1. Introduction

Idiopathic inflammatory myopathies (IIM) such as dermatomyositis (DM) and polymyositis (PM) are of major interest for the neurologist due to effective treatment. Nevertheless, there is an important proportion of patients who do not respond to some kind of treatment. Especially in patients with inclusion body myositis (IBM) treatment seems to be only partly effective in some and ineffective in most.

New therapeutic regimens such as intravenous immunoglobulin treatment and a combination of cytotoxic drugs with corticosteroids have been added during past years. Nevertheless, most of the therapeutic approaches in inflammatory myopathies are based on the personal experience of the specialist. Controlled studies are rare and suffer from major methodological shortcomings.

The aim of the workshop was to update the knowledge concerning inflammatory myopathies and to establish diagnostic criteria for DM, PM and IBM, which can be applied for future therapeutic studies.

2. Pathophysiology

N. Goebels (Munich, Germany) described the molecular immunopathogenesis of inflammatory myopathies. He stressed the different immune mechanisms involved in DM, PM and IBM. In DM muscle fiber damage is secondary to an immune response directed against the vascular endothelium. In PM there is a direct invasion of CD8+ T-cells into initially non-necrotic muscle fibers. The antigens against which the immune responses are directed are currently unknown. On the effector side of PM the molecule perforin, which is found in cytotoxic granules of T-cells, seems to induce damage of the muscle cell membrane. Perforin is expressed in T-cells in PM as well as in DM. However, its intracellular localization varies between PM and DM. In DM it is distributed in a diffuse way whereas in T-cells in PM perforin is expressed vectorially towards the target muscle cell. Fas-expression is found in numerous T-cells and the Fas-ligand is widely expressed on the surface of muscle fibers. Nevertheless, no significant signs of apoptosis could be detected in muscle nuclei. This could be due to the co-expression of the anti-apoptotic molecule Bcl-2.

Regarding the T-cell-receptor expression, identical clonal expansions of CD8+ T-cells could be detected in both the muscle and the blood of untreated PM patients.

Single cell PCR will help to clarify the pathophysiological significance of these clonally expanded T-cells.

The pathophysiology of IBM is still under debate. According to Karpati IBM seems to be a multi-factorial disease. Various factors which are not well understood (age, genetic, acquired) lead to an alteration of the nuclear matrix. The hypothesis of Karpati is that these nuclear changes can explain the major findings in s-IBM (sporadic inclusion body myositis) such as the myonuclear disintegration, the inflammatory response which can include expression of class I MHC at the surface of muscle and the appearance of ‘alien’ proteins which are caused by an aberrant gene expression. The disconnection of the nuclear and mitochondrial genome leads to a malfunction of the mitochondria with the morphological picture of cytochrome-c-oxidase-deficient ragged red fibers. The appearance of the rimmed vacuoles may be the result of altered pH values in the cytoplasm caused by basic components of the nucleus. Presently, the immunological response which is triggered by altered proteins at the surface of muscle cells is the only potentially treatable part of s-IBM. The poor response to any kind of anti-dysimmune treatment indicates that the immunological reaction plays a minor role in the causation of the clinical picture of the disease.

3. Clinical picture

A. Manzur (London, UK) reported on his experience with 70 children suffering from inflammatory myopathies. In infancy and childhood DM is much more common than
PM, which was found in two children only. DM was more frequently found in girls than in boys. The three cardinal symptoms of DM in children are weakness, misery and rash. The most common distribution of the rash is on the face and the knuckles, but may also occur over the knees, elbows and the axillary folds. Systemic manifestations of the disease such as affection of the gastrointestinal tract, joints and kidney may occur in children, but only in a minority.

K. Kunze (Hamburg, Germany) and St. Zierz (Halle, Germany) summarized the clinical features of adulthood PM and DM, emphasizing that the criteria established by Bohan and Peter in 1975 have not been replaced by clearly better ones. Proximal muscle weakness with or without myalgia is the main presentation in both diseases. However, both muscle weakness and the additional criteria of abnormal electromyographical findings and elevated serum activity of muscle enzymes (CK and aldolase) are non-specific and can be found in many other neuromuscular disorders. DM additionally is characterized by typical skin abnormalities (e.g. heliotropic exanthema, Gottron’s sign).

G. Karpati (Montreal, Canada) explained the clinical features of IBM as well as morphological characteristics of the different types of IIM. In contrast to PM and DM, patients are almost exclusively older than 50 years, and muscle weakness often involves distal muscles, especially the long finger flexors, or is asymmetrical. Bedside testing of the patients is the most important clue to the diagnosis of IBM. Patients never complain of myalgia. If pain is present it always can be explained as referring pain due to osteoarthritis or similar degenerative affections of bones and joints.

