Cerebrospinal Fluid Oligoclonal IgG Bands in Patients With Spinal Arteriovenous Malformation and Structural Central Nervous System Lesions

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Objective: To investigate the incidence and characteristics of patients with structural central nervous system (CNS) lesions and cerebrospinal fluid oligoclonal IgG bands.

Design: A retrospective study.

Method: The medical records of patients with cerebrospinal fluid oligoclonal IgG bands were evaluated for the presence of structural CNS lesions, their location and cause, and for clinical characteristics.

Setting: Cerebrospinal fluid oligoclonal IgG bands were examined in the Neuroimmunology Laboratory, Hadassah University Hospital, Jerusalem, Israel.

Patients: Two hundred seventy of 570 patients with positive cerebrospinal fluid oligoclonal IgG bands were available for analysis. Twenty patients had structural CNS lesions.

Results: Twenty (7.5%) of the 270 patients had structural CNS lesions: 3 patients had spinal arteriovenous malformation; 5 patients had tumors; 9 patients had compressive cervical myelopathy. Traumatic leukomalacia, Arnold-Chiari malformation type 1, and CNS hemosiderosis were present in 1 patient each. In 2 patients (1 patient with recurrent meningioma and 1 patient with post-traumatic encephalomalacia) the presence of a structural CNS lesion was followed by the development of multiple sclerosis. In all 3 patients with spinal arteriovenous malformation, oligoclonal IgG identification prolonged the time to diagnosis and therapy, which varied from a few weeks to 3 years.

Conclusions: Structural CNS lesions, responsible for the neurological disorder, were present in 20 patients (7.5%) with cerebrospinal fluid oligoclonal IgG bands. The mechanism underlying oligoclonal IgG presence in spinal arteriovenous malformation and the coexistence of multiple sclerosis and structural CNS lesions is unknown, but may be related to recurrent tissue damage with repeated presentation of CNS antigens to the immune system.

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RESULTS

GROUP CHARACTERISTICS

Oligoclonal IgG bands can be identified in the cerebrospinal fluid (CSF) of patients with a variety of infectious and inflammatory conditions involving the nervous system. These include multiple sclerosis (MS), acute disseminated encephalomyelitis, Guillain-Barré syndrome, subacute sclerosing panencephalitis, progressive rubella panencephalitis, and acute viral encephalitis. In some of these conditions, their presence serves as an auxiliary diagnostic tool and only occasionally they are identified in the CSF of patients without inflammatory or infectious neurological disorders. In recent years we have encountered several patients who had neurological disease due to structural central nervous system (CNS) lesions, in whom CSF oligoclonal IgG bands were detected. This prompted us to examine our medical records for the incidence and characteristics of CSF oligoclonal IgG bands in such patients.

Twenty (7.5%) of the 270 patients with CSF oligoclonal IgG bands had structural CNS lesions. These were 9 men and 11 women (age range, 33-79 years; mean age, 49 years). Thirteen patients had a spinal abnormality (Table 1), while in 7 patients the pathologic condition was located above the foramen magnum (Table 2). Three patients had spinal arteriovenous malformation (AVM), 5 patients had tumors, and 9 patients had compressive cervical myelopathy due to spinal stenosis, disk herniations, or degenerative changes. Traumatic leukomalacia, Arnold-Chiari malformation type 1, and CNS hemosiderosis were present in 1 patient each.

In all patients, the structural CNS lesion was sufficient to account for the neurological disorder, none of them had ini-
SUBJECTS AND METHODS

SUBJECTS

Between January 1, 1988, and May 31, 1998, 9987 CSF and serum samples were examined in the Laboratory of Neuroimmunology, Hadassah University Hospital, Jerusalem, Israel, for the presence of oligoclonal IgG bands. Of 570 patients with CSF positive for and serum negative for oligoclonal IgG bands, 270 patients were hospitalized, evaluated, and followed up in our institution. Their medical records were available for this retrospective study. Medical records were analyzed for demographic characteristics, nature of the neurological disorder or the systemic disability that led to CSF analysis, disease course, and laboratory findings.

METHODS

Oligoclonal IgG bands were assayed by agarose electrophoresis. Briefly, CSF is applied to an agarose gel slide (Pangel; Princeton Separations Inc, Freehold, NJ) composed of 1% prebuffered agarose solution (15.17 g of barbital per liter). An electric potential is applied across the slide causing different proteins to move at different rates from the point of application. After completion, the slide is fixed, dried, and stained with amido-black, and the separation patterns are evaluated.

