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Review article

Evolution of diagnostic criteria for multiple sclerosis

Joanna Przybek [a,1], Inga Gniatkowska [b], Dagmara Mirowska-Guzel [a,b], Anna Członkowska [a,b,*]

[a] Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland
[b] 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

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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

* *Corresponding author at*: 2nd Department of Neurology, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02-957 Warsaw, Poland. Tel.: +48 22 45 82 537/22 84 27 683; fax: +48 22 84 24 023.
E-mail addresses: neuro2@ipin.edu.pl (I. Gniatkowska), dmirowska@wum.edu.pl (D. Mirowska-Guzel), czlonkow@ipin.edu.pl (A. Członkowska).
[1] Tel.: +48 22 1166160; fax: +48 22 1166202.
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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

from another disease of the CNS, for example inflammatory diseases, such as Borrelia burgdorferi infection or CNS syphilis, autoimmune diseases, such as acute disseminated encephalomyelitis (ADEM), or degenerative disorders, such as vitamin B12 deficiency or Friedreich's ataxia. Therefore, special care was advised when diagnosing MS when both types of changes (clinical and laboratory) appeared at the same time [8,11].

4. McDonald criteria

The development of radiological scans, particularly MRI, as well as the introduction of the first disease-modifying drug-interferon beta, into the European market in 1996 called for the further changes in the MS diagnostic criteria. The researchers aimed for a quicker and more accurate diagnosis of MS in its early stage, when the potential treatment effect was thought to be the largest [13].

In 2001, the International Panel on MS Diagnosis chaired by Ian McDonald developed new criteria for diagnosing MS, now known as the ''McDonald criteria'' [14].

Several important changes were introduced to the Poser criteria. The classifications of clinically or laboratory supported definite or probable MS were abandoned because such divisions did not correlate with the further clinical course [14]. The number of diagnoses was reduced to three: ''MS'', ''possible MS'' and ''not MS''. The diagnosis of MS was given when the disease had a typical clinical course and met all the required criteria. Possible MS referred to a situation when the symptoms presented by the patient indicated MS, but did not meet the McDonald criteria; therefore further observation of the patient was required [15,16]. The ''not MS'' diagnosis excluded the disease [14].

McDonald et al. also modified the definition of relapse, stressing that the symptoms must have a duration of at least 24 h and may not be associated with fever or other symptoms of infection. The necessity of a 30-day gap between the two relapses remained, so they would be considered separately. They also modified the definition of such a gap. It was accepted that 30 days had to pass between the onset of neurological symptoms suggestive of a relapse and the appearance of the next neurological worsening (not since the ''early recovery'', recommended by Poser). It was also stated that the paroxysmal movements may be treated as a relapse only if they appeared several times within at least 24 h [14].

Another change was an increase in the importance of CNS imaging using MRI techniques in the process of diagnosing MS. In the Poser criteria, MRI played only a supporting role and was used mainly as a tool for finding a second, subclinical outbreak; while it became as important as a clinical evaluation, and was mandatory if DIT or DIS could not be documented by neurological examination.

Radiological DIS could be proven if there were sufficient numbers of lesions suggestive of demyelination (with clear edges, greater than 3 mm in diameter) and these lesions met the radiological criteria for MS (developed by Barkhoff, modified by Tintore) (Table 1) [11,17–19]. According to MRI criteria at al. these MRI criteria significantly raised the specificity of the diagnosis, while not greatly changing the sensitivity; thus, they were incorporated into the McDonald criteria.

The DIS was also proven when the MRI indicated the existence of lesions suggestive of demyelination, but their number and localization made them insufficient to satisfy the criteria. If such a situation occurred, the presence of two lesions typical of MS in MRI in conjunction with the presence of oligoclonal bands or an elevated IgG index in the CSF were considered sufficient to prove DIS.

The new criteria also introduced the possibility of radiological DIT. To prove DIT, the co-existence of new and old lesions had to be demonstrated by MRI (Table 2).

The relapsing-remitting form of MS (RRMS) could still be diagnosed only after the second relapse, but patients could meet the McDonald criteria for MS before the second relapse happened. This group is defined in the medical literature as 'McDonald MS' and includes patients:

Table 1 – Radiological criteria of 'dissemination in space' (DIS): a comparison.

