Idiopathic hypertrophic cranial pachymeningitis

Report of three cases

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Hypertrophic cranial pachymeningitis is a rare, idiopathic form of granulomatous pachymeningitis. This report describes three cases of hypertrophic cranial pachymeningitis and discusses the clinical, radiographic, and pathological findings in these and other reported cases. These lesions typically cause progressive cranial nerve palsies, headaches, and cerebellar dysfunction. They occur in patients of all age groups; the peak incidence is in the sixth decade. Hypertrophic cranial pachymeningitis is best identified by magnetic resonance imaging. The diagnosis is established by excluding all other granulomatous and infectious diseases. A dural biopsy is essential to confirm the diagnosis. Hypertrophic cranial pachymeningitis is initially responsive to steroid therapy, but in most cases it recurs or progresses despite treatment. Surgical excision of granulomas is occasionally necessary to alleviate a mass effect. The long-term outcome remains uncertain for most patients, but progressive disease is usually fatal owing to cranial neuropathies.

KEY WORDS • hypertrophic cranial pachymeningitis • granulomatous disease • sarcoidosis • cranial nerve palsy • multifocal fibrosclerosis

Hypertrophic cranial pachymeningitis is a diffuse inflammatory disease that causes thickening of the dura mater. This extremely rare, idiopathic, poorly understood form of granulomatous pachymeningitis has been reported in only six cases. This report describes three patients with hypertrophic cranial pachymeningitis and discusses the clinical, radiographic, and pathological findings in these and the other reported cases. The evaluation of patients with suspected hypertrophic cranial pachymeningitis, the differential diagnosis, and the relationship of hypertrophic cranial pachymeningitis to other forms of pachymeningitis and to fibrosclerotic diseases in other organ systems are also discussed.

Case Reports

Case 1

This 67-year-old woman developed a hearing loss in her right ear in 1988, and Ménière’s disease was diagnosed. Three years later, she noted a slight decrease in the visual acuity of her right eye. She also noticed a foul taste in her mouth, but did not have difficulty with tasting or smelling foods. Facial weakness and diplopia were absent. Over the next 4 months, she had progressive dysarthria, deviation of the tongue to the right, headache, and a sharp pain in the right occiput. Magnetic resonance (MR) images showed no abnormalities.

Examination. Physical and neurological examinations showed a right-sided sensorineural hearing loss, diminished corneal sensation in the right eye, a right 12th cranial nerve palsy, and dysarthria. All laboratory findings were normal, except for an elevated erythrocyte sedimentation rate of 43 mm/hr. Three lumbar punctures over the course of 2 months were normal, but a fourth lumbar puncture showed an elevated cerebrospinal fluid (CSF) protein level of 113 mg/dl and a white blood cell count of 45/cu mm (predominantly lymphocytes); all other CSF studies, including cytological, cryptococcal antigen, and venereal disease tests, and stains and cultures for fungi and acid-fast bacilli, were negative. All serum tests, including thyroid function, iron, and venereal disease tests, and cryptococcal and bacterial cultures, were also negative. Magnetic resonance images (Fig. 1A, B, and C) showed thickening of the meninges, which was greatest along the falx and tentorial edge. Gadolinium-enhanced T1- and T2-weighted MR images showed thickened meninges with hyperin-
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Tense edges. An enhancing mass lesion that compressed the brain stem was noted anterior to the pons; the center of the mass was hypointense on T1-weighted images.

Operation. A burr-hole biopsy of the right frontal meninges revealed thickened dura, leptomeninges infiltrated with large numbers of chronic inflammatory and multinucleated giant cells, and some areas of acute inflammation (Fig. 1D). Special stains for *Histoplasma*, *Coccidioides*, and *Mycobacterium* species revealed no organisms.

Postoperative Course. Treatment with prednisone, 40 mg/day, alleviated the dysarthria, but the hypoglossal nerve palsy persisted. Magnetic resonance images showed a reduction in the size of the dural skull base lesion. The prednisone was tapered very slowly, but the symptoms returned when the dose reached 20 mg/day; higher doses did not alleviate the symptoms. Six months after the biopsy, the patient developed facial pain. Magnetic resonance images showed dural hypertrophy and a retroclival mass that had not enlarged to presteroid dimensions. The patient declined to have the lesion resected and is being followed with MR imaging. The fifth, eighth, and 12th cranial nerve palsies are unchanged. She continues to take prednisone, at least 20 mg/day. Recently, she has developed blurred vision, nausea, neck pain radiating to the occiput, ataxia, left-sided hearing loss, and further difficulty with swallowing, and is being evaluated for immunosuppressive therapy with azathioprine and cyclophosphamide.

