B- and T-cell markers in opsoclonus–myoclonus syndrome

Immunophenotyping of CSF lymphocytes

M.R. Pranzatelli, MD; A.L. Travelstead, BS, MT (ASCP); E.D. Tate, FNP-C, MN; T.J. Allison, BS; E.J. Moticka, PhD; D.N. Franz, MD; M.A. Nigro, DO; J.T. Parke, MD; D.A. Stumpf, MD, PhD; and S.J. Verhulst, PhD

Abstract—Background: Although many lines of evidence suggest an autoimmune etiology, the pathophysiology of opsoclonus–myoclonus syndrome (OMS) remains poorly understood and no immunologic abnormalities have correlated with neurologic severity. Conventional immunotherapies often do not prevent relapse or permanent sequelae.

Objective: To test the cellular immune hypothesis of OMS in a cross-sectional study and determine if CSF lymphocyte subset analysis provides biomarkers of disease activity.

Methods: The expression of lymphocyte surface antigens was investigated in CSF and blood of 36 children with OMS and 18 control subjects, using a comprehensive panel of monoclonal antibodies to adhesion and activation proteins in combination with anti-CD3 and anti-CD45 antibodies in four-color fluorescence-activated cell sorting.

Results: Although most children with OMS had normal CSF cell counts, they exhibited expansion of CD19+/H11001 B-cell (up to 29%) and CD9253/CD9254 T-cell (up to 26%) subsets and a lower percentage of CD4+/H11001 T-cells and CD4/CD8 ratio, which persisted even years after disease onset and conventional treatments. The percentage of activated CSF T-cells was also higher. Abnormalities correlated with neurologic severity, as scored blinded from videotapes using a 12-item motor scale, and disease duration. No significant differences were found between tumor and no-tumor groups. In children with neuroblastoma, tumor resection or cancer chemotherapy did not alter immunologic abnormalities.

Conclusions: CSF B- and T-cell recruitment is linked to neurologic signs in pediatric OMS, which may relate to relapses and disease progression.

Opsoclonus–myoclonus syndrome (OMS) is a neuro-psychiatric disorder, in which autoimmunity may play an important role, characterized by relapses and often permanent sequelae. The brainstem and cerebellum are thought to give rise to the principal motor features. In children, neuroblastoma and viral infections are the most common causes.

The immunopathophysiology of childhood OMS has remained rather elusive. Basic information about the participant immune cell types in OMS is lacking, and there have been no convincing links between various autoantibodies and neurologic abnormalities. Because autoantibodies are not found in all cases and they do not cause OMS in laboratory animals when passively transferred from humans, we hypothesized cellular immune co-involvement. The same immune cell types involved in host tumor defenses, such as tumor-infiltrating lymphocytes and lymphokine-activated killer cells, could participate in the paraneoplastic syndrome through blood–brain barrier permeation after activation by onconeural antigens.

Lymphocytes traffic from brain capillaries through the CNS as part of a physiologic process of immune surveillance. Under various pathologic conditions, CSF can host increased numbers of αβ T-cells (helper/inducer; cytotoxic/suppressor), γδ T-cells, B-cells, natural killer (NK) cells, as well as cell types not normally found in CSF,
such as plasma cells and macrophages. Expanded lymphocyte subsets in CSF may reflect increased trafficking or proliferation within the CSF.

Flow cytometry, the most reliable method for quantitative analysis of lymphocyte subsets, allows cells to be analyzed simultaneously for expression of multiple immunologic markers. We now report a cross-sectional study of CSF leukocyte phenotype, activation, and maturation status in a carefully defined cohort of children with OMS.

