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ORIGINAL ARTICLE

Real-world challenges in the diagnosis of primary progressive multiple sclerosis

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Abstract

Background and purpose: Despite the 2017 revisions to the McDonald criteria, diagnosing primary progressive multiple sclerosis (PPMS) remains challenging. To improve clinical practice, the aim was to identify frequent diagnostic challenges in a real-world setting and associate these with the performance of the 2010 and 2017 PPMS diagnostic McDonald criteria.

Methods: Clinical, radiological and laboratory characteristics at the time of diagnosis were retrospectively recorded from designated PPMS patient files. Possible complicating factors were recorded such as confounding comorbidity, signs indicative of alternative diagnoses, possible earlier relapses and/or incomplete diagnostic work-up (no cerebrospinal fluid examination and/or magnetic resonance imaging brain and spinal cord). The percentages of patients fulfilling the 2010 and 2017 McDonald criteria were calculated after censoring patients with these complicating factors.

Results: A total of 322 designated PPMS patients were included. Of all participants, it was found that $n = 28/322$ had confounding comorbidity and/or signs indicative of alternative diagnoses, $n = 103/294$ had possible initial relapsing and/or uncertainly progressive phenotypes and $n = 73/191$ received an incomplete diagnostic work-up. When applying the 2010 and 2017 diagnostic PPMS McDonald criteria on $n = 118$ cases with a full diagnostic work-up and a primary progressive disease course without a better alternative explanation, these were met by 104/118 (88.1%) and 98/118 remaining patients (83.1%), respectively ($p = 0.15$).

Conclusion: Accurate interpretation of the initial clinical course, consideration of alternative diagnoses and a full diagnostic work-up are the cornerstones of a PPMS diagnosis. When these conditions are met, the 2010 and 2017 McDonald criteria for PPMS perform similarly, emphasizing the importance of their appropriate application in clinical practice.

KEYWORDS
diagnosis, McDonald criteria, primary progressive multiple sclerosis

Beatrijs Wokke and Janet de Beukelaar are shared last author, equal contribution.

INTRODUCTION

For a definite diagnosis of multiple sclerosis (MS), compatible symptoms and evidence for dissemination in space and time of an intrathecal inflammatory and demyelinating disease process are essential [1–5]. The first diagnostic criteria focused on the relapsing–remitting course of MS (RRMS) [1, 6]. For the 15% of MS patients who experienced a gradual neurological decline from onset, often localized in the spinal cord and often without superimposed relapses, the nature of the disease course meant that they often could not fulfill these diagnostic criteria of dissemination in space and time for MS [7–9]. Separate diagnostic criteria for this primary progressive form of MS (PPMS) [10, 11] were incorporated into the 2001 McDonald diagnostic criteria and—with alterations—in its revisions since [2–5]. In the latest 2017 revisions, slight alterations were made in these PPMS diagnostic criteria, with more inclusive magnetic resonance imaging (MRI) criteria and a preference for demonstration of unique oligoclonal bands (OCBs) by electrophoresis in cerebrospinal fluid (CSF) over the immunoglobulin G (IgG) index [3, 5].

Despite available diagnostic criteria, the diagnosis of PPMS remains challenging [8, 12–14]. Importantly, the McDonald criteria should only be applied in patients where MS-related demyelination is the most likely explanation. Application of the criteria in atypical clinical syndromes is one of the main causes of misdiagnosis of MS [5, 15, 16]. PPMS lacks the typical relapses and remissions of RRMS [14, 17], and the insidious disease course can hamper a complete and accurate history. The ruling out of possible earlier demyelinating attacks to distinguish PPMS from a secondary progressive disease course (SPMS) can also be challenging [14, 18, 19]. In addition, because PPMS patients are generally about 10 years older than RRMS patients at the time of diagnosis [20], differential diagnoses such as cervical spondylosis or concomitant vasculopathy are more common. These conditions can obscure both disease course and imaging results, thereby complicating the diagnostic process [8, 20].

However, a correct and timely diagnosis of PPMS is imperative for counseling of patients and treatment decisions. Although treatment options for PPMS are limited, recent data have shown that an early versus delayed start of ocrelizumab results in more favorable long-term outcomes on several measures of disease progression [21, 22]. Additionally, as our current understanding of mechanisms of progression in MS is limited, patients with PPMS are an important clinical group to study. Such research benefits from accurate PPMS diagnoses [17, 20, 23].

Although the diagnostic challenges for PPMS have been acknowledged [8, 9, 12, 14], most studies on MS misdiagnosis have focused on RRMS [16, 24, 25]. Also, to the best of our knowledge, the performance of the 2017 and 2010 McDonald criteria for PPMS diagnosis has not been assessed in association with these challenges. Insight into the current diagnostic process can help identify relevant pitfalls, improve clinical practice and could possibly benefit future diagnostic criteria. Therefore, the aim of our study was twofold: (i) to explore which factors complicate a definite PPMS diagnosis in a real-world cohort and (ii) to associate the performance of the 2010 and 2017 McDonald criteria with these challenges in a real-world cohort diagnosed with PPMS.