Case 2

This 50-year-old woman noted difficulty in moving her jaw and talking in 1985. Later that year, she began to have intrascapular and upper back pain. Evaluation of these symptoms, including four-vessel cerebral angiography and skull tomography, revealed no abnormalities. In the spring of 1986, she reported difficulty with concentrating. In January, 1987, she began to have slurred speech and developed retro-auricular pain, headaches, an unsteady gait, and, shortly thereafter, vertigo. In April, 1987, she noted a right-sided hearing loss. One month later, she began to have dysphagia and severe headaches, and neck extension was limited by pain.

Between 1968 and 1983, she had multiple admissions to the hospital for an urticarial skin condition. No diagnosis was ever established. A skin biopsy in 1969 showed an extensive chronic inflammatory infiltrate, scattered Langerhans giant cells, multiple foci of necrosis, and scattered plasma cells. Special stains for acid-fast bacilli, fungi, spirochetes, and bacteria were negative. Systemic assays for *Cryptococcus*, *Histoplasma*, *Coccidioides*, and *Mycobacterium* species were non-diagnostic. She was successfully treated with antipruritic agents and remained nearly asymptomatic until 1985.

Examination. Physical examination showed a right facial dysesthesias, diminished right corneal reflex, and slow rightward movement of the tongue. Magnetic resonance images (Fig. 2 upper pair) in 1987 revealed a 2.5-cm clival mass that distorted the brain stem and stretched the 10th to 12th cranial nerves. Treatment with dexamethasone, 16 mg/day, alleviated the dysphagia.
returned despite high doses of prednisone. Currently, she is being evaluated for treatment with azathioprine.

Case 3

This 75-year-old man suffered left-sided headache and otitis media in September, 1981. He was treated with oral antibiotic agents but the pain persisted. Intermittent treatment with prednisone for 4 months did not relieve the symptoms completely. No diagnostic workup was performed. In January, 1982, he developed retro-orbital pain and diplopia on left lateral gaze. Temporal arteritis was diagnosed presumptively without a formal workup. The pain was relieved by treatment with prednisone. One month later, a temporal artery biopsy was performed and was normal.

In May, 1982, the patient began to have persistent nausea and vomiting, and the diplopia returned. A cerebral angiogram and computerized tomography (CT) scans of the head showed no abnormalities. A lumbar puncture revealed an opening pressure of 230 mm H₂O, a protein level of 61 mg/dl, a glucose level of 87 mg/dl, oligoclonal bands, and an immunoglobulin (Ig) G index of 46 mg/dl. Multiple sclerosis was diagnosed. Steroid treatment was reinstituted but was discontinued in September, 1982, for unclear reasons. In November, 1982, the retro-orbital pain returned. The patient also reported a 50-lb weight loss.

Examination. In December, 1982, the patient was admitted to the hospital for a diagnostic workup. He was found to have left pupil-sparing third, fourth, sixth, and seventh cranial nerve palsies and a diminished left corneal reflex. The erythrocyte sedimentation rate was 61 mm/hr; a lumbar puncture revealed an opening pressure of 61 mm H₂O, and CSF analysis disclosed a glucose level of 51 mg/dl, a protein content of 110 mg/dl, a white blood cell count of 46/cu mm (predominantly lymphocytes), and an IgG index of 39.8 mg/dl. Cultures for fungi, acid-fast bacilli, bacteria, spirochetes, and parasites were negative. Both serum and CSF venereal disease tests were negative. Computerized tomography scans showed thickening of the left cavernous sinus and the inferior margin of the tentorium and enhancing, thickened pachymeninges over much of the cerebrum (Fig. 3 left).

Operation. A meningeal biopsy was performed through a left subtemporal craniotomy. Pathological examination of the biopsy specimen showed necrotic granuloma with lymphocytosis, fibrosis, and other chronic inflammatory changes (Fig. 3 right). Cultures for fungi and acid-fast bacilli were negative. Tolosa-Hunt syndrome was diagnosed.

Postoperative Course. Treatment with steroids reduced the neurological symptoms significantly. Soon after, the patient had congestive heart failure and upper gastrointestinal bleeding, and died of cardiopulmonary arrest in January, 1983. A postmortem examination of the brain revealed thickened, nodular, irregular basal dura, necrotizing granulomata, and acute and chronic inflammation of the cavernous sinus and entire dura. The adventitia of the left internal carotid artery showed chronic inflammation.