Table Clinical characteristics of children with OMS

<table>
<thead>
<tr>
<th>Variable</th>
<th>All OMS*</th>
<th>Tumor found†</th>
<th>No tumor found†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases (%)</td>
<td>36</td>
<td>16 (44)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>16 (44)</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Girl</td>
<td>20 (56)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Mean ± SD age at testing, y</td>
<td>4.1 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td>4.8 ± 0.9</td>
</tr>
<tr>
<td>Range, y</td>
<td>1.1–16.9</td>
<td>1.8–9.3</td>
<td>0.7–16.9</td>
</tr>
<tr>
<td>Infant &lt;1.5 y, no. (%)</td>
<td>2 (6)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Toddler ≥1.5 &lt; 3 y, no. (%)</td>
<td>15 (42)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Preschool ≥3 &lt; 5 y, no. (%)</td>
<td>12 (33)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>School age ≥5 y, no. (%)</td>
<td>7 (19)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Mean ± SD age at onset, y</td>
<td>1.9 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Range, y</td>
<td>0.5–5.6</td>
<td>0.5–3.6</td>
<td>0.7–5.6</td>
</tr>
<tr>
<td>Mean ± SD syndrome duration, y</td>
<td>2.2 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td>Range, y</td>
<td>0.1–14.4</td>
<td>0.3–7.7</td>
<td>0.1–14.4</td>
</tr>
<tr>
<td>Acute ≥0.3 y, no. (%)</td>
<td>5 (14)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Subacute ≥0.3 ≤ 1 y, no. (%)</td>
<td>13 (36)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Chronic &gt;1 y, no. (%)</td>
<td>18 (50)</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Neurologic severity‡</td>
<td>16.2 ± 1.9</td>
<td>15.7 ± 2.5</td>
<td>16.7 ± 2.8</td>
</tr>
<tr>
<td>Range</td>
<td>0–36</td>
<td>0–36</td>
<td>2–36</td>
</tr>
<tr>
<td>Mild, no. (%)</td>
<td>14 (39)</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Moderate, no. (%)</td>
<td>17 (47)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Severe, no. (%)</td>
<td>5 (14)</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Prior tumor chemotherapy,§ no. (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>27 (75)</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (25)</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Current immunotherapy,‖ no. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (28)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>15 (42)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Two or more agents</td>
<td>11 (30)</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

* The χ² goodness-of-fit test of all OMS subjects showed significant differences in numbers of subjects by age category, syndrome duration category, neurologic severity category, and prior tumor chemotherapy, but not by current treatment category (p < 0.05).
† In statistical comparisons between the tumor and no-tumor groups, there were significant differences in numbers of individuals receiving prior chemotherapy (p = 0.001, χ²) and current immunotherapy (p = 0.007, χ²).
‡ Total score indicates the neurologic motor abnormality was mild if 0–12, moderate if 13–24, and severe if 25–36.
§ Chemotherapy was cyclophosphamide given either alone, which was most often the case, or in combination with other agents such as adriamycin or cisplatin, doxorubicin, and etoposide.
‖ Treatments included adrenocorticotropic hormone (H.P. Acthar gel; Questcor, Union City, CA), steroids, or IV immunoglobulins (infused monthly).

OMS = opsoclonus–myoclonus syndrome.

Methods. Subjects. Thirty-six children with OMS were recruited through the National Pediatric Myoclonus Center, and their parents signed consent for this institutional review board–approved study. The clinical characteristics are shown in the table. A thorough search was made for occult neuroblastoma using neuroimaging and blood and urine tumor markers. Those with a previously identified tumor, which was either stage I or II in all but one case, had undergone tumor resection.

Scoring of neurologic status. Each child was videotaped (see the supplementary material on the Neurology Web site; go to www.neurology.org). A trained observer blinded to treatment status rated motor impairment using the OMS Evaluation Scale, which we devised and validated. Items of the 12-part scale were...
rated from 0 to 3 as an index of increasing neurologic severity or impairment. Total score, which was calculated as the sum of subscores, tallied 36 in the most extreme cases.

**Controls.** Control subjects included 18 children with myoclonus, ataxia, idiopathic intracranial hypertension, chronic daily headache, or developmental delay, who were undergoing a diagnostic lumbar puncture. Standardization of stress on immune function, and provision of compassionate care, an anesthesiologist administered IV propofol after brief sevoflurane induction to insert the IV line. The lumbar puncture was performed in the lateral decubitus position, and the first 4 mL was sent for routine studies. An additional 8 to 10 mL, not to exceed 15% of the calculated total CSF volume, was collected for flow cytometry.

