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Demographic and clinical profile of patients with multiple sclerosis diagnosed over the last 30 years according to different diagnostic criteria

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ABSTRACT

The aim of this study was to investigate the demographic and clinical characteristics of patients with multiple sclerosis (MS) diagnosed between 1986 and 2015.

333 patients with definite MS were divided into four subgroups according to the following diagnostic criteria: Group A) Poser (n = 145), Group B) McDonald 2000 (n = 66), Group C) McDonald 2005 (n = 62), and Group D) McDonald 2010 (n = 60). We investigated: 1) patient sex and age at diagnosis, 2) symptoms and number of relapses that prompted MS diagnosis, 3) time between first symptoms suggestive of MS and confirmed diagnosis, and 5) Expanded Disability Status Scale (EDSS) score at disease onset.

The overall female-to-male ratio was 2.3:1, but in the subgroups it differed significantly (A — 1.9; B — 1.6; C — 4.7; D — 3.6). The mean age at diagnosis (in years) decreased from 39.6 ± 13.3 in Group A to 29.9 ± 9.3 in Group D, $p < 0.001$. Pyramidal signs remained the most common manifestation regardless of the diagnostic criteria, although an increased trend of visual dysfunction was observed (A — 16%, B — 14%, C — 19%, D — 23,3%; A vs D, $p < 0.001$). The number of relapses before diagnosis decreased from median 4.0 to 2.5 in Group A and Group D, $p < 0.001$. Time from the first symptom to diagnosis shortened from 88.9 ± 80.2 months (Group A) to 33.6 ± 68.2 months (Group D), $p < 0.0001$. Mean EDSS score at diagnosis also decreased: A — 4.4 ± 2.3; B — 3.1 ± 1.7; C — 2.7 ± 1.3; D — 2.8 ± 1.4, $p < 0.001$.

Our study indicates significant differences in demographic and clinical characteristics of MS diagnosed according to the changing criteria.

Key words: multiple sclerosis, Poser criteria, McDonald criteria

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Introduction

Multiple sclerosis (MS), the most common demyelinating disease, is responsible for a considerable loss of quality and — to some extent — life expectancy in the developed world [1, 2]. Interestingly, an as-yet unexplained increase in the incidence of MS has been observed recently [3–5]. Between 1976 and 2006, the European prevalence of MS was estimated to be 83/100,000, whereas 10 years later it had reached nearly 100/100,000 [6].

However, it is worth pointing out that our perception of MS epidemiology might have become biased by a changing set of criteria which has allowed us to make a diagnosis at an earlier stage. Over the last 30 years, multiple sclerosis has been diagnosed according to five different sets of criteria, from the first so-called 'contemporary' criteria drawn up by Poser in 1983 through McDonald 2000, McDonald 2005, and McDonald 2010 right up to the current McDonald 2017. All of these were based mainly on a clinical assessment of the patient and, where there was insufficient data, supported by additional tests.

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The introduction of magnetic resonance imaging (MRI) shifted the diagnostic approach from a clinical examination supported by laboratory tests i.e. cerebrospinal fluid (CSF) analysis (Immunoglobulin G index and/or oligoclonal bands), and electrophysiology testing (in the Poser criteria) towards precise observations of lesions found in the brain and spinal cord in MRI (the McDonald 2000, 2005 and 2010 criteria) [7–9]. Importantly, the McDonald 2017 criteria underline once more the importance of CSF examination [10].

Even though the goal of each adjustment to the process has been to increase the sensitivity and specificity of the diagnosis, still today there is no one ideal test for MS available. Furthermore, the proportion of false positive diagnoses has risen over the years, reaching as much as 5–20% [11, 12]. It has been suggested that the explanation for this lies in simplification of diagnostic criteria, especially in the MRI era. Thus, it could be that not all of the patients labelled with MS nowadays would have been diagnosed with the disease according to the previous criteria.

There is no doubt that big data tools are required to address this issue. Unfortunately, the Global Report on MS Patients, launched in 2013, has highlighted the lack of epidemiological data from some European countries [13]. This situation partially changed in 2019 with the Swedish initiative of updating the national MS registries across Europe [14]. Brola's group from Końskie and AGH University of Science and Technology in Kraków was described as the local MS registry available in Poland [14]. Another paper from Kułakowska et al. tackled some selected aspects of MS epidemiology in Poland in 2010 [15]. However, the abovementioned groups represent local registries. To the best of our knowledge, no specific comparison of groups of patients diagnosed with MS according to subsequent modern diagnostic criteria exists in Poland.