METHODS

Patient selection

Medical files of all patients with the diagnosis PPMS recorded in their medical correspondence between 1 January 2000 and 21 February 2019 were reviewed retrospectively in two MS centers in the Netherlands: the Erasmus Medical Center (Erasmus MC, University Hospital) and the Albert Schweitzer Hospital (non-academic teaching hospital). Permission for this study was granted by the medical ethics committee of the Erasmus MC, and the study conforms with the World Medical Association Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013). No informed consent was obtained in accordance with Article 458, Book 7, of the Medical Treatment Contracts Act.

Data collection

The following data were extracted for each patient: sex, date of birth, prior medical history, date of first progressive symptoms, date of diagnosis, clinical symptoms at diagnosis, results of brain and spinal cord MRI if present, and results of CSF analysis and blood analyses if reported. Expanded Disability Status Scale (EDSS) scores [26] at the time of diagnosis were collected. If no EDSS score was recorded, an estimated EDSS score was formed based on the described neurological examination. Validation of the recorded disease course as compatible with PPMS was based on the description of patient history and neurological examinations. Available MRI images and neuroradiology reports were reviewed by medical doctors specialized in MS (KB and JB). In the case of disagreements between the radiology report and the judgement of these medical doctors, the images were reviewed by a neuroradiologist with expertise in MS, whose judgement was considered final (CMJ). If MRI images were unavailable, MRI scan results were based on the neuroradiology reports. The diagnostic work-up was considered to be complete if there were available results from MRI brain and spinal cord, as well as CSF analyses including both IgG index and electrophoresis. All data were collected in Castor Electronic Data Capture.

Evaluation of complicating factors and the 2010 and 2017 McDonald criteria

The 2010 and 2017 McDonald criteria for PPMS (Table 1) consist of (a) the requirement of at least 1 year of disease progression suspected of demyelination (identical in both criteria) and (b) decision rules based on MRI and CSF results (different between the two criteria). These two parts of the diagnostic criteria were analyzed separately. In the evaluation of the first requirement

TABLE 1 The 2010 and 2017 McDonald diagnostic criteria for diagnosis of primary progressive multiple sclerosis.

2010 McDonald criteria	2017 McDonald criteria
Primary progressive multiple sclerosis can be diagnosed in patients with	
1 year of disability progression (retrospectively or prospectively determined)	1 year of disability progression (retrospectively or prospectively determined)
Plus 2 of the 3 following criteria: [a]1. Evidence for DIS in the brain based on ≥1 T2-hyperintense lesions in the MS characteristic (periventricular, juxtacortical or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2-hyperintense lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)	Plus 2 of the 3 following criteria: [b]1. Evidence for DIS in the brain based on ≥1 T2-hyperintense lesions in the MS characteristic (periventricular, cortical or juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2-hyperintense lesions in the cord 3. Presence of CSF-specific oligoclonal bands

Note: Changes between the two sets of criteria are underscored.

Abbreviations: CSF, cerebrospinal fluid; DIS, dissemination in space; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis.

[a]Symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

[b]No distinction between symptomatic and asymptomatic MRI lesions is required.

(a), several possible complicating factors were identified, namely (i) signs indicative of alternative diagnoses that were not sufficiently investigated [27], (ii) comorbidity that could confound the MS disease course and (iii) patient histories with possible earlier relapses or indiscernible disease course. For the second requirement (b) the MRI and CSF results were evaluated at the time of diagnosis to determine if a patient fulfilled these decision rules for the 2010 and/or 2017 criteria.

Statistical analyses

In this cohort of people diagnosed with PPMS, the percentage of patients who fulfilled the MRI and CSF decision rules of the 2010 and 2017 McDonald criteria was calculated. Patients who did not meet either set of McDonald criteria because of incomplete diagnostic work-up were scored as negative for the fulfillment of the corresponding criteria in the descriptive statistics. Comparative analyses between the 2010 and 2017 criteria were performed with McNemar's test, the percentage of agreement and Cohen's kappa. To prevent bias, these comparative analyses were only performed in patients without any complicating factors and with a complete diagnostic work-up.

To determine whether patients with complicating factors were different on a more biological level their baseline demographic, clinical and radiological characteristics were compared with patients fulfilling the 2017 McDonald criteria without such complicating factors. These characteristics were compared using chi-squared tests for categorical outcomes (Fisher's exact tests if expected frequencies were below 5) and Mann–Whitney *U* tests for continuous outcomes.

