EXTENDED REPORT

Anti-signal recognition particle autoantibodies: marker of a necrotising myopathy

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Objective: To elucidate the clinical importance of the anti-signal recognition particle (SRP) autoantibody in patients with myositis.

Methods: Retrospective systematic assessment of the clinical, laboratory and histological characteristics of 23 anti-SRP-positive patients from six European centres. Data were compared with a large group of anti-SRP-negative patients with myositis published previously.

Results: Clinically, patients with anti-SRP autoantibodies often had a severe symmetric proximal muscle weakness resulting in marked disability, dysphagia and highly elevated levels of serum creatine kinase. Three patients had typical dermatomyositis rashes. The disease was associated with the occurrence of extramuscular signs and symptoms including interstitial lung disease. No association was found with an increased risk of cardiac involvement, and the disease carried a reasonably favourable prognosis with most patients responding to treatment. None of the patients had the typical histological features of myositis. Most muscle biopsy specimens showed the presence of necrotic muscle fibres and no inflammatory infiltrates.

Conclusions: Anti-SRP autoantibodies are associated with a syndrome of a necrotising myopathy in the spectrum of immune-mediated myopathies that differs from typical polymyositis. Further studies are needed to elucidate the pathogenesis and to clarify the role of the anti-SRP autoantibodies in this unique disease.

Defined autoantibodies are detected in about 50% of patients with myositis and are traditionally divided into myositis-specific autoantibodies and myositis-associated autoantibodies, the myositis-associated autoantibodies also occurring in autoimmune diseases without the presence of myositis.[1] One of the myositis-specific autoantibodies is the anti-signal recognition particle (SRP) autoantibody, which is directed against components of the signal recognition particle.[2]

Earlier studies suggested an association between anti-SRP autoantibodies and the presence of an acute and severe form of polymyositis with cardiac involvement, a poor response to immunosuppressive treatment and an increased mortality.[3–6] Others confirmed the presence of a relatively aggressive disease, but cardiac involvement was not found.[7] In a recent study, Miller *et al*[8] described the clinical and pathological features of seven patients with anti-SRP autoantibodies. They concluded that anti-SRP is associated with an immune-mediated necrotising myopathy and not with polymyositis, characterised by a rapidly progressive severe proximal muscle weakness with an incomplete response to corticosteroids and no clinical signs or symptoms suggestive of multiorgan involvement. Furthermore, they found a predilection for the disease to start in the autumn. Kao *et al*[9] were unable to confirm several of Miller's observations. In contrast with Miller *et al*,[8] their patients did not have a large number of necrotic muscle fibres, nor was there a clear seasonal onset. Furthermore, they found multiorgan involvement in 25% of their patients.

To elucidate whether anti-SRP is associated with a specific form of immune-mediated myopathy, we analysed the clinical and histological data of the largest group of anti-SRP-positive patients to date in a systematic manner and compared this group with a large group of patients with myositis published previously.[7]

PATIENTS AND METHODS

Patients and patient evaluation

Serum samples were collected from 417 patients with myositis from several European neurological and rheumatological institutes. The autoantibody profile of this large group has been reported previously.[1] In addition, serum samples were collected from all patients with myositis seen between 2000 and 2003 at the Neuromuscular Centre Nijmegen, Nijmegen, The Netherlands. All patients with anti-SRP autoantibodies were included in the study. In total, 27 patients were included from various European countries (Czech Republic three, Greece five, Italy five, The Netherlands eight, Slovenia one, Sweden two, Switzerland one and UK two).

