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Review article

Evolution of diagnostic criteria for multiple sclerosis

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ABSTRACT

Multiple sclerosis is a chronic demyelinating disease of the central nervous system that occurs primarily in young adults. There is no single diagnostic test to recognize the disease. The diagnostic criteria, based on clinical examination and laboratory tests, have changed considerably over time. The first guidelines involved only the results of the patient's neurological examination. The diagnostic criteria developed by Poser in 1983 were based largely on the results of additional tests, including visual evoked potentials and analysis of cerebrospinal fluid. The McDonald criteria, developed in 2001and updated in 2005 and 2010, reflected the diagnostic breakthrough caused by widespread use of magnetic resonance imaging (MRI). Currently, the diagnosis depends largely on the results of the MRI examination. An early diagnosis is particularly important for starting disease-modifying treatments.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS), and the aetiology is still not fully understood. There is currently no single diagnostic test for MS. The most common tool used to support the clinic-based diagnosis is magnetic resonance imaging (MRI). Over the last ten years the criteria for diagnosing MS have changed considerably, as have the improvements of MRI. Examination of the cerebrospinal fluid (CSF), to demonstrate an increase of immunoglobulin production, was formerly considered one of the basic diagnostic tests, but it lost its importance in the MRI era. Still, the diagnostic methods have many limitations and are often not specific enough for a diagnosis of MS, especially in the early stages of the disease. As early initiation of disease-modifying therapy is important, the diagnostic process is both a medical and ethical challenge.

2. The first guidelines for recognizing MS

The first physician who described the clinical features typical for MS was Jean-Martin Charcot (reviewed by [1]). Nystagmus, intention tremor, and scanning speech were the triad of

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symptoms presented in 1868. For many years Charcot's triad was said to be characteristic of MS. It turned out, however, that this group of symptoms typically occurred in advanced stages of the disease, and also appeared in a number of neurological disorders, particularly those associated with damage to the cerebellum [2,3].

In 1906, Marburg also attempted to develop criteria for the diagnosis of MS. He stated that the co-occurrence of Uhthoff's phenomenon (worsening of neurological symptoms when the body's temperature increases), pyramidal signs, and a lack of plantar reflex was enough to make a diagnosis. Both Charcot's triad and the criteria of Marburg had low specificity (reviewed by [4]).

In 1954, first clinical classification of MS made by Allison and Milliar appeared (reviewed by [1]). This classification recognized the appearance of clinical symptoms at different time points in different regions of the central nervous system (CNS) as typical for MS. Until then, the terms ''dissemination in time (DIT)'' and ''dissemination in space (DIS)'' were used to describe the characteristics of MS [5]. The authors of this first contemporary definition divided the patients into the following groups ''early'', ''possible'' and ''probable'' MS. That was the first time the patients' reports of symptoms were taken into account. The division of patients into the groups, mentioned above, was later used by Schumacher, who developed the first modern diagnostic criteria for MS [6]. According to Schumacher, 1965, all the following conditions had to be met to diagnose clinically definite MS:

a) the presence of objective symptoms during the neurological examination;
b) at least two symptoms suggesting the involvement of different regions of CNS present in the neurological examination or documented in the medical history;
c) the presence of symptoms resulting mainly from white matter lesions;
d) at least two documented relapses, with symptoms lasting a minimum of 24 h, and at least 1 month between the relapses or the progression of symptoms within 6 months of observation;
e) patient aged between 10 and 50 years;
f) other diseases causing similar symptoms were less probable.

Over the next few years, it was repeatedly pointed out that Schumacher's criteria were too restrictive. There were attempts to improve them (e.g. by McAlpine, Lumsden, Acheson) [4], but without much success. The only accepted change was removing the age limit from the criteria in the modification by Rose, published in 1976 [7].

3. Poser criteria

Poser et al. created new diagnostic criteria for MS in 1983 for clinical trials [8]. These were based on Schumacher's previous criteria. Five possible diagnoses were identified:

1) clinically definite MS;
2) clinically probable MS;
3) laboratory supported definite MS;
4) laboratory supported probable MS;
5) not MS [8].

Poser et al. suggested screening only patients that met the criteria of definite and probable MS [8].

The main clinical feature of MS was a ''relapse'', also called ''the neurological worsening.'' The definition of a relapse was an acute or subacute onset of neurological symptoms ''typical for MS'' which had to be present for at least 24 h and weren't due to an infection. These symptoms had to be observed during the patient's examination, or if they existed in the past, were reported accurately by the patient. Calling the symptoms ''typical for MS'' Poser discarded such unspecific symptoms as headaches, disturbances of consciousness or psychiatric symptoms. Also, the authors recommended caution when classifying relapse symptoms described only by the patient, and not documented by a clinical examination [8].

Poser criteria allowed a diagnosis of clinically definite MS to be made if there were at least two relapses (DIT) and if there was clinical evidence of damage to at least two structures of the CNS (DIS). The second neurological worsening was recognized as a second relapse if at least 30 days had passed since the start of the recovery from a previous exacerbation of the disease.

Laboratory supported definite MS could be diagnosed when there was clinical evidence of damage to one region of the CNS, but abnormalities in laboratory tests pointed to additional subclinical damage in a different placement.

A new part of the diagnostic criteria considered the laboratory tests (evoked potentials, CSF examination, and MRI scan), which had only a supporting role in the diagnostic process, – e.g. abnormalities in these studies equalled the clinical evidence of structural damage to the CNS. It was necessary to identify at least one clinical relapse to diagnose MS.

Of the above-mentioned laboratory tests, a special role was attributed to the CSF study (which confirmed the intrathecal synthesis of immunoglobulin). Widely used since the 1950s globulin tests and the colloidal gold test [9] were gradually replaced by the calculation of the IgG index and the presence of oligoclonal bands in the CSF that demonstrated intrathecal IgG synthesis. An elevated IgG index or the presence of oligoclonal bands in the CSF was used to diagnose laboratory supported MS [10].

Another group of laboratory tests useful in supporting the diagnosis were the electrophysiological examinations. Specific abnormalities found in evoked potentials were equivalent to the silent lesions of the CNS. Prolonged latencies of visual evoked potentials (VEP) indicated damage to the optic nerve or visual pathways, brainstem auditory evoked potentials (BAEP) indicated a lesion of the brainstem, and somatosensory evoked potentials (SSEP) indicated damage to the sensory pathways at the level of the spinal cord and brainstem.

At that time, there were no standard procedures for assessing MS lesions by MRI, nevertheless, showing lesions by MRI could support the diagnosis. Also, the availability of MRI in clinics was still very limited [11,12].

The authors advocated caution when diagnosing MS in patients with only one confirmed clinical relapse and abnormalities in the laboratory tests [8]. In this situation there was a risk of misdiagnosing a patient who could suffer