Inflammatory Diseases of the Brain

With Contributions by

M. Bendszus · B. Ertl-Wagner · J. Fiehler · S. Hähnel · C. Jacobi · T. Kollmann
B. Kress · M. Lettau · S. Rohde · A. Seitz · J. Spreer · C. Stippich · B. Storch-Hagenlocher
H. Tschampa · H. Urbach · B. Wildemann · M. Wengenroth · A. Wetter · S. G. Wetzel

Foreword by
M. Knauth

Springer
Dedication

For Claudia, Theresa, and Paulina.

And for my parents.
Foreword

Inflammatory diseases of the brain are caused by many different etiologies and come in various disguises; sometimes the diagnosis is straightforward, most of the time it is not. In fact, the diagnosis and differential diagnosis of inflammatory diseases of the brain often are very confusing.

There is a wide variety of causative agents and inflammatory pathways ranging from bacteria, fungi, parasites, viruses, prions, and toxins to autoimmune diseases.

Inflammatory diseases of the brain can mimic many other intracranial pathoentities, e.g., they can be tumefactive, disguised as meningiosis or intracranial hypotension, and sometimes can even be difficult to separate from infarctions, let alone telling them apart from each other.

Fortunately, the (neuro-)radiologist’s arsenal of weapons has grown over the years, especially with the advent of new MR techniques, e.g., diffusion- and perfusion-weighted imaging and MR spectroscopy, and other sophisticated methods of MR examination have added to the diagnostic options of the radiologist.

Stefan Hähnel and his team of coauthors extensively cover the variety of inflammatory diseases of the brain in child- and adulthood. A standardized approach is used throughout the book, which deals with epidemiology, clinical presentation, therapy, imaging, and differential diagnosis in each chapter. Emphasis is also placed on how the “new” MR techniques can be used in the diagnosis and differential diagnosis of inflammatory diseases of the brain. As building up a “mental library” of engrams is very important in the differential diagnosis, the book is richly illustrated.

Stefan Hähnel has managed to recruit a team of recognized experts in the field of inflammatory diseases of the brain. They have succeeded in creating this volume of “Medical Radiology” in a record-breaking period of time; if writing this book had been the Tour de France, everybody would have suspected the authors of doping!

Inflammatory Diseases of the Brain is not only of high relevance for the neuroradiologist and radiologist, but also for the neighboring clinical disciplines such as neurology, neuropediatrics, and neurosurgery. I am sure that this book will be a great success.

Göttingen

Michael Knauth
Inflammatory diseases of the central nervous system (CNS) are playing an increasingly important role in the clinical practice of neuroradiology: Infections of the CNS frequently involve immunocompromised patients and are being accompanied increasingly more with the employment of innovative and aggressive immunosuppressive and immunomodulatory therapies. Noninfectious inflammation, such as multiple sclerosis, accounts for about 10% of all neurological diseases.

In this textbook special attention is given to advanced MR techniques such as diffusion-weighted imaging, perfusion imaging, susceptibility-weighted imaging, as well as MR spectroscopy. These techniques provide important information for the differentiation between inflammatory brain diseases and other entities, such as neoplastic or ischemic diseases, which have to be considered in the differential diagnosis.

The chapters which highlight special topics deal with brain inflammation in childhood, granulomatous diseases, MR imaging, and spectroscopic specifics in the context of recommendations for imaging protocols.

The uniform structure of each chapter should help the reader to navigate the complexity of the diseases and understand the coherence of clinical, epidemiological, pathological, and radiological specifics of brain inflammation.

We are aware that there are some repetitions between the chapters and themes: They should support the learning and memorization of certain topics from different points of view.

We have taken special care to furnish the book with many instructive figures, because a good neuroradiological textbook derives its life from extensive illustration. For readers who prefer a quicker exploration of the subject, it would certainly be worthwhile to flick through the book with the intention of only looking at the images.

We hope that the book will be of value not only for neuroradiologists but also for neurologists, neuropediatricians, and general radiologists. The coauthors and myself would be thankful for any constructive criticism from the reader. Please let us know if anything can be improved for the next edition.

Many people not involved with the actual writing of the book contributed substantially to its development. Firstly, I thank my former chief, Klaus Sartor (Heidelberg), who awakened my interest in diagnostic neuroradiology as an academic teacher more than 15 years ago, and who inspired me to work on this book. Michael Knauth (Göttingen) accompanied me not only during the creation of the book but has also accompanied me during my professional career. I also thank Martin Bendszus (Heidelberg), who gave me substantial input and stimulation for the book. Finally, I thank Ursula Davis of Springer-Verlag, who patiently assisted me during the editing process and advised me excellently regarding the structure of the book.

