Serum autoantibodies to myelin peptides distinguish acute disseminated encephalomyelitis from relapsing–remitting multiple sclerosis


*Mult Scler* published online 23 April 2013
DOI: 10.1177/1352458513485653

The online version of this article can be found at: [http://msj.sagepub.com/content/early/2013/04/18/1352458513485653](http://msj.sagepub.com/content/early/2013/04/18/1352458513485653)
Serum autoantibodies to myelin peptides distinguish acute disseminated encephalomyelitis from relapsing–remitting multiple sclerosis

Keith Van Haren1,2, Beren H Tomooka3,4, Brian A Kidd3, Brenda Banwell5, Amit Bar-Or6, Tanuja Chitnis7, Silvia N Tenembaum8, Daniela Pohl9, Kevin Rostasy10, Russell C Dale11, Kevin C O’Connor12, David A Hafler12, Lawrence Steinman1 and William H Robinson3,4

Abstract
Background and objective: Acute disseminated encephalomyelitis (ADEM) and relapsing–remitting multiple sclerosis (RRMS) share overlapping clinical, radiologic and laboratory features at onset. Because autoantibodies may contribute to the pathogenesis of both diseases, we sought to identify autoantibody biomarkers that are capable of distinguishing them.

Methods: We used custom antigen arrays to profile anti-myelin-peptide autoantibodies in sera derived from individuals with pediatric ADEM (n = 15), pediatric multiple sclerosis (Ped MS; n = 11) and adult MS (n = 15). Using isotype-specific secondary antibodies, we profiled both IgG and IgM reactivities. We used Statistical Analysis of Microarrays software to confirm the differences in autoantibody reactivity profiles between ADEM and MS samples. We used Prediction Analysis of Microarrays software to generate and validate prediction algorithms, based on the autoantibody reactivity profiles.

Results: ADEM was characterized by IgG autoantibodies targeting epitopes derived from myelin basic protein, proteolipid protein, myelin-associated oligodendrocyte basic glycoprotein, and alpha-B-crystallin. In contrast, MS was characterized by IgM autoantibodies targeting myelin basic protein, proteolipid protein, myelin-associated oligodendrocyte basic glycoprotein and oligodendrocyte-specific protein. We generated and validated prediction algorithms that distinguish ADEM serum (sensitivity 62–86%; specificity 56–79%) from MS serum (sensitivity 40–87%; specificity 62–86%) on the basis of combined IgG and IgM anti-myelin autoantibody reactivity to a small number of myelin peptides.

Conclusions: Combined profiles of serum IgG and IgM autoantibodies identified myelin antigens that may be useful for distinguishing MS from ADEM. Further studies are required to establish clinical utility. Further biological assays are required to delineate the pathogenic potential of these antibodies.

Keywords
Pediatric disease, multiple sclerosis, acute disseminated encephalomyelitis, myelin, autoantibody, differential diagnosis, biomarker, immunoglobulin, autoimmune disease, immunoassay

Date received: 7th November 2012; accepted: 17th March 2013
Introduction

Acute disseminated encephalomyelitis (ADEM) and relapsing–remitting multiple sclerosis (RRMS) are distinct forms of autoimmune-mediated demyelination, yet they may share polysymptomatic neurological deficits, multifocal white matter lesions and laboratory findings. This can render a prediction of monophasic outcome (typical of ADEM) versus RRMS difficult. Observation over time is required for diagnosis. An improved understanding of the biological factors that distinguish transient immune targeting of the central nervous system (CNS) from chronic CNS-directed autoimmunity has both diagnostic and potential therapeutic implications. Therefore, molecular biomarkers that can distinguish between multiple sclerosis (MS) and ADEM are highly sought after.1–3

The etiology of MS is multi-factorial, with a role for both genetic and environmental factors. The natural history of MS involves episodic exacerbations overlying a chronic and progressive decline, though life-long immunomodulatory therapy can moderately attenuate the disease. The current diagnosis of MS is based on clinical and radiologic confirmation of relapsing inflammatory demyelination that occurs in multiple CNS regions, separated in both space and time.4 In contrast, ADEM is a monophasic disorder in more than 90% of cases and it affects primarily children. Many patients report recent upper respiratory illness, prompting consideration of an infectious trigger for that immune response. The criteria for diagnosing ADEM remain a subject of debate, though many clinicians apply the 2007 consensus criteria, which characterize ADEM as a first episode of inflammatory demyelination with multi-focal CNS involvement and encephalopathy.5