Before the collection of clinical data a standardised questionnaire was devised, and all evaluators agreed on study definitions and conventions for evaluation. The questionnaires were sent to the treating doctors and included detailed clinical and laboratory information. Clinical data of all patients presenting to the Neuromuscular Centre Nijmegen (n = 8) were obtained by questioning and examining the patients, reviewing their charts and consulting their treating doctor. Fifteen questionnaires were returned of the 19 included non-Dutch patients, thus making a total of 23 anti-SRP-positive patients. Whenever possible, muscle biopsy specimens were sent to the Neuromuscular Centre Nijmegen for evaluation by an experienced pathologist (HJtL) and for additional staining if indicated and feasible. Stains included haematoxylin–phloxine, myofibrillar ATPase, acid phosphatase, trichome stain and the following immunohistochemical stainings: membrane attack complex (MAC), human

Abbreviations: HLA, human leucocyte antigen; ILD, interstitial lung disease; MAC, membrane attack complex; SRP, signal recognition particle

leucocyte antigen (HLA)-ABC, CD8 and CD68. Necrotic fibres were identified on haematoxylin–phloxine staining (paling of the cytoplasm and absence of basophilia) and on subsequent MAC staining. The presence of necrotic fibres was semi-quantitatively assessed as follows: −, 0; +, <4; ++, 4–40; +++, >40 necrotic fibres in the muscle biopsy specimen consisting of approximately 500–1000 fibres.

Control group
Whenever possible, data were compared with those from a large group of patients with myositis published previously.[7] This group of 125 patients included five patients with anti-SRP autoantibodies; all other patients had negative test results for this autoantibody. These anti-SRP positive patients were excluded from the comparator myositis group.

Serological assay
The presence of anti-SRP autoantibodies was determined by immunoprecipitation and dot blot analysis as described previously.[1] Immunoprecipitated RNA, recovered after phenol/chloroform extraction, was spotted on to Hybond N+ membranes (Amersham, Buckinghamshire, UK). After drying and ultraviolet crosslinking, the dot blots were hybridised with radiolabelled anti-sense 7 SL RNA in a hybridisation mix (6× saline sodium citrate, 10× Denhardt's solution, 0.1% sodium dodecyl sulphate, 100 µg/ml denatured herring sperm DNA). After overnight incubation at 65°C, membranes were washed three times with 0.1× saline sodium citrate/0.1% sodium dodecyl sulphate at 65°C and exposed to a Kodak X-Omat AR imaging film (Eastman Kodak, Rochester, New York, USA).

Statistical analysis
Discontinuous grouped data were analysed by χ^2 frequency distribution. Fisher's exact test was used in cases of a predicted frequency $\leqslant 2$. Continuous data were analysed using the Wilcoxon Mann–Whitney U test. A p value <0.05 was considered significant. Patients whose data for a particular variable were not available were excluded from the analysis of that variable, and the number used for the calculation of percentages was adjusted accordingly.

RESULTS
Diagnosis
The clinical data of 23 patients with autoantibodies directed against components of the SRP were analysed. Three patients were diagnosed with dermatomyositis, whereas all other patients were diagnosed with polymyositis. All three patients with dermatomyositis had typical dermatomyositis rashes (heliotrope rash and Gottron's sign).

Demographic data
The average age at disease onset was 47.7 years, which did not differ from that in the comparator myositis group (table 1). As in the comparator myositis group, there was a clear female predominance in the anti-SRP group (table 1). Two of the 23 patients had a malignancy in their medical history (breast cancer and suspected gynaecological cancer), and one patient used potentially myotoxic drugs at the time of presentation (simvastatine and renitec).

Clinical signs and symptoms
Patients with anti-SRP autoantibodies had dysphagia and severe muscle atrophy significantly more often ($p<0.02$) and associated rheumatic diseases less frequently ($p<0.02$) than patients in the comparator myositis group (table 1). Other signs and symptoms did not differ significantly between the anti-SRP-positive patients and the patients in the comparator myositis group.

