研究用

EUROLINE Autoimmune Inflammatory Myopathies 20 Ag (IgG)
EUROLINE Cytoplasm profile 13 Ag (IgG)

Specificity, sensitivity and prevalence: In a study performed at the University of Uppsala, Sweden, 153 sera from patients with clinically characterised myositis (50 patients with dermatomyositis, 89 patients with polymyositis, 4 patients with juvenile dermatomyositis and 10 patients with inclusion body myositis) as well as 77 sera from control patients (26 patients with Sjögren's syndrome, 26 patients with SLE and 25 patients with systemic sclerosis) were tested for antibodies against Mi-2β, Ku, PM-Scl100, Jo-1, PL-7 and PL-12. The prevalence values ranged between 3% and 12%, with a specificity for myositis of 97% to 100%. The total detection rate for antibodies against Mi-2β, Ku, PM-Scl100, Jo-1, PL-7 and PL-12 in the myositis panel was 26%.

Anti-	Prevalence	Specificity
Mi-2β	3%	100%
Ku	3%	97%
PM-Scl100	7%	100%
Jo-1	12%	100%
PL-7	2%	100%
PL-12	0%	100%

A further study carried out at the University of Padua, Italy, showed similar results. In the investigation of 208 sera from patients with clinically characterised myositis and 214 sera from control patients (50 healthy persons, 13 patients with non-autoimmune myopathy, 23 sera from patients with CTD-associated myopathy, 65 patients with SLE, 34 patients with systemic sclerosis, 21 patients with primary Sjögren’s syndrome, 8 patients with arthropathies) prevalence values of 4% to 21% were obtained, with a specificity for myositis of 95% to 100%. The total detection rate for antibodies against Mi-2β, Ku, PM-Scl100, Jo-1, PL-7 and PL-12 in the myositis panel was 37%.

Anti-	Prevalence	Specificity
Mi-2β	4%	98%
Ku	5%	95%
PM-Scl100	4%	100%
Jo-1	21%	100%
PL-7 or PL-12	4%	100%

In another study 194 patients with SLE, 131 patients with systemic sclerosis, 179 patients with polymyositis/dermatomyositis (PM/DM) and 50 patients with rheumatoid arthritis (RA) were examined for antibodies against SRP, EJ, OJ and PM-Scl75. The prevalence of antibodies against SRP was 4%, at a specificity for myositis of 99%. The prevalence values for antibodies against EJ, OJ and PM-Scl75 in the myositis and systemic sclerosis panel ranged between 1% and 6%, with a specificity for these diseases of 98% to 100%.

Anti-	Prevalence	Specificity
SRP	4%	99%
EJ	1%	100%
OJ	1%	100%
PM-Scl75	6%	98%

Sera from 264 patients with clinically characterised myositis and 120 controls were tested for antibodies against Mi-2α, MDA5, NXP2 and SAE1. The prevalences ranged from 2% to 7%, with a specificity for myositis of 100%. The overall prevalence for antibodies against Mi-2α, MDA5, NXP2 and SAE1 in the panel of myositis patients was 14% (38/264).

Anti-	Prevalence	Specificity
Mi-2α	7%	100%
MDA5	2%	100%
NXP2	2%	100%
SAE1	4%	100%

In a further study 10 anti-TIF1γ positive sera, which had been precharacterised using immunoprecipitation, and 120 sera from controls were tested for antibodies against the TIF1γ antigen. The sensitivity was 100% (10/10) in comparison with the reference test. All patient samples from the 120 controls were negative.

In the framework of a further study, sera of 197 patients with inclusion body myositis (IBM), 175 patients with different collagenoses (PM/DM, mixed collagenoses, undifferentiated collagenosis, systemic sclerosis, SLE, primary Sjögren's syndrome) and 161 healthy blood donors were investigated for antibodies against cN-1A. There were prevalences of 35% in IBM and 11% in the collagenoses panel.

Disease	Prevalence of antibodies against cN-1A	
	Serum samples	Anti-cN-1A positive (%)
Inclusion body myositis	197	35
PM/DM	52	8
Mixed collagenoses	3	0
Undifferentiated collagenosis	18	11
Systemic sclerosis	27	11
SLE/primary Sjögren's syndrome	75	13
Healthy blood donors	161	2

In a study with 1194 patients with interstitial lung disease (ILD), prevalences of 2.0 to 6.1% were determined for antibodies against the aminoacyl-tRNA synthetases Ha, Ks or Zo. In a panel of 152 healthy blood donors the specificity of the EUROLINE for these antibodies was 100%.

Anti-	Prevalence		Specificity
	n = 131 ILD with connective tissue disease	n = 1063 ILD without connective tissue disease	n = 152 healthy blood donors
Ha	3.8%	4.0%	100%
Ks	2.3%	2.0%	100%
Zo	6.1%	2.5%	100%

Antibodies against Ro-52: Sera from 591 patients with rheumatic autoimmune diseases, from 260 patients with autoimmune and infectious liver diseases and from 50 healthy blood donors were tested for antibodies against Ro-52 using EUROLINE. Antibodies against Ro-52 are not associated with a specific disease, but they can be found in both autoimmune and infectious diseases with a prevalence of 5% to 81%.

