Cerebrospinal Fluid and Therapy of Isolated Angiitis of the Central Nervous System

Vitor Oliveira, MD; Pedro Póvoa, MD; Adília Costa, MD; José Ducla-Soares, PhD

Background Serial cerebral angiograms, computed tomography, and magnetic resonance imaging are among the proposed methods for monitoring disease activity and response to therapy in isolated angiitis of the central nervous system. Cerebrospinal fluid has not proved to be useful in monitoring clinical course.

Case Description We describe a 45-year-old man with histological diagnosis of isolated angiitis of the central nervous system that was treated with prednisone plus azathioprine and monitored for 2 years. Samples of the cerebrospinal fluid were obtained for cytological and routine chemical examination, as well as albumin and immunoglobulin content. Before treatment, cerebrospinal fluid showed marked plasmatic transudation of albumin and intrathecal synthesis of immunoglobulins. During the first year of immunosuppression no events were noticed, and the previously abnormal aspects of the cerebrospinal fluid showed improvement. During the weaning of azathioprine, a new stroke occurred in conjunction with a marked deterioration of cerebrospinal fluid parameters. Immunosuppression was resumed at previous levels, and during the following year no further events occurred. Once again, abnormal cerebrospinal fluid values improved significantly.

Conclusions We report a case of isolated angiitis of the central nervous system in which the serial cerebrospinal fluid examinations (albumin and immunoglobulin content) showed a close correlation with clinical course. This method may be useful in monitoring response to therapy.

Case Report A 45-year-old man was admitted to our hospital in March 1990 because of a right-sided hemiparesis and aphasia. He had an 11-month history of recurrent strokes. In May 1989 he presented with a right-sided hemiparesis and slurred speech lasting for 2 hours. General medical workup was normal. No risk factors for vascular disease were identified, except for an alcohol intake of 100 g/d. One month later (June 1989) he was admitted as a result of generalized seizures. Physical examination revealed a left-sided hemiparesis, and brain CT showed one right parietal subcortical hematoma, one small left capsular hematoma, and one left parietal cortical infarction. A four-vessel digital intraarterial cerebral angiogram was normal. He made a good recovery and was discharged on phenytoin. In December 1989 he was again admitted because of generalized seizures. Brain CT showed a right parietal subcortical hematoma. A good clinical recovery was observed, and phenytoin was maintained.

On admission the pulse rate was 80/min and rhythmic, and blood pressure was 130/80 mm Hg. Physical examination showed agitation, global aphasia, right-sided hemiparesis, diminished right tenden reflexes, and extensor plantar responses. General laboratory workup was unremarkable. Antithrombin III, protein C, and free protein S activities were normal. Antiphospholipid antibodies and lupus anticoagulant were absent. Antinuclear antibodies, anti-dsDNA antibodies, and anti-neutrophil cytoplasmic antibodies were within normal range. Tests for human immunodeficiency virus, Epstein-Barr virus, herpes simplex virus, herpes zoster virus, cytomegalovirus, and syphilis were negative.

Samples of CSF were obtained for cytological and chemical examination, as well as albumin and immuno-
Cerebrospinal Fluid Before and During Immunosuppression

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<tbody>
<tr>
<td>TProt, mg/L</td>
<td>1230</td>
<td>1230</td>
<td>1000</td>
<td>480</td>
<td>2760</td>
<td>1070</td>
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<td>810</td>
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<tr>
<td>PTAlb, mg/L</td>
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<td>336</td>
<td>350</td>
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<td>1200</td>
<td>425</td>
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<tr>
<td>ITSIg, mg/L</td>
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<td>55</td>
<td>20</td>
<td>5</td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IgG</td>
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<td>3</td>
<td>2</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>6</td>
<td>1</td>
<td>5</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IgM</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>5</td>
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AZA indicates azathioprine; PRD, prednisone; CSF, cerebrospinal fluid; TProt, total protein; PTAlb, plasmatic transudation of albumin; and ITSIg, Intrathecal synthesis of immunoglobulins.

Reference values are as follows: TProt, 200-550 mg/L; PTAlb, 0 mg/L; and ITSIg, (IgG, IgA, IgM), 0 mg/L.

globulin content (IgG, IgA, and IgM). Results were compared with albumin and immunoglobulin content in serum. Plasmatic transudation of albumin and intrathecal synthesis of immunoglobulins were assessed according to Tourtellote et al.8 and Schuller et al.9 CSF samples withdrawn before therapy showed a normal cell count, increased total CSF protein, marked plasmatic transudation of albumin, and intrathecal synthesis of immunoglobulins (Table).

On admission brain CT showed a right temporal and a left parietal hematoma. The MRI scan showed the same lesions plus several bilateral hemorrhagic lesions at different stages. Celiac and renal angiograms were normal. Cerebral and leptomeningial biopsies were performed. Histology revealed multiple granulomatous lesions with lymphocytes and giant cells involving the whole thickness of the wall of the small cerebral vessels and perivascular infiltration of mononuclear cells in the leptomeninges (Figure). A diagnosis of isolated angiitis of the CNS was established.

Treatment with prednisone 60 mg/d and azathioprine 150 mg/d was initiated in June 1990. For 1 year of immunosuppression no further events were noticed. Two CSF samples withdrawn during that period showed a normal cell count, reduction of total CSF protein, normalization of plasmatic transudation of albumin, and a marked reduction of intrathecal synthesis of immunoglobulins (Table).

During the weaning of therapy (prednisone 60 mg/d and azathioprine 50 mg/d) a new hemorrhagic stroke occurred in June 1991, and the CSF analysis revealed a marked deterioration of total protein, plasmatic transu-
dation of albumin, and intrathecal synthesis of immunoglobulins (Table). The cell count was normal. Immunosuppressive therapy was resumed at previous levels. No further events were noticed, and the CSF examination once again showed a decrease in the total protein as well as in plasmatic transudation of albumin and no intrathecal synthesis of immunoglobulins (Table). CSF cell count remained normal.

One year later (July 1992) the patient was admitted to our hospital because of bilateral pneumonia. He developed septic shock and died 4 days later.

Discussion

Several therapeutic agents have been tried in isolated angiitis of the CNS, but only steroids and cytotoxic agents have demonstrated some success.1-3,10 Accepted therapeutic approaches consist of the combination of steroids plus cyclophosphamide or azathioprine. The clinical and laboratory course (serial CSF analyses) in our patient suggested that azathioprine plus prednisone was an effective drug association. The initiation of azathioprine resulted in clinical stabilization, and its weaning was followed by a flare-up of the disease, which once again became quiescent when brought to previous levels.

Monitoring of therapy is also a matter of debate; however, the lack of specificity and the lack of sensitivity of the proposed methods are serious drawbacks.4-5,7 Angiograms are normal in half of the cases, and CSF, although usually abnormal, has never been used.1-2,6 In this case pretreatment CSF showed a marked plasmatic albumin transudation and intrathecal synthesis of immunoglobulins, mainly IgG. Serial CSF analyses showed a clear relation between clinical course and immunosuppression. After therapy was started, both plasmatic transudation of albumin and intrathecal synthesis of immunoglobulins showed a significant decrease. Weaning of azathioprine was followed by another stroke and CSF deterioration. The readministration of azathioprine at previous levels was followed by an improvement in clinical condition as well as CSF parameters. Thus, in our patient serial CSF analyses showed a close correlation between clinical course and immunosuppression.

Serial CSF analyses seem to be a reliable marker of the CNS inflammatory process and therefore a guideline for monitoring disease activity and response to therapy.

Acknowledgments

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References

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