**Lumbar puncture.** To prevent contamination of CSF with blood due to trauma, minimize sediment risks during lumbar puncture, standardize the degree of stress on immune function, and provide compassionate care, an anesthesiologist administered IV propofol after brief sevoflurane induction to insert the IV line. The lumbar puncture was performed in the lateral decubitus position, and the first 4 mL was sent for routine studies. An additional 8 to 10 mL, not to exceed 15% of the calculated total CSF volume, was collected for flow cytometry. Blood for parallel studies was also drawn.

CSF mononuclear cell count was 0 to 3 cells/mm² in all children except those with OMS, who had pleocytosis with counts of 5 to 20 cells/mm². The mean CSF white blood cell count of 1.3 ± 1 cells/mm² in control subjects was not statistically different from 1.5 ± 0.2 cells/mm² of healthy young adults as assessed by ANOVA to allow comparisons between OMS categories as well as with controls. The principal independent variables were diagnosis (OMS vs controls), etiology (tumor vs no tumor), neurologic severity (mild, moderate, severe), syndrome duration (acute, subacute, chronic), and treatment (current treatment vs no treatment, prior chemotherapy vs no chemotherapy). Pearson correlation coefficients were used for correlation analysis. Demographic data were analyzed by $\chi^2$ and $\chi^2$ goodness-of-fit tests. To evaluate unequal variances, we performed nonparametric tests, but as the results were substantially the same as the unequal-variance $t$-tests, only $t$-tests are reported here.

Because lymphocyte populations, in blood at least, may vary with age and there are no CSF data in healthy children, we looked for correlations between age and each type of lymphocyte in our control subjects. No significant correlations were found, so the data were pooled. This had the effect of increasing the mean age of our control subjects somewhat, but we felt it was more important, given the small sample size, to boost the statistical power. The same argument applies to blood, as the relative size of various lymphocyte populations in healthy children ages 2 to 5 years and 5 to 10 years differs by only 1 to 6%. Published normative CSF data for healthy young adults as well as children with various neurologic disorders were used to assess the comparability of our neurologic controls.

**Results.** **Distribution of lymphocyte population in CSF.** In control subjects, the prominent characteristic of normal CSF lymphocytes was the dominance of $\gamma$ T-cells (CD3\(^+\)) and almost total lack of B-cells. The rank order of CSF lymphocytes was helper/inducer T-cells (CD3\(^+\)CD4\(^+\)) > cytotoxic/suppressor T-cells (CD3\(^+\)CD8\(^+\)) > \gamma\delta T-cells (T-cell receptor [TCR]-\gamma\delta\)), NK cells (CD3\(^-\)CD16/56\(^+\)), NK-like T-cells (CD3\(^-\)CD16/56\(^-\)) > B-cells (CD45\(^+\)CD3\(^-\)CD19\(^+\)). In OMS, abnormalities in the percentage of various cell types were found in all cases, despite the absence of CSF leukocytosis in most (figure 1). Percentages were lower for CD3\(^-\)CD4\(^+\) cells (19%; $p = 0.0001$) and minimally higher for CD3\(^+\)CD8\(^+\) cells (5%; $p = 0.047$). As a result, the mean ratio of CD4\(^+\) to CD8\(^+\) T-cells was less (53%; $p = 0.017$). Percentages were higher for \gamma\delta T-cells (2.7-fold; $p = 0.0001$) and CD19\(^+\) B-cells (6.5-fold; $p = 0.0004$). There was a trend toward lower CD3\(^+\) cells ($p = 0.055$) but no intergroup difference in CD3\(^-\) or CD3\(^+\) NK cells. The immunophenotype was not changed by presence of tumor or treatment.

Certain cell types were found in neither controls nor OMS. Based on CD45 staining and light scatter characteristics, no plasma cells or macrophages were detected in CSF. Monocytes regularly constituted <5% within the lympho monocyte gate (data not shown).

