

Clinical Neurology and Neurosurgery

Clinical Neurology and Neurosurgery 110 (2008) 83-87

www.elsevier.com/locate/clineuro

Case report

Diffuse cortical lesions with hemorrhage in cerebral Whipple's disease

Liyong Wu, Xiangbo Wang*, Hua Wei, Cunjiang Li, Jianping Jia

Department of Neurology, Xuanwu Hospital, Capital University of Medical Sciences, Beijing 100053, PR China Received 7 February 2007; received in revised form 13 August 2007; accepted 24 August 2007

Abstract

A 30-year-old Chinese male with a history of diarrhea and arthralgia presented for evaluation of progressive dementia, epilepsy, and increased intracranial pressure. Imaging of the brain showed progressive cortical and subcortical lesions with hemorrhage involving the bilateral temporal and occipital lobes, the posterior parietal lobes, and the left frontal lobe. "Foamy" periodic acid–Schiff (PAS)-positive macrophages were demonstrated on brain biopsy. The patient showed clinical improvement following treatment with chloromycetin and sulfadiazine for 2 months. This constitutes the first reported case of cerebral Whipple's disease with diffuse cortical lesions with hemorrhage reported in a Chinese individual. Further, this case points out the significance of early recognition and treatment of cerebral Whipple's disease, especially in those cases with unusual manifestations.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Whipple's disease; Dementia; Magnetic resonance imaging; Diffuse brain lesions

1. Introduction

Whipple's disease (WD), first described in 1907 [1], was originally thought to be a gastrointestinal disease, but has become recognized as a multisystem, chronic, and relapsing infection. WD is considered to be a rare disease, with fewer than 1000 cases reported during the last century [2]. WD occurs worldwide, but most patients are Caucasian; only a few cases have been reported in the Asian population [3]. To our knowledge, no cases of cerebral WD have been reported in the Chinese population. The clinical features of cerebral WD are diverse, as the disease may affect the brain stem, the diencephalon, the rhinencephalon, the medial temporal lobe, and the meninges [4]. Multiple lesions with hemorrhage in cerebral WD have not been reported. We herein describe the first case of cerebral WD in a Chinese patient, which was characterized by diffuse cortical and subcortical lesions with hemorrhage.

2. Case report

2.1. History and physical examination

In September 2005, a 30-year-old Chinese male with a history of recurrent seizures for 7 months and progressive dementia for 5 months was admitted to our hospital. He had been in excellent health until 7 months prior to admission, when he had a seizure of 2 min duration, characterized by loss of consciousness and tonic-clonic movements of the extremities. On referral to the hospital, he was diagnosed with cysticercosis and treated with albendazole. Two months later, he had another seizure, accompanied by new symptoms, including headache, arthralgia of the right knee, difficulty expressing himself, and an inability to read newspapers or books. While receiving treatment with methylprednisolone and gamma globulin, the patient's symptoms progressively worsened. His words became scant, his memory was severely impaired, and he could not name objects. He reported a decline in both vision and hearing 3 months before admission to the hospital, and was treated concurrently with methylprednisolone and cyclophosphamide. Unfortunately, the patient lost his vision and hearing completely 2 weeks

^{*} Corresponding author. Tel.: +86 10 83198899 8850. E-mail address: xb90956@yahoo.com.cn (X. Wang).

^{0303-8467/\$ –} see front matter © 2007 Elsevier B.V. All rights reserved. doi:10.1016/j.clineuro.2007.08.017

before hospital admission. The patient's medical history included chronic diarrhea for 10 years and arthralgia for 5 years. He denied any history of fevers or weight loss. On physical examination, there was no fever, no peripheral lymphadenopathy, and no gastrointestinal or cardiorespiratory abnormalities. On neurologic examination, the patient was apathetic, had dementia, motor and sensory aphasia, and an inability to communicate. Fundoscopic examination revealed hemorrhage of the retinas and edema of the optic discs. Vision and hearing were absent bilaterally. No oculomasticatory myorhythmia (OMM) or oculofaxial-skeletal myorhythmia (OFSM) was found. Muscular tension was normal and muscle strength was 5/5 in all extremities. Reflexes were normal and no pathologic reflexes existed; both Kerning and Brudzinski signs were negative. The patient was uncooperative on examination of coordination and sensation.