Heidelberg

Stefan Hähnel
# Contents

## Brain Parenchyma

1 Multiple Sclerosis and Other Demyelinating Diseases ........................................ 3

1.1 Multiple Sclerosis ......................................................... 4  
Brigitte Storch-Hagenlocher and Martin Bendszus

1.2 Other Demyelinating Diseases ........................................... 16  
Brigitte Storch-Hagenlocher and Martin Bendszus

2 Cerebral Vasculitis ............................................................... 25

2.1 Epidemiology, Clinical Presentation and Therapy ........................................ 26  
Christian Jacobi and Brigitte Wildemann

2.2 Imaging and Differential Diagnosis ........................................... 30  
Martina Wengenroth

3 Pyogenic Cerebritis and Brain Abscess ........................................... 51  
Joachim Spreer

4 Neurulues ............................................................................. 71  
Bodo Kress

5 Neurotuberculosis ................................................................. 75  
Stephan G. Wetzel and Thilo Kollmann

6 Other Bacterial Infections ..................................................... 85  
Michael Lettau

7 Viral Encephalitis ................................................................. 97  
Stefan Hähnel

8 Spongiforme Encephalopathies ................................................. 113  
Horst Urbach and Henriette Tschampa

9 Fungal Infections ................................................................ 125  
Jens Fiehler
10  Parasitic Infections .......................................................... 143
    Christoph Stippich

Meninges

11  Inflammatory Diseases of the Meninges  ......................... 169
    Stefan Rohde

Specific Topics

12  Granulomatous Diseases ................................................ 187
    Bodo Kress

13  Specifics of Infectious Diseases of Childhood ...................... 197
    Birgit Ertl-Wagner and Angelika Seitz

14  MR Imaging and Spectroscopic Specifics and Protocols ....... 213
    Axel Wetter

List of Acronyms .......................................................... 223

Subject Index ........................................................... 225

List of Contributors .................................................... 233
Brain Parenchyma
Multiple sclerosis (MS) is the most frequent idiopathic inflammatory demyelinating disease of the central nervous system. Magnetic resonance imaging is the most important paraclinical parameter in the diagnosis of MS. If the MR criteria for dissemination in time and space are positive, the early diagnosis of MS may be established already after one clinical event; thus, MRI has an important impact on the initiation of early therapy in MS. Moreover, MRI is essential in monitoring disease activity and therapy effects. Atypical inflammatory demyelinating diseases include ADEM, neuromyelitis optica (Devic disease), Baló’s concentric sclerosis, Schilder’s disease, Marburg’s disease, tumefactive demyelinating lesions, and acute transverse myelitis. These entities may be separated from MS by a different clinical course and a particular appearance on MRI. Occasionally, these variants merge with MS.
**Multiple Sclerosis**

Brigitte Storch-Hagenlocher and Martin Bendszus

**Introduction**

Multiple sclerosis is a chronic autoimmune condition of the central nervous system (CNS) characterized by blood–brain barrier breakdown, inflammation, myelin damage, and axonal loss. The pathogenesis of MS is unknown; apart from a genetic predisposition, previous virus infections are thought to be relevant. Multiple sclerosis is estimated to affect 2.5 million individuals worldwide. Multiple sclerosis typically presents in young Caucasian adults, with a peak between 20 and 40 years. There is increasing evidence for first manifestations of MS at older ages as well. Multiple sclerosis is twice as common in women than men. The clinical courses include relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive-relapsing (PRMS) MS. Patients with RRMS exhibit neurological symptoms that remit over a period of weeks to months with or without complete recovery. A large proportion of patients with RRMS evolve after 10–15 years to the SPMS form of the disease, in which neurological deficits become fixed and cumulative. In contrast, patients with PPMS exhibit a continuous steady progression of neurological symptoms from the onset of the disease without periods of relapse or remission. Patients with PRMS also experience steady disease progression from the outset with or without superimposed relapses and remissions.

The clinical diagnosis of MS requires evidence for at least two anatomically distinct lesions consistent with (CNS) white matter damage in an individual with a history of at least two distinct episodes of focal neurological dysfunction (so-called symptom dissemination in time and space). These criteria are not difficult to demonstrate in well-established MS, but considerable problems can arise early in the course of the disease, and it is not possible to make a definite clinical diagnosis of MS when the patient first presents with a clinically isolated syndrome even if it is typical of MS (e.g., unilateral optic neuritis, internuclear ophthalmoplegia, or partial myelopathy). In recent years, new drugs have been introduced in the treatment of MS which have been proven to especially treat early stages of the disease. In order to establish an early diagnosis of MS and therefore initiate early treatment, new diagnostic criteria, including paraclinical parameters, have been introduced. Magnetic resonance imaging has become the most important of these paraclinical parameters. Already after one clinical event and positive MRI criteria, the diagnosis of MS may be established and treatment initiated; thereby, MRI has immediate impact on early treatment of MS.

**1.1.1 Epidemiology, Clinical Presentation, and Therapy**

Brigitte Storch-Hagenlocher

**1.1.1.1 Epidemiology**

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that affects mainly young adults and is yet the most frequent cause of invalidity at an early stage. The proportion of women to men affected is about 2–3:1, and disease most frequently occurs between the ages of 20 and 40 years but also during childhood or after the age of 50 years.

The prevalence of MS varies considerably around the world, increasing with the distance from the equator. It is highest in northern Europe, southern Australia, and the middle part of North America, with 80–150 per 100,000 persons. Germany also belongs to high prevalence regions with about 120,000 to 150,000 MS patients. There has been a trend toward an increasing prevalence and incidence, particularly in southern Europe. It is uncertain to which extent the observed increases are explained by an enhanced awareness of the disease and improved diagnostic techniques, but in some areas of northern Europe incidence has actually declined. The reasons for the variation in the prevalence and incidence of MS worldwide are not well understood. Environmental and genetic factors probably play a role. People who migrate from high- to low-prevalence areas during childhood only take on the risk of the host country, and vice versa; however, the nature of putative environmental factors remains unclear in numerous case-control studies.

