Hypertrophic chronic pachymeningitis as a localized immune process in the craniocervical region

Article abstract—Hypertrophic chronic pachymeningitis (HCP) is a rare disorder that causes intracranial or spinal thickening of the dura mater. This report describes a patient with progressive HCP in the craniocervical region associated with signs of rheumatic disease. A ventricular-atrial shunt had to be inserted because of increased intracranial pressure. The patient improved after suboccipital craniotomy, C1 to C6 laminectomy, and removal of the thickened dura. Additional therapy with methotrexate stopped progression, which was documented by MRI and PET.

NEUROLOGY 2001;56:107–109

B. Voller, MD; K. Vass, MD; J. Wanschitz, MD; K. Machold, MD; S. Asenbaum, MD; M. Hoberstorfer, MD; and E. Auff, MD

The etiology of hypertrophic chronic pachymeningitis (HCP) is unclear, although several causative factors have been recognized, including infections, autoimmune disorders, and neoplasms. However, most cases are classified as idiopathic. In a summary of 14 patients with cranial HCP of unknown origin, intracranial thickening was mainly found in the tentorium, posterior part of the falx, and the skull base.[1] Laboratory tests showed signs of systemic inflammation in all patients. In a review of 69 cases of spinal idiopathic HCP, the cervical and thoracic regions appeared to be more affected.[2] Signs of inflammation seemed to indicate a worse prognosis for these patients. Four cases of cervicocranial HCP have been reported in the literature, but only one with an identifiable cause (tuberculosis).[3-6] We present a case report of a patient with HCP in the craniocervical region that was effectively treated with surgery followed by methotrexate administration. The effect of immunosuppression in HCP was documented by both MRI and PET.

Case report. In 1991, a 54-year-old man was referred to an internal department with relapsing fever, weakness, myalgia, arthralgia, diplopia, conjunctivitis, and inflammation of the salivary glands. His medical history included cholesteatoma surgery, recurring otalgia, hearing loss, and diabetes mellitus for the previous 10 years. At that time, the findings from CT and gadolinium-diethylene-triaminepentaacetic acid (Gd-DTPA)–enhanced MRI scans, CSF analysis, and liver biopsy were normal. A tentative diagnosis of unspecified autoimmune disease was made. The patient received prednisolone for several months and improved slowly. Later he developed penis ulcers followed by iridocyclitis, but no oral ulcers. Biopsy of the penis showed inflammatory granulomatous tissue. Cultures of smears from the ulcers grew methicillin-resistant *Staphylococcus aureus*. The patient was treated with rifampicin and doxycycline for several months.

Thickening of the dura of the craniocervical region was first documented by MRI in October 1996. HCP was diagnosed. The C-reactive protein (CRP) level was 5.5 mg/dL (normal, <0.8 mg/dL). The protein level was elevated on CSF examination. The serum immunoglobulin (Ig) G level was 1,760 mg/dL (normal, <1,600 mg/dL); the IgA level was 507 mg/dL (normal, <400 mg/dL); and the C3 level was 119 mg/dL (normal, <90 mg/dL). IgM and complement component C4 levels were normal. Serum was nonreactive to the Venereal Disease Research Laboratory (VDRL) test; fluorescent treponemal antibody, absorbed (FTA-ABS) test; *Borrelia*; and HIV-1 and HIV-2 antibodies. Antibodies to mycoplasma and *Cryptococcus*, antinuclear antibodies (HEp-2), rheumatoid factor, antibodies to Sm, double-stranded DNA, U_1RNP, Ro (SS-A), La (SS-B), Jo-1, and tumor markers were negative. Antineutrophil cytoplasmatic antibody (p-ANCA and c-ANCA), antiparietal cell antibody (APCA), antimitochondrial antibody (AMA), and antismooth muscle antibody (ASMA) were negative. Thyroid function was normal. Results of CSF cultures were negative. The creatine kinase level was elevated (250 U/L). A muscle biopsy showed non-specific, mild, myopathic changes. Abdominal CT revealed no abnormalities. Treatment with rifampicin and doxycycline was restarted, followed by long-term methylprednisolone administration.

In April 1998, the patient was admitted to a neurologic department for headaches, myalgia and confusion. Gd-DTPA-enhanced MRI again showed thickening of the dura in the craniocervical region (figure 1A). Antibody titers were negative. The PCR for *Mycobacterium tuberculosis* DNA in CSF was also negative. Thoracic CT was normal. Clinical symptoms improved following IV high-dose steroid therapy. In May 1998 a ventricular-atrial shunt was inserted because the patient had developed obstructive hydrocephalus. A specimen of the dura taken from the frontoparietal region revealed no abnormalities.