In initial stages of IBM distal paresis of the muscles is not a mandatory feature. At that stage IBM can be indistinguishable from PM.

At the end of the meeting the participants defined the criteria for DM, PM and IBM which are shown in Appendix A.

4. Diagnostic evaluation

4.1. Electromyography

W. Müller-Felber (Munich, Germany) described the specific problems of clinical electromyography in the field of inflammatory myopathies. Efforts to quantify the electrical signal during voluntary activation have shown a low diagnostic yield. That is true for the noise-based techniques such as the assessment of the number of turns, the amplitudes, power spectrum and for the MUAP-based procedures like automatic-decomposition-EMG or multi-MUAP. In a series of 138 patients with DM or PM Müller-Felber showed that before treatment 10% of patients with DM had a normal EMG. Pathological spontaneous activity was found in 81% of patients with DM. Failure to detect changes in the electromyogram can be in some cases attributed to a focal involvement of muscles in inflammatory myopathies. In patients with anti-synthetase syndrome a very low yield of pathological findings was observed. During the course of the disease there is an increase of the MUAP duration. Nevertheless, in most patients there is a persisting decrease of fast-component duration. In a series of 23 patients with IBM, a wide spectrum of electrophysiological findings ranging from low amplitude, low duration to high amplitude, large duration MUAPs was found. Pathological spontaneous activity at rest was found in 13/23 patients.

4.2. Imaging

K. Kunze (Hamburg, Germany) and C.D. Reimers (Göttingen, Germany) stressed the value of muscle imaging for the diagnosis of inflammatory muscle disease. High signal intensities on T2-weighted or on fat-suppressive MR images in contrast to low signal intensities on T1-weighted images are the diagnostic hallmark of acute myositis. However, this constellation sometimes can also be found in non-inflammatory muscle disease such as metabolic myopathies or muscular dystrophies (especially in facioscapulohumeral muscular dystrophy) and even in healthy subjects after muscular exertion. These abnormalities should not uncritically be referred to muscle edema, because they probably are not caused by an increase of intramuscular water content in all cases. Presumably a shift of intra- and extracellular water into the other compartment without a change of the total water content results in increased signal intensity on T2-weighted and fat-suppressive MR images. Fat-suppressive MR sequences are more sensitive in depicting these abnormalities than T2-weighted images. In IIM, contrast-enhanced MR images do not provide more information than plain images. The signal intensity on T2-weighted and fat-suppressive MR images reflects the active inflammation. Thus, regions exhibiting these abnormalities are most suitable for muscle biopsies. Ultrasonography is also able to depict active myositis, which is characterized by homogeneously increased echo-intensity. In chronic myositis, lipomatose degeneration of muscles occurs. In these cases, increased signal intensities appear on both T1- and T2-weighted MR images. Ultrasonography exhibits inhomogeneously increased muscular echo-intensity. Judgement of ultrasonographical images is more difficult than that of MR images and needs considerable experience. Thus, it is still reserved for special units with high expertise in neuromuscular diseases.

4.3. Laboratory investigation

E. Genth (Aachen, Germany) presented his great experience on auto-antibodies in IIM. Depending on the selection of the patients up to 90% exhibit auto-antibodies, most of them, however, being non-specific such as antinuclear antibodies. Only one auto-antibody, i.e. signal recognition particle (SRP), is always associated with inflammatory muscle disease. In up to 60% of patients myositis-associated anti-
bodies can be detected. The most common among these are anti-synthetase antibodies. With few exceptions only one specific antibody can be detected in a single patient.

Patients with auto-antibodies may show muscular, extra-muscular or both manifestations of their disease.

Some auto-antibodies are associated with typical clinical features. Examples are the Jo-1-syndrome which consists of myositis, fibrosing alveolitis and skin involvement or patients with Pm-Scl-auto-antibodies, who exhibit scleroderma, Raynard’s phenomenon, and often myositis.

4.4. Histological evaluation

In PM cellular infiltrates can be found in more than 90% of all patients. Dalakas and Karpati stressed that in virtually all patients with PM, cellular infiltrates should be found. If not re-biopsy is indicated. Nevertheless, there are few patients with the histological picture of necrotizing myopathy without cellular infiltrates who show clinical symptoms of PM and who respond to immunosuppressive treatment. It cannot be decided whether this group of patients is an entity different from PM. An important clue is that in all forms of IIM, class I major histocompatibility complex products are present at the surface of muscle fibers. This is very widespread in PM but may be patchy in DM and IBM. Normally, muscle fibers do not express class I MHC.