Table 1 Clinical characteristics of anti-signal recognition particle (SRP)-positive patients compared with a large group of anti-SRP-negative patients with myositis[7]

Characteristics	Anti-SRP patients (n = 23)	Anti-SRP-negative patients with myositis (n = 120)	Significance
Demographic data			
Age at onset (years)	47.7	47.9	NS
Sex (F:M)	3.6:1	2.4:1	NS
Signs and symptoms			
Dry eyes/mouth	8	16	NS
CTS	10	16	NS
Dysphagia	69	43	p<0.02
Oedema	17	8	NS
Dyspnoea on exertion	34	38	NS
Chest pain	8	4	NS
Arthralgia	39	42	NS
Arthritis	13	22	NS
Raynaud's phenomenon	26	26	NS
Muscle atrophy	70	30	p<0.02
Myalgia	66	51	NS
Interstitial lung disease	21	19	NS
Associated disorders			
Rheumatic disorders	0	12	p<0.02
Laboratory investigations			
Normal EMG	4	6	NS
CK	6872 U/l	1535 U/l	p<0.001
Treatment response (clinical)			
Complete	26	15%	NS
Partial	60	70%	NS
None	13	14%	NS

CK, creatine kinase; CTS, carpal tunnel syndrome; EMG, electromyography; F, female; M, male.
Numbers are percentages of the total with exception of age at onset, sex and CK.

Muscle symptoms
Of the 23 patients, 22 had marked muscle weakness. The muscle weakness was symmetric in all cases and the proximal muscles were clearly more affected than the distal ones. The disease was rapidly progressive in all patients, with an average time to maximum disability of 6 months. Of the eight Dutch patients, one became bedridden, two were unable to stand, three were barely able to walk, one could walk a few hundred yards and one had severe exercise intolerance due to ILD.

Cardiopulmonary involvement
Dyspnoea on exertion was present in half of the patients, whereas palpitations, signs or symptoms suggestive of heart failure and chest pain were found in <20% of patients.

Ancillary investigations disclosed the presence of cardiomegaly in one patient, who was also diagnosed with interstitial lung disease (ILD). Electrocardiogram abnormalities were found in more than half of the patients who underwent this test. Abnormalities most often consisted of signs of prior myocardial infarctions in patients known to have coexisting coronary artery disease. Four other patients had asymptomatic conduction abnormalities (first-degree atrioventricular block (n = 1), sinus tachycardia (n = 1), ventricular extrasystole (n = 1), elongated PQ interval (n = 1)), and two patients had signs of left ventricular strain secondary to hypertension. The cardiac ultrasound was abnormal in 6 of the 12 patients who underwent an ultrasound. A hypokinetic left ventricle was seen in three patients secondary to myocardial infarctions, two patients had minor valve abnormalities and one patient had a reduced ejection fraction with traces of pericardial fluid. The patients

with reduced ejection fraction had signs of cardiac ischaemia on electrocardiogram, with clinical signs and symptoms suggestive of cardiac failure.

Almost half of the patients had an abnormal chest *x* ray, mostly consisting of abnormalities suggestive of ILD. In 75% of the cases, this diagnosis could be substantiated by high-resolution computed tomography. More than half of the patients had an abnormal pulmonary function test, usually a restrictive pattern secondary to muscle weakness. Six patients had a decreased carbon monoxide diffusion capacity consistent with the diagnosis of ILD.

Overall, 21% of the patients were diagnosed with ILD, whereas a diagnosis of myocarditis or pericarditis was not made in any of the patients.

Histopathology

A total of 15 muscle biopsy specimens were evaluated (table 2). Muscle biopsy specimens of seven patients were not available for evaluation and biopsy had not been performed in one patient. All muscle biopsies had been performed during the initial diagnostic investigation. Myopathic features were seen in almost all biopsy specimens. Atrophy of muscle fibres was not confined to any particular region of the fascicle or to a specific fibre type. Swollen capillaries were present in 85% of the biopsy specimens, whereas compact cellular inflammatory infiltrates were never found. Necrotic muscle fibres with or without myophagia were present in most patients, whereas they were absent in only four of the 15 biopsy specimens examined. Positive staining of the sarcolemma with HLA-ABC was not seen in any of the muscle biopsy specimens and endomysial fibrosis was encountered only sporadically. Deposition of MAC was only found in necrotic muscle fibres but not in the capillaries. None of the biopsy specimens showed features suggestive of pipe stem capillaries.