RESULTS

SPINAL AVM ASSOCIATED WITH OLIGOCLONAL IgG (PATIENTS 1-3)

During the study period 11 patients with spinal AVM were diagnosed in our institution. The 3 (27%) of them, who had CSF oligoclonal IgG bands, were all men, aged 34 to 67 years. Brain magnetic resonance imaging (MRI) was available in 2 patients and for both it was normal. The initial syndromes were progressive paraparesis in 2 patients and relapsing subacute paraparesis in the third patient. In all, oligoclonal IgG examination was done as part of the evaluation and in 2 patients it prolonged the time to diagnosis and therapy, which varied from a few weeks to 3 years.

In 2 patients a selective embolization of the structured CNS lesion was performed, and in 1 patient the AVM was surgically removed. The conditions of 2 patients markedly improved after the procedure.

REPORT OF A CASE (PATIENT 3)

A 48-year-old man with a medical history of posttraumatic epilepsy controlled by oral phenytoin sodium, 100 mg thrice daily, was admitted to the hospital because of the acute onset of leg weakness and urinary retention. Five months prior to hospital admission (2 weeks after a viral infection) he suffered from legs paresthesias and low back pain. Neurological examination findings revealed absent deep tendon reflexes in the right leg and nerve conduction studies demonstrated prolonged F waves in both legs.

Because his condition improved spontaneously over the course of several weeks, a probable diagnosis of postinfectious radiculopathy was made. Four months later he developed leg weakness and difficulty in micturition, progressing, within 1 month, to urinary retention and the inability to walk, which prompted his seeking medical advice. Results of a general medical examination on admission were unremarkable except for reduced rectal tone. Neurological examination results revealed intact cognitive functions and cranial nerves, bilateral brisk deep tendon reflexes in the hands, and a 3/5 (Medical Research Council scale) paraparesis, more prominent on the left side, with reduced deep tendon reflexes and bilateral extensor plantar response. The patient could not stand without assistance. He had a sensory level to all sensory modalities at D7 on the left side. No cerebellar signs were evoked. The following laboratory examination results were normal or negative: complete blood cell count and biochemistry studies, erythrocyte sedimentation rate, antinuclear antibodies, C3, immunoelectrophoresis, and antibodies to human immunodeficiency virus. Cerebrospinal fluid contained 1.2×10^7/L red blood cells, no white blood cells, a normal level of glucose, and a total protein level of 1.2 g/L (reference range, <0.65 g/L). Oligoclonal IgG bands were present. Thoracic and lumbar computed tomographic scans showed no abnormalities. Within the first few days of hospitalization he became paraplegic. A diagnosis of acute relapsing myeloradiculitis was considered and he was treated with methylprednisolone sodium succinate, 1000 mg intravenously, with no apparent improvement in the patient’s condition. Consequently, MRI and spinal angiography were performed and revealed a dural AVM at the level of D6 with a single-feeding artery on the left side. The patient was referred for selective embolization of the lesion. Six months later, following rehabilitation, he could walk again with crutches and regained partial urinary control.

CERVICAL MYELOPATHY ASSOCIATED WITH OLIGOCLONAL IgG (PATIENTS 5-13)

There were 7 women and 2 men, aged 35 to 79 years (mean age, 56.1 years). In all, the reasons for cervical spinal cord compression were spinal stenosis, disk herniations, or degenerative changes. Brain MRI was performed in 7 patients and did not reveal any white matter lesions compatible with MS. The initial symptoms were radicular pain in 3 patients, hand weakness in 2 pa-
patients, gait disturbances in 5 patients, legs weakness in 3 patients, tetraparesis in 2 patients, and paresthesias in the lower extremities in 2 patients. Disease course was chronically progressive in all patients, and no one had a relapsing course. Three patients were operated on with resultant clinical improvement.

PATIENTS WITH TUMORS
(PATIENTS 4 AND 14-17)

There were 3 women and 2 men, aged from 38 to 62 years (mean age, 48.8 years). In 1 patient, the tumor was spinal and in 4 patients intracranial. There were 2 meningiomas, 1 glioblastoma multiforme, 1 spinal meningioma, and 1 pontine intramedullary tumor for which no histological data were available.

MISCELLANEOUS (PATIENTS 18-20)

Arnold-Chiari malformation, cerebral hemosiderosis, and posttraumatic encephalomalacia were seen in 1 patient each (2 men, 1 woman, aged 33-50 years; mean age, 42.6 years). Disease course was remitting-relapsing in 1 patient (patient 19, Table 2) and chronic in 2 patients (patients 18 and 20). One patient (patient 18) with an initially chronic course eventually developed a relapsing course heralding the development of MS.

