Harmonization of Cerebrospinal Fluid Oligoclonal Banding Reporting

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INTRODUCTION

- Cerebrospinal fluid (CSF) oligoclonal banding (OCB) analysis can be used as one component to fulfill diagnostic criteria for multiple sclerosis (MS)
- Other associated tests (e.g., CSF immunoglobulin G (IgG), CSF albumin) and calculated indices (e.g., IgG index) may aid in clinical interpretation
- Presence of ≥2 CSF-specific OCBs can satisfy dissemination in time criteria for MS diagnosis (2017 McDonald Criteria[1])
- A recent survey revealed significant variability in processes and reporting practices across Canadian clinical laboratories[2]
- To address this issue, a subcommittee of the Canadian Society of Clinical Chemists (CSCC) Reference Interval Harmonization (hRI) Working Group was formed

OBJECTIVE

To harmonize laboratory processes and reporting for CSF OCB and associated tests for the diagnosis of MS.

METHODS

Establish a CSCC-hRI subcommittee of clinical chemists and neurologist across Canada (19 members).

Identify key areas requiring harmonized recommendations.

Formulate questions to address each key area.

1. Literature search and review of current laboratory practices in Canada.
2. Survey Canadian neurologists to understand how tests are used and reporting preferences.
3. Plan and perform studies to answer outstanding questions.

Draft statements to answer each question.

Use Delphi process to refine and finalize recommendation statements.

RESULTS

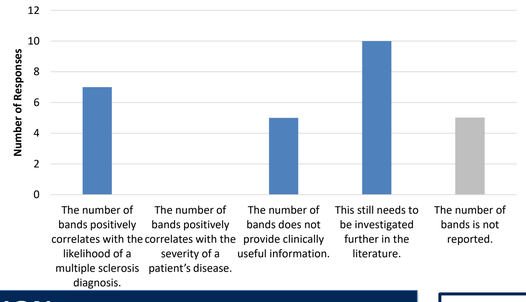
Key Areas, Associated Questions, & Literature Search