First Operation. A posterior fossa craniectomy was performed, and a dural-based granuloma with caseous necrosis was almost totally resected. Cultures of the mass were negative for bacteria, fungi, and acid-fast bacilli. The patient was largely asymptomatic until July, 1991, when she began to have nausea and vomiting, extreme disequilibrium, and right-sided hearing loss. A repeat MR image showed a large, solid dural lesion with a cystic component ventral to the pons.

Second Operation. Subtotal translabyrinthine resection of the lesion in late 1991 relieved the headaches and nausea. Pathological analysis of the surgical specimen showed well-formed chronic granulomas and inflammation but no organisms (Fig. 2 lower). These findings matched those from the previous surgical specimen and were remarkably similar to the description of the skin biopsy in 1969.

Postoperative Course. Approximately 6 months after the second operation, the patient was readmitted to the hospital with headache, nausea, and vomiting. The erythrocyte sedimentation rate was 6 mm/hr. A full diagnostic workup was unrevealing, and MR images did not show new skull base lesions. Treatment with prednisone, 20 mg/day, alleviated the nausea and vomiting initially; an additional workup was unrevealing. Recently, the nausea, vomiting, and dysphagia have
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Discussion

Pachymeningitis was first described in detail by Gowers, who divided it into two subtypes. External pachymeningitis was characterized as a local phenomenon caused by trauma or infection from "adjacent disease." Internal pachymeningitis was portrayed as a more diffuse process that was either hemorrhagic (probably representing chronic subdural hematoma) or purulent (probably representing the spread of leptomeningeal tuberculosis or syphilis). These descriptions do not match our current view of hypertrophic cranial pachymeningitis. However, in 1873, Charcot described a case of hypertrophic cervical pachymeningitis as a process in which "the neighboring leptomeninges always suffers as well, becoming opaque and thick, and firmly united to the dura and cord." This description is more consistent with what we know as hypertrophic cranial pachymeningitis, but it is unclear whether an infectious agent was responsible for the pathological findings in that case.

Clinical and Laboratory Findings

Only six other cases of idiopathic hypertrophic cranial pachymeningitis have been reported. In five patients the disease was limited to the pachymeninges and in one it extended into the orbit. These cases and our three cases are summarized in Table 1. In total, there were five men and four women, aged 20 to 75 years; most were in the sixth decade.

The most common symptoms are headache (100%) and cranial nerve palsies (78%). All cranial nerves except the olfactory nerve may be affected (Table 2). The eighth cranial nerve is most frequently involved, followed in equal frequency by the fifth, seventh, ninth, tenth, and 12th cranial nerves. Two patients had dural venous sinus occlusion or narrowing.

Cerebellar ataxia has been reported in five patients, including one in our series (Case 2). Masson, et al., found angiographic evidence of narrowed venous sinuses and delayed drainage in two patients with ataxia and confusion, and suggested that these symptoms and

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
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<td>55, M</td>
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<td>anti-TB drugs, ACTH</td>
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<td>52, M</td>
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<td>steroids</td>
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<td>Masson, et al., 1989</td>
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<td>HA, ataxia</td>
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<td>75, M</td>
<td>HA; 3rd-7th CN</td>
<td>steroids</td>
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* HA = headache; CN = cranial nerve palsy; TB = tuberculosis; ACTH = adrenocorticotropic hormone; HCP = hypertrophic cranial pachymeningitis; RT = radiation therapy.

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associated white matter changes in the cerebellum and cerebrum resulted from venous congestion of the draining sinuses. However, one of our patients with cerebellar ataxia (Case 2) and one reported by Berger, et al., both had normal angiograms and no white matter changes noted on MR images. Diffuse cerebral or cerebellar ischemia caused by compression of the cortical surface by tight, thickened, and adherent pachymeninges seems a more plausible cause of this diffuse dysfunction.

Studies of CSF are inconclusive in patients with hypertrophic cranial pachymeningitis. No microorganisms are identifiable. Lumbar puncture opening pressures, glucose levels, and cell counts are variable and nondiagnostic. The CSF protein level and the erythrocyte sedimentation rate are usually elevated, but other tests of chronic inflammatory states are nondiagnostic. The angiotensin-converting enzyme level, which often helps to confirm the diagnosis of sarcoidosis, was normal in one patient with hypertrophic cranial pachymeningitis, but has not been measured in other patients.