In both ADEM and MS, autoantibodies to specific myelin proteins and lipids may contribute to disease pathogenesis6–8 and activate complement in some patients.9,10 We have developed antigen arrays for profiling autoantibodies in a variety of autoimmune diseases, including demyelinating disorders.11–13 Preliminary studies suggest that the two diseases (ADEM and RRMS) have distinct autoantibody profiles,2,14 including differences in immunoglobulin (Ig) subtype.1,8,15–17 Based on the available literature, we hypothesized that IgG and IgM autoantibodies in ADEM and MS patients might offer disease-specific profiles. In this study, we used antigen arrays to identify serum anti-myelin autoantibody profiles that can distinguish between ADEM and MS.

Materials and methods

Patient samples

 Archived serum samples from patients with pediatric ADEM (n = 15), pediatric MS (Ped MS; n = 11), or adult MS (n = 15) were available for analysis. Demographic data are summarized in Table 1. The samples were collected at several sites, under protocols approved by the local Institutional Review Board. Informed consent was obtained from all subjects. Samples were stored at −80ºC until used. The patient’s neurological history, relapse features, neurological examinations, MRIs and CSF findings were reviewed when available. Each clinical diagnosis was validated using the data from the clinical intake form or available records. Patients diagnosed with pediatric or adult MS met the 2001 McDonald criteria for lesion dissemination in time and space, at the time blood was drawn.18 Ped MS was defined as cases of MS with an onset of symptoms prior to 18 years of age. The definitions proposed by the International Pediatric MS Study Group were used to distinguish ADEM and Ped MS.19 Patients were diagnosed with ADEM if they experienced a polysymptomatic inflammatory demyelinating event accompanied by encephalopathy, seizure or coma, without subsequent evidence of further inflammatory disease. ADEM patients were drawn from four international sites located in Argentina, Canada, Germany and the UK. Adult MS patients were diagnosed at a single center in the USA.

Table 1. Patient demographics.

<table>
<thead>
<tr>
<th></th>
<th>Adult MS</th>
<th>Ped MS</th>
<th>ADEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort #1 (n = 7)</td>
<td>Cohort #2 (n = 8)</td>
<td>Cohort #1 (n = 10)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>41 (29, 62)</td>
<td>40 (18, 74)</td>
<td>14 (6, 15)</td>
</tr>
<tr>
<td>Female, %</td>
<td>71.4%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Patients within 3 months of acute demyelinating event, %</td>
<td>14.3%</td>
<td>0%</td>
<td>80%</td>
</tr>
<tr>
<td>Median EDSS at blood draw (range)</td>
<td>1 (0, 2.5)</td>
<td>2 (0, 4)</td>
<td>1 (0, 3.5)</td>
</tr>
<tr>
<td>Median disease duration at time of blood draw, months (range)</td>
<td>16 (1, 101)</td>
<td>120 (36, 516)</td>
<td>10 (1, 36)</td>
</tr>
<tr>
<td>Median total duration of clinical follow-up, months (range)</td>
<td>16 (1, 101)</td>
<td>120 (36, 516)</td>
<td>17.5 (4, 50)</td>
</tr>
</tbody>
</table>

ADEM: acute disseminated encephalomyelitis; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; Ped MS: pediatric MS.
Pediatric MS cases were drawn from the USA, Germany, Russia and Canada. Samples were classified as acute, if collected within 90 days of an attack, and convalescent if collected > 90 days after an attack. None of the pediatric or adult MS patients were taking disease modifying therapies at the time of sample acquisition.

**Antigen arrays**

We generated antigen arrays containing overlapping peptide sequences derived from several myelin proteins, each selected based on previously published reports of possible antigenicity in demyelinating disorders: myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated oligodendrocyte basic protein (MOBP), myelin oligodendrocyte glycoprotein (MOG), 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), oligodendrocyte-specific protein (OSP) and the heat shock protein alpha-B-crystallin (abCrys). Whole-protein human IgG, IgA and IgM were included as positive controls; plus influenza virus, mouse, bovine and chicken proteins as negative controls. The full set of peptides and proteins are listed in Supplemental Table 2. In total, each array contained 125 unique peptide sequences, with each putative antigen printed twice. Thus, each serum sample was screened against a total of 264 features (Supplemental Table 1). The antigen arrays were custom ordered from JPT Peptide Technologies, Inc. (Berlin, Germany), which uses short molecular strands to fasten and orient each individual peptide and protein to the glass array, a technique that ensures a high degree of uniformity in protein orientation and concentration.