Müller-Felber (Munich, Germany) showed that in patients showing the histopathological picture of PM who did not respond to treatment, 50% turned out to suffer from s-IBM. The other patients suffered from muscular dystrophies (mainly inflammatory FSH-dystrophy).

Karpati reported that rimmed vacuoles, 15–18 nm tubulofilaments, nuclear abnormalities and intracellular amyloid deposits are characteristic signs. As mentioned above, the diagnosis can be missed in patients with otherwise typical signs of IBM.

Pongratz (Munich, Germany) showed that in contrast to PM and IBM, in DM the dominant immunoeffector mechanism is the membrane attack complex (MAC) which can be demonstrated by immunohistochemistry. The primary target cells for the inflammatory process are the blood vessels and not muscle fibers. The histopathological consequences are capillary necrosis, vascular thrombosis, and finally ischemic myopathy.

5. Therapy

C.D. Reimers (Göttingen, Germany) reported that corticosteroids should be administered first in all cases of IIM, although their efficacy has never been proven in randomized, controlled studies. However, clinical evidence is so overwhelming that beneficial effects in DM and PM are beyond any doubt. In IBM, effects are missing or rather low. The optimal dosage has also never been studied systematically. However, a daily administration of 1 mg/kg body weight has generally been accepted. High dosages can be given in divided portions. Lower doses should be given early in the morning. Their is no clear evidence that corticosteroids endanger the patient in relation to developing a gastric ulcer, so that H2-proton pump inhibitors must not be given if the patient has no corresponding history. Due to numerous adverse effects (e.g. osteoporosis, cataracts) other immunosuppressants should be added in those patients in whom muscle weakness cannot be alleviated considerably and the CK levels should be normalized within a few months.

J. Hoogendijk (Utrecht, The Netherlands) presented new data, still not published as an original article, indicating that a very high dose of prednisolone administration of 1000 mg or even more on 2 or 3 days a week might be more effective than conventional treatment and have only minor side effects. This cycle must be repeated after intervals of a few weeks.

M. Dalakas (Bethesda, MD, USA) reviewed the therapeutic regimes in PM and DM, focusing on the high-dose immunoglobulins. He also stressed that corticosteroids (prednisone or prednisolone) are still the agents of first choice with a dosage of 1 mg/kg body weight per day. After 3 or 4 weeks the dosage should be decreased. In case of insufficient efficacy, additional immunosuppressants are needed. In contrast to former recommendations, he would use high-dose intravenous immunoglobulins (ivIG) as the medication of second choice due to its proven efficacy and relatively few and mild adverse effects. The recommended dosage was 2 g/kg body weight within 2–5 days. This should be repeated roughly every month for a few months, the intervals being lengthened corresponding to the course of the disease. According to present knowledge, ivIG act by means of suppression of C3 complement and reduction of lymphocytes. Azathioprine and methotrexate would be drugs of third choice.

Presently, high-dose immunoglobulins are the only therapeutics resulting in slight improvement or delayed worsening of IBM, although the results of treatment studies are not really convincing and the numbers of patients treated in randomized, controlled studies are rather low. Intravenous immunoglobulins 2 g/kg body weight per circle plus 60 mg prednisone did not improve muscle strength, but subjects who were treated felt better than those who received placebo instead of ivIG.

Manzur reported that children are treated initially with prednisolone 1 mg/kg body weight, which can be increased when indicated in the occasional case with a poor response. He recommended cyclosporin-A for those patients who do not tolerate reduction of corticosteroids or who are refractory to corticosteroids. In 24 out of 26 patients treated by cyclosporin-A, corticosteroids could be withdrawn. Finally, in 15 of these patients, cyclosporin-A could be withdrawn without a new exacerbation of the disease. Monitoring of therapy in children is mainly based on the clinical manifestations. Measurement of CK levels may further help to monitor these children.
6. List of workshop participants

- M. Dalakas (USA)
- E. Genth (Germany)
- N. Goebels (Germany)
- J. Hoogendijk (The Netherlands)
- G. Karpati (Canada)
- K. Kunze (Germany)
- T. Kyriakides (Cyprus)
- P. Lotichius (Germany)
- A. Manzur (UK)
- W. Müller-Felber (Germany)
- D. Pongratz (Germany)
- C. Reimers (Germany)
- R. Rüdel (Germany)
- A. Urtizberea (France)
- M. De Visser (The Netherlands)
- A. Wintzen (The Netherlands)
- S. Zierz (Germany)

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Appendix A

Abbreviations: I, inclusion criterion; E, exclusion criterion; C, comment.