The patient was readmitted to the neurologic department in August 1998 with frequently occurring headaches, cervical pain with bilateral arm radiation, gait difficulties, and confusion. Corticosteroids were gradually tapered because of intractable type II diabetes. The erythrocyte sedimentation rate was 80 mm/h and the CRP level was 5.3 mg/dL. Monoclonal gammopathy was excluded by serum immunoelectrophoresis. The CSF contained 9 white blood cells/mm^3, 4.6 mmol/mm^3 glucose, 1,640 mg/dL protein, and 1,081 mg/dL albumin. CSF and serum angiotensin-

From the Department of Neurology (Drs. Voller, Vass, and Auff), Institute of Neurology (Dr. Wanschitz), Department of Internal Medicine III, Division of Rheumatology (Dr. Machold), and Department of Nuclear Medicine (Dr. Asenbaum), University of Vienna; and Department of Neurology, Lainz Hospital (Dr. Hoberstorfer), Vienna, Austria.

Received April 12, 2000. Accepted in final form August 24, 2000.

Address correspondence and reprint requests to Dr. Bernhard Voller, University of Vienna, Department of Neurology, Waehringerguertel 18-20, A-1090 Wien, Austria; e-mail: bernhard.voller@akh-wien.ac.at

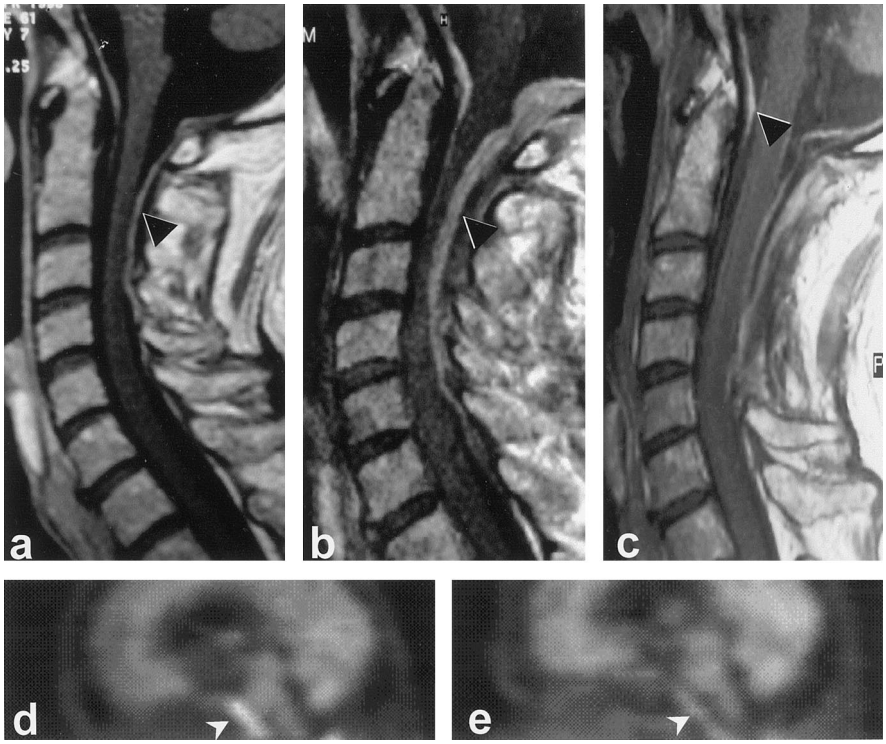

Figure 1. (a) MRI 16 months before surgery. Sagittal T1-weighted scans after gadolinium-diethylene-triamine-pentaacetic acid (Gd-DTPA) administration demonstrates enhancement of the thickened dura in the craniocervical region. (b) Preoperative MRI shows compression of the spinal cord. (c) Postoperative MRI after 20 months of methotrexate therapy. Sagittal T1-weighted scans following Gd-DTPA administration demonstrate the synthetic patch and slight reduction of the meningeal mass in the clivus (arrow). (d) A fluorodeoxyglucose PET scan before treatment shows high activity in the clivus. (e) Nine months after treatment a reduction of activity in the clivus is shown.

converting enzyme (ACE) findings were normal. Antihuman T-cell lymphotropic virus-I antibody was negative. Human leukocyte antigen (HLA) typing revealed DR2 and DR7. Purified protein derivative (PPD) skin testing was negative. Cultures of urine, CSF and sputum were negative for anaerobes, mycobacteria, and fungi. MRI showed marked enhancement of the thickened craniocervical dura (figure 1b). There was no intracerebral lesion on MRI scans. A fluorodeoxyglucose (FDG) PET study demonstrated extracerebral hypermetabolism at the clivus and the upper cervical spine (figure 1d).

The patient's condition worsened until finally he developed acute quadriplegia with urine retention in September 1998. An emergency suboccipital craniotomy was performed, along with a C1 to C6 laminectomy. The entire posterior part of the dura was removed. Microscopic examination showed dense fibrous tissue with a granulomatous inflammatory reaction composed of a mixed granulo-lymphoplasmocellular infiltrate, and multinucleated giant cells of Langhans type (figure 2). Perivascular accentuation and occasional invasion of small vessel walls by neutrophils was compatible with the histologic picture of leukocytoclastic vasculitis. Stains for bacteria (including Ziehl-Neelsen), fungi, and amyloid were negative.