Ad hoc analyses were performed to elucidate the discrepancies between the IgG index and electrophoresis in the CSF results in the subgroup of patients without complicating factors and with full diagnostic work-up. A multivariable logistic regression analysis was performed for the presence of OCBs, including covariates: year of CSF analysis and IgG index.

All statistical analyses were performed in IBM SPSS Statistics 25, with a two-sided significance level of 0.05.

RESULTS

Participants

A total of 322 patients diagnosed with PPMS by their treating neurologist were included; baseline data are displayed in Table 2. The year of diagnosis ranged between 1974 and 2019, median 2007 (interquartile range 2001–2014). Median age at diagnosis was 48 years, and 180 patients were female (55.9%). Spinal cord symptoms were the most common presentation (87.9%) (Table 2). Brain MRI was performed in 97.8%, spinal cord MRI in 84.6% (Table 3) and CSF analysis in 80.7% of patients (Table 4). Overall, of these patients with a PPMS diagnosis in clinical practice, 240 (74.5%) matched the ancillary (MRI and CSF) study profile of the 2010 McDonald criteria for PPMS and 228 (70.8%) matched those of the 2017 McDonald criteria for PPMS (Figure 1). The factors underlying this limited accordance between these MRI and CSF criteria and a diagnosis of PPMS in clinical practice were explored. All cases were systematically reviewed for the previously described challenges in diagnosing PPMS (i.e., signs indicative of alternative diagnoses, confounding comorbidity, possible earlier relapses and incomplete diagnostic work-up) and how these influenced the performance of MRI and CSF rules of the McDonald criteria for PPMS was investigated (Figure 1).

Challenges in PPMS diagnosis: concomitant disease and/or signs of an alternative diagnosis

On review of the patients' charts concomitant disease and/or signs of an alternative diagnosis were identified in 28 of our 322 patients (group A in Figure 1). In 22 patients this concerned confounding

TABLE 2 Comparison of demographic and clinical characteristics between patients in the entire cohort and in several diagnostic subgroups.

Demographic and clinical characteristics	Entire cohort	Group A ($n=28$)	p value	Group B ($n=103$)	p value	Group C ($n=98$)
Sex (female) (n, %)	180 (55.9)	12 (42.9)	0.391	64 (62.1)	0.148	51 (52.0)
Age at onset (median, IQR)	44.02 (35.63–51.45)	44.27 (36.02–52.24)	0.530	43.23 (33.67–51.09)	0.122	45.11 (37.76–53.27)
Age at diagnosis (median, IQR)	48.17 (41.51–55.39)	50.41 (43.06–56.83)	0.783	46.87 (39.57–54.44)	0.055	49.83 (44.31–55.99)
Year of diagnosis (median, IQR)	2007 (2001–2014)	2007 (2001–2015)	0.092	2004 (1995–2013)	**<0.001**	2010 (2006–2015)
(Estimated) EDSS at diagnosis (median, IQR)	4.0 (2.5–4.5) ($n=261$)[a]	4.0 (3.5–6.0)	0.182	3.5 (2.5–4.0)	0.083	4.0 (3.0–4.5)
CNS localization presenting symptoms:[b]						
Spinal cord (n, %)	283 (87.9)	27 (96.4)	0.682[c]	86 (83.5)	0.269	89 (90.8)
Cerebral (n, %)	194 (60.2)	15 (53.6)	0.802	63 (61.2)	0.293	54 (55.1)
Cerebellar (n, %)	77 (23.9)	3 (10.7)	0.150	23 (22.3)	0.896	22 (22.4)
Brainstem (n, %)	74 (23.0)	5 (17.9)	0.768[c]	31 (30.1)	**0.004**	14 (14.3)
Optic nerve (n, %)	48 (14.9)	4 (14.3)	0.235[c]	21 (20.4)	**0.002**	6 (6.1)[d]

Note: Group A, patients with confounding comorbidity and/or signs indicative of alternative diagnosis that were insufficiently investigated; group B, patients without comorbidity or alternative diagnosis but with possible earlier attacks of demyelination, or with indiscernible disease onset; group C, patients without comorbidity or alternative diagnosis, disease onset definitely progressive, with complete diagnostic work-up, and who fulfilled 2017 McDonald criteria for PPMS. Statistical analyses were performed by comparing groups A and B with reference group C.Bold type denotes statistical significance.

Abbreviations: CNS, central nervous system; EDSS, Expanded Disability Status Scale; IQR, interquartile range; PPMS, primary progressive multiple sclerosis.

[a]The number in parentheses indicates the number of patients for whom the information was available.

[b]Patients could present with symptoms in multiple CNS localizations.

[c]Fisher's exact test.

