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ORIGINAL COMMUNICATION

High performance of cerebrospinal fluid immunoglobulin G analysis for diagnosis of multiple sclerosis

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Abstract

Background The 2017 revision of the McDonald criteria highlights the usefulness of cerebrospinal fluid (CSF) immunoglobulin G (IgG) analysis to diagnose multiple sclerosis (MS). The objective of this study was to assess the diagnostic performances of CSF IgG analysis in the absence of a gold standard.

Methods All patients who underwent CSF IgG analysis for events suggestive of MS in Nancy University Hospital (France) from 2008 to 2011 were retrospectively included. A latent class analysis with Bayesian approach was used to infer MS prevalence (latent variable) as well as the diagnostic properties of the 2005 and 2010 McDonald criteria and CSF IgG analysis (observed variables).

Results Data from 673 patients were analysed. For CSF IgG analysis, the Bayesian latent class analysis estimated sensitivity of 0.93 (95% CrI 0.89–0.96) and specificity of 0.81 (95% CrI 0.77–0.85). The true prevalence estimate was 36% (95% CrI 0.33–0.40). Sensitivity and specificity estimates for patients with events suggestive of remitting-onset MS were similar to those for the whole sample—0.92 (95% CrI 0.85–0.96) and 0.80 (95% CrI 0.76–0.84), respectively—but higher for patients with signs of progressive-onset MS—0.95 (95% CrI 0.84–0.99) and 0.88 (95% CrI 0.78–0.94), respectively.

Conclusions In the absence of a gold standard, latent class analysis indicates good diagnostic properties of CSF IgG analysis for MS. This test could thus be useful, especially for patients who tested negative for the 2005 and 2010 McDonald criteria. These findings deserve to be confirmed prospectively.

Keywords Multiple sclerosis · Bayesian analysis · Cerebrospinal fluid · Diagnostic test assessment · Latent class model

Introduction

The diagnosis of multiple sclerosis (MS) has always been challenging. In the absence of a single test with sufficient sensitivity and specificity, it has always been based on a body of clinical and paraclinical arguments. Since the first set of criteria published in 1965 [1], the cornerstone of diagnosis has been the proof of dissemination in space (DIS) and time (DIT) of the pathological process, both in remitting-onset MS (ROMS) and progressive-onset MS (POMS) disease courses [2–5]. The diagnostic criteria include clinical history, physical examination, magnetic resonance imaging (MRI) scans and cerebrospinal fluid (CSF) immunoglobulin G (IgG) analysis. However, the recent introduction of the "2017 revision of the McDonald criteria" has somewhat modified the playing field: according to this revision, while DIS is still a valid parameter to suggest MS, DIT is no longer

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necessary when CSF IgG analysis reveals oligoclonal bands (OBs) on isoelectrofocusing [6].

The prominent role of CSF IgG analysis in the new diagnostic criteria is based on large prognostic cohort studies. When present, OBs are associated with a clear increase of the risk of a second relapse over the following years, independently of other baseline covariates (especially MRI data) [7, 8]. Moreover, the presence of OBs increases the risk of being McDonald 2010 positive in following years in patients with DIS only [9].

Obviously, CSF IgG analysis is unavoidable in cases of suspected MS and is already performed in many countries. A positive CSF IgG analysis after a clinically isolated syndrome (CIS) or in case of a progressive neurological disability suggestive of MS makes the neurologist confident enough to initiate discussion about the disease, or even to make the diagnosis.

This raises the question of the diagnostic performances of CSF alone. To address this issue, several case-control studies focusing on series of patients who had a spinal tap and a final diagnosis of MS (cases) or other diseases (controls) were published [10]. Sensitivity and specificity were based on the final diagnosis and their values vary largely whether controls suffered from inflammatory diseases of the central nervous system or not. This major bias is compounded by a second one, as the diagnosis of MS was based on tests or a body of argument that cannot be considered as a perfect *gold standard*, cases were probably patients with the clearest manifestations of the disease, i.e. severe patients. This might have overestimated the accuracy of the CSF tests.