After surgery, immunosuppression with low dose methotrexate was started. The dose was gradually increased to 15 mg weekly. The patient was transferred to our neurorehabilitation department, and neurologic symptoms improved within 3 months. Since January 1999, he has remained in a stable clinical condition, and is able to walk with assistance and eat unassisted. MRI in September 1999 showed a slight regression of the thickened dura in regions where surgery had not been performed, and FDG-PET showed a reduction of activity (figure 1e). In December 1999, the patient was treated with antibiotics because of a suspected shunt infection, and recovered completely. MRI was repeated in June 2000 and again revealed regression of the thickened dura (figure 1c). In an FDG-PET scan, no activity at all could be detected (data not shown).

Discussion. Exhaustive efforts to identify the cause of the dural thickening in our patient were unsuccessful. Focal inflammatory dural lesions have been described in the literature as radiologic features or occurring on autopsy.[1] Whereas the frontoparietal part of the dura in our patient was unaffected (biopsy 1998), we found bioptic evidence for a localized granulomatous inflammatory process in the craniocervical region. There was no history of trauma or intrathecal drug administration. The patient had received several courses of antibiotic and

Figure 2. Surgical specimen from cervical dura shows noncaseating epithelioid granulomatous tissue with giant cell of Langhans type (arrow) and mixed inflammatory infiltrate composed of neutrophils, lymphocytes, and plasmocytes. Hematoxylin and eosin ×110.

antituberculous drugs, and intermittent corticosteroid treatment from 1991 on. He had multiple relapsing rheumatic symptoms, which could not be classified according to clinical or serologic criteria. Disorders such as rheumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa, mixed connective tissue disease, orbital pseudotumor, and Behçet's disease were excluded.

Four cases of craniocervical pachymeningitis have been reported in the literature.[3-6] The clinical courses of these patients suggested that cranial HCP extends downwards to the spine. In our case there was no neuroradiologic evidence for this pattern.

Medical treatment of HCP is not well defined due to the rarity and variability of the disorder. High-dose corticosteroid therapy is often effective initially, but usually there is progression of the disease. In addition, antituberculous, chloroquine immunosuppression, and radiation therapy have been discussed.[7,8] Methotrexate was chosen in our patient because of the granulomatous nature of the process.[9,10]

Considering the possible irreversible damage to the CNS, the need for early extensive excision of the hypertrophic dura is mandatory in pachymeningitis in the spinal and craniocervical regions.[2,6] Biopsy is usually sufficient for pathologic confirmation of the diagnosis. Neurosurgery is required in patients with hydrocephalus. We are aware of the fact that methotrexate therapy does not cure HCP. However, the clinical improvement and reduction of metabolic activity as seen in the PET scan in the case presented demonstrate impressively the long-lasting effect of this drug in a clinical situation where corticoid treatment is not possible.

References

1. Masson C, Henin D, Hauw JJ, Rey A, Raverdy P, Masson M. Cranial pachymeningitis of unknown origin: a study of seven cases. Neurology 1993;43:1329–1334.
2. Mikawa Y, Watanabe R, Hino Y, Hirano K. Hypertrophic spinal pachymeningitis. Spine 1994;19:620–625.
3. Botella C, Orozco M, Navarro J, Riesgo P. Idiopathic chronic hypertrophic craniocervical pachymeningitis: case report. Neurosurgery 1994;35:1144–1149.
4. Okimura Y, Tanno H, Karasudani H, Suda S, Ono J, Isobe K. A case of hypertrophic cranial pachymeningitis [in Japanese]. No Shinkei Geka 1991;19:259–262.
5. Yuh WTC, Drew JM, Rizzo M, Ryals T, Sato Y, Dell W. Evaluation of pachymeningitis by contrast-enhanced MR imaging in a patient with rheumatoid disease. AJNR Am J Neuroradiol 1990;11:1247–1248.
6. Yamashita K, Suzuki Y, Yoshizumi H, Takahashi JB, Nogawa T. Tuberculous hypertrophic pachymeningitis involving the posterior fossa and high cervical region. Neurol Med Chir (Tokyo) 1994;34:100–103.
7. Parney IF, Johnson ES, Allen PB. "Idiopathic" cranial hypertrophic pachymeningitis responsive to antituberculous therapy: case report. Neurosurgery 1997;41:965–971.
8. Mamelak AN, Kelly WM, Davis RL, Rosenblum ML. Idiopathic hypertrophic cranial pachymeningitis. Report of three cases. J Neurosurg 1993;79:270–276.
9. Gutierrez-Urena S, Espinoza IR. Methotrexate: the agent of choice for chronic inflammatory disorders. A perspective ten years later. Clin Exp Rheumatol 1995;13:281–284.
10. Kaye O, Ribbens C, Kahn MF, Malaise MG. Sarcoidosis: recognition and treatment guidelines. BioDrugs 1997;7:441–447.