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EDITORIAL

Live-cell based assays are the gold standard for anti-MOG-Ab testing

E. Ann Yeh, MD, and Ichiro Nakashima, MD, PhD

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Correspondence
Dr. Yeh
ann.yeh@sickkids.ca

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Page XXX

Over the last decade, knowledge regarding antibodies (Abs) associated with inflammatory disorders of the CNS has revolutionized diagnosis and clinical care. Examples of highly specific Ab assays that are now widely used to diagnose and make rapid treatment decisions in this area include those for Abs directed at the aquaporin-4 water channel and NMDA receptor. This has resulted in the acceleration of knowledge regarding treatment and has decidedly improved outcomes among these patient populations. Challenging the field is the vast majority of patients who have syndromes that lack a specific biomarker.

In this issue of *Neurology*®, Waters et al.[1] provide important information on the comparative sensitivity and specificity of assays for 1 such Ab that has clinical importance, the anti–myelin oligodendrocyte glycoprotein (MOG) Ab.[1–5] Widespread interest and excitement about Abs against MOG, a cell-surface protein, have emerged in recent years, due in part to good concordance between the presence of MOG-Ab in the serum and distinct clinical syndromes. In pediatrics, MOG-Abs are present at onset in almost one-quarter to one-third of children with neuroinflammatory disease[6,7] who satisfied phenotypic classification but defied biologically based classification, regardless of whether they have monophasic or relapsing disease. A relapsing phenotype with persistent positivity of MOG-Ab may account for individuals who, until the advent of this marker, may have been labeled as having atypical multiple sclerosis (MS), Ab-negative neuromyelitis optica spectrum disorders (perhaps with atypical features), or even, if biopsied, small vessel CNS vasculitis.

Excitement about this biomarker is warranted. The reports above underline the potential value of this marker in a large group of individuals with a previously unidentified etiologic pathway. Doubt about the value of anti-MOG-Ab was for years due to the variability of ELISA based testing; the development of cell-based testing in more recent years showed, convincingly, specificity for clinical phenotypes. On the heels of this has come the development of a commercial kit that uses fixed cells (Euroimmun), which has increased potential access to cell-based testing for this biomarker. Thus, the important question of sensitivity and specificity of each cell-based method has arisen.

Waters et al.[1] address this question by using 3 different methods on the same samples (n = 394) to compare anti-MOG-Ab results. All 3 were cell-based assays (CBAs) with cells that have been transfected with MOG but with slightly different methodologies. One CBA was performed at Oxford, 1 at the Mayo laboratories, and 1 by Euroimmun using a commercial CBA kit. Both the Oxford and Mayo assays used live cells and differed in how positivity was determined. The Oxford assay relies on microscopic visual inspection of stained MOG-transfected and nontransfected cells. The Mayo assay measures median fluorescence intensity on MOG-transfected and nontransfected cells and determines their ratio to determine positivity. The Euroimmun assay uses fixed MOG-transfected and nontransfected cells and relies on microscopic visual inspection of staining. The serum samples came from 91 cases, patients who were considered to have an anti-MOG-Ab–like clinical phenotype, and controls, represented by patients with MS (n = 244), hypergammaglobulinemia (n = 42), and other neurologic diseases (n = 17). The 2 assays using live cells had higher positive predictive values

From the Division of Neurology (E.A.Y.), Department of Pediatrics, Division of Neuroscience and Mental Health, SickKids Research Institute, The Hospital for Sick Children, and University of Toronto, Ontario, Canada; and Department of Neurology (I.N.), Tohoku Medical and Pharmaceutical University, Sendai, Japan.

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than the fixed cell assay, and the fixed cell assay had more false-positive results than the live cell assays. The positive predictive values of the tests performed with the Euroimmun kit, Mayo, and Oxford were 82.1%, 95.5%, and 100%, respectively. The negative predictive values were 79.0%, 78.8%, and 79.8%, respectively. Sensitivity was relatively low (25.3%, 23.1%, and 27.5%, respectively), but specificity was high (98.1%, 99.6%, and 100%).

This article provides important information on anti-MOG-Ab testing and emphasizes the superiority of live CBA testing. This observation is of importance because a fixed cell assay is more likely to be widely used in diagnostic laboratories able to purchase prepared slides from a commercial source like Euroimmun.

The report also highlights another issue that looms in the background. Of 91 patients who had a clinical phenotype suggestive of MOG-related disease, only 25, or 27%, were anti-MOG-Ab positive using any assay: thus, it emphasizes the present dearth of knowledge about biological markers in individuals with neuroinflammatory disorders.

This report has set the scene for further improvement of fixed CBA and allows clinicians greater understanding of the utility of the testing that they are sending. The higher positive predictive value and lower number of false-positives in the live cell assays than in the fixed cell assay suggest to the observer 2 things: (1) laboratories capable of performing live CBA currently provide superior clinical information, and (2) there is a pressing need to develop methods to increase the sensitivity and specificity of assays that can be accessed via kit form. While the very high specificity in the 2 large laboratories performing live CBA is commendable, access to this testing may be limited for many practitioners; access to testing in these laboratories may be delayed by unwieldy insurance paperwork for external laboratory testing. Thus, there is a pressing future need for highly sensitive and specific kits that can be used locally to allow practitioners to make rapid and definitive diagnoses. Rapid access to this testing will certainly have effects on future morbidity and psychological well-being of patients and their families.

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