Our objective in this study was to evaluate the diagnostic properties of CSF IgG analysis for MS (presence of OBs and/or an elevated IgG index) in a prospectively acquired cohort of patients who underwent CSF analysis after a clinical event suggestive of MS. The patients of the cohort who were finally diagnosed with MS are part of ReLSEP (*Registre Lorrain des Scléroses En Plaques*), a population-based registry of North-Eastern France [11, 12].

Methods

Source population and sampling

MS is suspected by various clinico-radiological presentations, which we will refer to in this article as "event suggestive of MS". Every patient with such a clinical presentation in our neurology unit undergoes a spinal tap to collect CSF and detect OBs and/or an elevated IgG index, with only a few exceptions. Our sample consisted of all patients who underwent these tests at the Neurology Unit of Nancy University Hospital (ReLSEP reference center) between January 1, 2008 and December 31, 2011. They were identified through the hospital's exhaustive database of CSF biochemical analysis. As some patients might have had these tests whereas MS was not suspected, every case with CSF IgG analysis were reviewed by the authors, and cases without reasonable evidence of MS suspicion at the time of the spinal tap (e.g., dementia with normal brain MRI or suspicion of amyotrophic lateral sclerosis with normal spinal MRI) were excluded. Despite the initial event that had to suggest MS, the final diagnosis might have been set on another cause of CNS inflammation such as neurosarcoidosis or neuromyelitis optica, or even a non-inflammatory disease of the central nervous system. These cases correspond to MS-mimics. Whatever the final diagnosis was—MS, CIS, MS-mimics—every patient with events suggestive of MS and having underwent a spinal tap for this reason were included (Fig. 1).

Identification of variables

CSF protein and glucose concentrations were determined by the AU480® chemistry analyser (Beckman Coulter System). Concentrations of albumin and IgG were determined in the CSF and serum by automated turbidimetry kits (Kone Delta biochemistry analyser, ThermoFischer Scientific, Waltham, MA, USA). The presence of OBs in unconcentrated CSF was determined by isoelectrofocusing (SAS-3®, Helena Biosciences, Gateshead, UK) on agarose gels after double-antibody staining with a secondary IgG peroxidase conjugate. The IgG index was defined as the quotient of the CSF/serum ratios of IgG: CSF-IgG/serum-IgG divided by the ratio of albumin: CSF-albumin/serum-albumin was used for data analysis. Positive CSF IgG analysis was defined as ≥ 2 IgG OBs (presence of OBs) and/or an IgG index > 0.70 [4, 5, 10, 13].