We probed the arrays as previously described. Briefly, we blocked the arrays overnight at 4°C, then incubated secondary antibodies for 1 hour at 4°C (1:1000 Cy3-conjugated goat anti-human IgG and 1:1500 Cy5-conjugated goat anti-human IgM (both from Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA). Representative array results are shown in Supplemental Figure 1. The probed arrays were scanned with a GenePix 4000B scanner (MDS Analytical Technologies, Sunnyvale, CA, USA). Antibody reactivity was quantified in fluorescence units (FU).

**Data analysis**

We used Significance Analysis of Microarrays (SAM) software (version 3.09; http://www-stat.stanford.edu/~tibs/SAM/) and the statistical package R (version 3.10) to identify antigens whose autoantibody reactivity differed between patient groups, with statistical accuracy presented as false discovery rate “q.” We arranged the results of the SAM analysis into relationships, by using the hierarchical clustering software Cluster® (http://rana.lbl.gov/EisenSoftware.htm), and then displayed the results of the Cluster analysis as autoantigen heatmaps, by using TreeView® software (http://rana.lbl.gov/EisenSoftware.htm).

We used Prediction Analysis of Microarrays (PAM) software (version 2.1 http://www-stat.stanford.edu/~tibs/PAM/), as previously described, to identify a subset of serum autoantibody markers that could correctly determine whether the tested serum sample is from a patient with ADEM or from a patient with MS (i.e. diagnostic class prediction). Briefly, we divided the ADEM and adult MS patients into two non-overlapping cohorts (see Figure 2 in the Results section and Supplemental Table 3). This allowed us to create completely independent “training” and “validation” groups, such that our validation cohorts never contained patients from our training cohorts. Moreover, to replicate real-world interassay variability, our training and validation cohorts were drawn from array experiments performed on separate dates. To allow for a larger validation cohort, we analyzed the pediatric MS samples only in the validation experiments. The allotment of patients to Cohort 1 and Cohort 2 was determined empirically, before beginning the analysis. We next applied the PAM algorithm to the autoantibody profiles of the “training” sample set, allowing PAM to establish mean levels of autoantibody reactivity to each protein or peptide in each group of patients with a given diagnosis (i.e. class). We narrowed the hierarchical list of antigens generated by PAM by using the cross-validation results (Supplemental Figure 2) to select the threshold that offered the best sensitivity and specificity with the fewest number of antigens. We then applied this final algorithm to our independent patient cohorts to determine if our algorithm was capable of accurate “class prediction” when tested on a wholly novel group of patients (see Figure 2 in the Results section). To validate further, we used the same process in reverse, training with the original validation cohorts and validating with the original training cohorts (see Figure 2 in the Results section and Supplemental Table 3).

**Results**

**ADEM and MS sera have distinct anti-myelin autoantibody profiles**

SAM analysis of the autoantibody profiles comparing ADEM versus adult MS, and ADEM versus Ped MS, showed that several antigens were differentially targeted by autoantibodies in ADEM sera, compared to those in MS sera (Figure 1; Supplemental Figure 3). SAM analysis comparing the adult and Ped MS cohorts did not yield any significant differences (data not shown).

In Cohort 1, six antigens were differentially targeted by IgG antibodies (q < 8.8%) and 15 by IgM antibodies (q < 23.1%) in ADEM sera, as compared to adult MS sera (Figure 1(a); Figure 1(b)). The IgG-targeted antigens comprised three MBP peptides (amino-acid sequences 81–100; 150–171; 180–198), two MOBP peptides (1–20;
Multiple Sclerosis Journal 0(0)

171–183), and one abCrys peptide (110–131). The IgM-targeted antigens comprised six OSP peptides (81–100; 91–110; 111–130; 121–140; 161–180), three MOBP peptides (11–30; 101–120; 111–130), three PLP peptides (21–40; 151–170; 231–250), one MOG peptide (N-terminus), one abCrys peptide (81–100) and one CNPase peptide (356–375).