**1.1.1.2 Genetics**

Evidence that genetic factors have a substantial effect on susceptibility to MS is unequivocal. The concordance rate is highest among monozygotic twins (about 30%) and only about 2–5% among dizygotic twins; however,
the risk of disease in a first-degree relative of a patient with MS is 20–40 times higher than the risk in the general population. In 1972 the association between MS and the HLA region of the genome was established since narrowed down to the HLA-DRB1 gene on chromosome 6p21. Populations with a high frequency of the allele have the highest risk of MS. Furthermore, there is evidence of the involvement of other two interesting genes: IL2RA, which encodes the alpha subunit of the interleukin-2 receptor (synonym CD25) on chromosome 10p15; and IL7RA, which encodes the alpha chain of the interleukin-7 receptor on chromosome 5p13. These two interleukin-receptor genes are important in T-cell-mediated immunity regulating T-cell responses and homeostasis of the memory T-cell pool and may be important in the generation of autoreactive T-cells in MS.

1.1.1.3 Clinical Presentation

The heterogeneity of clinical symptoms and the temporal evolution of clinical findings may suggest the diagnosis of MS. In relapsing–remitting MS (RRMS), the type present in about 80% of cases, symptoms and signs evolve over a period of some days, stabilize, and often improve spontaneously or in response to corticosteroids, within several weeks. A relapse is defined by symptoms lasting more than 24 h. Relapsing–remitting MS generally begins in the second or third decade of life with a female predominance. With the first treatment, symptoms usually respond very well to corticosteroids, within several weeks. A relapse is defined by symptoms lasting more than 24 h. Relapsing–remitting MS defined by only mild symptoms being present 30 years after disease onset is found only in about 10% of cases. In the majority of cases disease passes into secondary progressive MS (SPMS) within 20–30 years.

Twenty percent of affected patients suffer from primary progressive MS (PPMS), which is characterized by a gradually progressive clinical course and a similar incidence among men and women. Relapsing–remitting MS frequently starts with sensory disturbances and Lhermitte's sign (trunk and limb paresthesias evoked by neck flexion). Further initial signs are unilateral optic neuritis or diplopia (internuclear ophthalmoplegia). Limb weakness, clumsiness, gait ataxia, and neurogenic bladder and bowel symptoms at the beginning of disease more often indicate a less favorable course. The onset of symptoms post-partum and symptomatic worsening with increases in body temperature (Uhthoff’s symptom), as well as pseudooexacerbations with fever, are suggestive of MS. Recurring, brief, stereotypical phenomena (paroxysmal pain or paresthesias, trigeminal neuralgia, episodic clumsiness or dysarthria, tonic limb posturing) also suggest the diagnosis of MS. Even at the beginning of the disease cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, spasticity, progressive quadriaparesis and sensory loss, pain, ataxic tremor, sexual dysfunction, and other manifestations of central nervous system dysfunction may impair affected patients; however, cortical signs (aphasia, apraxia, recurrent seizures, visual-field loss) as well as extrapyramidal symptoms generally only rarely occur.

Patients with primary progressive MS often develop a “chronic progressive myelopathy” with gradually evolving upper-motor-neuron symptoms of the legs. Over time this variant worsens with quadripareisis, cognitive decline, visual impairment, brain-stem syndromes, and cerebellar, bowel, bladder, and sexual dysfunction.

There are several standardized clinical parameters and scales to evaluate disease progression. Relapse rates are important for determining disease severity in the short term. Neurological disability is most directly measured with the Expanded Disability Status Scale (EDSS), an ordinal rating scale that defines transitions between different disability states ranging from 0 = normal neurological examination, to 10 = death from MS. The cognitive decline can be assessed by several neuropsychological tests, such as the Paced Auditory Serial Addition Test (PASAT), which measure speed of information processing. The nine-hole peg test (9HPT) is a specific measure of upper-limb function, whereas ambulation tasks, such as the 25-ft. walk, measure lower-limb function. The combination of these function-specific measures is more sensitive for following clinical outcome than the individual measures alone and is provided by the Multiple Sclerosis Functional Composite (MSFC).

1.1.1.4 Clinical Diagnosis

To increase specificity of diagnosis, the use of both clinical and paraclinical criteria must be obtained including information MRI, evoked potentials (EP), and cerebrospinal fluid (CSF), all being only supportive and not diagnostic itself. In 2001, the “International Panel on the Diagnosis of Multiple Sclerosis” presented new diagnostic criteria for MS with particular emphasis on determining dissemination of lesions in time and space. That allows the diagnosis of MS even in “clinically iso-
lated symptoms” (CIS) in the presence of new lesions on MRI controls during the time. The value of CSF analysis is stressed in primary progressive MS. These criteria were revised in 2005 with more consideration for the relevance of spinal lesions. When the results of the paraclinical tests are normal, this strongly suggests an alternative diagnosis, whereas when they are abnormal, they would support the diagnosis of MS. In addition, diagnostic criteria also demand that “there be no better explanation other than MS to account for the historical and objective evidence of neurological dysfunction”; therefore, other differential diagnoses must be ruled out very carefully (Table 1.1.1.1).

On MRI, findings of multifocal lesions of various ages, especially those involving the periventricular and subcortical white matter, brain stem, cerebellum, and spinal cord white matter, support the clinical impression of MS. The presence of gadolinium-enhancing lesions on MRI indicates current active lesions. In the past few years numerous studies have also demonstrated brain atrophy due to early axonal loss resulting in progression of neurological deficits and development of cognitive impairment.