Original McDonald criteria (2000)	Modified McDonald criteria (first revision, 2005)	Modified McDonald criteria (second revision, 2010)
Three conditions out of four must be met: 1. At least one gadolinium-enhancing lesion must be present or at least 9 T2 hiperintensive lesions must be present if gadolinium-enhancing lesions are absent. 2. At least one infratentorial lesion must be present. 3. At least 1 subcortical lesion must be present. 4. At least 3 periventricular lesions must be present.	Three conditions out of four must be met: 1. At least one gadolinium-enhancing lesion must be present or at least 9 T2 hiperintensive lesions must be present if gadolinium-enhancing lesions are absent. 2. At least one infratentorial lesion must be present. 3. At least 1 subcortical lesion must be present. 4. At least 3 periventricular lesions must be present.	'Dissemination in space' may be demonstrated by a presence of at least 1 T2 hiperintensive lesion[a] in 2 out of 4 typical locations: • periventricular • subcortical • infratentorial • in the spinal cord[b].

Important: The lesion in the spinal cord is equivalent to the infratentorial lesion. The gadolinium-enhancing lesion in the spinal cord is equivalent to the gadolinium-enhancing lesion in the brain. The lesions in the spinal cord can be counted together with the brain lesions to meet the required number of 9 lesions.

[a] Gadolinium-enhancing lesions are not required for DIS.

[b] If the patient has a relapse with spinal or truncal symptoms, the lesion responsible for these symptoms should not be counted.

Table 2 – Radiological criteria of 'dissemination in time' (DIT): a comparison.

Original McDonald criteria (2000)	Modified McDonald criteria (first revision, 2005)	Modified McDonald criteria (second revision, 2010)
DIT can be proven by: a) By a presence of at last one gadolinium-enhancing lesion in the brain in the MRI scan performed at least 3 months after the onset of first clinical symptoms*. This lesion should not be the one responsible for the clinical symptoms.	DIT can be proven in two ways: a) By a presence of gadolinium-enhancing lesion in a MRI scan performed at least 3 months after the onset of first clinical symptoms. This lesion should not be the one responsible for the clinical symptoms.	DIT can be proven in two ways: a) By a presence of a new T2 hiperintensive lesion or a gadolinium-enhancing lesion in the next MRI scan. The time of the previous MRI scan is not important.
b) By a presence of a new T2 hiperintensive lesion or a gadolinium-enhancing lesion in the second MRI scan performed not sooner than 3 months after the first.	b) By a presence of a new T2 hiperintensive lesion in the next MRI scan if the previous one was done at least 30 days after the onset of first clinical symptoms.	b) By a presence of both gadolinium-enhancing and non-enhancing lesions in the first MRI scan. The time of the MRI scan is not important.

* If the first MRI scan is done too early, it cannot be used for diagnosing DIT. Performing a second MRI scan no sooner than 3 months after the onset of clinical symptoms is recommended.

- after the first multifocal relapse,
- after two relapses with a single neurological symptom and those
- with clinically isolated syndrome (CIS) [11,20,21].

With the increasing importance of MRI of the brain, the role of other laboratory tests diminished. An MRI of the spinal cord was not included in the criteria, despite all the evidence suggesting lesions typical for MS may exist there, due to a lack of data from clinical trials. To satisfy the criteria, CSF examination was indicated only when MRI alone could not prove the DIS. McDonald at al. recommended VEP only if subclinical damage to the optic nerve was suspected. Other evoked potentials (SSEP, BAEP) were not included in the criteria because they did not contribute relevant data for the diagnosis of MS [20].

To summarize, MS according to the original McDonald criteria could be identified solely on the basis of clinical evaluation or with the help of additional laboratory tests (Table 3). It should be noted that McDonald at al. did not allow the symptoms reported by the patient to be counted as a relapse. In each case the lack of clinical proof for DIT or DIS indicated the need to perform an MRI scan of the brain. For the patients with CIS it was necessary to prove both DIS and DIT by MRI.