2.2. Laboratory tests

A routine blood count, urinalysis, blood chemistries (including creatine phosphokinase [CPK]), lymphocyte subgroups, lactic acid, erythrocyte sedimentation rate, and C-reaction protein were all within normal limits. Thyroid function, serum vitamin B12, and folate levels were also normal. Markers of autoimmune diseases, such as antinuclear antibodies (ANA), extractable nuclear antigen (ENA), and anti-neutrophilic cytoplasmic antibodies (ANCA) were all negative. Viral antibodies, syphilis serology, and HIV antibodies were negative. Serum antibodies against cysticercus, distoma pulmonale, toxoplasma, and schistosoma were also negative. Results of paraneoplastic tests (i.e., carcinoembryonic antigen and prostate-specific antigen) were within normal ranges. An ultrasound of the abdomen was normal. Electromyography showed no significant abnormalities. A muscle biopsy showed no ragged red fibers. An electroencephalogram (EEG) revealed a moderate diffuse disturbance in the cerebral cortex. Lumbar puncture showed a high intracranial pressure (>300 mmH₂O). Analysis of the cerebrospinal fluid (CSF) was significant for increased protein (1.41-2.03 g/L) and myelin basic protein (MBP; 7.22 nmol/L). Oligoclonal band (OB) was positive, but the cell count and glucose level were normal. Laboratory screening examination of the CSF for causative infectious agents, including cryptococcus, viruses, fungi, and tuberculosis, were all negative. No tumor cells were observed in the CSF. In February 2005, MRI of the brain revealed multiple confluent lesions with hyperintensity in the left temporal-occipital and right temporal grey matter and grey-white junction (Fig. 1). Over the ensuing 4 months, the lesions in both sides of the temporal-occipital lobes extended and a new lesion appeared in the left frontal lobe, accompanied by hemorrhage in the cortex. In October 2005, serial MR scans (Fig. 2A–D) revealed diffuse mixed signals in T1WI and T2WI; the lesions involved the bilateral temporal and occipital lobes, posterior parietal lobes, and the left frontal lobe, involving nearly

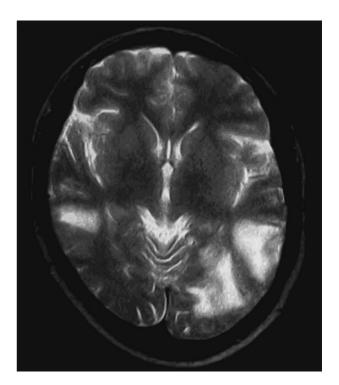


Fig. 1. Axial T2-weighted MR image, obtained in February 2005, revealed multiple confluent lesions with hyperintensity in the left temporal–occipital and right temporal grey matter and grey–white junction.

the entire brain. A contrast image showed diffuse or patchy enhancement. Brain tissue herniation was evident, consistent with the high intracranial pressure. Brain PET showed a mild high uptake in the affected cortices, indicating an infection. Stereotactic brain biopsy of the left occipital lobe performed in May 2005 showed that brain tissue was infiltrated with T lymphocytes and "foam" macrophages, suggestive of an infective disease.

2.3. Diagnosis and treatment

On admission, the patient was treated with mannitol, prednisone, and sodium valproate. His symptoms progressively worsened, accompanied by persistently elevated intracranial pressure and brain tissue herniation occurring in the area of the brain biopsy. For the purpose of symptomatic treatment and diagnosis, a craniotomy of the bilateral frontal lobe was performed 1 month after admission. During the operation, high pressure of the dura and disappearance of the sulci and gyri were observed. A biopsy of the left frontal lobe was performed. The specimen obtained was approximately $5 \text{ cm} \times 5 \text{ cm} \times 3 \text{ cm}$ in size, with visible hemorrhage and necrosis. Light-microscopic studies revealed numerous "foam" macrophages with gliosis. The macrophages contained intracytoplasmic rod-shaped or granular structures that were stained by periodic acid-Schiff (PAS). Special staining for acid-fast bacilli and fungi were negative. These findings were considered typical for WD.