The CSF examinations include white blood cell (WBC) count, quantitative and qualitative protein analysis as well as glucose and/or lactate level measurement. Higher than normal \( (N < 5 \times 10^6/l) \) WBC counts are found in approximately 35% of MS cases, but very high \( (> 50 \times 10^6/l) \) CSF WBC counts are unusual. Plasma cells can be detected in about 70–80% of cases, even in normal cell counts. CSF glucose and lactate levels usually are in normal ranges. Total protein and albumin quotient to indicate the blood–brain barrier function usually are normal. In MS the most important CSF findings are the detection of intrathecally produced IgG (“raised IgG index”) in about 70–90% of MS patients and oligoclonal bands different from those in serum in about 98% of MS. Intrathecally produced IgM can also be detected in about 30–40% of cases. Although revised McDonald criteria do not require CSF analysis in either case for diagnosis of MS, in Europe CSF analysis is recommended to eliminate alternative conditions that might “mimic” the disease.

Dissemination in space, even only subclinically, may be pointed out by changes in evoked potentials, especially in visual-evoked responses, somatosensory evoked potentials, and transcranial magnetic stimulation.

### 1.1.1.5 Pathology and Pathogenesis

Multiple sclerosis is an immune-mediated disease with a complex pathogenesis involving both inflammatory and neurodegenerative components. The basic pathology is characterized by perivascular infiltration of lymphocytes and lipid-containing macrophages, as well as axonal transection even in an early stage of disease. The destroying process not only involves white matter areas, but also thinly myelinated areas of gray matter and basal ganglia. The margins of the acute lesions can be indistinct due to ongoing demyelination and the lesion center may be edematous.

<table>
<thead>
<tr>
<th>Table 1.1.1.1.</th>
<th>Clinical differential diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variants of MS</strong></td>
<td><strong>Optic neuritis, neuromyelitis optica, acute disseminated encephalomyelitis</strong></td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Sjögren’s syndrome, systemic lupus erythematosus, Behçet’s disease, sarcoidosis, antiphospholipid-antibody syndrome, paraneoplastic disorders</td>
</tr>
<tr>
<td>Infections</td>
<td>HIV-associated myelopathy, HTLV-1-associated myelopathy, neuroborreliosis, meningovascular syphilis</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Disorders of B12 and folate metabolism, leukodystrophies</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Central nervous system vasculitis inclusive variants (e.g., Susac’s syndrome, Cogan’s disease), cerebral autosomal–dominant arteriopathy with subcortical infarcts and leukoencephalopathy</td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>Hereditary ataxias and hereditary paraplegias, Leber’s atrophy, other mitochondrial cytopathies</td>
</tr>
<tr>
<td>Lesions of the posterior fossa and spinal cord</td>
<td>Arnold–Chiari malformation, nonhereditary ataxias, spondylotic or other myelopathies</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Conversion reaction</td>
</tr>
</tbody>
</table>
Even though exact details of MS pathogenesis remain elusive, it is assumed that activated autoreactive T-cells from the periphery pass the blood–brain barrier and initiate a cascade of inflammatory immune reactions within the CNS. This includes activation of macrophages and B-cells, production of antibodies, and release of proinflammatory cytokines. Initially, the generation of autoimmune T-cells may be promoted by an impaired suppressive function of CD4+ CD25 high-regulatory T-cells (Treg), a phenotype that may be relevant in controlling autoimmune diseases. In MS lesions CD4+ and CD8+ T-cells are present, with CD4+ T-cells being predominantly in the perivascular cuff, and CD8+ T-cells being more prevalent in the center and border zone of the lesion. Axonal damage may be promoted by activated CD8+ T-cells that directly target neurons, by destructive macrophages, inflammatory mediators, and toxic molecules, as well as binding of antibodies to neuronal surface antigens, followed by complement activation and antibody-mediated phagocytosis of axons. In addition, indirect mechanisms, such as loss of protective myelin, mitochondrial dysfunction, or release of glutamate nitric oxide, might contribute to axonal damage. Clinical course and histopathological findings suggest that in MS patients these multiple mechanisms of disease are present to a different extent. According to Lucchinetti and colleagues (2000), four different immunopathogenic patterns in acute MS lesions can be observed histopathologically. Two patterns (I and II) display T-cells as the predominant cell population. Additional deposits of immunoglobulins and complement characterize pattern-II lesions. Patterns III and IV show primary oligodendrocyte dystrophy and pattern III also shows apoptotic oligodendrocytes. Patients with pattern I and II often show remyelinated plaques, but remyelination is absent in pattern-III and pattern-IV lesions.

1.1.1.6
Therapy

1.1.1.6.1
Relapse Treatment

Glucocorticoids are the standard treatment for acute relapses. They restore the blood–brain barrier, induce T-cell apoptosis, and decrease the release of proinflammatory cytokines; therefore, they have beneficial effects on inflammation, apoptosis, and demyelination. Although these drugs may shorten the duration of a relapse, they have no effect on the exacerbation rate or on the development of long-term disability. A relevant MS relapse should be treated with high-dose pulse therapy of methylprednisolone IV optionally followed by oral tapering. In case improvement is not satisfactory, treatment should be escalated either by solely repeating high-dose methylprednisolone or administering it in combination with a cytotoxic immunosuppressive agent (cyclophosphamide, mitoxantrone).

Plasma exchange (PE) is also an alternative escalating immunotherapy in patients with severe steroid-resistant relapses. In small trials the mean time point of improvement was after the third plasmapheresis session, and early initiation of plasma exchange therapy (within 1 month after start of relapse) was associated with better outcome.