Analysis of the antibody profiles obtained from a second, confirmatory experiment (Array Experiment 2) yielded similar results (Supplemental Figure 3). Here, 13 antigens (q < 16.7%) were differentially targeted by IgG antibodies in ADEM sera, compared to pediatric MS sera: seven MBP peptides (1–20; 51–70; 81–100; 111–129; 140–161; 150–171; 180–198), three MOBP peptides (1–20; 71–90; 161–180), two abCrys peptides (110–131; 161–176) and one CNPase peptide (343–362) (Supplemental Figure 3(a)). Six antigens (q < 33.3%) were differentially targeted by IgM antibodies: three OSP peptides (91–110; 111–130; 161–180), one PLP peptide (151–170), one MOBP peptide (171–183) and one abCrys peptide (81–100) (Supplemental Figure 3(b)).

Together, these findings suggest that ADEM and MS have distinct profiles of autoantibody reactivity to myelin peptides. Notably, we found that nearly all of the differentiating IgG-targeted antigens showed higher autoantibody reactivity among ADEM patients (Figures 1(a) and 1(c); Supplemental Figure 3(a)), whereas nearly all of the differentiating IgM-targeted antigens showed higher autoantibody reactivity among MS patients (Figures 1(b) and 1(d); Supplemental Figure 3(b)). We had noted a similar pattern

Figure 1. Differences in IgG and IgM autoantibody reactivity differentiate between ADEM and MS. SAM-generated heat maps highlight differences between IgM- and IgG-specific autoantibody reactivity between serum samples from patients with pediatric ADEM, adult MS, or Ped MS. Individual patients are listed above the heat map and the individual antigens are listed to the right of the heat map. Autoantibody reactivity is conveyed with blue, yellow and red hues representing low, medium and high reactivity, respectively. Figure 1 panels show differences in serum IgG (a) and IgM (b) reactivity between patients with ADEM and patients with adult MS, respectively; and differences in serum IgG (c) and IgM (d) reactivity between patients with ADEM, and patients with Ped MS, respectively. No significant differences were observed between Ped MS and Adult MS. Q values for individual SAM analyses are 8.8% in (a), 23.1% in (b), 16.7% in (c), and 33.3% in (d).

MOBP: myelin-associated oligodendrocyte basic protein; abCrys: alpha-B-crystallin; PLP: proteolipid protein; OSP: oligodendrocyte-specific protein; MBP: myelin basic protein; CNPase: 2',3' cyclic nucleotide phosphodiesterase; ADEM: acute disseminated encephalomyelitis; Ig: immunoglobulin; MS: multiple sclerosis; Ped MS: pediatric MS; SAM: Significance Analysis of Microarrays software.
in our preliminary studies, in which we found higher myelin-specific IgG reactivity among ADEM patients (Supplemental Figures 4(a) and 4(d)), when compared to MS. Analysis of these reactivity profiles using PAM yielded prediction algorithms (Supplemental Figures 4(b) and 4(e)) with greater sensitivity for ADEM than MS patients (Supplemental Figures 4(c) and 4(f)). These preliminary results encouraged us to add IgM reactivity profiles to our IgG profiles, with the goal of achieving greater predictive accuracy.

**Distinct autoantibody profiles can be used to distinguish ADEM from MS**

We used the prediction software PAM to determine whether the autoantibody profiles we identified could be used to reliably classify a patient’s clinical diagnosis as ADEM or MS. Using samples from seven adult MS patients and seven ADEM patients as the “training” cohort, PAM generated a prediction algorithm, comprising five IgG-targeted antigens (MBP 150–171; PLP 201–220; MOG 51–70; abCrys 1–20; abCrys 110–131) and three IgM-targeted antigens (MOBP 11–30; MBP 31–50; MOBP 61–80) (Figure 2). We then validated this algorithm using an independent set of 27 patient samples from Cohort 1. Our algorithm correctly classified 5/8 (62%) ADEM patients, 7/8 (87%) adult MS patients, and 8/11 (73%) Ped MS patients (Figure 2, see Prediction on Cohort 1). The sensitivity (SN) and specificity (SP) for each patient group in this analysis were as follows: ADEM SN 62%, SP 79%; adult MS SN 87%, SP 62%; and Ped MS SN 73%, SP 62%.