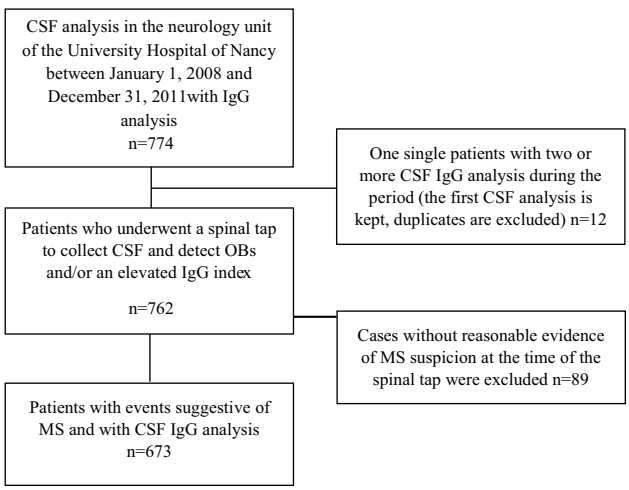

Fig. 1 Flowchart of patient recruitment

Statistical analysis

To minimize the *reference test bias*, we performed a latent class analysis (LCA) statistical model to evaluate the diagnostic properties of CSF IgG analysis. LCA states that the observed values of two or more tests used to diagnose a pathological condition (MS in this case) are conditional to a latent categorical variable: the true diagnosis of MS (yes or no) [14–17]. The assumption is that it is not possible to know with certainty the true state of the latent variable because of the lack of a gold standard, but the combination of the measured test values in a given patient depends on the class of the latent variable to which he/she belongs. Subsequently, the latent variable class can be inferred from the combination of observed values of the test variables. The observed variable of interest was the CSF IgG analysis results. We considered 2005 and 2010 McDonald criteria as the two other diagnostic tests for the LCA model. For the purpose of this study, the two sets of McDonald criteria were applied as screening tests rather than as predictive tools in case of a CIS (original purpose of these criteria). They were applied even if the final diagnosis was different from MS, using imaging and CSF data as for MS patients. For example, a patient finally diagnosed with neurosarcoidosis and assessed by the McDonald 2005 and 2010 criteria was sometimes noted as positive because of MRI lesions or clinical events meeting the DIS and DIT criteria. These "tests" were defined as positive if the criteria corresponded to published guidelines for ROMS or POMS [4, 5]. The criteria have been taken in their entirety with all the possibilities of DIT and DIS they include. If the criteria were only partially met, or not at all, the test was considered to be negative. We checked each part of the criteria against the clinical, CSF and MRI data available throughout the follow-up period (i.e., up to the date of extraction: March 30, 2016) and determined DIT by successive MRI exams and the occurrence of any new lesions.

The 2005 and 2010 McDonald criteria and CSF IgG analysis were taken as the observed variables of the LCA. This model assumes that the observed variables are independent conditional to the latent variable. However, obviously, our three tests were not independent: CSF results are part of the 2005 criteria for ROMS diagnosis and of the 2005 and 2010 criteria for POMS, and the same MRI scans are used to establish 2005 and 2010 criteria positivity. As previously proposed [18, 19], we introduced a random effect with a Bayesian approach to draw inferences about the disease prevalence and test properties while adjusting for the possibility of conditional dependence between tests. The Bayesian approach combines previous knowledge about parameters (from the literature) and the observed results of the tests to obtain a posterior probability distribution for the studied parameters [19–22].

We derived median estimates and 95% credible intervals (95% CrI) for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) for each test. Prior sensitivity and specificity values for the tests were identified based on published literature [23, 24] and elicited 95% prior probability intervals were derived (Table 1).

LCA also provides a median value and 95% CrI as estimates of the "true prevalence" of the disease—namely the "latent" variable the analysis is based on.

As a secondary analysis, we determined the performances of the CSF IgG analysis in the subsample of patients with an event suggestive of ROMS and in the subsample of patients with an event suggestive of POMS at the time of the spinal tap.

To determine whether any differences found between the 2005 and 2010 McDonald criteria were attributable to CSF, we also used a model with the 2005 McDonald criteria without considering the CSF (i.e., positivity for McDonald 2005 determined by MRI and clinical information alone).

To assess the validity of our results, we performed sensitivity analysis with different prior values for each parameter with wider prior intervals.

LCA does not require a gold standard so the final diagnosis established by the clinician was not used in the analysis. Nevertheless, we collected final clinician diagnosis from the medical files for descriptive purposes, and the percentages of MS cases and demyelinating events without all the criteria for MS (mentioned in the patient's medical records at the end of follow-up) were used to estimate a 95% probability interval of MS prevalence in our sample. When the reports were ambiguous, two expert neurologists (MD and GM) reinterpreted the MRI scans and clinical details. Data about socio-demographics were also gathered.