1.1.1.6.2
Immunotherapy in Relapsing–Remitting MS

The therapy escalation and de-escalation scheme is illustrated in Fig. 1.1.1.1. In relapsing–remitting MS (RRMS), on the basis of the inflammatory nature of the disease, targeting at the immune response has thus far been the most widely used and only successful treatment. Strategies have been developed that range from nonselective immunosuppression to highly specific immune intervention. Such treatments bring undoubted benefits in reducing the risk of relapse and, potentially, the risk of acquiring irreversible neurological disability. Evidence from research suggests that many patients with clinically isolated syndromes or early MS should be treated with disease-modifying drugs at an early stage, since disease experience during the first few years is likely to have significant impact on the long-term evolution of disease. Natural-history studies have also shown that the number of relapses occurring during the first few years of disease is related to the amount of accrued disability.

Immunomodulation and Global Immunosuppression

Most people with immunotherapy in relapsing–remitting MS (RRMS) are currently treated with the immunomodulatory substances interferon (INF-β) or glatiramer acetate (GA). INF-β has multiple immunomodulatory effects: it curtails T-cell trafficking, redresses a Th1–Th2 imbalance that is in favor of proinflammatory Th1 responses in MS patients, and exhibits antiviral properties. Glatiramer acetate, a synthetic polypeptide composed of the most prevalent amino acids in myelin basic protein (MBP), is a main target antigen in
MS-related immune response. Glatiramer acetate is believed to modulate autoreactive T-cells, inhibit monocyte activity, and induce bystander immune suppression at lesion sites in the CNS. As GA-reactive T-cells have been reported to release neurotrophic factors, GA might theoretically also promote neuroregeneration. These drugs have shown a reduction of relapse rates at about 30−35% and reduction of inflammatory activity and lesion load at about 60% as measured by MRI.

Other immunomodulating substances (fumaric acid, teriflunomide, laquinimod, phosphodiesterase inhibitors) are being tested for therapeutic properties in phase-II or phase-III trials.

Alternatively global immunosuppression can be applied with immunosuppressant drugs, most frequently with azathioprine or cyclosporine, both well-known drugs in other autoimmune diseases. Mycophenolate mofetil, another member of the antimetabolite group of immunosuppressants, has also shown positive effects on relapsing rates in a small number of patients. Additional immunosuppressant drugs (e.g., cladribine, treosulfan, temsirolimus) are also being investigated in clinical trials at this time.

In addition, combination therapies with azathioprine and INF-β or azathioprine and GA are being explored.

Intravenous immunoglobulin G (IVIG) can modify the balance between Th1 and Th2 subtypes and produce a downregulation of proinflammatory cytokines. It is applied to several autoimmune diseases and has also shown reduced relapse rates and gadolinium-enhancing lesions in RRMS but failed to show a benefit in secondary progressive MS (SPMS). Presently, IVIG is a therapeutic option in pregnancy and post-partum to prevent new relapses.

**Selective Immune Intervention**

With the introduction of humanized monoclonal antibodies and small specific molecules (e.g., receptor agonists or antagonists), specific ablation of distinct immune populations or selective blockade or activation of immune molecules has become possible. Antibodies that bind cell-specific surface molecules allow depletion of T-cells, B-cells, and other immune-cell subsets via antibody binding and complement-mediated cell lysis.
Modulation of Immune-Cell Migration

If first-step immunomodulation fails in controlling disease activity, an escalating therapy should be adopted. Natalizumab, a humanized monoclonal antibody against the adhesion molecule α-4 integrin, blocks this epitope on leukocytes and therefore prevents leukocyte binding to the vessel wall and thereby hampers leukocyte passage across the blood–brain barrier. This drug effectively reduces disease activity and has already been approved for very active RRMS. Side effects may be severe and patients must be controlled very carefully.

FTY20 (fingolimode), a fungal metabolite with sphingosine-1-phosphate-receptor agonist activity, induces homing of lymphocytes to the lymph nodes and traps them at this site, thereby preventing their migration to inflamed organ departments. This orally administered drug is effective in transplantation and in autoimmune animal models. A phase-II trial in patients with MS revealed positive results, and a phase-III trial is currently ongoing.

Depletion of Immune Cells

The monoclonal antibodies mentioned below have already demonstrated effectiveness in reducing contrast-enhancing lesions and improving clinical scores in patients with RRMS in phase-II or small open-label trials. Further studies are intended or have already been started.

Alemtuzumab (Campath1H) is a humanized anti-leukocyte (CD52) monoclonal antibody that is cytolytic and produces prolonged lymphocyte depletion. Positive effects in RRMS have been shown, and a study in SPMS has generated not unequivocal results; thus, there is a need for more data. A phase-III trial will soon be started.

Daclizumab is a humanized monoclonal antibody specific for the IL-2-receptor alpha chain that inhibits activation of lymphocytes. Further clinical trials and more data about long-term efficacy and safety are required. Phase-II studies of daclizumab as monotherapy or combined with other treatments are now underway.

Rituximab, a human-murine chimeric monoclonal antibody that binds specifically to the CD20 antigen, causes rapid depletion of CD20-positive B-cells in the peripheral blood. In small studies patients with progressively relapsing myelitis and neuromyelitis optica experienced an improvement of ambulation and relapse-free phases. Rituximab seems to be beneficial in a subgroup of patients with high humoral activity. A phase-III study with rituximab is now under way as well.