A.1. Diagnostic criteria for polymyositis

A.1.1. Clinical features

- I, Symmetrical subacute progressive proximal muscle weakness.
- E, Predominant distal muscle weakness.
- E, Skin lesions of dermatomyositis.
- E, Presence of microbial etiologies associated with myositis.
- E, History of drugs associated with myositis.
- C, Significant involvement of the pharyngeal muscles and neck flexors may occur.
- C, Arthralgias, myalgias and Raynard’s phenomenon may occur.
- C, Sometimes weakness is primarily chronic.
- C, HIV and other infections (toxoplasmose) may be associated with polymyositis.
- C, Auto-immune diseases including graft versus host disease can be associated with polymyositis.
- C, Association with malignancy is not disproportionately enhanced.

A.1.2. Ancillary investigations

- I, Muscle biopsy (two out of the four following features are obligate):
  - endomysial lymphocytic infiltrates containing predominantly CD8 lymphocytes.
  - invasion of non-necrotic fibers by CD8 lymphocytes and macrophages.
  - scattered necrotic and regenerating fibers.
  - expression of class I MHC product in most muscle fibers not only regenerating fibers.
- E, Rimmed vacuoles, filamentous inclusions.
- C, COX-negative/ragged red fibers may occur.
- C, Serum creatine kinase activity moderately to markedly elevated.
- C, Electromyography: usually myopathic. Fibrillations and/or positive sharp waves can also occur.
- C, MRI: increased signal on T2-weighted images, contrast enhancement.
- C, Auto-antibodies are found in about 30%.

A.1.3. Age at onset

Any age but only seldomly found in children.

A.1.4. Course

Slowly to moderately progressive.
A.2. Diagnostic criteria for sporadic inclusion body myositis

A.2.1. Clinical features

I, Progressive muscle weakness and wasting with insidious onset.
C, Initially, muscle weakness can be proximal or distal.
C, Significant involvement of the pharyngeal muscles and neck flexors may occur.
C, Some patients may have facial weakness.
C, Muscle weakness can be asymmetric.
E, Consistent and prominent muscle pain.
E, Positive family history.

A.2.2. Ancillary investigations

I, Muscle biopsy (three out of the five following features are obligate):
- endomysial infiltrates containing predominantly CD8+ lymphocytes.
- invasion of non-necrotic fibers by CD8+ lymphocytes.
- rimmed vacuoles.
- congophilic deposits seen with Texas Red fluorescence optics.
- typical filamentous inclusions by electron microscopy.
C, Necrotic fibers are rare.
C, COX-negative/ragged red fibers may occur.
E, Serum creatine kinase activity >10× elevated.
C, Electromyography: usually myopathic/mixed pattern.
EMG may erroneously indicate a neurogenic disease.
C, MRI: increased signal on T2-weighted images, fatty replacement of the muscle tissue.
C, Auto-antibodies: only rarely found.

A.2.3. Age at onset

Mainly in patients elder than 50 years. Seldomly found in juvenile patients or young adults.

A.2.4. Course

Slowly progressive.

A.3. Diagnostic criteria for dermatomyositis

A.3.1. Clinical features

I, Symmetrical subacute progressive proximal and axial muscle weakness.
I, Dysphagia.
I, Typical skin changes.
- heliotropic erythema with periorbital edema.
- sign of Gottron.
- sign of Keinig.
- de- and hyperpigmentation.
- mechanics hands.
- subcutaneous calcifications.
- erythematous rash on knuckles and elbows.
- petecchie of nailbeds.
C, Significant involvement of the pharyngeal muscles and neck flexors may occur.
C, Exclusive skin lesions without muscle weakness can occur.
C, Cancer may be an associated phenomenon.
C, Extramuscular manifestations are not rare (including arthralgias and Raynaud’s phenomenon).
C, Exercise-induced muscle pain is often encountered.
E, Predominant distal muscle weakness.
E, Lupus erythematous, scleroderma, eosinophilic fascitis, trichinosis.
E, Positive family history.
E, Drug-induced myopathy.

A.3.2. Ancillary investigations

I, Any of the following features in muscle biopsy:
- vasculopathy: capillary loss, MAC deposits in capillaries, microtubular inclusions at the ultrastructural level.
- perifascicular atrophy.
- infiltrates, including CD4 + lymphocytes at perimysial sites.
C, (Micro)infarcts may be present.
C, MHCI positivity is often found.
C, Serum creatine kinase activity is usually elevated, but may be normal in approximately 10%.
C, Electromyography: usually myopathic, fibrillations and positive waves may be present.
C, MRI: increased signal on T2-weighted images, contrast enhancement.
C, Auto-antibodies are found in about 30%.

A.3.3. Age at onset

Any age.

A.3.4. Course

Acute or relapsing/remitting or progressive.