The original criteria were characterized by a good predictive value. In two large clinical trials evaluating the usefulness of McDonald criteria, Dalton et al. found that both the sensitivity

Table 3 – McDonald diagnostic criteria for Multiple Sclerosis: a comparison.

Clinical symptoms:	Additional conditions that must be met to make diagnosis of MS (the original McDonald criteria and a 2005 revision of the McDonald criteria):	Additional conditions that must be met to make diagnosis of MS (a 2010 revision of McDonald criteria):
Two or more relapses *and* at least two different clinical symptoms.	Not needed	Not needed
Two or more relapses *and* only one clinical symptom.	Dissemination in space proven by MRI scan *or* Wait for the relapse with different symptomatology.	Dissemination in space proven by MRI scan *or* Wait for the relapse with different symptomatology.
One relapse *and* at least two different clinical symptoms.	Dissemination in time proven by MRI scan *or* Two or more T2 hiperintensive lesions in MRI scan together with presence of oligoclonal bands or elevated IgG index in cerebrospinal fluid *or* Wait for the second relapse.	Dissemination in time proven by MRI scan *or* Wait for the second relapse.
One relapse and only one clinical symptom (clinically isolated syndrome).	Dissemination in time proven by MRI scan *or* Two or more T2 hiperintensive lesions in MRI scan together with presence of oligoclonal bands or elevated IgG index in cerebrospinal fluid *and* Dissemination in space proven by MRI scan *Alternatively* Wait for the second relapse with different symptomatology.	Dissemination in time proven by MRI scan *or* Wait for the second relapse *and* Dissemination in space proven by MRI scan *or* Wait for the second relapse with different symptomatology.

and specificity for the likelihood of a second attack were 83%. Tintore et al. defined the sensitivity of the criteria at 74% and specificity at 86% [12,22].

4.1. *Modifications to the McDonald criteria in 2005 and 2010*

Since the year 2000, the experts of the Panel on MS Diagnosis (further referred to as the Panel) gathered twice (2005, 2010) to develop modifications to the McDonald criteria [16,17]. The modifications were meant to facilitate and speed up the diagnostic process.

In the introduction the Panel stressed that the McDonald criteria should serve as an aid, not as a basis in the diagnostic process. McDonald criteria have been developed for a group of patients whose clinical symptoms are characteristic of the demyelinating process. It should be noted that they were tested for a Western adult population and do not apply to children and people from other ethnic groups [17]. The clinical features typical for the demyelinating process were symptoms lasting over 24 h suggesting structural damage of the brain hemispheres, brainstem, cerebellum or partial lateral damage of the spinal cord [16]. Patients with non-characteristic symptoms, both because of their nature (such as cognitive dysfunction, encephalopathy or seizures) or clinical course (one-phase) should not be assessed by McDonald criteria. In such patients a search for other diseases should be performed. Lesions on MRI that appear similar to MS lesions can occur in a number of other diseases, including:

- Acute disseminated encephalomyelitis (ADEM),
- Transverse myelitis,
- Devic's disease,
- Sarcoidosis of CNS,
- Behcet's disease,
- CNS vasculitis,
- Systemic Lupus Erythematous,
- CNS lymphoma [16,21].

The examples of differential diagnosis, divided into radiological and clinical groups, can be found in Table 4. A full list of 'red flags' that were atypical for MS features and should prompt the search for a different diagnosis was created in 2008 by Miller et al. [20].

Table 4 – Differential diagnosis of MS.

Differential diagnosis group	Diseases
Radiological	- Tumour (glioma, isolated CNS lymphoma, tumefactive MS) - neuromyelitis optica - ADEM - Balo's concentric sclerosis
Clinical	- neuroboreliosis - myelopathy - vasculitis - sarcoidosis - syphilis - neurocysticercosis - Behcet's disease

The modification in 2005 reduced the time needed to prove a radiological DIT (Table 2). The clinician could adopt a strategy of a 3-month wait after the first relapse. If an MRI, performed after that time, showed even one lesion enhanced after administering gadolinium to the patient, it was enough to satisfy the radiological criteria for DIT. An MRI scan performed before that time (between 30 days and 3 months after the onset of clinical symptoms) was treated as a reference test. An occurrence of any new lesion in the next MRI scan proved the DIT.

