The diagnostic value of IgG index versus oligoclonal bands in cerebrospinal fluid of patients with multiple sclerosis

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Abstract

Background: Diagnostic criteria for multiple sclerosis have been developed to guide the diagnostic process. In the latest revision of the McDonald criteria, the presence of oligoclonal bands may replace the need for dissemination in time. The aim of this study is to investigate if the less time-consuming analysis of immunoglobulin G index in cerebrospinal fluid can safely predict the findings of oligoclonal bands.

Methods: This is a retrospective study of patients with multiple sclerosis at three hospitals in South-East Norway where lumbar puncture is performed routinely. We included patients diagnosed with multiple sclerosis after 2005 with known oligoclonal band status and an immunoglobulin G index score.

Results: Of 1295 patients diagnosed during or after 2005, 93.8% were oligoclonal band positive at diagnosis. Of 842 multiple sclerosis patients with known immunoglobulin G index and oligoclonal band status, 93.3% were oligoclonal band positive and 76.7% had an elevated immunoglobulin G index. The positive predictive value of a high immunoglobulin G index when oligoclonal bands are positive was 99.4% (95% confidence interval 98.4–99.8%). The negative predictive value of a normal immunoglobulin G index when oligoclonal bands are negative was 26.5% (95% confidence interval 23.5–29.9%).

Conclusion: An immunoglobulin G index >0.7 has a positive predictive value >99% for oligoclonal bands. An elevated immunoglobulin G index adds diagnostic value versus oligoclonal bands and saves time in the diagnostic process.

Keywords: Biomarkers, multiple sclerosis, oligoclonal bands, IgG index

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Introduction

Multiple sclerosis (MS) is an inflammatory disease with secondary neurodegeneration that causes significant disability in patients over time. Disease onset is usually between 20 and 40 years of age and MS is one of the most common non-traumatic causes of disability in young adults.1 Recent studies have shown increasing evidence of a better prognosis when disease-modifying drugs are initiated early in the disease course.2,3

The diagnostic criteria for MS are based on a combination of clinical, imaging and laboratory evidence for disease in the central nervous system (CNS). The impact of each of these elements has changed, although the need for evidence of dissemination in time (DIT) and dissemination in space (DIS) for a secure diagnosis has remained.4–7 Cerebrospinal fluid (CSF) analysis is not mandatory for the diagnosis of MS in patients with a clinical syndrome suggestive of the disease. However, in the 2017 revision of the McDonald diagnostic criteria, presence of ≥2 CSF-specific oligoclonal immunoglobulin G (IgG) bands (OCB) can be used in place of demonstrating DIT,8 possibly leading to an earlier diagnosis. Several authors have erroneously assumed the newest McDonald criteria allow for OCB to prove DIT. In fact, the presence of OCB in patients with a...
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In total 23.3% had a normal IgG index, whereas 76.7% had an elevated index. We found that 99.8% of patients with an IgG index above 0.8 had OCBs in their CSF. All patients with IgG index above 0.86 had OCBs (Figure 1).

All 842 patients with a known IgG index had a known OCB status (93.3% OCB positive, Table 2). The sensitivity of the IgG index predicting OCB outcome was 81.7% (95% CI 78.8–84.3%), and the specificity was 92.9% (95% CI 82.7–98.0%). The positive predictive value of an elevated IgG index was 99.4% (95% CI 98.4–99.8%), whereas the negative predictive value of a normal IgG index was 26.5% (95% CI 23.5–29.9%). Each of the three hospitals had similar individual positive predictive values (OUS 99.0%, VVHF 100%, STHF 99.4%) (Figure 2).

Discussion

The current study demonstrates that an elevated IgG index has a positive predictive value above 99% predicting the presence of intrathecal OCBs. Thus, an elevated IgG index can be used as a proxy to OCB and DIT is not required.

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In a Northern European population, around 95% of MS patients have OCB in the CSF. Different
ethnic populations have significantly lower prevalence of OCB\textsuperscript{16–18} although this difference may not be as obvious in immigrants to high-risk countries\textsuperscript{19} and may in fact represent less-sensitive methodology and misdiagnosis.\textsuperscript{20} In our population, which is mostly Northern-European, 93.8\% had OCB.