Treatment and prognosis

The disease was responsive to immunosuppression and immunomodulation in almost all patients. The treatment response in general did not differ significantly from that of the comparator myositis group (table 1). Most patients were treated with corticosteroids combined with other immunomodulators. Only two patients were treated with prednisone alone. Other drugs or treatments used were methotrexate (n = 15 patients), azathioprine (n = 11), ciclosporin (n = 5), intravenous immunoglobulins (n = 5), cyclophosphamide (n = 2) and plasmapheresis (n = 2). Hardly any patient became drug free. At the time of the study, 19 of the 23 patients were still being actively treated. In general, the relapse rate on tapering of dosages or stopping of drugs was high (70%).

Most patients had a fairly good clinical recovery, although most still had residual muscle weakness. At the time of the study, 75% had a (near) normal walking pattern. Of the 23 patients, 5 had died, on average 12 years after the myopathy was diagnosed. Death was clearly not associated with the inflammatory myopathy in three patients and possibly associated in two (one patient who had ILD died of pneumonia and one patient who had a severely reduced walking distance and breast cancer died of a pulmonary embolism).

DISCUSSION

To elucidate whether anti-SRP autoantibodies are associated with a specific form of myositis, we analysed the clinical and histological data of the largest group of anti-SRP-positive patients to date. Several interesting conclusions can be made, keeping the retrospective nature of the study in mind.

Clinically, the disease had a rapidly progressive course and caused severe disability within months, with most patients barely able to stand, let alone walk. Dysphagia was a prominent symptom and serum creatine kinase levels were highly elevated. The disease was responsive to immunosuppression and immunomodulation, and patients in general had a moderate to good recovery. Treatment seemed to be needed for a long time (years) because most patients studied were not drug free and the relapse rate was high, although not significantly different from polymyositis and dermatomyositis in general.[10]

None of the patients studied was diagnosed with any other inflammatory connective tissue disorder. ILD was present in almost one quarter of the patients, thus not differing from polymyositis and dermatomyositis in general.[11] The type and frequency of abnormalities on the electrocardiogram was comparable to that found in a large series of patients with polymyositis and dermatomyositis.[12]

Muscle biopsy showed the presence of a necrotising myopathy. The typical histological features of myositis (presence of inflammatory infiltrates and positive HLA-ABC staining of the sarcolemma) were absent.[13 14] Necrotising

Table 2 Characteristics of muscle biopsy specimens of 15 patients with anti-signal recognition particle autoantibodies

	Patient														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	48	32	31	38	53	56	61	55	33	57	63	44	40	47	62
Sex	M	F	F	F	F	F	M	M	F	F	F	M	F	F	F
Country	GR	GR	GR	GR	GR	NL	NL	NL	NL	NL	NL	S	S	CZ	CZ
Necrotic fibres	+++	+	−	++	+	++	++	++	+	++	+++	+	−	−	−
Necrotic fibres with myophagia	+++	−	−	++	−	+	−	+	−	+	++	+	−	−	−
Basophilic fibres	+++	−	+	−	++	++	++	++	+	+++	+++	++	−	−	−
Swollen nuclei	+	ND	+	ND	+	+	+++	+	−	++	+++	−	−	+	+
Swollen capillaries	+	ND	+	ND	+	++	+++	+	+	++	++	−	−	+	+
Pipe stem capillaries	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
% Internal nuclei	10	0	16	3	2	2	8	13	15	9	3	21	4	4	1
Fibre splitting	−	−	+	−	−	−	−	+	−	−	+	−	−	−	−
Atrophic fibres	+++	−	−	+	+++	++	++	+	+	++	+++	+	+	−	+
Hypertrophic fibres	+++	−	+	++	+	−	+	++	+	+	−	+	+	+	+
Endomysial fibrosis	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Cellular infiltration	−	+	−	−	+	+	−	−	−	−	−	−	+	−	−
CD8	ND	ND	ND	ND	ND	−	−	+	−	−	++	ND	ND	ND	ND
CD68	ND	ND	ND	ND	ND	+	−	++	−	−	+++	ND	ND	ND	ND
MAC	ND	ND	ND	ND	ND	+	−	++	+	−	+++	ND	ND	ND	ND
Sarcolemmal HLA-ABC	ND	ND	ND	ND	ND	−	−	−	−	−	−	ND	ND	ND	ND