PATIENTS WITH STRUCTURAL CNS LESION WHO DEVELOPED MS (PATIENTS 14 AND 18)

Two patients in our series, with no initial clinical or radiological evidence for a demyelinating disorder, eventually developed MS. A 33-year-old man (patient 18), with right hemiparesis and generalized tonic-clonic epilepsy following head trauma, developed, 12 years later, left optic neuritis and left hemiparesis with a relapsing course compatible with MS. Diagnosis was confirmed by a typical MRI. The second patient’s, a 38-year-old woman’s (patient 14), case history is described below:

This previously healthy woman, developed headache and left hemiparesis due to right frontal meningioma. Craniotomy was performed and the tumor was resected. Six years later a local recurrence necessitated a reoperation that was complicated by osteomyelitis of the right frontal bone, for which a cranioplasty operation was performed. Two years later, a meningioma involving the frontal and ethmoidal sinuses was diagnosed. The lesion

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### Table 1. Patients With Spinal Disorders and Cerebrospinal Fluid (CSF) Oligoclonal IgG Bands

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>Medical History</th>
<th>Clinical Presentation</th>
<th>Clinical Findings</th>
<th>CSF</th>
<th>Imaging Procedure</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/34</td>
<td>Spinal AVM</td>
<td>. . .</td>
<td>L leg monoparesis and erectile dysfunction</td>
<td>Spastic paraparesis</td>
<td>AC and elevated protein level</td>
<td>Spinal angiography</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>2/M/67</td>
<td>Spinal AVM</td>
<td>Depression</td>
<td>Paraparesis and urinary retention</td>
<td>Flaccid paraparesis</td>
<td>130 RBC/mL and NP</td>
<td>Spinal angiography</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>3/M/48</td>
<td>Spinal AVM</td>
<td>Posttraumatic epilepsy</td>
<td>LBP and gait disturbances</td>
<td>Flaccid paraparesis</td>
<td>AC and NP</td>
<td>Spinal angiography</td>
<td>Remitting relapsing</td>
</tr>
<tr>
<td>4/F/45</td>
<td>Thoracic meningioma</td>
<td>. . .</td>
<td>R leg hypoesthesia and weakness</td>
<td>Parapyramidal syndrome</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Subacute</td>
</tr>
<tr>
<td>5/F/45</td>
<td>Cervical disk herniation</td>
<td>. . .</td>
<td>Gait disturbances</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>6/F/42</td>
<td>Cervical disk herniation</td>
<td>. . .</td>
<td>Weakness in the legs</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>7/F/74</td>
<td>Cervical spinal stenosis</td>
<td>IHD and IBD</td>
<td>Gait disturbances</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>8/F/35</td>
<td>Cervical discopathy</td>
<td>. . .</td>
<td>L radicular pain</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>9/F/79</td>
<td>Cervical discopathy</td>
<td>. . .</td>
<td>Leg pain and gait disturbances</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>10/M/69</td>
<td>Cervical degenerative changes</td>
<td>Peptic ulcer disease</td>
<td>L leg pain and gait disturbances</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>11/F/64</td>
<td>Cervical spondylosis</td>
<td>HTN and osteoarthritis</td>
<td>Hand weakness and gait disturbances</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>12/M/38</td>
<td>Cervical discopathy and stenosis</td>
<td>. . .</td>
<td>Tetraparesis</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>13/F/59</td>
<td>Cervical discopathy and stenosis</td>
<td>NIDDM</td>
<td>Tetraparesis</td>
<td>Tetrapaumidal syndrome</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Chronic progressive</td>
</tr>
</tbody>
</table>