Stem Cell Transplantation

Experimental and clinical observations suggest that high-dose immunosuppression followed by autologous stem cell transplantation can induce remissions in severe, refractory autoimmune diseases, including MS. Stem cells have the capacity to enter the CNS and transdifferentiate into microglia and possibly neurons, and therefore might be of significant importance in producing remyelination and neuron repair. Initial studies were associated with significant morbidity and mortality but were promising in terms of clinical stability and impact on disease activity at MRI. Patients with severe, rapidly worsening MS who are unresponsive to approved therapies could be candidates for this treatment, but only within clinical trials.

1.1.1.6.3 Therapy of Secondary Progressive Multiple Sclerosis

In secondary progressive multiple sclerosis (SPMS) treatment options are limited. Interferon-β might ameliorate disease progression slightly, although this effect could not be demonstrated in all studies. Nevertheless, interferon-β (Betaferon, Bayer Schering Pharma, Berlin, Germany) is approved for this indication, especially in the presence of relapses. In MS patients with rapidly progressive disease activity (e.g., deterioration in the EDSS of ≥1 point within 1 year) mitoxantrone, an antineoplastic agent, has shown efficacy on disability progression. Due to restricted cumulative life dose, mitoxantrone can be given for about 2 years, and thus far there is ambiguity as to which immunotherapy should be applied after mitoxantrone treatment.

1.1.1.6.4 Therapy of Primary Progressive MS

In primary progressive multiple sclerosis (PPMS) treatment only limited data are available from small studies. Beneficial effects in reducing progression of disability could be achieved by combined low-dose mitoxantrone and methylprednisolone therapy. Also repeated IV methylprednisolone administration has the ability to decelerate disease progression. An alternative therapy op-
tion is the treatment with low-dose oral methotrexate resulting in a slowed deterioration of motor function.

1.1.1.6.5 Symptomatic Therapy

A large panel of various symptomatic therapies to treat MS patients is necessary and available. Physiotherapy and occupational therapy are essential as well as anti-spastic, anticholinergic or analgetic drugs. Therapeutically, problems in coping with the disease should be considered as well as fatigue or depression, which are the main problems in about half of all MS patients.

Further Reading


1.1.2 Imaging

Martin Bendszus

1.1.2.1 Technical Aspects

Magnetic resonance imaging is the imaging modality of choice in MS. Lesion conspicuity is related to the field strength of the MR scanner; therefore, high-magnetic-field scanners (≥ 1 T) should be preferred. Lower-field-strength magnets with an open configuration, however, may be the only option for examining extremely claustrophobic or obese patients. With the advance of 3-T scanners in clinical routine detection and delineation of MS, lesions have once again increased (Wattiès 2006). Most MS patients undergo serial MR examinations. In order to assure intraindividual comparability, exact and reproducible slice positioning is essential; therefore, a scout sequence in three directions should be performed initially. Axial slices should be aligned with the subcallosal line on the mid-sagittal scout image (Simon et al. 2006). Another approach to assure exact slice repositioning is the acquisition of 3D data sets with secondary image reconstruction with isotropic voxel. Sequence parameters, angulation, and the amount of contrast medium should be kept identical for every patient. For clinical routine, a concentration of 0.1 mmol Gd-DTPA per kilogram body weight is well established (Simon 2006); however, higher concentrations (e.g., 0.2 or 0.3 mmol) reveal more contrast-enhancing lesions (Fillipi 1998). Another factor that directly influences the number and extent of contrast-enhancing lesions is the time between application of contrast medium and the beginning and duration of the MR sequence. This time should be at least 5 min and always be kept constant (Simon 2006). Magnetization transfer sequences may increase sensitivity in detecting contrast-enhancing lesions (Fillipi 1998). Lesion number and volume is directly related to slice thickness. For MR studies in a slice thickness of 3 mm for the axial slices is recommended (Polman 2005). In clinical practice, a slice thickness of 3–5 mm has been suggested (Simon 2006). For routine imaging of the brain in MS, the following sequence protocol has been suggested: sagittal FLAIR images, axial fast spin-echo (FSE) PD- and T2-weighted images, and axial T1-weighted images spin-echo (SE) images before and administration of Gd-DTPA (Simon 2006). For MRI of the spine sagittal T1-weighted and T2-weighted FSE sequences have been proposed, supplemented by axial T1-weighted and T2-weighted sequences (see also Chap. 5).

1.1.2.2 Imaging Findings in Typical MS

Magnetic resonance imaging is the most relevant para-clinical diagnostic criterion for MS as well as a surrogate parameter for monitoring disease activity. Unenhanced T2-weighted images are highly sensitive for the detection of hyperintense MS lesions and therefore useful for diagnosing MS, monitoring short-term disease activity, and assessing the overall disease burden; however, these lesions are nonspecific for the underlying pathologic findings, and correlations with clinical status seem to be weak. Hypointense lesions on T1-weighted images (so-called black holes) may represent areas with severe
tissue damage as demyelination and axonal loss. Hyperintense lesions on unenhanced T1-weighted images are possibly related to a local deposition of free radicals, and recent studies indicate an association between the presence of hyperintense T1-lesions and disability; therefore, post-gadolinium T1-weighted sequences should always be preceded by unenhanced T1-weighted images. Enhancement of gadolinium on T1-weighted images allows discrimination between active and inactive MS lesions, since Gd-DTPA enhancement is a consequence of a disruption of the blood–brain barrier and corresponds to areas with acute inflammation.