Table 1 Prior probability intervals for the prevalence of multiple sclerosis in the sample and sensitivity and specificity for the three diagnostic tests of the latent class analysis

	Variable	95% probability intervals
Multiple sclerosis	Prevalence	[0.30; 0.50]
2010 McDonald criteria	Sensitivity	[0.72; 0.99]
	Specificity	[0.87; 0.99]
2005 McDonald criteria	Sensitivity	[0.60; 0.99]
	Specificity	[0.88; 0.99]
CSF IgG analysis	Sensitivity	[0.53; 0.99]
	Specificity	[0.50; 0.99]

Positive CSF IgG analysis: presence of oligoclonal bands and/or IgG index > 0.70

CSF cerebrospinal fluid, *IgG* immunoglobulin G

Standard protocol approvals and registrations

The study was registered with the French National Commission for Data Protection and Liberties (CNIL; reference R2016-13). All the patients had been informed that their data were recorded and that they may be used for research purposes, in compliance with the French legislation about non-interventional epidemiological research.

Results

Description

Among the 673 recruited patients, 67.3% were women. The mean age was 41.58 ± 14.49 years (range 13–82 years) at the time of the spinal tap (Table 2). Overall, 316 (47.0%) patients had OBs, and 317 (47.1%) patients had CSF IgG OBs and/or an IgG index > 0.70 (only one patient had a positive IgG index and no OBs). According to the clinician, at the end of the mean follow-up of 2.65 ± 2.35 years, 36.4% of patients were diagnosed with MS, and 14.4% have had one single clinical event suggestive of MS without meeting diagnosis criteria. Clinically isolated syndrome without DIS and/or DIT on MRI are in this category, as well as patients with progressive disability without criteria for primary progressive MS.

Main analysis

Table 3 shows the number of patients undergoing the various combinations of the three tests. According to the LCA, the estimated true prevalence of MS was 36% (95% CrI 0.33–0.40). All the tests had high sensitivity for the diagnosis of MS: 0.96 for the 2010 criteria; 0.98 for the 2005 criteria; and: 0.93 for CSF IgG analysis (Table 4). The PPVs had a similar pattern: 0.93 and 0.98 for 2010 and 2005 McDonald criteria, respectively, and 0.74 for the CSF IgG. Specificity was similar for the 2010 and 2005 McDonald criteria (0.96 and 0.99, respectively), and 0.81 for the CSF IgG. The NPVs were high and the difference between the tests low: 0.98, 0.99 and 0.95 for the 2010 and 2005 McDonald criteria and CSF IgG analysis, respectively. The PLRs were 24 and 105 for the 2010 and 2005 McDonald criteria and 5 for the CSF IgG analysis. The NLRs were similar: 0.04 and 0.02 for the 2010 and 2005 McDonald criteria and 0.09 for CSF IgG.

Analysis in patients with an event suggestive of ROMS before the spinal tap led to similar but slightly reduced results for CSF IgG analysis: 0.92 for sensitivity and 0.80 for specificity. The results were higher for the POMS-suggestive events subsample: 0.95 and 0.88, respectively.

Furthermore, in the model where the 2005 McDonald criteria were used without CSF data (i.e., without the possibility of DIS by positive CSF IgG analysis and two or more white matter lesions) the sensitivity changed in the subsample patients with ROMS-suggestive events: 0.99 (95% CrI 0.97–0.99) for the 2010 McDonald criteria and 0.97 (95% CrI 0.94–0.99) for the 2005 McDonald criteria. In the same model, specificity for the 2010 McDonald criteria was lower at 0.93 (95% CrI 0.90–0.95) but unchanged for the 2005 McDonald criteria at 0.99 (95% CrI 0.98–0.99).

Sensitivity analysis

Reanalysing with less informative priors, within wider range than those found in the literature, in the Bayesian model than those in Table 1 led to the same results (not shown).

Discussion

This study reports the high specificity and sensitivity of CSF IgG analysis for the diagnosis of MS (81% and 93%, respectively) in a sample of 673 patients with a clinical event suggestive of MS and an estimated 36% with a final diagnosis of MS. The CSF IgG analysis PLR was five, indicating a moderate increase in the likelihood of developing the disease while the NLR was 0.09, indicating a tenfold decrease in the likelihood of developing the disease (often considered conclusive, when the test is negative) [25, 26]. CSF IgG positivity was mainly driven by the presence of OBs, since only one patient in the whole population had an elevated IgG index and no OBs. This confirms a low—if not inexistent—role of the IgG index, in line with the use of OBs but not the IgG index in the latest version of the McDonald criteria [6]. Moreover, 11.6% patients who did not meet the McDonald 2005 or 2010 criteria (i.e., suspected of having MS even if not diagnosed because of negative criteria), were CSF IgG positive underlining the interest of a spinal tap in this setting.