[d]The visual symptoms were never the only symptoms in these patients.

comorbidity, mostly cervical spinal stenosis and neurovascular events, which could have influenced the interpretation of the MS disease course (Table 5). In seven of these 28 patients the authors agreed that an alternative diagnosis other than MS was insufficiently investigated (Table 6). Accordingly, four out of seven patients did not fulfill the CSF and MRI criteria for PPMS. One patient had both concomitant disease (neurovascular events) and signs indicating an alternative diagnosis that was insufficiently investigated (systemic auto-inflammatory disease). In the total group of 28 patients either with confounding comorbidity or with signs indicating an alternative diagnosis other than MS, unique OCBs in CSF were significantly less frequent (54.2% vs. 80.6%) (Table 4), and significantly fewer spinal cord MRIs were performed (in 87.5% vs. 100%) (Table 3) compared with the definite PPMS group (group C in Figure 1). Since the McDonald criteria should only be applied in the absence of a better explanation of the clinical presentation, the performance of the MRI and CSF rules of the McDonald criteria were evaluated with these cases censored. A minor increase in fulfillment of the 2017 (72.1%) but not the 2010 McDonald criteria was noted (Figure 1).

Challenges in PPMS diagnosis: possible clinically relapsing MS disease course

Consequently the disease course of the remaining 294 patients was critically reviewed, based on the available data. This resulted in a total of 103 patients without an unequivocally progressive disease course (group B in Figure 1). Four groups within this subgroup were identified. The first group of patients were those who experienced and had been reviewed for neurological symptoms prior to their progressive symptoms. This group consisted of 19 patients ($n=15$ reviewed by a neurologist, $n=2$ reviewed by an ophthalmologist, $n=2$ by a general practitioner; in 13 of these cases the symptoms were localized in the central nervous system at the time). The second group of 22 cases consisted of patients where the patient history revealed possible earlier relapses without medical evaluation at that time. Thirdly, a group also of 22 patients were identified with an 'attack onset progressive MS', that is, the first symptoms constituted an attack with onset of symptoms within 2 weeks, with (in)complete recovery and subsequent progression within a year of this attack. Lastly, in 40 patients there were incomplete or conflicting reports for various reasons regarding the patient's history in the medical file (data not shown).

Compared to definite PPMS patients (group C in Figure 1), in the 103 patients in whom possible earlier attacks of demyelination could not be ruled out, the diagnosis had been made about 6 years earlier (median year of diagnosis 2004 vs. 2010). They presented more frequently with brainstem or optic nerve symptoms (30.1% vs. 14.3% and 20.4% vs. 6.1%, respectively) (Table 2), and also had significantly fewer spinal cord MRIs performed at diagnosis (Table 3). Since the McDonald criteria for PPMS should only be applied to patients with a primary progressive disease course, the performance of these criteria was evaluated with censoring of all cases with relapsing or

TABLE 3 Comparison of MRI characteristics at diagnosis between patients in several diagnostic subgroups.

MRI characteristics	Entire cohort	Group A ($n=28$)	p value	Group B ($n=103$)	p value	Group C ($n=98$)
MRI brain at diagnosis (n, %)	305 (97.8) ($n=312$)	27 (100) ($n=27$)	1.000[a]	93 (97.9) ($n=95$)	0.241[b]	98 (100) ($n=98$)
With gadolinium (n, %)	144 (60.3) ($n=239$)	9 (42.9) ($n=21$)	**0.019**	43 (60.6) ($n=71$)	0.206	59 (70.2) ($n=84$)
Gadolinium-enhancing lesions (n, %)	30 (21.4) ($n=140$)	1 (11.1) ($n=9$)	1.000[b]	8 (18.6) ($n=43$)	0.963	11 (19.0) ($n=58$)
≥9 lesions (n, %)	125 (60.1) ($n=208$)	6 (37.5) ($n=16$)	0.109	33 (55.9) ($n=59$)	0.694	48 (59.3) ($n=81$)
Periventricular lesions (n, %)	248 (90.8) ($n=273$)	22 (91.7) ($n=24$)	1.000[b]	69 (89.6) ($n=77$)	0.659	87 (91.6) ($n=95$)
≥3 periventricular lesions (n, %)	146 (75.3) ($n=194$)	10 (66.7) ($n=15$)	0.537[b]	42 (77.8) ($n=54$)	0.652	55 (74.3) ($n=74$)
Juxtacortical lesions (n, %)	140 (63.6) ($n=220$)	8 (42.1) ($n=19$)	0.088	39 (61.9) ($n=63$)	0.852	52 (63.4) ($n=82$)
Infratentorial lesions (n, %)	164 (63.1) ($n=261$)	12 (50) ($n=24$)	0.582	53 (69.7) ($n=76$)	0.077	49 (56.3) ($n=87$)
Cortical lesions (n, %)	5 (4.4) ($n=113$)	1 (11.1) ($n=9$)	0.428[b]	1 (3.3) ($n=30$)	1.000[b]	2 (4.4) ($n=45$)
Black holes (n, %)	121 (69.9) ($n=173$)	7 (58.3) ($n=12$)	0.753[b]	35 (71.4) ($n=49$)	0.383	44 (63.8) ($n=69$)
MRI spinal cord at diagnosis (n, %)	253 (84.6) ($n=299$)	21 (87.5) ($n=24$)	**0.007**[b]	69 (77.5) ($n=89$)	**<0.001**	98 (100) ($n=98$)
With gadolinium (n, %)	61 (30.3) ($n=201$)	6 (33.3) ($n=18$)	0.8072	20 (36.4) ($n=55$)	0.468	24 (30.4) ($n=79$)
Gadolinium-enhancing lesions (n, %)	7 (11.1) ($n=63$)	1 (16.7) ($n=6$)	1.000[b]	2 (10) ($n=20$)	1.000[b]	3 (12.5) ($n=24$)
Lesions in spinal cord (n, %)	183 (73.8) ($n=248$)	15 (71.4) ($n=21$)	0.772	56 (83.6) ($n=67$)	0.165	73 (74.5) ($n=98$)
≥2 lesions (n, %)	112 (70.9) ($n=158$)	12 (85.7) ($n=14$)	0.496[b]	35 (66.0) ($n=53$)	0.540	45 (72.6) ($n=62$)