Radiographic Findings

The radiographic appearance of hypertrophic cranial pachymeningitis is characteristic but not diagnostic. Unenhanced CT scans show thickened, hyperdense dura, typically along the tentorium, tentorial ridge, falx, and preopticine brain stem. After administration of iodinated contrast material, the hypertrophic dura enhances markedly. Gadolinium-enhanced T1-weighted MR images show conspicuous enhancement of the dural edges. The T2-weighted MR images typically show relative hypointensity of the thickened meninges, which may be bordered by a thin margin of hyperintensity. Cellular compactness and abundant collagenous material or fibrosis (Case 1) are ultrastructural characteristics associated with restricted micromolecular water motion, short T2 relaxation times, and resultant hypointensity on T2-weighted images. Hypervascularity at the affected dural margins may explain the thin, wafer-like edges of hyperintensity noted on T2-weighted images. Diffuse hypointensity of the dura may also be observed without central hypointensity.

Differential Diagnosis

The diagnosis of hypertrophic cranial pachymeningitis is made by exclusion. Patients with cranial nerve palsies and headache should undergo a lumbar puncture to rule out infectious causes of meningitis, and CT or MR imaging studies should be obtained to identify mass lesions in the brain stem or skull base. If dural-based mass lesions and thickened pachymeninges are noted on imaging studies, a systemic evaluation for other causes of granulomatous disease, such as sarcoidosis or tuberculosis, should be undertaken. The evaluation should include a chest x-ray film and a purified protein derivative skin test; a workup for metastatic cancer may also be useful.

A dural biopsy is essential to confirm the diagnosis in cases of suspected hypertrophic cranial pachymeningitis. It is a diffuse rather than a focal process and can usually be distinguished from other noninfectious granulomatous diseases. Sarcoidosis, for example, causes non-necrotizing granulomas with a predilection, often focal, for the facial nerve; however, isolated intracranial sarcoid occurs in less than 2.5% of cases. The level of angiotensin-converting enzyme is often elevated in patients with sarcoidosis and may help to rule out hypertrophic cranial pachymeningitis. Moreover, neurosarcoidosis responds well to steroid therapy and is usually self-limiting, whereas hypertrophic cranial pachymeningitis responds to corticosteroid therapy in only about 50% of cases and often recurs or progresses despite continuing treatment.

Wegener's granulomatosis, a vasculitic disease of uncertain etiology, must also be included in the differential diagnosis. It usually causes signs of nasopharyngeal or sinus inflammation; peripheral neuropathies are the most common neurological manifestations. Unlike hypertrophic cranial pachymeningitis, which progresses slowly and is associated with a low mortality rate, Wegener's granulomatosis usually progresses rapidly and is almost always fatal unless it is treated aggressively with steroids and cyclophosphamide, in which case remission is achieved in over 90% of cases. None of our patients had evidence of pharyngeal or sinus inflammation on CT scans or MR images; we have no information about such findings in the other cases. Wegener's granulomatosis can involve the nerves in the cavernous sinus and was considered in the differential diagnosis of Case 3; however, the absence of evidence of vasculitis in other organ systems at autopsy argues against this diagnosis. Similarly, other vasculitides, such as polyarteritis nodosa, are unlikely to cause pachymeningitis without signs of systemic involvement.

Tuberculomas can usually be diagnosed by staining for acid-fast bacilli and by a positive purified protein derivative skin test. Diffuse tuberculomas pachymeningitis is rare in the United States; it causes severe illness and can usually be diagnosed by biopsy or CSF studies. Syphilis, another infectious cause of granulomatous pachymeningitis, is easily detectable by testing for venereal disease or by culturing Treponema pallidum from biopsy samples and can therefore be differenti-

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Associated Diseases

Hypertrophic Spinal Pachymeningitis. Ashkenazi, et al., note that hypertrophic spinal pachymeningitis was originally described by Charcot and Joffroy in 1869, and at least 55 cases have been reported. This pachymeningitis has a strong predilection for the cervical and high thoracic regions of the spinal cord. Trauma, infection, mucopolysaccharidosis, rheumatoid arthritis, and intrathecal toxins have been implicated in the development of hypertrophic spinal pachymeningitis, but no single agent has proven to be causative. Noninfectious hypertrophic spinal pachymeningitis is histologically similar to hypertrophic cranial pachymeningitis; however, the former preferentially involves the lower brain stem and skull base, whereas the latter affects the upper cervical spinal cord. Most patients with hypertrophic cranial pachymeningitis have multiple cranial nerve palsies, and most patients with hypertrophic spinal pachymeningitis have symptoms of nerve root compression. These similarities suggest that hypertrophic spinal pachymeningitis and hypertrophic cranial pachymeningitis are different presentations of a single disease.