The same characteristics for CSF IgG analysis were found in the subsample of ROMS-suggestive clinical presentation as in the entire sample. In contrast, CSF IgG analysis showed better performances in the POMS-suggestive clinical presentation subsample. CSF analysis is thus important when diagnosing POMS. However, the 95% credible intervals were less accurate because of the size of the subsample.

Overall, both the 2010 and 2005 McDonald criteria were more specific than CSF IgG analysis. This is logical because both sets of criteria include clinical and paraclinical laboratory assessments as well as 2.65 ± 2.35 years of follow-up, which means that of the occurrence of a second clinical or "radiological" event can be taken into account (ensuring DIT and sometimes DIS). Moreover, CSF IgG analysis is part of the 2005 McDonald criteria, explaining the highest performances for this set of criteria in diagnosing MS. After

Table 2 Characteristics of 673 patients who underwent a spinal tap for a clinical history suggestive of multiple sclerosis at the time of the spinal tap

	N	%	Mean	SD
Age at spinal tap				
Years	673		41.58	14.49
Sex				
Female	453	67.3		
Male	220	32.7		
Follow-up				
Days	673		966	857
Type of event suggestive of MS				
Progressive onset MS suggestive	101	15.0		
Relapsing onset MS suggestive	572	85.0		
Final diagnosis according to the clinician				
MS	245	36.4		
Event suggestive MS (symptoms and MRI) but not fulfilling McDonald criteria for MS	97	14.4		
Myopathy	1	0.2		
Oncology disease	4	0.6		
Metabolic or toxic encephalopathy	7	1.0		
Psychiatric disease	10	1.5		
Infectious disease	13	1.9		
Physical or traumatic disease	17	2.5		
Degenerative disease	23	3.4		
Non-MS inflammatory disease of the central nervous system	2731	4.0		
Neuropathy	33,161	4.6		
Vascular disease	4	4.9		
Functional and/or pain syndrome		23.9		
Indefinite		0.6		
CSF IgG OB				
No	357	53.0		
Yes	316	47.0		
IgG index > 0.70				
No	503	74.7		
Yes	170	25.3		
CSF IgG OB/or IgG index > 0.70				
Negative	356	52.9		
Positive	317	47.1		
2005 McDonald DIS				
Negative	377	56.0		
Positive	296	44.0		
2005 McDonald DIT				
Negative	445	66.1		
Positive	228	33.9		
2005 McDonald criteria				
Negative	433	64.3		
Positive	240	35.7		
2010 McDonald DIS				
Negative	342	50.8		
Positive	331	49.2		
2010 McDonald DIT				
Negative	411	61.1		
Positive	262	38.9		
2010 McDonald criteria				
Negative	422	62.7		
Positive	251	37.3		

CSF cerebrospinal fluid, *DIS* dissemination in space, *DIT* dissemination in time, *IgG* immunoglobulin G, *MS* multiple sclerosis, *OB* oligoclonal bands, *SD* standard deviation

Table 3 Combinations of test results for 2010 and 2005 McDonald criteria and CSF IgG analysis (presence of oligoclonal bands and/or immunoglobulin G index > 0.70)

2010 McDonald criteria	2005 McDonald criteria	CSF IgG analysis	N	%
+	+	+	216	32.0
+	+	−	16	2.4
+	−	+	15	2.2
+	−	−	4	0.6
−	+	+	8	1.2
−	+	−	0	0.0
−	−	+	78	11.6
−	−	−	336	50.0

CSF cerebrospinal fluid, *IgG* immunoglobulin G

excluding CSF analysis data from the 2005 criteria, sensitivity seems to be lower.