*Ellipses indicate unremarkable data; AC, acellular; AVM, arteriovenous malformation; RBC, red blood cells; NP, normal protein level; LBP, low back pain; MRI, magnetic resonance imaging; IHD, ischemic heart disease; IBD, inflammatory bowel disease; HTN, hypertension; and NIDDM, non-insulin-dependent diabetes mellitus.
bands had a disease presentation and course that could be
 Twenty (7.5%) of 270 patients with CSF oligoclonal IgG
spinal cord involvement.
ally developed a secondary progressive course with mainly
was established. During 6 years of follow-up, she gradu-
changes and many hyperintense lesions in the white mat-
was acellular, with normal protein and glucose content, but
factor, C3, and Rose-Waller latex test. Cerebrospinal fluid
chemistry studies, immunoelectrophoresis, antinuclear
lowing laboratory test results were negative or normal: com-
was surgically resected and a cranioplasty using a silicon
graft was performed. About 6 months after this fourth op-
operation, she developed progressive right hemiparesis. Brain
computed tomographic scan did not reveal recurrence of
the lesion. Over the next months a gradual spontaneous
improvement in her condition was evident. However, a few
months later she developed vertigo and unsteadiness of gait
and was hospitalized for evaluation of her condition. Gen-
eral physical examination results were unremarkable. Neu-
rological examination results were unremarkable. Neu-
rological examination results revealed mild ptosis of the
right upper eyelid, bilateral horizontal nystagmus more
prominent on the left side, increased limb tone, mild hyper-
reflexia, and extensor plantar response on the right side.
Sensory examination results were normal and she had mild
bilateral adiadochokinesis. Her gait was ataxic. The fol-
looming laboratory test results were negative or normal: com-
plete blood cell count, erythrocyte sedimentation rate, bio-
chemistry studies, immunoelectrophoresis, antinuclear
factor, C3, and Rose-Waller latex test. Cerebrospinal fluid
was acellular, with normal protein and glucose content, but
again contained oligoclonal IgG bands. Magnetic reso-
nance imaging revealed postoperative right frontal lobe
changes and many hyperintense lesions in the white matter,
some of them pereventricular and the other cerebellar.
A diagnosis of clinically definite, laboratory-supported MS
was established. During 6 years of follow-up, she gradu-
devolved a secondary progressive course with mainly
spinal cord involvement.

**COMMENT**

**FREQUENCY AND CHARACTERISTICS
OF STRUCTURAL CNS LESIONS IN PATIENTS
WITH CSF OLIGOCLONAL IgG BANDS**

Twenty (7.5%) of 270 patients with CSF oligoclonal IgG
bands had a disease presentation and course that could be
related to a CNS structural lesion(s). While the presence
of CSF oligoclonal IgG bands in noninflammatory neuro-
logical disorders has been previously documented,2,3 the
quoted estimation that 5% to 10% of patients with non-
MS, noninflammatory neurological diseases will have in-
creased intrathecal IgG synthesis2 related to a large spec-
trum of conditions. These include amyotrophic lateral
sclerosis, cerebrovascular diseases, primary cerebral neo-
plasms, meningeal carcinomatosis, parkinsonism, sarcoid-
osis of the CNS, anterior spinal artery occlusion, and sub-
dural hematoma.6 By comparison, our study suggests that
CSF oligoclonal IgG bands are present in 20 (7.5%) of 270
patients with structural CNS lesions. These findings could
even represent an underestimation, since it may be as-
sumed that CSF analysis was not performed in patients in
whom the diagnosis of a structural CNS lesion was prob-
able or evident.

In at least 2 of our patients the presence of oligo-
clonal IgG bands was misleading and prolonged the time
required for diagnosis and therapy.

The patients with structural CNS lesions and oli-
goclonal IgG bands can be roughly divided into the fol-
loowing 4 categories: (1) patients with spinal AVM, (2)
patients with cervical spine disease, (3) patients with tu-
mors, and (4) miscellaneous.

**CSF OLIGOCLONAL IgG BANDS IN PATIENTS
WITH SPINAL AVM AND THE PATHOGENESIS
OF OLIGOCLONAL IgG PRODUCTION
IN STRUCTURAL CNS LESIONS**

Of special consideration is the association of spinal AVM
with CSF oligoclonal IgG bands. While it might be an
incidental association, oligoclonal IgG bands were ident-
ified in 3 of 11 patients with spinal AVM; spinal AVM
was present in 3 of 20 patients with structural CNS les-
sions and CSF oligoclonal IgG bands. Therefore, the pos-