Note: Group A, patients with confounding comorbidity and/or signs indicative of alternative diagnoses that were insufficiently investigated; group B, patients without comorbidity or alternative diagnosis but with possible earlier attacks of demyelination, or with indiscernible disease onset; group C, patients without comorbidity or alternative diagnosis, disease onset definitely progressive, with complete diagnostic work-up, and who fulfilled the 2017 McDonald criteria for PPMS. Statistical analyses were performed by comparing groups A and B with reference group C. The added numbers in parentheses in columns indicate the number of patients for whom the information was available.Bold type denotes statistical significance.

Abbreviations: MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis.

[a]no measures of association could be computed because in both groups 100% had a MRI brain at diagnosis.

[b]Fisher's exact test.

uncertain disease courses (Figure 1). In these 191 patients with an unequivocally primary progressive course and without better alternative explanations, 81.2% fulfilled the 2010 and 77.5% the 2017 criteria.

Challenges in PPMS diagnosis: completeness of diagnostic work-up in PPMS

It was noted that, of the $N=191$ patients with a primary progressive course without better alternative explanations, only $N=118$ received a full diagnostic work-up. In this last group, application of the diagnostic criteria resulted in $N=104$ patients (88.1%) meeting the 2010 and $N=98$ patients (83.1%) meeting the 2017 McDonald criteria for PPMS ($p=0.15$) (Figure 1). The percentage agreement between the criteria in this group was 89.8% and Cohen's kappa was moderate: 0.59 (95% confidence interval 0.38–0.79). This higher fulfillment of the 2010 McDonald criteria than of the 2017 revisions was due to patients in whom the CSF analysis showed no OCBs but did show an elevated IgG index; the latter is not incorporated in the 2017 revisions. Ad hoc analyses revealed that these discrepancies were dependent on year of CSF analyses. In this clinical PPMS group with full diagnostic work-up, an odds ratio of 1.13 (95% confidence interval 1.06–1.21, $p<0.001$) for positive OCBs per later year of CSF analysis was found, adjusted for IgG index. In these patients diagnosed in or after 2010 ($n=58$), both the 2010 criteria and the 2017 criteria were met by 53 patients (91.4%).

In the 118 patients with a clinical PPMS disease course and a full diagnostic work-up, 11 patients met neither set of McDonald criteria. This was due to a lack of spinal cord lesions and/or CSF abnormalities. Whilst the clinical course was suggestive of PPMS, the brain MRI showed lesions suggestive of MS, and evoked potential results—if available—were consistent with MS. The authors therefore considered PPMS to be the most likely diagnosis in these cases.

DISCUSSION

This retrospective study explored complicating factors in the diagnosis of PPMS in a real-world cohort of designated PPMS patients. In our cohort of patients diagnosed with PPMS by their treating neurologist, in over one-third of the patients it was found that on critical review of the available data the diagnosis of PPMS could be challenged. In this subgroup of patients four key factors contributing to these results were identified. It was also shown that, in patients in whom there were no doubts as to the diagnosis of PPMS and who had a full diagnostic work-up, there was no significant difference in the 2010 and 2017 McDonald criteria for PPMS with 88% and 83% of patients fulfilling these criteria. These findings show that a thorough and critical review, and sometimes reevaluation of the disease course, is essential in a diagnosis of

TABLE 4 Comparison of cerebrospinal fluid characteristics at diagnosis between patients in several diagnostic subgroups.