Therefore, we investigated the demographic, clinical and laboratory aspects of a population diagnosed with MS according to the different criteria between 1986 and 2015.

Materials and methods

Types of data collected

Our study included patients (n = 402) who were hospitalised to confirm an MS diagnosis between 1986 and 2015 due to criteria applicable at the time. Notes of the patients were collected from the MS sub-register kept at the 2nd Neurology Department of IPiN so that scientific studies and clinical trials can be conducted. The Bioethics Committee of the Medical University of Warsaw approved our study in 2015. Every patient who met the relevant criteria was included in the study. We excluded patients who were eventually diagnosed with a different disease responsible for their neurological deficit symptoms (e.g. tumour, vascular or infectious disease) as well as those whose available documentation was insufficient to fulfil the criteria.

Firstly, patients were divided into groups according to diagnostic criteria used to confirm the diagnosis of MS. Secondly, selected demographic and clinical features were used to characterise patients included in the study: age, sex, type of first symptom, number of confirmed relapses before diagnosis, time from first symptom to diagnosis (in months), disability level measured in Expanded Disability Status Scale (EDSS) at the time of diagnosis, and severity of functional systems impairment (pyramidal, sensory, cerebellar, brainstem, visual, bowel and bladder, other systems). Finally, we analysed the frequency of using additional tests such as: oligoclonal bands detection in CSF, IgG index, MRI performance and pattern visual evoked potentials examination (since these became available).

Statistical analysis

Data was analysed using SAS 15.1. Continuous data is presented as mean and standard deviation and categorical data is shown as percentages with frequency. Skewed data is presented as median with range or mean with standard deviation. Quantitative variables were assessed using the Kruskal-Wallis test when more than two groups were considered. Two paired groups were compared using the non-parametric Mann-Whitney test. Chi-square and Fisher exact test were applied to assess differences in quantitive features. For all of the analyses, $p < 0.05$ was considered statistically significant.

Results

Overview of studied group

Data on 402 patients with suspected MS who were hospitalised between 1986 and 2015 was collected. Considering our exclusion criteria, 69 patients were not included in the study due to either a final diagnosis "other than MS" (13 patients), or a lack of data regarding disease onset or insufficient data provided to confirm the diagnosis (56 patients). Finally, 333 patients were included for further assessment. 43.5% of these were diagnosed according to the Poser criteria (Group A, n = 145), whereas 19.8% (Group B, n = 66), 18.6% (Group C, n = 62), and 18% (Group D, n = 60) were diagnosed according to the McDonald 2000, McDonald 2005, and McDonald 2010 criteria, respectively.

Demographic features

We found statistically significant differences between groups in terms of age ($p < 0.001$), and female-to-male ratio ($p < 0.001$) (Tab. 1). Patients diagnosed with McDonald 2010 criteria were younger than in any other group (e.g. mean ± SD: 29.3 ± 9.3 years vs. 39.3 ± 13.3 years for McDonald 2010 vs. Poser group). There were also significant changes in female-to-male ratio between groups (from 1.94 in the Poser group to 4.65 in the McDonald 2005 group, $p < 0.001$).

Table 1. Demographic features and clinical characteristics of patients diagnosed due to changing criteria of multiple sclerosis