**Expression of T-cell activation markers in CSF.** We evaluated both human leukocyte antigen (HLA) DR and CD25 (interleukin-2 receptor) T-cell activation markers. HLA-DR\(^+\) T-cells accounted for approximately 12% of CD3\(^+\) cells in the CSF of control subjects, whereas few T-cells were CD25\(^+\) (figure 2). In OMS, the percentage of HLA-DR\(^+\) T-cells was 51% greater ($p = 0.0006$), as can be seen in representative flow cytometric displays (see figure E-1 on the Neurology Web site). The percentage of CD3\(^-\)CD25\(^+\) cells was not significantly different in OMS. OMS etiology and treatment had no significant effect.

**CSF T-cell markers of maturation.** In a comparison of CD45R isofoms on CD3\(^+\) cells from control subjects, the percentage of “memory” (CD45RO\(^+\)) T-cells was about two-fold higher than that of “naive” (CD45RA\(^+\)) T-cells ($p = 0.0004$). However, there were no significant differences between controls and OMS for CD45RO\(^+\) (47.3 ± 4.4 and 43.5 ± 4.0, respectively) or CD45RA\(^+\) (21.7 ± 4.8 and 18.5 ± 1.9) T-cells. OMS etiology and treatment also had no significant effects with the exception of slightly lower
CD45RA+ cells in the no-tumor group (−9%; p = 0.019) (data not shown).

Relation of neurologic severity of OMS to CSF cell types. The effect of neurologic severity on the percentage of CD19+ B-cells as well as CD4+ and TCR-γδ+ T-cells was statistically significant (figure 3). Reciprocal relations were seen between αβ T-cells and γδ T-cells. The two children with the highest percentage of CSF γδ T-cells (26%) or B-cells (29%) were most severe (total scores 34 and 36, respectively). Severity correlated negatively with the percentage of CD3+ cells (r = −0.56, p = 0.0012) and CD3−CD4+ cells (r = −0.38, p = 0.024). A positive correlation was found with the percentage of CD19+ cells (r = 0.37, p = 0.03), TCR-γδ+ cells (r = 0.54, p = 0.0019), and CD3−NK cells (r = 0.38, p = 0.04). There were no other significant correlations.

Relation of syndrome duration to CSF cell types. The duration of illness correlated with the CD4/CD8 ratio (r = 0.40, p = 0.015) and the percentage of CD4+ T-cells (r = 0.44, p = 0.007) and CD3+ cells (r = 0.38, p = 0.039). There was a negative correlation with TCR-γδ+ cells (r = −0.37, p = 0.043) and total score (r = −0.45, p = 0.008).

CSF/blood lymphocyte ratios. In control subjects, the percentage of all cells in CSF exceeded that in paired peripheral blood, except for B-cells and CD45RA+ T-cells. The magnitude of CSF/blood ratios differed significantly between cell types (figure 4). The percentage of CD3+ HLA-DR+ cells was sevenfold higher in CSF than in blood, whereas the percentage of CSF CD19+ B-cells was only one-twentieth of that in blood. The means of other ratios were just above 1.0, with the exception of the CD3+ NK cell ratio and CD45RO+ cell ratio, which were about threefold higher.

In OMS, the CSF/blood ratio for CD19+ B-cells was threefold higher than in control subjects (p = 0.0005). The γδ T-cell ratio was 2.4-fold higher (p = 0.0005) and correlated with total score (r = 0.61, p = 0.0004), syndrome duration (r = −0.42, p = 0.022), and the CD4/CD8 ratio (r = −0.49, p = 0.0075). There was a 2.4-fold higher ratio for CD3−NK cells in OMS (p = 0.04). Presence of a tumor and treatment had no effect. There were no other significant differences in lymphocyte ratios, with the exception of a lower HLA-DR+ cell ratio in chemotherapy-treated children (−57%; p = 0.0019).

The relative size of the peripheral blood mononuclear cell pool did not reflect the lymphocyte subset abnormalities found in CSF. There were no significant differences between control and OMS subjects. In the tumor group, approximately 1.5-fold higher percentages of CD19+ B-cells (p = 0.038) and HLA-DR+ T-cells (p = 0.048) were found (data not shown).