In the current practice, it can take several days or weeks to get the OCB result and thus the MS diagnosis is potentially delayed. Meanwhile, calculating the IgG index takes less time and is cheaper and can be done within a day. In addition, it is rater independent. However, the IgG index and other quantitative IgG analysis are not equivalent to qualitative analysis using IEF due to lower sensitivity.\textsuperscript{12,21} Quantitative analysis has a diagnostic sensitivity of 60–70\%\textsuperscript{15,22} and only 75\% of patients will turn out to be OCB positive.\textsuperscript{12} In our study, the probability of a patient with OCB having an elevated IgG index was 81.7\%.

Although the IgG index itself cannot predict the OCB outcome, our findings show an elevated IgG index has a very high predictive value of forecasting OCB. A normal IgG index, however, cannot be used to predict the presence or lack of OCB.

**Table 2:** Cross table of OCB and IgG index findings. Percentage of elevated or normal IgG index with OCB or without OCB.

|               | OCB+   | OCB−   | Sum   |
|---------------|--------|--------|-------|
| Elevated IgG index | 642 (99.4\%) | 4 (0.6\%) | 646   |
| Normal IgG index    | 144 (73.5\%) | 52 (26.5\%) | 196   |
| **Sum**            | 786 (93.3\%) | 56 (6.7\%)  | 842   |

IgG: immunoglobulin G; OCB: oligoclonal bands; IgG index: (CSF/serum IgG) / (CSF/serum albumin)

Like most hospitals, we use 0.6–0.7 as the cut-off for an elevated IgG index. We found that 99.8\% of MS patients had positive OCB when the IgG index was above 0.8 and 100\% of MS patients had ≥2 OCB when the IgG index was more than 0.86. Other studies have also proven strong correlations between a positive IgG index and the presence of intrathecal OCBs, with 96–100\% of patients with an IgG index above 0.8 having positive OCB.\textsuperscript{15,23} A few smaller studies have found no correlation.\textsuperscript{24,25} However, most studies on OCB and IgG index have had small sample sizes or have been subject to testing bias, as patients with complicated disease history are more likely to undergo lumbar puncture. Moreover, many of the cited OCB and IgG index studies were done before the introduction of IEF. Our study includes a large and near-complete MS population, as lumbar puncture is performed routinely when diagnosing MS in Norway. In addition, our study only included patients diagnosed after the introduction of IEF in 2005.

CSF findings used in the routine diagnosis of MS serve two purposes: to confirm a diagnosis of MS early in the disease course, and support exclusion of differential diagnoses.\textsuperscript{26,27} A meta-analysis found that OCB has a specificity of 94\% for MS.\textsuperscript{13} However, when considering patients with MS or other neuroinflammatory conditions, the specificity fell to 61\%. This underlines the importance of context. We emphasise that our findings cannot be extrapolated to all neurological patients with a high IgG index, but are reserved for those patients where other neurological conditions have been excluded and the clinician is merely waiting for a positive OCB or DIT to be able to diagnose MS. We found that MS patients without OCB or with a normal IgG index were on average more likely to have progressive disease at onset and were older.

**Sensitivity** (probability of a patient with OCB having an elevated IgG index) = 81.7\%
(95\% CI 78.8–84.3\%)

**Specificity** (probability of a patient without OCB having normal IgG index) = 92.2\%
(95\% CI 98.4–99.8\%)

**Positive Predictive Value** (probability of a patient with elevated IgG index having OCB) = 99.4\%
(95\% CI 98.4–99.8\%)

**Negative Predictive Value** (probability of a patient with normal IgG index not having OCB) = 26.5\%
(95\% CI 23.5–29.9\%)

**Figure 2.** Sensitivity, specificity, positive predictive value and negative predictive value. CI: confidence interval; IgG: immunoglobulin G; OCB: oligoclonal bands.
than those with OCB or elevated IgG index. This is in line with findings from Siritho et al.,\textsuperscript{28} though not others.\textsuperscript{29,30} One likely explanation for the significant difference in disease phenotype between those with and those without OCB and elevated IgG index is misdiagnosis.\textsuperscript{20} The lack of OCB has a very high negative predictive value.\textsuperscript{31} Although the current ethos is to diagnose MS as early as possible, this can sometimes decrease the accuracy of the diagnosis. If one suspects other neuroinflammatory disorders or there is presence of red flags in the diagnostic work up,\textsuperscript{32} both the presence of OCB and a positive IgG index score should be interpreted with caution.

A faster diagnosis of MS is important to initialize treatment early.\textsuperscript{33} This study of data from routine lumbar punctures over many years in a large Norwegian MS population demonstrates that an IgG index \textgreater{}0.7 has a very high positive predictive value for the presence of OCB. A positive IgG index can therefore replace OCB and thus lead to an earlier diagnosis.

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