CZ, Czech Republic; F, female; GR, Greece; HLA, human leucocyte antigen; M, male; MAC, membrane attack complex; ND, not done or not measured; NL, The Netherlands; S, Sweden; −, normal or not present; +, slightly increased; ++, moderately increased; +++, very increased.

myopathies occur most often as a paraneoplastic phenomenon or as secondary to myotoxic drugs or toxins.[15] Several muscle biopsy specimens in our study showed diffuse staining of the necrotic muscle fibres with antibodies to MAC as has been described for paraneoplastic necrotising myopathy.[16] In our study, only two patients had a neoplastic disease and only one patient had used drugs associated with a myopathy (in this particular patient cessation of the drug did not stop the progression of the disease, thus making the diagnosis of a drug-induced myopathy unlikely).

A few cases have been published of patients with a necrotising myopathy who responded more or less favourably to immunosuppressive drugs.[17] Inflammatory infiltrates were not found in the muscle biopsy specimens of these patients, and in some of these cases signs and symptoms suggestive of an inflammatory connective tissue disorder were present.[17] The disease was named ''necrotising myopathy with pipe stem capillaries'' because the capillaries had thick walls with accumulation of periodic acid Schiff-positive material and a small lumen. Furthermore, microvascular deposits of MAC were present. None of our patients with anti-SRP autoantibodies had capillary abnormalities suggestive of pipe stem capillaries, and none of the muscle biopsies showed capillary deposition of MAC. Therefore, the necrotising myopathy seen in our patients with anti-SRP autoantibodies seems to be a distinct disease entity. The clinical syndrome of the described patients with necrotising myopathy with pipe stem capillaries also differs from that seen in our anti-SRP-positive patients with a relatively mild myopathy, and marked extramuscular involvement in the few patients who have been described in the literature so far.[17 18]

Three anti-SRP-positive patients were diagnosed with dermatomyositis. The observation of anti-SRP autoantibodies in dermatomyositis and the presence of these autoantibodies in systemic sclerosis have been reported before.[1 5 7 9] Whether this implies that anti-SRP autoantibodies can be formed in several distinct disorders resulting in muscle fibre necrosis is unknown. However, it does illustrate that anti-SRP autoantibodies are not solely seen in polymyositis-like disorders.

The presence of a disease-specific autoantibody and a favourable response to immunosuppressive and immunomodulating agents suggest an immune-mediated pathogenic mechanism underlying the anti-SRP myopathy despite the absence of clear inflammation. On the basis of the findings of deposition of MAC in capillaries, a reduction in the capillary density and an increase in endomysial connective tissue, it has been suggested that the myopathy is secondary to multifocal ischaemia.[8] We were unable to confirm these observations, with the exception of the presence of swollen capillaries.

The major shortcoming of our study is the large amount of missing data, caused by the retrospective design. Diagnostic investigation of extramuscular manifestations was not routinely performed but was guided by clinical judgement. Hence, subclinical extramuscular involvement could have remained unnoticed. Histological data were available only for two thirds of the included patients although no other selection bias had occurred other than availability. Furthermore, treatment responses could not be defined using quantifiable outcome measures such as standard muscle strength measurements because this was not the routine in daily practice in all participating centres. Nevertheless, the study does provide a useful descriptive view of a rare disorder that differs strongly from regular myositis. The pathogenesis of this disorder, which probably should be placed in the spectrum of immune-mediated myopathies, is unclear. Further, preferably prospective studies are needed to fully define the disease and to elucidate the pathogenesis, including the role of the anti-SRP autoantibodies.

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