Comparability of pediatric neurologic control subjects and healthy young adults. No major discrepancies were found between our control subjects and data from healthy young adults in the general distribution and relative proportions of CSF lymphocyte subsets. Our controls had a slightly lower percentage of CD3+ cells, CD4+ T-cells, and NK-like T-cells and a slightly higher percentage of NK cells and HLA-DR+ T-cells. Although we could find no study of CSF γδ T-cells in normal individuals, the percentage of γδ T-cells in our controls was comparable with that of a group of pediatric neurologic control subjects.

Discussion. To our knowledge, this is the first immunophenotyping study of CSF lymphocytes in OMS. We found multiple immunologic abnormalities involving B-cells and T-cells, as is the case with mul-
Multiple sclerosis and a growing number of human autoimmune diseases. Both lymphocyte populations infiltrate neuroblastomas to a high degree and may provide a link between peripheral indication of autoimmunity and CNS immunopathology. Because both B-cell and T-cell abnormalities were linked to neurologic dysfunction, they could account for relapses and disease progression. Although the pattern of abnormalities may suggest immune dysregulation, this is a descriptive observation; prospective longitudinal studies, which are in progress at our center, will be required. Long-term persistence of CSF abnormalities despite tumor resection, multiantigen cancer chemotherapy, or prior treatment with conventional immunotherapies emphasizes the need for more effective therapies in OMS. The absence of a detectable tumor had little impact on the immunologic abnormalities in CSF, which, taken together with neuroblastoma's high incidence of spontaneous regression, emphasizes the need for very careful tumor screening. However, some of our patients, even a substantial percentage, may not have had a tumor.

Our data suggest that one component of OMS may be B-cell mediated. The intrathecal expansion or

Figure 2: CSF CD3+ T-cell activation markers in control subjects vs opsoclonus–myoclonus syndrome (OMS) (A), tumor vs no tumor (B), and untreated vs treated OMS (C). Data are means ± SEM. Asterisks signify statistical significance by t-tests: ***0.0001 ≤ p < 0.001. In OMS, 21 of 36 children had values above the upper confidence limit of the control group for human leukocyte antigen DR+ T-cells (up to 34%) but only 11 children for CD3+CD25+ cells (up to 25%).

Figure 3: Relation between neurologic severity (total score) in opsoclonus–myoclonus syndrome (OMS) and percentage of CSF CD4+ T-cells (A), γδ T-cells (B), and CD19+ B-cells (C). Sample size is shown at the base of each column. Data are means ± SEM. Asterisks indicate statistically significant differences between OMS severity categories on Duncan test, p < 0.05. Dagger indicates significant differences between OMS and control subjects. Analysis of variance with linear trend analysis revealed that the more severely affected children (higher total score) had a lower percentage of CSF CD4+ T-cells (F = 20.6, p ≤ 0.0001). In contrast, the percentage of CSF γδ T-cells increased with severity (F = 25.6, p ≤ 0.0001), being nearly double in the severe category, and the percentage of CSF CD19+ B-cells was also higher (F = 21.2, p ≤ 0.0001).
crease in relative size of the B-cell pool is clinically important because B-cells usually are negligible in normal CSF and the high percentage of CSF B-cells in severe OMS indicates pronounced recruitment to the CNS. B-Cell expansion implies potential for au-
toantibody production, as B-cells are capable of syn-
thesizing antibodies even if they are not plasma
cells, and autoantibodies have been found in some
children with OMS.6,12,13 However, autoreactive
B-cells also may contribute to autoimmune disease
merely by enhancing antigen presentation to T-cells.
Studies of various inflammatory CNS disorders have
revealed that CSF B-cells may be a particularly reac-
tive population compared with peripheral blood,29
preferentially compartmentalized to the CSF and
lacking systemic feedback control.30 The next step
will be to determine if CSF B-cells in OMS are highly
activated and lead to a humoral response that is
pathogenic.