Many studies have analyzed the McDonald criteria [27–30]. We will focus on a parallel with Swanton et al.'s study, which assessed the 2001, 2005 and 2010 criteria in a cohort of patients with CIS (CSF IgG analysis was not performed) [24]. This work demonstrated the superiority of the 2010 criteria to diagnose ROMS. In our study, CSF IgG sensitivity was higher than the 2010 criteria in Swanton's study (71.8%, 95% confidence interval 61.0–81.0) and the PLR was approximately the same (5.5, 95% confidence interval 3.4–8.9). Conversely, CSF specificity was lower in our study than for the 2010 criteria in Swanton's study (87%, 95% confidence interval 79.7–94.2) although CSF IgG NLR was lower and better than the NLR of the 2010 criteria. Moreover, our data showed a superiority of the 2005 over the 2010 criteria while Swanton's study and others have always found better sensitivity for the 2010 over the 2005 criteria. We assume that these findings are due in part to the incorporation of the criteria "two or more characteristic lesions and positive CSF" in the 2005 DIS criteria, but above all to the considerable differences in study design. In previous works, the 2005 and 2010 McDonald criteria were applied at the time of CIS, and incidental new demyelinating clinical events occurring during follow-up was taken to be the gold standard. In our design, the 2005 and 2010 McDonald

Table 4 Posterior medians and 95% credible intervals for the estimated "true" prevalence of multiple sclerosis and for each test variables in the entire sample, the subsample with events suggestive of ROMS and the subsample with events suggestive of POMS

Parameter	Entire sample		ROMS suggestive events subsample		POMS suggestive events subsample	
	Estimate	95% CrI	Estimate	95% CrI	Estimate	95% CrI
Prevalence	0.36	[0.33; 0.40]	0.22	[0.18; 0.25]	0.40	[0.33; 0.47]
CSF IgG analysis						
Sensitivity	0.93	[0.89; 0.96]	0.92	[0.85; 0.96]	0.95	[0.84; 0.99]
Specificity	0.81	[0.77; 0.85]	0.80	[0.76; 0.84]	0.88	[0.78; 0.94]
PPV	0.74	[0.69; 0.79]	0.56	[0.48; 0.63]	0.84	[0.73; 0.92]
NPV	0.95	[0.93; 0.97]	0.97	[0.95; 0.99]	0.96	[0.89; 0.99]
PLR	5.00	[4.0; 6.2]	4.56	[3.7; 5.7]	7.69	[4.3; 16.5]
NLR	0.09	[0.05; 0.14]	0.099	[0.05; 0.19]	0.06	[0.01; 0.18]
2010 McDonald criteria						
Sensitivity	0.96	[0.93; 0.98]	0.95	[0.89; 0.99]	0.97	[0.88; 0.99]
Specificity	0.96	[0.94; 0.98]	0.96	[0.93; 0.99]	0.94	[0.87; 0.98]
PPV	0.93	[0.90; 0.96]	0.87	[0.80; 0.93]	0.92	[0.86; 0.97]
NPV	0.98	[0.96; 0.99]	0.99	[0.97; 0.99]	0.98	[0.92; 0.99]
PLR	24.00	[15.6; 41.9]	24.89	[15.4; 45.9]	17.12	[7.60; 48.3]
NLR	0.04	[0.02; 0.08]	0.05	[0.02; 0.12]	0.04	[0.007; 0.13]
2005 McDonald criteria						
Sensitivity	0.98	[0.95; 0.99]	0.96	[0.89; 0.99]	0.97	[0.87; 0.99]
Specificity	0.99	[0.98; 0.99]	0.99	[0.97; 0.99]	0.97	[0.93; 0.99]
PPV	0.98	[0.96; 0.99]	0.96	[0.91; 0.99]	0.96	[0.89; 0.99]
NPV	0.99	[0.97; 0.99]	0.99	[0.97; 0.99]	0.98	[0.91; 0.99]
PLR	105.00	[41.04; 316.8]	89.08	[36.6; 280.9]	35.44	[12.74; 123.6]
NLR	0.02	[0.004; 0.05]	0.04	[0.008; 0.11]	0.04	[0.005; 0.14]