	A) Poser n = 145	B) McDonald 2000 n = 66	C) McDonald 2005 n = 62	D) McDonald 2010 n = 60	P value
Age (years), mean ± SD	39.6 ± 13.3	37.75 ± 12.8	35.4 ± 13.0	29.9 ± 9.3	*p < 0.001 **p < 0.0001
Female sex, n (%)	94 (65)	41 (62)	51 (82)	47 (78)	*p < 0.001 **p = 0.05
female: male ratio	1.9:1	1.6:1	4.7:1	3.6:1	
Symptom type at disease onset, %:					
pyramidal	50	55	32	32	*p < 0.001 **p < 0.001
visual	16	14	19	23	*p < 0.0001 **p < 0.001
sensory	20	15	19	23	*p = 0.1776 **p = 0.0260
brainstem	4	4.5	14.5	13	*p = 0.003 **p = 0.0004
cerebellar	9	9	13	8	*p = 0.001 **p = 0.0005
Number of relapses before diagnosis, mean ± SD	4.1 ± 2.4	2.2 ± 1.6	1.6 ± 0.8	1.6 ± 1.0	*p = 0.0039 **p < 0.001
Time from first symptom to diagnosis (months), mean ± SD	88.9 ± 80.2	39.1 ± 68.4	36.2 ± 58.5	33.6 ± 68.2	*p < 0.0001 **p < 0.0001
EDSS at diagnosis, mean ± SD	4.4 ± 2.3	3.1 ± 1.7	2.7 ± 1.3	2.8 ± 1.4	*p < 0.001 **p < 0.0001

*p value for comparison between all groups; **p value for difference between groups A) and D); p < 0.05 considered significant

Clinical data

The most common first symptom observed in all studied groups was motor dysfunction. It became less prevalent in patients diagnosed with McDonald 2010 criteria (McDonald 2010 vs. Poser, p < 0.001). In contrast, ocular dysfunction (including optic neuritis) was observed more often as a primary finding in the McDonald 2010 group compared to the Poser group, p < 0.0001. Brainstem and cerebellar symptoms were more often found at disease onset in patients diagnosed with McDonald 2000 and 2005 compared to Poser criteria, p = 0.003 and p = 0.001 respectively (Tab. 1). A statistically significant decrease in the number of relapses before the confirmed diagnosis was found when comparing the Poser group (median 4.0) to the McDonald 2010 group (median 2.5), p < 0.001. Mean time from the first MS-suggesting symptom to diagnosis has shortened significantly over the years, from 88.91 months on average in the Poser group to 33.55 months in the McDonald 2010 group (Tab. 1). EDSS score was also significantly lower in the McDonald 2010 group compared to the Poser group [2.81 ± 1.37 vs. 4.36 ± 2.25, respectively (Tab. 1)]. Furthermore, we found a statistically significant decrease in the severity of brainstem, pyramidal, cerebellar, bowel and bladder symptoms in patients diagnosed with McDonald 2010 criteria compared to Poser. In contrast, sensory and visual function was more impaired in individuals diagnosed with McDonald 2010 criteria (Tab. 2).

Diagnostic tests

The rate of performing CSF oligoclonal bands and IgG index analysis did not change with the introduction of newer criteria in our studied group (p > 0.05). However, a downward trend for CSF sample examination was observed between the Poser and the McDonald 2000 groups (97.9% vs. 84.9%, p < 0.001).

Statistical difference in performing MRI was found (Poser — 11%, McDonald 2000 — 95.5%, McDonald 2005 — 95.2%, and McDonald 2010 — 98.3%, p < 0.0001). Generally, no statistically significant difference was found in frequency of using visual evoked potentials for MS diagnosis in the whole group (n = 333), however pattern-VEP examination was performed in 88.3% of the McDonald 2010 group but only 60% of the McDonald 2005 group (p < 0.01) (Tab. 3).

Discussion

Despite a growing interest in MS epidemiological studies, data on epidemiology of the disease in some parts of the world remains limited [3, 14–19].

Table 2. Percentages of patients with functional loss in main neurological systems comprising the Expanded Disability Status Scale (EDSS) found at disease onset according to different diagnostic criteria

Functional system EDSS	Impairment (according to EDSS)	A) Poser n = 145	B) McDonald 2000 n = 66	C) McDonald 2005 n = 62	D) McDonald 2010 N = 60	P value
Pyramidal	Proportion with impairment [%]	83.4	84.8	96.8	88.3	*p < 0.001
	Median score (range)	3 (0–5)	2 (0–5)	2 (0–4)	1 (0–4)	**p < 0.001
Sensory	Proportion with impairment [%]	49.7	60.6	58.1	66.7	*p = 0.177
	Median score (range)	0 (0–4)	1 (0–3)	1 (0–4)	2 (0–4)	**p = 0.0625
Cerebellar	Proportion with impairment [%]	43.4	60.6	35.5	25	*p < 0.001
	Median score (range)	0 (0–4)	1 (0–2)	0 (0–2)	0 (0–3)	**p = 0.0005
Bowel and bladder	Proportion with impairment [%]	17.2	37.9	17.7	23.3	*p = 0.0071
	Median score (range)	0 (0–4)	0 (0–3)	0 (0–4)	0 (0–1)	**p = 0.0013
Brainstem	Proportion with impairment [%]	20	43.9	35.5	41.7	*p = 0.0003
	Median score (range)	0 (0–3)	0 (0–3)	0 (0–2)	0 (0–3)	**p = 0.0004
Visual	Proportion with impairment [%]	9.7	28.8	33.9	56.7	*p < 0.0001
	Median score (range)	0 (0–3)	0 (0–9)	0 (0–5)	1 (0–9)	**p < 0.0001