The γδ T-cell is regarded as an “unconventional”
T-cell, one with a unique role in immunologic dis-
ease. Also called “fetal-type lymphocytes,” γδ T-cells
are the first T-cells to develop and a possible third
arm of immune response.31 Because they possess in-
herent autoreactivity, γδ T-cells may recognize anti-
gens directly in tissues rather than relying on the
professional antigen-presenting cells for antigen rec-
nognition required of conventional T-cells.31

CSF expansion of γδ T-cells is abnormal; the TCR
of most CSF T-cells in normal individuals expresses
α- and β-chains, rather than γ- and δ-chains.32 How-
ever, our data do not allow us to determine if the
expansion in OMS is primary or secondary or
whether it is deleterious or helpful. The γδ T-cells
could be involved in the primary immune response
against the tumor,33 triggering a cascade of immuno-
logic events that lead to inflammation once they
have entered the brain. Alternatively, they may be
drawn only secondarily to CNS inflammation al-
ready involving other T-cells and B-cells.34 In con-
trast, γδ T-cells could fulfill an anti-inflammatory
role in OMS by down-regulating autoimmune dis-
ease,35 because they normally do not function as
helper cells35 and they suppress B-cell expansion in
vivo.31 Whatever role γδ T-cells do have in OMS, it is
likely to be important.

The principal abnormalities involving “conven-
tional” T-cells in OMS were increased T-cell activa-
tion, greatly reduced helper/inducer T-cells, and
slightly increased suppressor/cytotoxic T-cells. T-Cell
activation, an important factor in the development of
autoimmune disease, is required for optimal antigen

Figure 4. CSF/blood lymphocyte ratios. (A) In opsoclonus–myoclonus syndrome (OMS), the ratios for γδ T-cells, CD19+
B-cells, and CD3+CD16/56+ cells were significantly increased. The B-cell ratios were 0.05 ± 0.01 for controls and 0.16 ±
0.03 for OMS. (B) There were no statistically significant differences between the tumor and no-tumor groups. Data are
means ± SEM. Asterisks signify statistical significance by t-tests: *0.01 ≤ p < 0.05, **0.0001 ≤ p < 0.001.
presentation by B-cells to T-cells. An increased percentage of activated T-cells in the CSF is evidence of significant T-cell recruitment in OMS.

In a study of three adults with paraneoplastic cerebellar degeneration (PCD), 20 to 40% of CSF cells were activated conventional T-cells, which is above the normal range and similar to what we found in OMS. A specific inhibitor of activated T-cells markedly reduced these cells in CSF. In PCD, antigen-specific cytotoxic T-cells also have been found in peripheral blood. Although PCD and OMS are different disorders clinically, increased T-cell activation is a feature of both, and there may be other shared immunologic traits as well.

The explanation for the reduced percentage of CSF helper/inducer T-cells we found in OMS is unclear. Although circulating blood helper T-cells and the helper/suppressor T-cell ratio are reduced in epilepsy and a subset of autism, we are not aware of CSF helper T-cell reduction in other neurologic disorders. Because of the importance of helper T-cell subsets in autoimmune diseases, the next stage will be to evaluate Th1- and Th2-helper T-cell subsets in OMS.

We propose that CSF B-cell and T-cell abnormalities be factored into the design and monitoring of immunotherapy for OMS. We realize it is hazardous to draw conclusions about functional properties of immune cells from their phenotypic markers. However, given the cytotoxic capacity of these cells, their potential role in the pathophysiology of pediatric OMS warrants serious attention. Our study shows that some children who manifest neurologic abnormalities years after presentation appear to have an active autoimmune process and are potentially salvageable. CSF lymphocyte immunophenotyping allows this subgroup to be identified for further treatment.

Acknowledgment

The authors thank the children and families for participating in the research. They also thank Janet Butler and Sarah Kirsch for typing the manuscript, Janice Vines and Susan Ball for scheduling the manuscript, Janice Vines and Susan Ball for scheduling the manuscript, and the St. John's Hospital and Memorial Medical Center Anesthesia Departments for providing anesthesia for lumbar punctures.

References