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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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.

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 structure 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 1.2×10^6/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-
tients, 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 postradiographic 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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<td>Spinal angiography</td>
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<td>Leg pain and gait disturbances</td>
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<tr>
<td>12/M/38</td>
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</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.
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 neurological disorders has been previously documented, the quoted estimation that 5% to 10% of patients with non-MS, noninflammatory neurological diseases will have increased intrathecal IgG synthesis related to a large spectrum of conditions. These include amyotrophic lateral sclerosis, cerebrovascular diseases, primary cerebral neoplasms, meningeal carcinomatosis, parkinsonism, sarcoidosis of the CNS, anterior spinal artery occlusion, and subdural hematoma. 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 assumed that CSF analysis was not performed in patients in whom the diagnosis of a structural CNS lesion was probable or evident.

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

The patients with structural CNS lesions and oligoclonal IgG bands can be roughly divided into the following 4 categories: (1) patients with spinal AVM, (2) patients with cervical spine disease, (3) patients with tumors, and (4) miscellaneous.

**CSF OLIGOCOLONAL IgG BANDS IN PATIENTS WITH SPINAL AVM AND THE PATHOGENESIS OF OLIGOCOLONAL 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 identified in 3 of 11 patients with spinal AVM; spinal AVM was present in 3 of 20 patients with structural CNS lesions and CSF oligoclonal IgG bands. Therefore, the pos-
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 studies 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 literature 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.

Accepted for publication November 18, 1999.

This study was supported in part by the Hilda Katz-Blaustein Fund, Baltimore, Md.

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