*p value for comparison between all groups; **p value for difference between groups A) and D)

Table 3. Additional examinations performed in patients of subsequent diagnostic criteria groups (number and percentage of tests done in whole group)

	A) Poser n = 145	B) McDonald 2000 n = 66	C) McDonald 2005 n = 62	D) McDonald 2010 n = 60
OCBs,	123	54	48	53
n (%)	(84)	(82)	(77)	(88)
IgG index, n	113	37	42	56
(%)	(78)	(56)	(68)	(93)
MRI, n	16	63	59	59
(%)	(11)	(95.5)	(95)	(98)
VEP, n	138	52	37	53
(%)	(95)	(80)	(60)	(88)

OCBs — oligoclonal bands; IgG — immunoglobulin G; MRI — magnetic resonance imaging; VEP — visual evoked potentials

To the best of our knowledge, this is the first analysis in central-eastern Europe to describe groups of patients diagnosed according to successive criteria introduced between 1983 and 2015.

Our study shows that patients nowadays are diagnosed at a younger age, that MS prevalence in females is higher, and that disability is less pronounced regardless of sex. Interestingly, our study shows that although motor neuron dysfunction remains the most common first symptom in MS patients, subjects diagnosed with the McDonald 2010 criteria present an increased prevalence of visual symptoms compared to those diagnosed with the Poser criteria.

The upward F/M ratio trend, declining age, and less pronounced function deficit by the time of diagnosis are in accordance with changes observed worldwide in previous studies undertaken in Europe [20], Asia, Australia and New Zealand [4, 21]. However, the 4:1 female:male ratio of patients diagnosed with McDonald 2010 observed in our study surpasses the numbers presented by other authors [22]. A Canadian report showed 3.2:1 (n = 27,074) [23] followed by European studies with an F:M ratio of 3.1:1 [24] and Asian ones with a similar rate [25]. Japanese neurologists have described an increasing F:M ratio trend over the years starting with 2.63:1 until 2001, increasing to 2.75:1 in 2006 and to 3.38:1 in 2011 [26, 27]. A similar surge has been observed in American studies [28]. Only a Danish study from 2017 involving females aged under 18 showed similar results concerning the distribution of MS across the sexes [29]. Similar results to our study were obtained in the Polish study by Kułakowska et al., with a 2.4:1 female-to-male ratio. However, the material for their paper was collected in 2008–09 and so according to McDonald 2005 criteria [15].

Hypotheses have been coined to explain these observations. The higher prevalence of MS among women might reflect

the role of hormones or epigenetic factors [30]. On the other hand, younger age and better neurological function at the time of diagnosis are probably linked to increased awareness of the disease and better healthcare accessibility [31]. It is not uncommon nowadays to encounter patients with only surreptitious deficits, who fully meet MRI-based criteria of the disease.