The Panel pointed out that the new lesion should be large enough to ascertain that it was not omitted in the previous MRI scan due to technical reasons [17,19].

The Panel included MRI of the spinal cord in the 2005 modified criteria (Table 1). A lesion in the spinal cord was the equivalent of an infratentorial lesion, according to the Barkhoff and Tintore criteria. It could be also counted together with the lesions of the brain to meet the required number of lesions. The Panel determined that an MRI of the spinal cord could also be used to meet the radiological criteria for DIT. For that, the presence of at least one gadolinium-enhancing lesion was required. However, it was not recommended to routinely scan the spinal cord. Such an MRI was justified only if there were new symptoms suggesting damage of the spinal cord [12].

In 2010, the McDonald criteria were modified for the second time.

The Panel based on the study results demonstrated by the MAGNIMS (European Magnetic Imaging in MS) group, changed the criteria for radiological DIS (Table 1). The new criteria stated at least one lesion typical for MS lesion in at least two out of four locations typical for MS should be present in the MRI. The typical locations are: periventricular, subcortical, infratentorial, and in the spinal cord. It was emphasized that at the time of the MRI scan, the patient has clinical symptoms indicating the involvement of one of the CNS lesions, this lesion should not be counted [19].

In 2010, the Panel also rejected the radiological criteria of Barkhoff and Tintore. The modifications were dictated by the higher sensitivity of the new criteria in making the diagnosis, while the specificity remained unchanged [13,16,19].

The Panel also recognized that MRI scans to prove the DIT may be performed earlier than recommended in the previous criteria (which was a minimum of 30 days after the onset of clinical symptoms). The coexistence of gadolinium-enhancing and non-enhancing lesions was considered sufficient to prove DIT (Table 2). The lack of a reference MRI did not change the specificity in diagnosing MS. In the most recent McDonald criteria, DIT can be proven on the basis of the result of the first MRI without specifying a time frame in which the scan should be performed. This applies to both the MRI of the brain and the spinal cord [19].

Due to the change in the criteria of DIS, once again the role of CSF testing was diminished. The earlier McDonald criteria made it possible to bypass the Barkhoff radiological criteria if the results of CSF tests were positive (elevated IgG index, presence of oligoclonal bands) [18,19]. With the modification proposed by the MAGNIMS group, CSF testing was removed from the McDonald criteria for RRMS. This does not mean that it should not be performed. It continues to play an important role in the differential diagnosis of MS and in diagnosing the primary progressive form of MS [21].

The panel has also returned to the concept of recognizing as relapse-typical symptoms reported by the patient only. However, it was stressed that the diagnosis of MS requires confirmation by clinical examination or by additional tests after at least one clinical relapse.

To summarize, the newest criteria make it possible to identify MS 3 months earlier than allowed by the original McDonald criteria and 1 month earlier than the 2005 criteria, provided that DIT and DIS are proven by MRI (Table 3). It is not necessary to repeat the brain MRI if the first one meets the criteria. The number of MRI scans performed depends on the clinical situation. The new criteria also allow the start of disease-modifying therapy when the first clinical symptoms of MS appear.

4.2. *Subtypes of MS*

Originally, in 1996, the course of MS was categorized into four main subtypes: relapsing-remitting, primary progressive, secondary progressive, and progressive relapsing MS [23].

According to the 2014 revision, the newly described subtypes were:

1) clinically isolated syndrome (CIS),
2) relapsing-remitting MS (RRMS),
3) secondary progressive MS (SSMS),
4) primary progressive MS (PPMS) [24].

Clinically isolated syndrome is the first clinical manifestation of the disease. In CIS there is no evidence of previous episodes of demyelination, not even from the patient's medical history [24].

The vast majority of patients suffering from MS have the relapsing-remitting subtype [23,24].

During the course of RRMS, we observe clearly defined relapses with full recovery (or residual deficit upon recovery). There is no disease progression during the periods between relapses. The SPMS is characterized by an initial RRMS course followed by gradual worsening with or without relapses. The diagnosis of SPMS is made retrospectively [25,26]. The PPMS could be described as a progressive accumulation of disability from the disease onset with occasional plateaus, temporary minor improvements, or acute relapses still consistent with the definition [27].