Other Fibroelastic Diseases. There is some evidence that hypertrophic cranial pachymeningitis is related to other fibroelastic diseases. This diverse class of maladies, which can affect almost every organ system, includes sclerosing cholangitis, episcleritis, orbital pseudotumor, Riedel's thyroiditis, testicular fibrosis, mediastinal fibrosis, and subcutaneous fibrosis. Orbital pseudotumor with intracranial extension has been reported in seven cases. Berger, et al., described a patient with episcleritis, orbital pseudotumor, sclerosing cholangitis, and hypertrophic cranial pachymeningitis. Adler, et al., reported a patient with cervical pachymeningitis and a pathologically identical pulmonary nodule. One of our patients had a long history of chronic skin inflammation with histiocytic changes; 15 years later, she developed hypertrophic cranial pachymeningitis. Although the skin biopsy specimens could not be located for direct comparison with the meningeal biopsy, the description of the skin biopsy findings suggests an unmistakable similarity to hypertrophic cranial pachymeningitis. This similarity supports the possible connection between hypertrophic cranial pachymeningitis and other chronic inflammatory conditions, such as multifocal fibrosclerosis. Multifocal fibrosclerosis is a process dominated by chronic inflammatory changes and fibrosis, with some small areas of acute inflammation. These findings are also noted in hypertrophic cranial pachymeningitis. Hypertrophic cranial pachymeningitis may be detected earlier than other fibroelastic diseases because the brain stem and cranial nerves are less tolerant of space-occupying lesions than other organ systems.

Tolosa-Hunt syndrome, first described by Tolosa, in 1954 and later by Hunt and colleagues, is characterized by painful ophthalmoplegia due to inflammation of the anterior wall of the cavernous sinus that is not caused by a benign steroid-sensitive granuloma such as sarcoidosis. In Case 3, the walls of the cavernous sinus and the entire dura were inflamed. Initially, the cavernous sinus was affected; the subsequent involvement of multiple cranial nerves underlines the diffuse nature of this disease. To our knowledge, this is the only reported case of hypertrophic cranial pachymeningitis associated with Tolosa-Hunt syndrome. Orbital pseudotumor with intracranial extension, in which painful ophthalmoplegia is caused by a granulomatous mass in the orbit rather than by inflammation of the cavernous sinus, is a much more common etiology for the Tolosa-Hunt syndrome and should probably be excluded before a diagnosis of hypertrophic cranial pachymeningitis is entertained. Orbital pseudotumor has been reported both in isolation and in association with intracranial extension.

Treatment

The treatment of hypertrophic cranial pachymeningitis is not well defined, owing to the rarity of the disease and uncertainty regarding its etiology. Corticosteroid therapy is often effective initially, but the disease usually progresses despite such treatment. In the case reported by Berger, et al., steroid therapy stopped progression of the disease, although some symptoms persisted. In the series of Masson, et al., steroid therapy halted progression in one case, worked temporarily in another, and failed in the third. Of the remaining cases, one patient died from progressive disease and one had slowly progressive symptoms. Excluding our three cases, four patients worsened despite steroid therapy and two were stabilized. Azathioprine and other immunosuppressive drugs have been administered, but the follow-up times in all reported cases are too short to determine the efficacy of these agents. Based on the notion that hypertrophic cranial pachymeningitis may behave like sarcoidosis, radiation therapy has also been tried, but without proven benefit. A burr hole biopsy is usually sufficient for pathological confirmation of the diagnosis; in some cases, surgical excision may be required to relieve compression by a granuloma. This approach was used twice in one of our patients. Her symptoms were well controlled for 5 years, but after each excision the disease progressed.

A better understanding of the pathophysiological mechanisms that lead to the development of hypertrophic cranial pachymeningitis and other fibroelastic diseases seems essential for improving the treatment of hypertrophic cranial pachymeningitis. At present, high-dose corticosteroid therapy is the treatment of choice, followed by immunosuppressive agents, such as azathioprine and cyclophosphamide, if necessary. Further long-term follow-up study of these patients is needed to clarify the outcome of this rare disease.

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References


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