In terms of the first symptom of the disease, although the proportion of first clinical signs at the diagnosis has changed over time, motor impairment has remained the most frequent in all groups (Poser — 50.3%, McDonald 2000 — 54.6%, McDonald 2005 — 32.3%, McDonald 2010 — 31.7%). Simultaneously, an increasing trend for the rate of retrobulbar neuritis has been found (from 15.9% in the Poser group to 23.3% in the McDonald 2010 group). This observation reflects the worldwide trend regarding initial MS manifestation. Several groups of neurologists have obtained similar ratios of motor and ocular disturbances (e.g. 43.5% motor, 32.4% ocular) being the first clinical symptom of MS [33, 34]. However, our study showed a relatively higher incidence of ocular abnormalities compared to motor ones, especially in the McDonald 2010 group. We must point out that Gharagozli et al.'s study was conducted in 2008-10, whereas our investigation lasted until 2015, by which time optic neuritis was being reported even more often than previously. Moreover, the aforementioned study comprises an Asian subpopulation solely, whereas our study group consists of Caucasians only [33]. In recent years, more attention has been paid to fatigue and other motor dysfunctions but this was not within the scope of our study. However, some reports show that fatigue may dominate within MS clinical characteristics (61%) [35] but is closely followed by ocular and sensory symptoms (~ 50%) in polysymptomatic onset of the disease. Additionally, we must remember that there is an increasing number of new MS-suspect cases based mainly on MRI findings (RIS) in asymptomatic patients. That might explain the lower level of motor dysfunction reported nowadays [36] or the rise in cognitive dysfunction before physical symptoms appear [37].

Mean EDSS at the time of diagnosis has changed significantly over the years, from mean 4.36 ± 2.25 in the Poser group to 2.81 ± 1.37 in McDonald 2010. This aligns with other epidemiological studies [15, 31].

To the best of our knowledge, such an increased prevalence of optic neuritis among MS patients diagnosed with McDonald 2010 criteria has not been previously reported. There may be several reasons for this. First of all, even though we know that ocular issues may be the first symptoms of MS, it is not routine management that an ophthalmologist refers a patient to a neurologist for a neurological examination. Nowadays, almost all patients with any neuro-ophthalmological sign are subjected to meticulous examination by both types of specialists. Moreover, each retrobulbar neuritis case undergoes obligatory MRI of the central nervous system in our site. This is not routine elsewhere. Finally, over the last 30 years patient awareness of MS has increased substantially. Today they tend to report their symptoms immediately and to seek ophthalmology and neurology help simultaneously.

Cases of optic neuritis, which are often characterised by subtle clinical findings and lack of changes in physical examination, might have been labelled as subjective visual deficits in the pre-MRI era. Therefore, the actual incidence of optic neuritis detection is much higher in the MRI era.

CSF evaluation was a mandatory test in laboratory-supported MS only under the Poser criteria. However, in our centre, regardless of the recommendations, the vast majority of MS-suspected patients underwent a CSF evaluation as a part of their differential diagnosis. It has become part of routine management. Numerous studies have verified the importance and significance of CSF evaluation. Firstly, it was proven that positive oligoclonal bands (OCBs) present high sensitivity (98%) in distinguishing MS from conditions mimicking MS [38]. Secondly, positive OCBs may have prognostic value in the probability of CIS converting into MS [39, 40]. Thirdly, positive OCBs at the initial manifestation correlate positively with severity of the disease in long-term prognosis [42]. Finally, OCBs and IgG index may play crucial roles in the differential diagnosis of MS [42, 43]. Additionally, the current (McDonald 2017) criteria emphasise the value of OCBs and have brought them back into the diagnostic sphere [11].

MRI is nowadays widely used for MS diagnosis [18]. This can be seen in our results: since the introduction of McDonald 2000 more than 95%, and since McDonald 2010 more than 98%, underwent MRI scans. In the case of the population diagnosed according to the Poser criteria, it was not so commonly performed in our group; at that time, it was a new diagnostic tool and not widely used. The sensitivity and specificity of VEP have been questioned numerous times over the past decade. In our study, there was some fluctuation in VEP performance over the years. A surge from laboratory to neuro-imaging tests in diagnostic criteria might explain that difference.

In conclusion, we must underline that the population of patients diagnosed with subsequent criteria has changed. Early recognition, higher female-to-male ratio, and increased prevalence or detection rate of optic neuritis might affect our approach to diagnosis, then to the treatment decision.

We are aware of limitations of our study. These include small groups, a single-centre study, a high level of reference hospital and thus an unrepresentative group of patients (i.e. we may have selected difficult cases), and bias in first symptom reported by the patient (not always confirmed by the clinician).

Yet ours is still a promising pilot study that helps to better describe how the profile of MS patients has changed over the years. Nevertheless, more epidemiological data is still needed to more fully delineate MS patient characteristics.

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Conflicts of interest

None

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