The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

EASi™
European Autoimmunity
Standardisation Initiative


ThermoFisher
SCIENTIFIC

The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

Pabst Science Publishers
Lengerich, Berlin, Bremen, Miami,
Riga, Viernheim, Wien, Zagreb

Bibliographic information published by Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

http://www.pabst-publishers.de

Printing: MercedesDruck, Berlin
Typesetting: Hilmar Schlegel, Berlin
Cover: Agentur für zeitgemäße Kommunikation Kaner Thompson
www.kanerthompson.de

ISBN 978-3-89967-770-6

Multiple sclerosis

Stephanie Knippenberg, Jan Damoiseaux, Raymond Hupperts

1 Introduction

Multiple Sclerosis (MS) is a chronic, invalidating disease of the central nervous system (CNS), characterized by focal inflammation, demyelination, and loss of neurons within the CNS. The inflammation causes areas of scars within the CNS, giving the disease its name: multiple areas of hard scars (sclerosis). The inflammation is believed to be of autoimmune origin. In MS, white blood cells are able to cross the blood brain barrier. Inflammation, demyelination and loss of neurons is caused by the release of soluble factors by infiltrating leukocytes and resident microglial cells [1].

Clinically, the inflammation within the CNS causes a variety of neurological complaints depending on the location of the inflammation. Muscle weakness and sensory loss are the most common first symptoms of MS, especially in the limbs. Other common first symptoms are optic neuritis (ON) and double vision (Table 1) [2]. Most patients start with a relapsing remitting form of MS (RRMS) that generally becomes progressive overtime, while patients become more severely disabled. In this progressive phase, the disease is referred to as secondary progressive (SP) MS. A small proportion of patients experiences progressive disability from disease

Table 1. Common first symptoms of MS.

Presenting symptom	Percentage of patients
Motor weakness of the limbs	43–46 %
Sensory problems	41–49 %
Optic neuritis	22.5–36 %
Double vision	13–19 %
Ataxia	8 %
Bladder dysfunction	1.25 %
Cranial nerve dysfunctions	1.25 %

onset onwards without relapses and remissions, and in these patients the disease is called primary progressive (PP) MS [1].

Globally the estimated median incidence of MS is 2.5 per 100 000 (minimum-maximum range is 1.1–4.0) and the median prevalence of MS is 30 per 100 000 (minimum-maximum range of 5–80). MS is more prevalent in countries further from the equator. Women are affected twice as frequently as men and this ratio may be increasing. The age at disease onset is typically between 20 and 50 years of age, although MS can occasionally have its onset during childhood or in the elderly [3].

2 Diagnostic measurements for experts

MS can be hard to diagnose since it can have a heterogeneous first presentation (Table 1). The diagnosis is made clinically, based upon the appearance of MS lesions in different parts of the CNS that have occurred at different points in time. To facilitate and standardize the diagnostic process, diagnostic criteria were defined. Historically, the Schumacher and Poser criteria were both popular. Nowadays, the McDonald criteria are most recommended. The McDonald diagnostic criteria were inaugurated in 2001, making a diagnosis possible after a first clinical attack. These criteria were revised in 2005 and are updated again in 2010. The McDonald criteria focus on the demonstration of the dissemination of MS lesions in time and space by predominantly clinical and radiologic data (Table 2).

Table 2. Diagnostic criteria according to McDonald criteria 2010.

Clinical presentation (neurological attacks)	Objective clinical evidence (MRI lesions)	Additional data needed to confirm MS diagnosis
Two or more	Two or more **or** Objective clinical evidence of 1 lesion with historical evidence of another prior attack	None
Two or more	One	Dissemination in space – verified by MRI [a] **or** – verified by second clinical neurological attack implicating a different CNS site
One	Two or more	Dissemination in time – verified by MRI [a] **or** – verified by second clinical neurological attack

Clinical presentation (neurological attacks)	Objective clinical evidence (MRI lesions)	Additional data needed to confirm MS diagnosis
One	One	Dissemination in space: – verified by MRI [a] **or** – verified by second clinical neurological attack implicating a different CNS site **and** dissemination in time: – verified by MRI [a] **or** – verified by second clinical neurological attack
Neurological progression suggestive of MS without attacks (PPMS)		One year of neurological disease progression (either retrospectively or prospectively determined) and two of the following points: – Evidence for dissemination in space in the brain based on ≥ 1 MRI brain lesions [a] – Evidence for dissemination in space in the spinal cord based on ≥ 2 MRI spinal cord lesions [a] – Positive CSF [b]

[a] Verification by MRI must fulfil specific MRI criteria

[b] CSF is determined positive if oligoclonal bands are found in CSF

Abbreviations: CSF, cerebrospinal fluid; CNS, central nervous system; MS, multiple sclerosis; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.