Cerebrospinal fluid	Entire cohort	Group A (*n* = 28)	*p* value	Group B (*n* = 103)	*p* value	Group C (*n* = 98)
Total protein (g/L) (median, IQR)	0.43 (0.35–0.53) (*n* = 200)	0.38 (0.31–0.44) (*n* = 20)	0.236	0.45 (0.38–0.56) (*n* = 54)	0.054	0.41 (0.33–0.49) (*n* = 84)
Leukocytes (10^6/L) (median, IQR)	4.0 (2–8) (*n* = 174)	3.0 (1.0–8.0) (*n* = 19)	0.993	4.0 (2.0–8.0) (*n* = 43)	0.433	4.0 (2.0–8.0) (*n* = 78)
IgG index (median, IQR)	0.91 (0.63–1.39) (*n* = 225)	0.68 (0.57–1.05) (*n* = 22)	0.146	0.90 (0.63–1.29) (*n* = 57)	0.957	0.92 (0.64–1.40) (*n* = 98)
Presence of unique oligoclonal bands (*n*, %)	175 (72.6) (*n* = 242)	13 (54.2) (*n* = 24)	**0.007**	48 (76.2) (*n* = 63)	0.502	79 (80.6) (*n* = 98)

Note: Group A, patients with confounding comorbidity and/or signs indicative of alternative diagnoses that were insufficiently investigated; group B, patients without comorbidity or alternative diagnosis but with possible earlier attacks of demyelination, or with indiscernible disease onset; group C, patients without comorbidity or alternative diagnosis, disease onset definitely progressive, with complete diagnostic work-up, and fulfilled the 2017 McDonald criteria for PPMS. Statistical analyses were performed by comparing groups A and B with reference group C. The added numbers in parentheses in columns indicate the number of patients for whom the information was available.Bold type denotes statistical significance.

Abbreviations: IgG, immunoglobulin G; IQR, interquartile range; PPMS, primary progressive multiple sclerosis.

PPMS and that even in patients with a complete diagnostic work-up the diagnosis can be challenging.

The biggest challenge encountered in the diagnosis of PPMS was patients without a definite progressive disease onset. This varied between suspected previous demyelinating events, either solely in patient history or objectified by a clinician, indiscernible disease course in available data and 'attack onset progressive MS' of which there was incomplete recovery followed by progression in the same year. Compared to definite PPMS patients, these patients more frequently presented with brainstem and optic nerve symptoms, localizations more common in RRMS than in PPMS [20]. This is further suggestive of an initial relapsing phenotype in at least some of these patients.

Although never as a main focus of research, such retrospective findings of possible earlier relapses on secondary review of medical files have been reported previously [8, 28, 29]. Due to the current therapeutic consequences to the distinction between SPMS and PPMS, it is possible that there is currently more attention for these possible earlier relapses. Patients with a single attack before progression were once reported as a separate phenotype called 'transitional progressive MS' [30–32]. Moreover, recent studies have shown that disability accumulation in RRMS occurs mostly independently of relapses [33, 34], making the transition to SPMS difficult to identify [19, 35].

The common factor of these findings is that they illustrate the challenges in distinguishing relapsing from pure progressive MS. Furthermore, even though there are subgroups at both ends of the spectrum with truly relapsing and truly progressive disease course, it is likely that there is also a subgroup of patients in whom this differentiation is not so certain. This raises questions about the validity of differentiating between them. It is therefore felt that a single set of diagnostic criteria for any phenotype of MS should be considered to facilitate the diagnostic process. Variants within this MS spectrum might then be more relevantly described using markers of several different biological disease mechanisms possibly holding different therapeutic consequences, as also discussed by Kuhlmann et al. [36]. Although such a new framework still requires additional studies and validation, there are already some promising radiological and fluid markers currently known that could aid in developing such a new framework [36].

Another challenge in terms of the diagnosis was a small subgroup of patients with confounding comorbidity. Cervical spinal stenosis was the most common confounding comorbidity. Besides being an important differential diagnosis for patients with progressive myelopathy [7, 14, 27], there is some evidence that people with progressive MS are more susceptible to cervical spinal stenosis [37]. This stresses the need to perform and critically review an MRI spinal cord in patients suspected of PPMS, especially since cervical spine decompression can improve myelopathy, neck pain and radiculopathy in patients with coexistent cervical stenosis and MS [38]. Signs indicative of an alternative diagnosis were found in seven patients. In most of these patients, simple additional diagnostics could have provided more certainty about an