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**Table 2. Patients With Cranial Disorders and Cerebrospinal Fluid (CSF) Oligoclonal IgG Bands**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Diagnosis</th>
<th>Medical History</th>
<th>Clinical Presentation</th>
<th>Clinical Findings</th>
<th>CSF</th>
<th>Imaging Procedure</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/F/38</td>
<td>Recurrent R frontal meningioma</td>
<td>. . .</td>
<td>L hemiparesis</td>
<td>L hemiparesis</td>
<td>AC and NP</td>
<td>CT</td>
<td>. . .</td>
</tr>
<tr>
<td>15/F/51</td>
<td>R parietal meningioma</td>
<td>. . .</td>
<td>Paraparesis</td>
<td>Tetrapyrimal signs</td>
<td>AC and NP</td>
<td>CT+ and MRI</td>
<td>Chronic progressive</td>
</tr>
<tr>
<td>16/M/62</td>
<td>L occipital glioblastoma</td>
<td>HTN</td>
<td>Headache and R hemiparesis</td>
<td>R hemiparesis</td>
<td>AC and NP</td>
<td>CT</td>
<td>Secondary progressive</td>
</tr>
<tr>
<td>17/M/46</td>
<td>Pontine intramedullary tumor</td>
<td>. . .</td>
<td>L leg monoparesis</td>
<td>Parapyrimal syndrome</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Subacute</td>
</tr>
<tr>
<td>18/M/33</td>
<td>Posttraumatic encephalomalacia</td>
<td>MS</td>
<td>. . .</td>
<td>. . .</td>
<td>MRI</td>
<td>MRI</td>
<td>Chronic</td>
</tr>
<tr>
<td>19/F/45</td>
<td>Arnold-Chiari type 1</td>
<td>. . .</td>
<td>Diplopa and headache</td>
<td>Tetrapyrimal signs</td>
<td>AC and NP</td>
<td>MRI</td>
<td>Remitting relapsing</td>
</tr>
<tr>
<td>20/M/50</td>
<td>Cerebral hemisclerosis</td>
<td>. . .</td>
<td>Dysarthria and ataxia</td>
<td>Bilateral cerebellar signs</td>
<td>AC and elevated protein level</td>
<td>MRI</td>
<td>Progress</td>
</tr>
</tbody>
</table>

* Ellipses indicate unremarkable data; AC, acellular; NP, normal protein level; CT, computed tomography; MS, multiple sclerosis; MRI, magnetic resonance imaging; HTN, hypertension; AVM, arteriovenous malformation; RBC, red blood cells; LBP, low back pain; IHD, ischemic heart disease; IBD, inflammatory bowel disease; and NIDDM, non–insulin-dependent diabetes mellitus.
sibility that there might be a cause-effect relationships between structural CNS lesions and intrathecal synthesis of IgG cannot be ruled out. It may be speculated that recurrent bleedings into the CNS may disrupt the blood-brain barrier and lead to exposure of CNS antigens to the immune system with resultant intrathecal synthesis of IgG.

Alternatively, a structural CNS lesion, particularly AVM, may behave as a space-occupying lesion, which causes disruption of the adjacent tissue and blood vessels and recurrent tissue damage, leading to a continuous release of CNS antigens that are repeatedly presented to the immune system. Moreover, the breakdown of the blood-brain barrier in the area of the AVM may also contribute to such an “antigen leak,” and facilitate the penetration of inflammatory cells and proinflammatory cytokines. Whatever the mechanism(s), to our knowledge, this is the first report of CSF oligoclonal IgG bands in patients with spinal AVM. Besides the theoretical consideration, awareness of this association is of clinical significance. Their identification in the context of a recurrent or “remitting-relapsing” course might be misleading and postpone the correct diagnosis and treatment, as indeed happened in 2 of our patients.

STRUCTURAL CNS LESIONS AND MS

Two of our patients with structural CNS lesions, who had no clinical or MRI evidence for a demyelinating disease, eventually developed, over the years, new symptoms and signs, which could not be explained by the previous structural CNS lesions. These patients were finally diagnosed as having clinically definite MS. Although the coexistence of 2 disorders may be incidental, it is interesting to point that an association between MS and cervical spondylosis was previously documented. The mechanisms underlying the development of MS in a patient with structural CNS lesions, and the coexistence of MS and cervical myelopathy, are yet unknown but may also be related to recurrent tissue damage and a continuous release of CNS antigens leading to an inflammatory process. This concept of trauma-induced autoimmunity is controversial. On one hand, animal studies9 demonstrated that T cells isolated from spinal-injured rats are capable of causing neurological deficits and histopathological changes similar to experimental allergic encephalomyelitis when injected intravenously into naive animals. On the other hand, a review of the current literature10 provides class 2 evidence against an association between head trauma and MS.

CONCLUSIONS

Our study demonstrates that CSF oligoclonal IgG bands are present in a number of patients with structural CNS lesions, in whom no evidence for an infectious or inflammatory condition affecting the CNS can be found. Awareness to their presence in spinal AVM may avoid delay in the correct diagnosis and treatment.

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