4.3. *Clinically isolated syndrome*

The first clinical sign of MS with no radiological evidence (can be a single or multiple lesions, possibly of demyelinating origin, but no DIT) could be classified as CIS [28]. A symptom that is classified as CIS should last for at least 24 h so it is isolated in time but not necessarily in space [29]. Most often a patient with CIS presents with one of the following:

a) sensory symptoms such as: numbness, coldness, tightness, tingling, pins-and-needles, swelling of the limb or trunk;
b) ophthalmological manifestations: most commonly optic neuritis (presented as unilateral eye pain that is aggravated by ocular movements and variable decreases of visual acuity decrease);
c) motor symptoms: weakness of arms, legs, spasticity, pathological reflexes;
d) diplopia (result of lesions in the brainstem or cerebellar pathways);
e) coordination problems such as gait imbalance, slurred speech, dysmetria, intention tremor (cerebellar or cerebello-vestibular connection dysfunction);
f) vertigo [30].

A distinct portion of patients presenting with CIS convert to MS within 10 years [28]. There is discussion among neurologists on how to treat CIS, because a lot of evidence suggests that an early start of disease-modifying therapies for CIS patients may delay the conversion to MS [31].

4.4. *Radiologically isolated syndrome*

In the era of the new developments in MRI techniques, more and more often T2 hyperintense lesions could be found in locations typical for MS in the brains of patients with a history suggestive of MS. The most frequent reasons for performing MRI are: migraine and other headaches, depression, head injury, loss of consciousness and tinnitus [32–34]. In such cases, caution should be exercised. Informing the patient of the suspected MS in the absence of clinical proof can lead to stigmatization of the patient and huge psychological strain [35]. It is worth noting that radiologist often described lesions in the brain as 'hyperintense lesions in the white matter that might be inflammatory, vascular or demyelinating', which demonstrates the difficulties in characterizing such lesions during routine scans [36]. Nevertheless, such a radiological description may cause a great deal of anxiety to the patient [37].

The newly described RIS is a clinical condition in which there may be suspicion of a demyelinating process, but the lack of typical clinical features prevents the physician from diagnosing MS. The RIS can be identified only when the radiological criteria of Barkhoff and Tintore are met in the absence of clinical relapses or neurological symptoms characteristic of MS [38]. Changes seen in MRI can be observed as DIS and DIT. The DIS can be demonstrated by a minimum of one T2 lesion (not necessarily gadolinium-enhanced) in at least four areas of the CNS:

1) periventricular,
2) juxtacortical,
3) infratentorial,
4) spinal cord (if a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to the lesion count).

The DIT can be demonstrated by:

1) a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI;
2) simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.

In a large randomized clinical trials, around 30% of subjects with RIS developed CIS within 2 years [16,33,39].

Until recently, it was unclear how to deal with patients with RIS. Sellner et al. proposed to adopt a strategy of 'waiting' or a strategy of 'follow-up' [38]. The first strategy of 'waiting' was reduced to wait for the first clinical relapse; while, the strategy of 'follow-up' was to repeat imaging studies: after 6 months, then after 24 months, to follow the possible progression of MR changes [39,40].

Distinguishing between demyelinating and natural age-related radiological MRI changes can be one of the most difficult diagnostic issues [41]. The majority of studies evaluating age-related changes were confirmed on post-mortem examination [42]; thus it is extremely demanding to discriminate these two types of changes on MRI scans. Typical age-related MRI changes are:

1) enlarged perivascular (Virchow-Robin) spaces,
2) reduction in white-matter volume,
3) enlarges perivascular spaces,
4) small vessel ischaemia,
5) degeneration of myelin and axons [42,43].

5. Diagnostic criteria for children with MS

From the first cases of MS diagnosed in children neurologist have had particular problems distinguishing MS from other disorders. Due to high similarity between the first MS clinical manifestation and ADEM in childhood, it is a diagnostic challenge for clinicians to diagnose MS accurately after the first relapse [44]. The McDonald diagnostic criteria are adequate for children older than 12 years but are not specific and sensitive enough for those younger [45,46].