Conversely, when we performed this prediction in reverse, by using adult MS and ADEM samples from Cohort 1 as the training group, we generated a classification algorithm comprising one IgG-specific (abCrys 110–131) and three IgM-specific (PLP 231–250; OSP 161–180; MOBP 11–30) antigens (q < 1.6) (Figure 2). We then validated this algorithm using an independent set of 25 patient samples from Cohort 2. This algorithm correctly classified 6/7 (86%) ADEM patients, 5/7 (71%) adult MS patients, and 4/10 (40%) Ped MS patients (Figure 2, see Prediction on Cohort 2). The sensitivity and specificity for each patient group in this prediction analysis were as follows: ADEM SN 86%, SP 56%; adult MS SN 71%, SP 86%; and Ped MS SN 40%, SP 86%. A comparison of the prediction algorithms derived from Cohort 1 and Cohort 2 suggested that IgG and IgM antibodies targeting portions of PLP, abCrys, and MOBP provide the greatest diagnostic value in our sample (Figure 2; Supplemental Table 4).

In total, our SAM and PAM analyses from Cohorts 1 and 2 resulted in eight independently-generated lists of antigens (six from SAM; two from PAM). Several of these antigens appeared in more than one statistical analysis (Supplemental Table 4). Two antigens appeared in both prediction matrices: IgM-targeted MOBP 11–30 and IgG-targeted abCrys 110–131. Both of these antigens had higher antibody reactivity with ADEM sera than with MS sera.

**Discussion**

Using antigen arrays, we identified distinct profiles of anti-myelin autoantibody reactivity in a trial population of ADEM and MS patients. We used these profiles to generate prediction algorithms based on a small number of antigens capable of distinguishing our ADEM and MS patients with reasonable accuracy and reproducibility within this trial population. Several myelin autoantigens were validated in multiple analyses and should be considered for use in future studies seeking to develop diagnostic tools for classifying acquired demyelinating syndromes. This represents, to our knowledge, the first use of autoantibody array technology to distinguish between clinically distinct demyelinating syndromes.

Our results indicate that MS is characterized by the presence of serum autoantibodies of the IgM isotype targeting PLP, MOBP and OSP; whereas ADEM is characterized by serum autoantibodies of the IgG isotype, targeting MBP and MOBP. Because IgM is a non-class-switched isotype, our findings indicate that the autoantibody response to MBP in MS has not undergone the class-switching that is typically observed in antigen-driven immune responses, consistent with previous findings that many of the autoantibodies observed in MS are of the IgM isotype.

In contrast, the fact that ADEM is characterized by class-switched IgG responses to MBP and MOBP supports the notion that the immune response is primed during the prodromal illness that often precedes the onset of demyelination in ADEM. These findings are consistent with recent work demonstrating that levels of clonal IgG are higher in the serum of ADEM patients than in MS patients. Several of us (BB, AB, DP, KR) have previously described higher levels of IgG reactivity in monophasic ADEM patients that disappear in the months following event resolution, yet persist in a small subset of MS patients. In the present study, both ADEM and pediatric MS patients had blood collected within the same proximity to a demyelinating event (3 months or less), yet only the ADEM patients demonstrated the tendency toward elevated IgG reactivity. This suggests that the higher IgG reactivity observed in our ADEM cohorts is not simply an artifact of disease acuity.

Identifying biologically-relevant antigens is a critical early step in developing autoantibody-based biomarker tests. In the current study, several myelin antigens were implicated in multiple analyses (Supplemental Table 4). Of the MBP peptides that were selectively targeted in our arrays, MBP 81–100 has the greatest precedence. The presence of peptides outside this region (MBP peptides 51–70 and 150–171) has been previously noted. The presence of diverse antibody reactivity in these regions may be related to the complementary roles that T cells and B cells, which function synergistically to recognize a...
Multiple Sclerosis Journal 0(0)

variety of epitopes from both intact and damaged proteins.\textsuperscript{30} While T cells recognize only linear epitopes, B cells and their antibodies recognize both linear and conformational epitopes, which do not always overlap with T-cell targeted regions.\textsuperscript{31} It is also possible that the sera of ADEM patients (and EAE mice) more accurately reflect the autoantibodies present in the CSF,\textsuperscript{3} when compared to MS patients.\textsuperscript{27} This distinction may provide advantages when using serum autoantigen arrays for discriminating between these two disorders.