Typical localizations for MS lesions include the fossa posterior (in particular, pons, pedunculus cerebelli, and cerebellar white matter), the optic radiatio, the internal and external capsule, the corpus callosum, and the periventricular and subcortical region. Subcortical lesions typically include the subcortical U-fibers and are also referred to as “juxtacortical” lesions. In 2001, an international panel suggested diagnostic MR criteria for MS (so-called McDonald criteria; McDonald 2001). These criteria were revised and simplified in 2005 (Polman 2005). According to these criteria, the early diagnosis of MS may be established after one clinical event. The clinical concept of dissemination in space and time was adapted to MRI. Similar to the clinical diagnosis of MS, the MR diagnosis of MS requires a dissemination of lesions in space and time. Dissemination in space is dependent on the number and localization of lesions on T2-weighted images and contrast enhancement of lesions. In particular, dissemination in space includes the following four criteria: (1) at least one infratentorial lesion (Fig. 1.1.2.1); (2) at least one juxtacortical lesion (Fig. 1.1.2.2); (3) at least three periventricular lesions (Fig. 1.1.2.3); and (4) at least nine lesions overall (Fig. 1.1.2.4) or, alternatively, at least one contrast-enhancing lesion (Fig. 1.1.2.4). If three of these four criteria are positive, dissemination in space is fulfilled (Table 1.1.2.1). Spinal cord imaging can be extremely helpful in excluding other differential diagnoses. Whereas lesions in the brain can develop in healthy aging people, this is not typical in the spinal cord. Lesions on spinal MRI may contribute to the dissemination in space. Spinal cord lesions should be focal (i.e., clearly delineated and circumscribed as seen on heavily T2-weighted images) in nature for consideration in MS diagnosis. Moreover, they should be at least 3 mm in size, but less than two vertebral segments in length and occupying only part of the cord cross section. Spinal cord lesions may contribute to the dissemination in space on MRI: (1) one spinal lesion may replace an infratentorial lesion (Fig. 1.1.2.5); (2) the number of spinal lesions is added to the overall number of cerebral lesions; and (3) one spinal contrast-enhancing lesion may replace a cerebral contrast-enhancing lesion (Fig. 1.1.2.5); thereby, spinal MRI may fulfill two of four criteria of dissemination in space on MRI.

Dissemination in time requires new lesions on MRI follow-up. New lesions are defined as (1) detection of a gadolinium-enhancing lesion at least 3 months after the onset of the initial clinical event, if not at the site cor-
responding to the initial event (Fig. 1.1.2.6), or (2) detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event (Fig. 1.1.2.7). For the first criterion only one MR examination is necessary (no reference scan), whereas for the second criterion two MR examinations are required (Table 1.1.2.2).

Recently, simplified criteria for the early diagnosis of MS have been suggested. According to these criteria, dissemination in space may be fulfilled by at least one lesion in at least two of the four typical regions (i.e., periventricular, juxtacortical, infratentorial, and spinal cord). Dissemination in time may be fulfilled by one or more new T2 lesions at a 3-month follow-up. These new criteria improved sensitivity for the development of clinically definite MS without a reduction in specificity, which underlines the tendency toward an earlier and less rigid early diagnosis of MS by MRI (see also Chap. 5; Swanton 2007).

1.1.2.3 Imaging Findings in PPMS

Besides acute relapsing–remitting, the beginning of MS onset may be primarily chronic in 10–15% of patients. Clinically, the diagnosis of primarily chronic MS repre-

Fig. 1.1.2.2a,b. Multiple periventricular lesions. a Axial PD-weighted image. b Sagittal FLAIR image. These lesions typically have an ovoid shape with immediate contact to the lateral ventricles (“Dawson finger”). The immediate contact to the lateral ventricles is demonstrated best on sagittal FLAIR images (b). One criterion for dissemination in space is given if at least three periventricular lesions are present.

Fig. 1.1.2.3. Subcortical lesions. Axial PD-weighted image. Hyperintense subcortical lesions. One subcortical lesion can fulfill one criterion for dissemination in space. In contrast to microangiopathic lesions, MS lesions involve the subcortical U-fibers (so-called juxtacortical lesions).
Fig. 1.1.2.4a–c. MS plaques. a, b Axial PD-weighted images. c Axial T1-weighted image after contrast administration. Multiple (more than nine) hyperintense lesions fulfill one criterion for dissemination in space (a). Equivalent to these more than nine hyperintense lesions one contrast-enhancing lesion (c) may fulfill this criterion for dissemination in space.

Presents a challenge. Compared with a relapsing–remitting course of disease, patients with PPMS are older at onset and a higher proportion is male. Inflammatory white matter lesions are less evident, but diffuse axonal loss is seen in normal-appearing white matter, in addition to cortical demyelination. Spinal cord atrophy corresponds to the frequent clinical presentation of progressive spastic paraplegia. In 2005, new diagnostic criteria were introduced by an international panel to diagnose primarily chronic MS. Apart from 1 year of disease progression (retrospectively or prospectively determined), the diagnosis of PPMS requires any two of the following...
Fig. 1.1.2.5a,b. Spinal lesions.  
- (a) Sagittal T2-weighted image.  
- (b) Sagittal T1-weighted image after contrast administration.  
Hyperintense lesions in the cervico-thoracic spine on sagittal T2-weighted images (a) extending over one to two segments. One of these lesions reveals enhancement of Gd-DTPA on sagittal T1-weighted images (b). For the criteria for dissemination in space one spinal cord lesion can replace an infratentorial lesion, the number of spinal lesions can be added to the overall number of cerebral T2 lesions, and one contrast-enhancing spinal cord lesion can replace a contrast-enhancing cerebral lesion; thereby, spinal cord MRI can fulfill two of four criteria for dissemination in space.
three criteria: (1) positive brain MRI (defined as nine T2 lesions or four or more T2 lesions with positive visual-evoked potential); (2) positive spine MRI (defined as two focal T2 lesions); and (3) positive cerebrospinal fluid (defined as oligoclonal IgG bands and/or increased IgG index).