Positive CSF IgG analysis: presence of oligoclonal bands and/or IgG index > 0.70

95% CrI 95% credible interval, *CSF* cerebrospinal fluid, *IgG* immunoglobulin G, *NLR* negative likelihood ratio, *NPV* negative predictive value, *PLR* positive likelihood ratio, *POMS* progressive at onset multiple sclerosis, *PPV* positive predictive value, *ROMS* relapsing at onset multiple sclerosis

criteria were used after many years of follow-up, with the inclusion of any further lesions or relapses and chance of DIT and DIS as mentioned above. Thus, the sensitivity and specificity of the McDonald 2005 or 2010 criteria may have had the same value in our study than those of the CSF IgG analysis if these were used with the data available at the moment of the spinal tap. Moreover, the central point of our analysis was the use of LCA with a random effect model and Bayesian approach, totally different from previous methodologies.

Other studies have evaluated CSF IgG analysis properties, by comparing the results in MS patients vs non-MS controls. Non-MS conditions were non-neurological syndromes or inflammatory or non-inflammatory neurological conditions. A meta-analysis of these studies [23] found that sensitivity ranges from 0.53 to 1.00 and specificity from 0.26 to 1.00 for CSF IgG analysis [31–33]. Results seem to vary according to the studied population. In particular, the specificity of CSF IgG analysis is low in studies with controls with inflammatory conditions. In our study, we extended the control sample to every patient with symptoms more or less suggestive of MS and having undergone a spinal tap for this reason. This fits in with daily clinical practice, and thus underscores the representativeness of our results. Our cohort of 673 patients is one of the largest used to evaluate CSF IgG analysis for MS diagnosis. The fact that we used the latest information available for each patient means that we were able to have more reliable results for the McDonald criteria, which in turn increased the quality of our model. Furthermore, the CSF IgG OBs and index were systematically measured by the same standardized methods.

Interestingly, our model estimated the true prevalence of MS as 36%, compared with the 36.4% of MS cases diagnosed by clinicians at the end of follow-up (14.4% more with an event suggestive of MS but not fulfilling McDonald criteria). Thus, while the latent variable distribution—the true condition "MS/not MS"—was established by the model, based on the distributions of the observed variables we used, the similarity of the estimated prevalence and the one derived from clinicians diagnosis is a good indication of the coherence of our model with clinical data.

Limitations

Our study has some limitations. We did not include patients with suspected MS who did not undergo CSF analysis, and we do not know how many patients fall into this category. Nevertheless, we can assume that the number of such patients was low due to the nearly systematic use of spinal tap in this setting in our local practice. We decided to use CSF IgG analysis as a single test as if no MRI had been performed. So we did not adjust our analysis of « CSF alone » properties on these imaging data. But MRIs have been taken into account as indicated in the McDonald criteria.

Conclusions

Bayesian LCA revealed good diagnostic properties of CSF IgG analysis in a large cohort of patients being assessed for MS in daily clinical practice in an expert Neurology Unit. This suggests that CSF IgG analysis improves confidence in the diagnosis of MS. After a clinical event suggestive of MS, patients not meeting McDonald 2005 and 2010 criteria on MRI but with OBs on CSF analysis might be considered at high risk for MS. This is in line with the "the 2017 revision of the McDonald criteria [6], where DIS of inflammation on clinical or MRU data is sufficient to make the diagnosis if CSF analysis is positive for IgG synthesis, even if DIT is missing.

A prospective study focusing on a cohort of CIS and using the same methodology is required to properly assess the use of CSF IgG analysis in comparison with McDonald criteria.

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Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical standards The study was approved by the institutional review board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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