

Reporting of cerebrospinal oligoclonal bands in Switzerland: Recommendations of the Swiss Society for Allergology and Immunology (SSAI) - Commission on Laboratory Diagnostics (CLD) and the Swiss Society of Clinical Chemistry (SSCC)

August, 2021

Introduction

In 2019, a survey was organized among laboratories in Switzerland that routinely perform isoelectric focusing (IEF) for the detection of oligoclonal bands in cerebrospinal fluid (CSF) for the diagnosis of multiple sclerosis (MS). The survey was prepared by the Commission of Laboratory Diagnostics (CLD) of the Swiss Society for Allergology and Immunology (SSAI) and was distributed to 15 laboratories participating in the national quality assurance schemes for CSF analysis. The aim of the survey was to assess the degree of variation between laboratories when reporting IEF results. The survey did explicitly not address the pre-analytical and analytical phases of CSF analysis.

The results of the survey, which was returned by 13 labs, allowed the identification of the main reporting items that show a high variation between laboratories and -as a consequence- may thus cause confusion and misinterpretation when read and interpreted by health care professionals receiving the reports. In an effort to reduce this reporting variation, we set out to define recommendations in order to harmonize reporting of CSF oligoclonal bands analysis by clinical laboratories in Switzerland.

Terminology

Laboratories use different terminology when reporting the results of CSF. Basically, one of the three following alternatives is used on the report of the laboratories participating in the survey:

- A) "oligoclonal bands" (without specifying the sample material)
- B) "oligoclonal bands in CSF" and "oligoclonal bands in serum"
- C) "CSF-specific oligoclonal bands"

It was noted that laboratories using terminology A ("oligoclonal bands") report objectively identical results differently. For example, when labs were asked how they would report a type 4 pattern (i.e., multiple bands in CSF and identical bands in serum), some labs using terminology A answered to report a type 4 pattern as "negative", while other labs using this terminology report pattern 4 as "positive". Centers using terminology B ("oligoclonal bands in CSF" and "oligoclonal bands in serum") also report cases differently. For example, one lab using terminology B indicated to report a type 4 as "identical" for both parameters, whereas another lab that uses terminology B reports a type 4 as "positive" for both of the listed parameters. In contrast, all laboratories that report according to option C ("CSF-

specific oligoclonal bands”) reported all cases of the survey uniformly. For example, a type 4 pattern was reported by all these laboratories as “negative”.

Therefore, considering that 1) the terminology of option A and B is not clearly defined, 2) the use of terminology A and B leads to discrepant reporting between laboratories, 3) the use of terminology C was not associated with discrepant reporting, and 4) the current international criteria guideline for the diagnosis of multiple sclerosis (Thompson et al., 2018) consistently uses the terminology as in option C, the CLD recommends the following:

Recommendation I:

Results of CSF/serum isoelectric focusing should be reported as “CSF-specific oligoclonal bands” (“Liquor-spezifische oligoklonale Banden”; “Bandes oligoclonales spécifiques au liquide cerebrospinal”). Other or additional terminology should not be used.

Isotype specification

When reporting oligoclonal bands, most labs participating in the survey do not specify or comment on the isotype (e.g., IgG) of the bands their method detects and just use terminology such as “oligoclonal bands” to describe the analysis.

Intrathecal Ig synthesis can be analyzed qualitatively by the determination of CSF-specific oligoclonal bands or quantitatively by mathematical formulas (e.g., IgG index, hyperbolic “Reiber” functions). Laboratories usually report results of IEF accompanied by the numerical and graphical representation of such quantitative Ig measurements, in particular for IgG, but also IgA and IgM. Since the isotypes of the quantitative Ig measurements are reported as such, it also seems appropriate to communicate the isotype of the oligoclonal bands detected by the IEF method in order to avoid misunderstanding.

Recommendation II:

In case the used isoelectric focusing method is isotype-restricted (e.g., isoelectric focusing with IgG-immunoblot or -immunofixation), the isotype should be specified on the report (e.g., “CSF-specific oligoclonal bands (IgG)” (“Liquor-spezifische oligoklonale Banden (IgG)”; “Bandes oligoclonales (IgG) spécifiques au liquide cerebrospinal”).

Pattern interpretation

Most, but not all laboratories participating in the survey report the interpretation of the observed IEF patterns in terms of the 5 standardized patterns originally defined by Andersson et al. 1994. These labs explicitly mention the type (i.e., 1-5) of the pattern observed, and most of them also include an explanation of the reported type. However, some labs give the type without further additional description or explanation. The few labs that do not report the pattern type according to Andersson et al. 1994, also do not describe the observed pattern.