### Differential Diagnosis

The differential diagnosis of MS includes other white matter lesions such as unspecific or microangiopathic white matter changes, acute disseminated encephalomyelitis (ADEM), cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), neurosarcoidosis, viral encephalitis, cerebral vasculitis, and metastasis. Microangiopathic...
white lesions have a more bandlike configuration and have no preferential manifestation in the corpus callosum, as is true for MS. In contrast to cerebral microangiopathy, MS only rarely manifests in the central gray matter (basal ganglia, thalamus). Lesions from ADEM are often more asymmetric than MS plaques, may also be manifested in the central gray matter, and have no predilection for the corpus callosum, as is the case with MS. Furthermore, ADEM lesions are mostly in the same stage regarding contrast enhancement. The CADASIL lesion typically involves the subcortical white matter of the frontal and temporal lobes, and the inner capsule. Neurosarcoidosis often involves the cranial nerves, the pituitary gland, the hypothalamus, and the leptomeninges, and the signal of granulomas on T2-weighted images is mostly iso- to hypointense (see also Chap. 3). The most common viral encephalitis which may mimic MS in imaging is neuroborreliosis (Lyme disease). In neuroborreliosis cranial nerves are often involved (see also Chap. 6). The imaging pattern in CNS vasculitis depends on the number, the site, and the size of the involved vessels; therefore, in contrast to MS, cerebral vasculitis may also involve cerebral gray matter. In some patients with vasculitis vessel stenoses or occlusions may be detected using MRA or DSA (see also Chap. 2.2). Cerebral metastases are typically located at the gray−white matter interface (corticomedullary junction), are space occupying, sometimes reveal hemorrhage, and show contrast enhancement throughout.

References

1.2
Other Demyelinating Diseases

Brigitte Storch-Hagenlocher and Martin Bendszus

Summary
In addition to MS there are several other idiopathic inflammatory demyelinating diseases (IIDDs) which differ in clinical course, severity, and lesion distribution as well as in imaging, laboratory, and pathological findings. Some IIDDs have a restricted topographical distribution such as optic neuritis, transverse myelitis, and neuromyelitis optica. (Devic) Acute disseminated encephalomyelitis (ADEM) is a clinical monophasic inflammatory disease with a broad spectrum of clinical and radiologic features. The differentiation of tumor-like lesions sometimes may be challenging. Fulminant variants of IIDDs are Marburg’s disease, Baló’s concentric sclerosis, and Schilder’s disease characterized by acute and severe attacks, and lesions seen as typical on MRI.

1.2.1
Introduction
Demyelinating lesions of the brain most frequently present with a typical clinical and morphological pattern of MS; however, atypical findings also exist and may represent differential diagnostic problems. Herein the most frequent types of idiopathic inflammatory demyelinating lesions of the brain are outlined.
1.2.2 Clinically Isolated Symptoms

Patients with monofocal inflammatory demyelinating symptoms, such as transverse myelitis, optic neuritis, or isolated brain-stem manifestation, not always but frequently develop MS especially in the presence of positive MRI and cerebral spinal fluid (CSF) findings. Patients with isolated symptoms who present with disseminated demyelinating lesions on MRI and oligoclonal bands present in the CSF have an 88% chance of developing clinically definite MS within 10−15 years, as compared with about 20% of such patients with normal MRI and CSF findings.

1.2.3 Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated acute inflammatory disorder of the central nervous system characterized by extensive demyelination predominantly involving the white matter of the brain and spinal cord. Most frequently, the disease is precipitated by a vaccination or viral infection. Patients commonly present with nonspecific symptoms, including headache, vomiting, drowsiness, fever, and lethargy, all of which are relatively uncommon in MS. Gender ratio of the disease is equal, but children and young adults are more affected than elderly. The CSF findings usually differ from those of MS patients. The CSF cell count is frequently elevated (>50/µl) but also may be normal, and the presence of oligoclonal bands is variable. Thus far, however, the diagnosis of ADEM is still based on the clinical and radiological features, since no other typical biological markers are available. Lesions in ADEM are typically large, multiple, and asymmetric (Fig. 1.2.1). In most cases, lesions involve the subcortical and central white matter as well as the cortical gray–white matter junction of cerebral and cerebellar hemispheres, brain stem, and spinal cord. Moreover, the deep gray matter of the thalami and basal ganglia are commonly involved. A symmetrical pattern of lesion distribution is common. The corpus callosum is not typically involved but may be affected in large lesions. Four patterns of cerebral involvement have been proposed to describe the MRI findings in ADEM: (1) ADEM with small lesions (<5 mm); (2) ADEM with large, confluent, or tumefactive lesions, with frequent extensive perilesional edema and mass effect; (3) ADEM