Clinically, two distinct episodes of neurological impairment, for which different inflammatory or demyelinated lesions within the CNS are presumed, can be sufficient for the diagnosis of MS, provided that the neurological impairment has been objectively observed for at least 24 hours [4]. Since many people seek medical attention after one episode, additional testing is often necessary. The most commonly used additional diagnostics are magnetic resonance imaging (MRI) and analysis of the cerebrospinal fluid (CSF). MRI of the brain and spine may show areas of inflammation or demyelination (Fig. 1). Gadolinium can be administered intravenously as a contrast to highlight active inflammatory lesions and demonstrate the existence of older lesions not associated with symptoms at the moment

of the evaluation. The sensitivity of MRI criteria for MS is between 35 % and 100 %, and specificity is between 36 % and 92 %. CSF obtained by lumbar puncture can provide information about inflammation of the CNS by testing it for oligoclonal bands of immunoglobulin G (IgG). This is preferentially tested by isoelectric focusing, which is considered to be the gold standard. Oligoclonal bands are found in 75–85 % of subjects with MS. Combination of MRI and CSF criteria for MS enhance sensitivity (56–100 %) and specificity (53–96 %) [4, 5]. Furthermore, the nervous system of a person with MS responds less actively to stimulation of the optic nerve and sensory nerves due to demyelination. These diminished responses can be examined using visual and sensory evoked potentials [4].

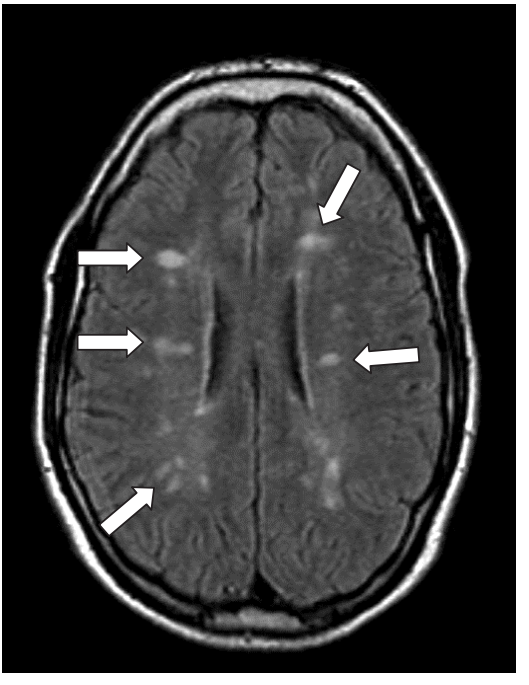

Figure 1. MRI showing multiple periventricular white matter lesions, consistent with multiple sclerosis.

3 Requirements for family practitioners

MS patients can suffer from a wide variety of neurological complaints, which are diverse in quantity and quality, and can arise from dysfunction of each component of the CNS. Although loss of motor function is the most well recognized symptom, symptoms can also include sensory impairment, visual impairment,

balance disorders, bowel and bladder dysfunction and sexual dysfunction. Cognitive impairment of varying degrees and emotional symptoms of depression or unstable moods are also common. Lifetime prevalence of fatigue is reported by 92 % of patients with MS. Patients suspected of having MS typically consult their general practitioner with muscle weakness, sensory symptoms or optic neuritis. Other neurological complaints may have occurred before the initial presentation. This should be carefully investigated as part of the medical history. When MS is suspected, the patient should be referred to a neurologist for further examination. This ensures that required treatments are started, and reduces anxiety and uncertainty. The presence of 2 clinical neurological attack and 2 or more MRI-detected lesions consistent with MS confirms the diagnosis, according to the McDonald criteria. If this is not the case, dissemination in space and time should be demonstrated by MRI or by a second clinical attack to confirm the diagnosis [4].

4 Follow up

Clinical observations

Patients with RRMS, experience episodic periods of worsening of neurological functions, called relapses. The relapse rate hardly ever exceeds 1.5 per year. The occurrence of relapses is unpredictable. However, viral infections and stress may increase the risk of a relapse. Other patients, SPMS or PPMS patients, experience a gradually progressive deterioration of neurological functions, or a combination of relapses and progressive deterioration. To rate the neurological deterioration in MS patients, the Kurtze expanded disability status scale (EDSS) is frequently used. The EDSS score is based upon neurological testing and examination of 7 areas of the CNS; pyramidal (motor), cerebellar (coordination), brainstem (speech and swallowing), sensory (touch and pain), bowel and bladder functions, visual, and mental functions (mood and fatigue).The EDSS is an ordinal scale in half-point increments ranging from 0 (normal neurologic examination) to 10 (death due to MS).

Expectations

MS is a chronic disease and there is no cure. The reduction in life expectancy is 5 to 10 years, with a median time to death about 30 years from onset. Prognosis depends on the subtype of the disease, gender, and initial symptoms. Relapsing remitting onset of the disease, optic neuritis as initial symptoms, and female gender are associated with a better prognosis [3].