Nowadays to diagnose a child with MS we need to find at least one of the following features:

a) two or more nonencephalopatic (especially not ADEM) clinical central nervous system events connected with more than one area of the CNS, with possible inflammatory origin, separated by more than 30 days;
b) one nonencephalopathic MS typical episode associated with MRI findings (consistent with 2010 McDonald criteria for DIS), in which a follow-up MRI shows at least one new enhancing or nonenhancing lesion consistent with the criteria for DIT;
c) one ADEM attack followed by a nonencephalopathic clinical event, 3 or more months after symptom onset, that is associated with new MRI lesions fulfilling the 2010 McDonald DIS criteria;
d) a first, single, acute event that does not meet ADEM criteria, and MRI findings that are consistent with the 2010 McDonald criteria for DIS and DIT (applies to children ≥12 years old) [47].

6. MS diagnosis in different ethnic groups

Although there is one set of diagnostic criteria for MS in adults of any origin, there are some differences in clinical characteristics between ethnic groups. The majority of studies that contributed to the MS criteria included Caucasian subjects [48]. However, there is some distinctiveness among Asians, Africans and Hispanics. First, MS is recognized less frequently in each of these groups compared with Caucasians [48–50]. People in Asia present with optic nerve and spinal cord disturbances more often than Caucasian population [49]. A recent publication demonstrated that the incidence of neuromyelitis optica (NMO) among Asians may be higher than previously though [50]. Africans are theoretically have the same risk as Caucasians, but only for males [48]. Several papers demonstrated the special importance of a differential diagnosis in Africans because this group is characterized by a high burden of neurological infections which can mimic MS [49]. The incidence of MS is lower in Hispanics than Caucasians [48].

7. Conclusions

Changes made over the past few years in the criteria for diagnosing of MS were aimed at facilitating and speeding up the diagnostic process. The result of successive modifications is a more frequent diagnosis of MS at a very early stage of the disease [34,51,52].

Currently, the diagnosis, beyond clinical symptoms, is based primarily on the results of MRI. Non-specific changes in the T2 sequence in patients with such symptoms as headache, dizziness, paraesthesias, pain, or excessive fatigue may be considered a symptom of MS [53]. This may lead to the over-interpretation of MRI results, as the lesions in the white matter are found in 40–95% of patients with other neurological diseases and in 44% of otherwise healthy individuals (those over 65 years old) [54]. On the other hand, including MRI in the criteria has increased the sensitivity of the MS diagnosis (66% before the era of McDonald criteria, compared with 94% in 2000) [1]. Based on these data, it can be assumed that MRI could have more value as an exclusion test for other neurological conditions than as part of the diagnostic criteria for MS [55].

The importance of the differential diagnosis should also be emphasized. It is estimated that the most frequent pathologies misdiagnosed as MS are: cerebrovascular disease, migraine headaches, CNS lymphoma, and fibromyalgia [19]. Many studies have shown that misdiagnoses are made in up to 20% of patients [15,19,52,53]. Moreover, it is estimated that 75% of patients diagnosed incorrectly receive disease- modifying therapies [54]. At best, the only disadvantage is a lack of treatment efficacy but it might also be harmful to the patient (e.g. in cases of neuromyelitis optica when the treatment worsens the patient's clinical condition) [55]. Moreover, misdiagnosis retards the introduction of proper treatment. That might be especially important in some potentially curable diseases such as CNS lymphoma, neuroborreliosis, and neurosarcoidosis [56]. It is important to establish a single panel of additional tests to exclude pathologies that mimic MS. It would be useful to train the radiologists in the differentiation of demyelinating lesions. We also have to understand that, in times of greater access to different sources of information, many patients try to interpret the results of radiological scans on their own [41].

Until a single 'fail-safe' diagnostic test is developed, neurologists will have to base their diagnosis on the current or future clinical criteria. It seems that the key to success in diagnosing MS is a careful analysis. One has to start with a proper assessment of clinical symptoms, including determining whether relapse can be diagnosed. The evaluation of the first symptoms is of special importance [56]. The correct interpretation depends largely on the experience of the clinician [19].

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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