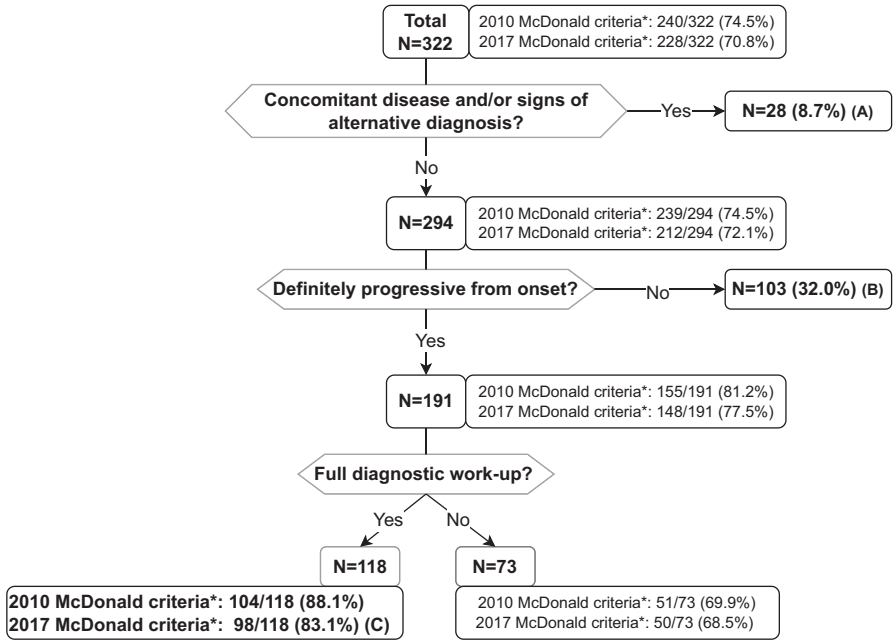

FIGURE 1 Flowchart of factors complicating a definite primary progressive multiple sclerosis (PPMS) diagnosis. *Fulfillment of 2010 and 2017 McDonald criteria for diagnosis of PPMS was based on cerebrospinal fluid and MRI results. Groups correspond to Tables 2–4: A, patients with confounding comorbidity and/or signs indicative of alternative diagnosis that were insufficiently investigated (see Tables 5 and 6 for specification); B, patients without confounding comorbidity and/or signs indicative of alternative diagnoses but with possible earlier relapses or indiscernible disease course; C, no complicating factors and 2017 McDonald criteria for PPMS fulfilled.

TABLE 5 Concomitant diagnoses blurring multiple sclerosis disease course.

Concomitant diagnosis	*n*
Cervical spinal stenosis	8
Neurovascular event(s)	4
Lumbar spinal stenosis	2
Traumatic injuries	2
Post-polio syndrome	2
Other[a]	4

[a]Other diagnoses included critical illness neuropathy, progressive spinal muscular atrophy, functional neurological disorder, recurrent keratitis.

alternative diagnosis. Therefore, clinicians should be alert about red flags and atypical findings to guide differential diagnostic considerations before applying the McDonald criteria. Patients in our cohort with concomitant confounding diagnoses and/or signs indicative of alternative diagnoses less frequently had unique OCBs in the CSF. This emphasizes the value of additional CSF evaluation in the diagnostic work-up of these patients.

Surprisingly, in our cohort, it was found that more patients fulfilled the 2010 than the 2017 McDonald criteria, although not statistically significant in the patients without complicating factors and with full diagnostic work-up. This finding was due to the more restrictive CSF interpretation in the 2017 revisions [5]. Our cohort includes patients diagnosed as far back as 1974, when less sensitive CSF analysis techniques were used [5, 39, 40]. Accordingly, it was found that more recent CSF analyses employing improved techniques were associated with the presence of OCBs in our cohort, even after adjusting for the IgG index.

It was found that inclusion of symptomatic spinal cord lesions resulted in a few extra patients fulfilling the 2017 versus the 2010 criteria (not statistically significant), but the addition of cortical lesions did not. This could be explained by the fact that the performed routine clinical MRI scans were without dedicated sequences for cortical lesions. This would be a valuable item to review in future data.

Limitations and strengths

Limitations of the study include its retrospective nature, reliance on incomplete or conflicting data from medical files, and the lack of clinical reevaluation of patients with inclusion of possibly misdiagnosed patients. Additionally, the time span of diagnoses in the cohort is extensive, and the McDonald criteria were not routinely used during the earlier years, which may have resulted in an underestimation of the number of patients fulfilling the criteria. The study's strengths lie in its real-world representation of the clinical diagnostic process, the demographic characteristics aligning with formal cohorts [20, 41] and the inclusion of a diverse range of PPMS patients from both academic and non-academic hospitals. In addition, to our knowledge, there are no previous data comparing the 2010 and 2017 McDonald criteria for PPMS.