Blood tests to be done

There are no blood tests available for monitoring disease activity.

5 Management

Since there is no cure for MS, current treatments attempt to prevent relapses and disability progression. Acute relapses are treated with high-dose intravenous corticosteroids, such as methylprednisolone. The registered maintenance therapies for MS are either immune modulating therapies or immune suppressive therapies. First-line maintenance therapies are beta-interferons and glatiramer acetate. Both therapies are administered by subcutaneous injections, varying from once a day to once a week. The first-line therapies are immune-modulating drugs; they skew the balance between a pro-inflammatory and anti-inflammatory immune response towards an anti-inflammatory immune response. Both beta-interferons and glatiramer acetate reduce the number of relapses by 30 %. Common side effects are irritation at the injection site and symptoms similar to influenza.

Non-responders to first-line drugs need more aggressive therapy to prevent increasing disability. Second-line therapies include Mitoxantrone and Natalizumab. Mitoxantrone is an immuno-suppressive drug developed to treat malignancies. It is used for the treatment of very active RRMS or SPMS and gives a significant reduction in relapses, an overall clinical improvement, and a reduction in active lesions on MRI. It is administered intravenously once per month. However, due to rare but serious side effects as cardiotoxicity, infertility, and acute myeloid leukaemia, it is not a physician's first choice. Natalizumab is the most recent drug in the group of disease modifying drugs available for the treatment of MS. It is a monoclonal antibody directed to an adhesion molecule expressed by white blood cells. Natalizumab is administered intravenously once per month. Its primary function is to inhibit migration of leukocytes towards the site of inflammation, i. e., the CNS. Natalizumab has shown a great efficacy, both in terms of relapse rate reduction and halting disability progression. However, long term effects are unknown and it is linked to the development of progressive multifocal leukoencephalopathy in a few patients. Currently, numerous new drugs are being tested for their efficacy in MS treatment [1].

6 Diagnostic tests

The presence of oligoclonal bands in CSF has long been considered an important supportive criterion for the diagnosis of MS. The term oligoclonal was coined because a restricted number of intrathecal B cells are triggered to produce immunoglobulins (Ig) of the IgG class. The IgG have a restricted heterogeneity with respect to their mobility in an electric field as is preferentially tested by isoelectric focusing. Isoelectric focusing is a technique which separates molecules based on their difference in isoelectric point. The charge of a protein is dependent on the sum of its ionisable acidic and basic amino acids. When protein is placed in a gel with a linear pH gradient and subjected to an electrical field, it will initially move

to the electrode with the opposite charge. During migration through a changing pH, the protein will either lose or pick up protons, thereby changing its net charge. Eventually, the protein will be uncharged, and will stop migrating. It has reached its isoelectric point. After isoelectric focusing, separated proteins are passively transferred to a cellulose nitrate membrane. Next, the membrane is incubated with sheep anti-human IgG antiserum as primary antibody, and anti-sheep IgG peroxidase conjugate as secondary antibody. The IgG bands are then visualized by the addition of 3-amino-9-ethylcarbazole. The IgG patterns seen in healthy individuals reveal a polyclonal smear which is similar in CSF and corresponding serum. In contrast, the patterns observed in patients with MS reveal discrete bands of IgG in CSF which is not reflected in the serum (Fig. 2).

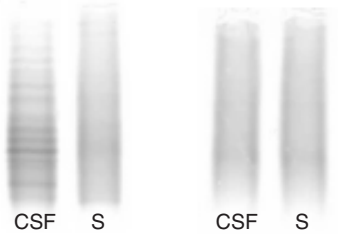

Figure 2. Patterns from isoelectric focusing of paired serum (S) and concentrated cerebrospinal fluid (CSF) adjusted to the same amount of IgG applied. A patient with multiple sclerosis (left) and a healthy control (right) are displayed.

7 Testing methods

The great benefit of the diagnostic tests and the McDonald criteria is the possibility of diagnosing MS at an early stage, which enables the MS patient to start treatment as soon as possible.

Limitations are the necessity of combining the different diagnostics, which puts extra burden on the patient. Lumbar puncture, in particular, is experienced as unpleasant and stressful by MS patients. In addition, tests run in the laboratory require expertise and are subjective. Currently there is an ongoing search for biomarkers which may facilitate the diagnosis of MS.

References

[1] Compston A, Coles A. Multiple sclerosis. Lancet 2008; 372: 1502–17.
[2] Sanders JAM, Beenakker CIM. Multiple Sclerosis Manual. 3rd ed. The Netherlands: Academic Pharmaceutical Productions bv, 2010

[3] W.H.O. Atlas Multiple Sclerosis Resources in the World 2008 (Accessed Nov 22, 2011, at http://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf)
[4] Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292–302.
[5] Schäffler N, Köpke S, Winkler L, et al. Accuracy of diagnostic tests in multiple sclerosis — a systematic review. Acta Neurol Scand, 2011; 124: 151–64.