IgM-targeted MOBP 11–30 and IgG-targeted abCrys 110–131 were validated in two independently-generated prediction algorithms. Both of these antigens reacted more strongly with antibodies in ADEM sera than with those in MS sera. Although MBP has been previously implicated in ADEM,\textsuperscript{1} this is, to our knowledge, the first report of selective targeting of MOBP in ADEM sera. Here we saw that MOBP peptides were differentially targeted by both IgG (1–20; Figure 1(a)) and IgM (11–30; Figure 1(b)) isotype antibodies in the ADEM sera, with the latter playing a prominent role in our prediction

**Figure 2. Performance of serum autoantibody profiles in the differential diagnosis of ADEM and MS.** We used PAM to generate and validate prediction algorithms based on autoantibody reactivity profiles. For prediction on Cohort 1 (starting top left), we generated an algorithm (antigens and scores, as listed) by “training” PAM, using the reactivity profiles from Cohort 2. We validated this algorithm using the autoantibody reactivity profiles from Cohort 1. The prediction accuracy of the algorithm is listed at the bottom left. To further test the validity of our autoantibody prediction paradigm, we reversed the order of training and validation (starting at bottom right) such that the training analysis was done using reactivity profiles from Cohort 1 and validated using serum samples from Cohort 2. Shown in bold are the IgG-targeted antigens that differentiated between ADEM and MS in both prediction trials. There were no overlapping patients in Cohorts 1 and 2.

ADEM: acute disseminated encephalomyelitis; Ig: immunoglobulin; MS: multiple sclerosis; PAM: Prediction Analysis of Microarrays software; RRMS: relapsing–remitting MS; SN: sensitivity; SP: specificity; MOBP: myelin-associated oligodendrocyte basic protein; abCrys: alpha-B-crystallin; PLP: proteolipid protein; OSP: oligodendrocyte-specific protein; MBP: myelin basic protein; CNPase, 2', 3' cyclic nucleotide phosphodiesterase; MOG: myelin oligodendrocyte glycoprotein.
Our findings support previous work suggesting that autoantibody profiles in our cohorts.

The proximity to an acute event had a significant impact on the antigenic triggers of ADEM and MS, perhaps eventually shedding insight on the very different natural histories associated with these two disorders.

Declaration of conflicting interests

None declared, for: KVH, BHT, BAK, RD, KCO, DAH, LS and WHR.

B Banwell has received speaker’s honoraria and/or has served on pediatric advisory boards for Biogen-Idec, Novartis, Merck-Serono and Teva Neuroscience. A Bar-Or has received honoraria and/or research support from Amplimmune, Aventis, Biogen Idec, Bayhill Therapeutics, Berlex, Biogenix, Eli-Lilly, GlaxoSmithKline, Merck Serono, Novartis, Ono Pharma, Receptos, Roche/Genentech and Teva Neuroscience. T Chitnis has acted as an advisor/consultant/advisory board member or speaker for Biogen-Idec, Merck-Serono, Novartis, Sanofi-aventis and Teva. S Tenembaum has received research support from Merck-Serono. S Tenembaum has received speaker’s honoraria and/or has served on pediatric advisory boards for Biogen-Idec, Merck Serono, Genzyme and Teva Neuroscience. D Pohl has received speaker’s honoraria and/or has served on pediatric advisory boards for Bayer-Schering, Biogen-Idec, MerckSerono and Teva Neuroscience.

Funding

KVH’s work was supported by funding from the US National Institutes of Health (NIH; grant number R25-NS070698), the NIH Loan Repayment Program, the Child Neurology Foundation and the Lucile Packard Foundation Sprague/McHugh Multiple Sclerosis Fund. BB and ABO’s work was supported by the Canadian Multiple Sclerosis Scientific Research Foundation; BB was previously supported by the Wadsworth Foundation. KCO’s work was supported by the Nancy Davis Foundation for Multiple Sclerosis and a Career Transition Fellowship from the National Multiple Sclerosis Society. DAH’s work was supported by the US NIH (NIAID grant number U19-AI070352; NINDS grant numbers R01-NS024247, P01-AI039671 and P01-NS038037). LS’s work was supported by the NIH (NINDS grant number R01 NS55997). WHR’s work was supported by the NIH NHLBI Proteomics Center (contract N01-HV-00242) and a Veteran’s Administration (VA) Merit Award.

References