Sample cohort	Prevalence of antibodies against Ro-52	
	Serum samples	Anti-Ro-52 positive (%)
Sjögren´s syndrome	88	81
Systemic sclerosis	81	28
Myositis	26	31
SLE	210	38
MCTD	21	19
Rheumatoid arthritis	165	5
Primary biliary cholangitis	100	27
Autoimmune hepatitis	60	35
Hepatitis B	50	10
Hepatitis C	50	22
Healthy blood donors	50	0

Clinical significance

Idiopathic inflammatory myositis (IIM) is a rare autoimmune disease of the skeletal musculature. There are different types of the disease: polymyositis, dermatomyositis, inclusion body myositis, necrotising myositis, anti-synthetase syndrome and overlap syndromes, that is, myositis combined with another autoimmune disease. The clinical manifestation of myositis mainly involves the skin, muscles and lungs. Around 10% of IIM cases are associated with a malignant tumour [1-7].

Symptoms of **polymyositis (PM)** are proximal muscle weakness, fever episodes, joint aches, Raynaud's syndrome and dysphagia. PM occurs more frequently in adults than children and accounts for around 5% of myositis cases [5, 6, 8].

Classic **dermatomyositis (DM)** manifests as symmetric proximal muscle weakness with characteristic skin symptoms: deep red exanthema on the eyelids, nose and cheeks, periorbital oedema, local erythema on the face, throat and neck ("shawl sign"), Gottron papules (papules and plaques on the extensor sides of the hands and fingers), "mechanic's hands" and calcinosis cutis. Furthermore, fever, dysphagia, myalgia, Raynaud's syndrome, interstitial lung disease and polyarthritis may occur. 31% of myositis cases are DM [2, 4-6, 8-10]. **DM sine dermatitis** is associated with muscle weakness and histological symptoms of DM without skin involvement, while **amyopathic DM** is defined by the typical DM skin symptoms without involvement of the muscles [6, 8, 10].

The clinical manifestations of **inclusion body myositis** are dysphagia, muscle weakness and atrophy. It is differentiated from other IIM by the presence of an asymmetric weakness of the proximal and distal muscles. Patients with inclusion body myositis are mainly above 50 years of age, men being more frequently affected than women [2, 6, 8].

Patients with **necrotising myositis (NM)** develop a rapidly progressive proximal muscle weakness within months after the onset of the disease. NM may occur in patients who have been treated with statins. It accounts for 19% of IIM cases [2, 6, 8].

Anti-synthetase syndrome (ASS) is a severe disease with extramuscular involvement. It is characterised by autoantibodies against aminoacyl-t-RNA synthetases (anti-synthetase antibodies) [1-3]. Typical manifestations are myositis, interstitial lung disease (ILD) and arthritis. Raynaud's syndrome, "mechanic's hands" and fever may also occur. The ASS phenotype can vary depending on the anti-synthetase antibodies and overlap with other autoimmune diseases [1, 5-10].

Overlap syndromes (**overlap myositis**, **OM**) typically occur in systemic sclerosis (14–96% of patients), systemic lupus erythematosus (4–16%), Sjögren's syndrome (5–73%) and rheumatoid arthritis (up to 8%). Patients with OM suffer from acute or subacute weakness of the arms and legs [4, 6, 8].

Myositis-specific antibodies (MSA) are directed against Mi-2α, Mi-2β, SAE1, NXP2, MDA5, cN-1A, TIF1γ, SRP and diverse tRNA synthetases as well as against HMGCR [5-7]. The frequency of MSA and the associated clinical phenotype vary considerably in different populations [4].

Autoantibodies against Mi-2α, Mi-2β, MDA5, TIF1γ, SAE1 or NXP2 can be found in patients with DM. The involvement of the musculature may be from mild or amyopathic in the case of anti-MDA5, anti-SAE1 or anti-TIF1γ antibodies to severe in the presence of anti-NXP2 antibodies [4, 5, 10].

Myositis-associated antibodies (MAA) also occur in other autoimmune diseases which can overlap with IIM. They are directed against, e.g., Ku, PM-Scl75, PM-Scl100 and Ro-52. MAA are detected in up to 50% of myositis patients [1, 2, 4-7, 9, 10].

Mi-2 (component of the nucleosome-remodelling deacetylase complex; isoforms **Mi-2α** (CHD3) and **Mi-2β** (CHD4)) is a transcription repressor. Anti-Mi-2 antibodies are associated with the characteristic skin manifestations and a mild course. They occur in adult or adolescent DM patients (frequency up to 31%). DM with anti-Mi-2β antibodies can be associated with a malignant tumour [1, 4, 6, 7, 9, 10].

SAE1 (SUMO-1 activating enzyme) is involved in the post-translational modification of proteins. The majority of patients with anti-SAE autoantibodies are adults with amyopathic DM with later transition to myositis. Malignant tumours can be found in patients with anti-SAE antibodies. Anti-SAE antibodies were detected in around 8% of adult DM patients in Europe and in around 3% of DM patients in Asia [1, 2, 4, 6-9].