Key Area	Questions
1. Quality control practices *Members: Michelle Parker, Karina Rodriguez-Capote, Yu Chen, Cassandra Ringuette-Goulet*	1. What is the recommended frequency of QC for CSF OCB (frequency per gel – e.g., number of lanes dedicated to QC, placement on the gel)? 2. What is the recommended QC material for CSF OCB (e.g., patient sample vs commercial material, CSF vs serum, pos and/or neg samples)? 3. What is the recommended documentation for CSF OCB QC results (e.g., counting bands or just pos/neg)?
2. Acceptable time interval for collection of paired CSF and serum samples *Members: Lily Olayinka, Daniel Beriault, Karina Rodriguez-Capote, Basma Ahmed, Yu Chen, Joe Macri*	1. What is the acceptable time limit for considering CSF and serum are paired samples? What is the stability of IgG in serum and CSF? What is IgG *in vivo* metabolism (synthesis and turnover) in serum and CSF? Does this differ in patients with MS, acute inflammation, taking specific medications, etc.? 2. How should CSF samples received without a paired serum be handled/reported? E.g., if no bands are identified on the CSF (reported as negative), if bands are identified in the CSF (report as inconclusive, try to schedule recollection with X amount of time)
3. Reporting protocols for band counts *Members: Daniel Beriault, Michelle Parker, Mark Freedman, Ron Booth, Basma Ahmed, Yu Chen, Raphael Schneider, Ilia Poliakov, Fabrizio Giuliani*	1. Should we report the number of CSF-specific bands observed? Is there utility in reporting the number of CSF-specific bands? Do number of CSF-specific bands relate to prognosis? To likelihood of diagnosis? To severity of diagnosis? 2. How should we report the number of CSF-specific bands observed (absolute counts vs. a range of bands (2-4, 5-8, etc.))? What is the intra- and inter-observer variability in reporting the number of CSF-specific bands? What is the analytical reproducibility of band counts? 3. Should we report the number of CSF-serum matched bands? Is there utility in reporting the number of CSF-serum matched bands? 4. How should we report the number of CSF-serum matched bands (absolute counts vs. a range of bands (2-4, 5-8, etc.))? What is the intra- and inter-observer variability in reporting the number of CSF-serum matched bands?
4. Interpretation and follow-up for other patterns *Members: Victoria Higgins, Mark Freedman, Jessica Gifford, Ron Booth, Karina Rodriguez-Capote, Ashley Newbigging, Yu Chen, Joe Macri, Vipin Bhayana, Liju Yang, Fabrizio Giuliani*	**Monoclonal Gammopathy Pattern:** 1. Should laboratories report on the presence of a monoclonal gammopathy pattern? How does this pattern agree with SPEP/IFE results? 2. What action should be taken by the laboratory and what should the interpretive comments include when a monoclonal gammopathy pattern is observed? **Inflammatory Response Pattern:** 1. Should laboratories report on the presence of a systemic inflammatory response pattern? 2. What threshold of CSF-serum matched bands should be used to identify the presence of a systemic inflammatory response pattern? 3. What should the interpretive comment include when an inflammatory response pattern is present? What conditions are associated with this pattern?
5. Handling matched band intensity variations *Members: Victoria Higgins, Yu Chen, Cassandra Ringuette-Goulet, Vipin Bhayana, Liju Yang*	1. For bands that are present in both serum and CSF, but differ in intensity, what process should be followed and how should they be reported? What if all bands and/or some bands vary in intensity?
6. Defining panel components and reference intervals/decision limits *Members: Christine Collier, Daniel Beriault, Mark Freedman, Ron Booth, Ashley Newbigging, Yu Chen, Joe Macri, Raphael Schneider, Ilia Poliakov, Fabrizio Giuliani*	**Defining Panel Components** 1. Should we report all components of calculations/indices? (i.e., CSF IgG, CSF albumin, serum IgG, and serum albumin) 2. Should we report CSF and serum total protein concentrations as part of the panel? 3. What associated tests, calculations, and indices should be reflexively included in a CSF OCB ordering panel? (e.g., albumin index, IgG index, IgG/albumin index, IgG/total protein index, CSF/serum IgG/Total protein ratio, CSF IgG synthesis rate, kappa FLC index)? What is their clinical value? 4. What terminology, units, and equations should be used? **Reference Intervals/Decision Limits** 1. What should the diagnostic cut-off for CSF-specific bands be? 2. Can we harmonize the reference intervals/decision limits for the associated lab tests and indices? What should the reference intervals/decision limits be? 3. What is the OCB positivity rate in healthy/other neurological conditions individuals?

Neurology Survey

- 16-question survey developed with Google Forms
- Disseminated to neurologists across Canada via colleagues of clinical chemists and neurologists and through the Canadian Network of MS Clinics, January 2022
- Responses obtained from 22 neurologists, March 2022

Key Area 3



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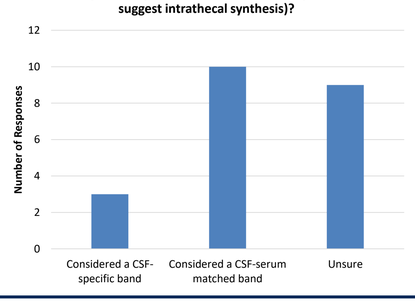

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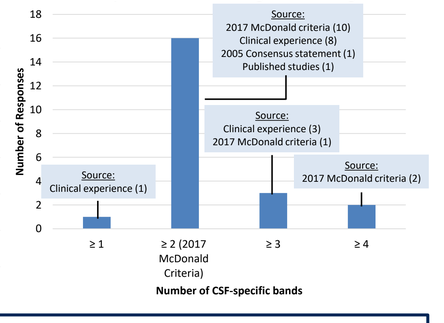

CONCLUSION

Recommendations to harmonize laboratory reporting will promote alignment of CSF OCB reporting practices with the latest evidence, ultimately enhancing diagnostic accuracy and patient care.

REFERENCES

1. A.J. Thompson, et al. Lancet Neurol. 17 (2) (2018) 162–173.
2. V. Higgins, et al. Clin Biochem. 116 (2023) 105–112.