Implications

Our data stress the need for a critical review of the patients' prior medical history and possible confounding factors before making a diagnosis of PPMS. However, in a subgroup of patients it is likely that some uncertainty as to the disease course will remain and it could be argued that a single set of diagnostic criteria for any disease course of MS would simplify the diagnostic process. However, also with a single set of diagnostic criteria, clinicians should be alert on possible differential diagnoses and perform adequate testing before applying

TABLE 6 Patients with signs indicative of alternative diagnoses that were insufficiently investigated.

		Clinical signs		MRI results					CSF results			
Patient number	Putative alternative diagnosis	≥1 year disability progression	Atypical clinical signs [27]	PV	JC	IT	SC	Atypical findings	OCB	Atypical findings	2017 MD criteria[a]	Missing diagnostics
1	Neuro-infectious disease (e.g., Lues)	Yes	Neuropsychiatric symptoms (behavioral changes)	Yes	No	No	NA	NA	No	Leucocytes 54 $\times 10^6$/L	No	E.g., Lues serology, MRI spinal cord
2	Neuro-infectious disease (e.g., TB)	Yes	Increased risk for infections due to homelessness	Yes	NA	Yes	Yes	NA	Yes	Leucocytes 76 $\times 10^6$/L	Yes	E.g., Borrelia, HTLV-1, TB testing
3	Systemic auto-inflammatory disease (e.g., SLE, sarcoidosis)	Yes	Undifferentiated arthritis and elevated ESR	Yes	No	No	Yes	No	Yes	No	Yes	E.g., ACE, sIL2R, ANCA
4	Systemic auto-inflammatory disease (e.g., Sjögren)	Yes	Livedo reticularis, interstitial nefritis	Yes	NA	Yes	Yes	Large confluent white matter lesions, microbleeds	No	No	Yes	Sjögren diagnosed after PPMS, possibly CNS manifestation of Sjögren but not considered in medical file
5	Arteriovenous dural fistula	Yes		No	No	No	Yes	Large lesion in conus with flow voids	No	No	No	MRA spinal cord
6	Antiphospholipid syndrome	No	Acute symptoms in pregnancy. Deep venous thrombosis. Minimal recovery followed by stable phase	No	No	Yes	No	Infratentorial lesion more suspicious of lacune with gliosis	No	No	No	Antiphospholipid antibodies
7	Hereditary spastic paraplegia	Yes	Age of onset <18 years	No	No	No	No	No	NA[b]	No	No	Genetic testing

Note: This table shows the atypical signs, the most important results from MRI and CSF, and some diagnostics that are considered to be missing to examine an alternative diagnosis. Diagnostics that were performed at the time that showed normal results are not shown.

Abbreviations: ACE, angiotensin-converting enzyme; ANCA, anti-neutrophil cytoplasmic antibodies; CNS, central nervous system; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; HTLV-1, human T-lymphotropic virus type 1; IT, infratentorial lesions; JC, juxtacortical lesions; MD, McDonald; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not available (in the case of MRI, no images available, not mentioned in report); OCB, oligoclonal bands; PPMS, primary progressive multiple sclerosis; PV, periventricular lesions; SC, at least two spinal cord lesions; sIL2R, soluble IL-2 receptor; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Fulfillment of the 2017 McDonald criteria for PPMS based on MRI and CSF results; see Table 1.

[b]Medical file reports 'no abnormalities' in CSF performed elsewhere; unclear if electrophoresis was performed.

the McDonald criteria. Lastly, diagnostic criteria are per definition a trade-off between sensitivity and specificity [42]. Therefore even in PPMS patients with a complete diagnostic work-up without possible confounders, not all patients will fulfill diagnostic criteria, as was also found in our cohort.

CONCLUSION

This study highlights the challenges in diagnosing PPMS. For an accurate PPMS diagnosis, a comprehensive assessment of the clinical course is essential, with particular attention given to possible relapses in the initial disease course and signs indicative of an alternative diagnosis. Furthermore, conducting a thorough diagnostic work-up including CSF analysis is crucial. The 2010 and 2017 McDonald diagnostic criteria for PPMS perform similarly when these factors are taken into account, emphasizing the importance of their appropriate application in clinical practice.

AUTHOR CONTRIBUTIONS

Katelijn M. Blok: Conceptualization, resources, data curation, formal analysis, investigation, methodology, project administration, visualization, writing—original draft. Joost Smolders: Conceptualization, supervision, writing—review and editing. Joost van Rosmalen: Methodology, writing—review and editing. Carine O. Martins Jarnalo: Data curation, writing—review and editing. Beatrijs Wokke: Conceptualization, project administration, supervision, writing—review and editing. Janet de Beukelaar: Conceptualization, resources, investigation, data curation, project administration, supervision, writing—review and editing.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. Raw data of this study are available from the corresponding author upon reasonable request.

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