Considering that 1) consensus papers have defined the most common patterns of oligoclonal bands when analyzing CSF and serum with the recommended IEF method (Andersson et al. 1994, Freedman et al. 2005), 2) standardized patterns help both laboratory specialists and neurologists to interpret and communicate the results, and 3) not all health professionals reading the report are familiar with the pattern types and understand the meaning of these without an explanatory comment, the CLD recommends:

Recommendation III:

Results of CSF/serum isoelectric focusing should be interpreted in terms of one of the standardized patterns of oligoclonal banding (Andersson et al. 1994). The report should mention both the pattern type as well as a description of the type.

Reporting of a single CSF band

Laboratories participating in the survey report the presence of a single CSF-specific IgG band differently. When asked how a single CSF band would be reported, some labs answered to report this as “negative”, whereas others classify one CSF band as “positive”. Alternatively, some labs report a single CSF band as “questionable”. Likewise, discrepancies were observed between laboratories regarding the reported pattern type. Both type 1 and type 2 were used when labs were asked how one single CSF band would be classified. Some laboratories did not commit to a specific type and/or added a comment explaining the clinical significance of the presence of one band.

Currently, there is no explicit threshold established on the number of CSF-specific bands to classify a case as positive (Andersson et. 1994, Freedman et al. 2005). Studies have evaluated the clinical significance of a single CSF IgG band and found that such a finding indicates a possible but not reliable proof of intrathecal IgG synthesis (Ferraro et al. 2017). As such, the current MS diagnostic criteria state that the demonstration of at least two CSF-specific oligoclonal bands reliably indicates intrathecal antibody synthesis (Thompson et al. 2018). However, even a cut-off of 2 CSF bands may have suboptimal diagnostic specificity (Hegen et al. 2019). In general, since a proper IEF is dependent on local factors, such as method, reagents and equipment, an optimal cut-off for CSF bands is most likely best defined locally. Such a clinical evaluation may however not be feasible for all laboratories. Therefore, the CLD, considering 1) the current MS diagnostic criteria and 2) the fact that single CSF IgG bands may not be specific, but tend to associate with diseases of the central nervous system characterized by intrathecal IgG synthesis, recommends that:

Recommendation IV:

The detection of at least two CSF-specific bands may be regarded as an indication for intrathecal IgG synthesis. The presence of a single CSF-specific IgG band, with or without bands equal in serum and CSF, should be reported by using an additional diagnostic reporting category (e.g., “borderline” and/or “possible intrathecal IgG synthesis”) not being classified as one of the five standard pattern types.

Discrepancy between qualitative (IEF) and quantitative CSF analysis

As already mentioned above, intrathecal Ig synthesis can be analyzed qualitatively by the determination of CSF-specific oligoclonal bands, or quantitatively by mathematical formulas (e.g., IgG index, Reiber functions). Although IEF with IgG-immunoblot or -immunofixation is currently considered the gold standard (Freedman et al, 2005), laboratories usually also report results of quantitative calculations for intrathecal IgG synthesis. Since the two methods (IEF and mathematical formulas) are different, their results may be discrepant. Such discrepant results on one report may cause confusion, especially when results of the two methods are both reported as, for example, “intrathecal IgG synthesis”. The survey addressed this issue by confronting the laboratories with a case that demonstrated a type 2 oligoclonal bands pattern, but for which the quantitative analysis (IgG index and Reiber functions) yielded a negative result. The report of one third of the laboratories contained the apparent discrepancy (i.e., “intrathecal IgG synthesis detectable by OCB” and “no intrathecal IgG synthesis by quantitative analysis”), but also included a text commenting on this discrepancy. Most of these labs explained the difference by mentioning the differences in sensitivity of the methods and referring to the IEF as the standard. However, another third of the laboratories report the results as a discrepancy, but do not give any explanatory comment or interpretation. Finally, a number of labs routinely report results of quantitative analyses, but do not describe this as intrathecal or local IgG synthesis. As a consequence, reports of these labs do not contain obvious discrepancies when reporting the case mentioned.

Considering that 1) intrathecal IgG synthesis can be assessed by both qualitative IEF as well as quantitative analysis, 2) results of these methods may be discrepant, 3) discrepancies may have different explanations and interpretations, and 4) health professionals reading the report may not be familiar with the analytical performances of the methods the laboratory is using, the CLD recommends:

Recommendation V:

In case of a discrepancy between results of qualitative IgG analysis using IEF and quantitative IgG analysis (e.g., IgG index, hyperbolic and exponential functions), a specific comment should be added that mentions the discrepancy and explains the clinical significance to help health professionals interpret the discrepant results. In case the terminology “intrathecal IgG synthesis” is used in the report, it should be clear from the report to which method is referred to.

Literature

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