) the articular symptoms were mild. In both patients, MG preceded the SLE by several years. The initial symptoms were from extrinsic ocular muscles, a finding indicating that the muscular symptoms were not due to a polymyositis. It is of
interest that one of these patients (case 4) gave birth to a child with neonatal myasthenia. In both patients, the myasthenic symptoms gradually faded as indices of SLE appeared. Both exacerbation and remission of muscular symptoms during development of SLE have been reported by several authors (Harvey et al., 1954; Alarcón-Segovia et al., 1963; Goldin and Robbins, 1963; Piemme, 1964; Oosterhuis and de Haas, 1968). Thymectomy was performed in case 5 without influencing the course of SLE.

The progression of MG in case 6 resembled that of case 2. The former developed a classical ankylosing spondylitis. During the disease, he had a period with myasthenic, edrophonium-sensitive ocular symptoms followed by spontaneous remission of the muscular symptoms. Coexisting ankylosing spondylitis and MG is also reported by Simpson (1960). The data are however, insufficient to exclude the possibility of this being a pure coincidence.

To summarize, arthritis may develop during the course of MG. The clinical and serological data demonstrate a close relationship between the two disorders. In some patients, the articular symptoms indicate the development of RA. In other patients, the myasthenia may be a prelude to SLE. In still other patients, unspecified arthralgia occurs, where only the future clinical development may reveal the definite diagnosis.

REFERENCES