NXP2 (nuclear matrix protein 2, also MJ, MORC3, p140) is a nucleic matrix protein that is involved in the regulation of the transcription factor p53. The autoantibodies are associated with severe muscle disease, skin ulcerations and calcinosis. Anti-NXP2 antibodies were found in adolescent (around 22%) and adult (1.6–30%) DM patients. The cancer risk in adult patients is increased [1, 2, 4, 7-10].

MDA5 (melanoma differentiation antigen 5, CADM-140) is an adhesion molecule and a resistance factor against double-stranded RNA viruses. It plays an important role in the regulation of the innate immune response. The typical clinical manifestation in adult IIM patients with anti-MDA5 antibodies is amyopathic DM with rapidly progressive ILD. Further symptoms are skin ulcerations, arthritis and fever. Anti-MDA5 antibodies are detected in 11% to 22% of Japanese adult DM patients, 0% to 13% of DM patients in Europe and the USA and 7.4% of adolescent DM patients [1, 2, 4, 6, 7, 9, 10].

Autoantibodies against the skeletal muscle antigen **cN-1A** (cytosolic 5'-nucleotidase 1A) are the only antibodies associated with inclusion body myositis. They are prevalent in around 30% to 50% of the patients. They have also been found in juvenile DM, Sjögren's syndrome and SLE [2, 4, 5, 10].

The nuclear protein **TIF1γ** (transcription intermediary factor-1 gamma, TRIM33, p155/140) is involved in gene transcription. Anti-TIF1γ antibodies can be found in adult and adolescent DM patients (41% in the USA and Europe, 17% in Japan). These antibodies are associated with severe skin lesions. They can be found in 35% of the patients with juvenile IIM and are the most frequent marker of this disease. Anti-TIF1γ antibodies are strongly associated with a tumour in adults with DM [1, 2, 7-10].

SRP (signal recognition particle), a cytoplasmic ribonucleoprotein, is responsible for the transport of proteins to the endoplasmic reticulum. Adults with anti-SRP antibodies typically develop acute, severe NM without skin involvement. Anti-SRP antibodies were detected in around 3% to 7% of adults with IIM and in 1.6% of juvenile patients [1, 4, 5, 7, 10].

Aminoacyl-t-RNA synthetases are cytoplasmic, ribosome-associated enzymes that catalyse the binding of the corresponding amino acid to the specific t-RNA during protein biosynthesis. So far, autoantibodies against histidyl- (**Jo-1**), threonyl- (**PL-7**), alanyl- (**PL-12**), glycyl- (**EJ**), isoleucyl- (**OJ**), tyrosyl- (**YRS/Ha**), asparaginyl- (**Ks**) and phenylalanyl- (**Zo**) t-RNA synthetases have been described [1, 2, 5-7, 9]. In most cases, anti-synthetase antibodies are directed against Jo-1 (in 20% to 30% of IIM patients). In adults, the titers of anti-Jo-1 antibodies correlate with the disease activity [1, 2, 8, 10]. Anti-EJ, anti-OJ, anti-Ha, anti-Ks and anti-Zo antibodies can be found in less than 2% of IIM patients [1, 5, 8]; up to 5% are positive for antibodies against PL-7 and PL-12. These patients also frequently have ILD, also acute, without signs of myositis. Pericarditis was observed in up to 50% of the anti-PL7-positive patients [1, 7, 8].

The enzyme **HMGCR** (3-hydroxy-3-methylglutaryl-CoA reductase) catalyses the conversion of HMG-CoA to mevalonic acid, which is an important step in cholesterol biosynthesis. It is located in the membrane of the endoplasmic reticulum. A small proportion of patients who take statins develop NM

with anti-HMGCR autoantibodies. Anti-HMGCR antibodies occur in up to 70% of NM patients. The titers correlate with the clinical activity. NM with anti-HMGCR antibodies can also develop without statin therapy. It is characterised by severe muscle weakness and, independent of statin therapy, with an increased risk of cancer. Anti-HMGCR autoantibodies are detected in 6% to 7% of cases with IIM [1-3, 8, 10].

Ku is a DNA binding protein involved in the repair of double-stranded DNA. Anti-Ku antibodies are associated with systemic sclerosis, SLE and other collagenoses. They can be found in 1% to 3% of patients with IIM and in up to 19% of cases with overlap syndrome with myositis [1, 4, 5, 8].

Antibodies against the exoribonuclease **PM-Scl** (subunits PM-Scl75, PM-Scl100) are associated with systemic sclerosis. They can be detected in up to 12% of IIM cases [1, 2, 8, 10].

Antibodies against **Ro-52** (TRIM21) can be found in up to 35% of myositis patients and in connection with many other autoimmune diseases. Anti-Ro-52 antibodies frequently occur together with anti-Jo-1 antibodies [8, 11].

MSA play a significant role in the diagnosis of IIM in addition to the creatin kinase level, electromyography and muscle biopsy [10]. They can be determined using enzyme immunotests and multiparametric line blots. IIM patients often only show one type of MSA. MAA may additionally occur [2, 4, 7, 9, 10].

Literature

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