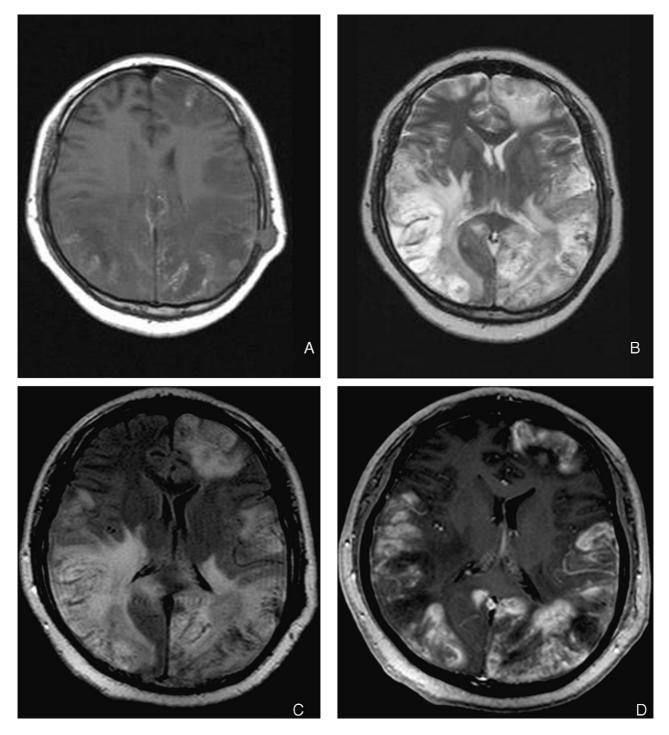


Fig. 2. (A) Axial T1-weighted MR image, obtained in October 2005, showed bilaterally decreased signal intensity mixed with a high signal in affected lobes, and brain tissue herniation occurred in the location of the brain biopsy. (B) Axial T2-weighted MR image showed increased signal intensity mixed with decreased signal in the bilateral temporal and occipital lobes, and the left frontal lobe. (C) Axial T2-weighted fluid-attenuated inversion recovery MR image showed increased signal intensity in the same areas. (D) Axial T1-weighted MR image after intravenous gadolinium–DTPA showed diffuse or patchy intensive enhancement in the same areas.

According to the clinical manifestations and pathologic features, a diagnosis of cerebral WD was established. Post-operatively, the patient became comatose secondary to the pulmonary infection. Except for mannitol, intravenous chlormycetin (0.5 g twice daily) and sulfadiazine (2 g twice

daily) were administered for 2 months and the patient's clinical condition improved; however, he still could not communicate and maintained a posture with the upper extremities in flexion and the lower extremities in extension, indicating a decorticate state.

3. Discussion

The symptoms of cerebral WD include oculomotor abnormalities, ataxia, seizures, psychiatric disturbances, dementia, and aseptic meningitis [4,5]. The protean manifestations of the disease make a diagnosis challenging, but oculomasticatory myorhythmia (OMM) and oculo-facial-skeletal myorhythmia (OFSM) are considered to be pathognomonic for central nervous system (CNS) WD [6]. Unfortunately, only 20% of the cases of CNS WD demonstrate one of these two pathognomonic features [6,7]. Louis et al. [6] has proposed guidelines for the diagnosis of CNS WD based on an extensive review of all previously reported cases. A definite diagnosis of CNS WD requires the presence of OMM or OFSM, a positive biopsy, or a positive PCR analysis. Given the low incidence of OMM and OFSM, diagnosis is mostly dependent on laboratory findings.

The clinical characteristics of the patient presented herein included a history of chronic diarrhea and arthralgia for many years, progressive dementia, and an elevated intracranial pressure accompanied by epilepsy. Although OMM or OFSM were not present, the patient was diagnosed with WD involving the CNS based on the findings obtained from the brain biopsy. A MRI of the patient's brain revealed diffuse lesions in the grey matter and at the grey-white junction, which made it challenging to distinguish from parasitic infections (e.g., cysticercosis and toxoplasmosis), unusual infectious diseases (e.g., mycobacterial and fungal infections), and metabolic disorders, such as mitochondrial encephalomyopathy with lactic acidosis and stroke (MELAS) or, less likely, a tumor. Progressively elevated intracranial pressure and cerebral edema suggested the diagnosis of a tumor, but this possibility was excluded after PET scanning and stereotactic brain biopsy. Cortical or subcortical lesions mainly affect the posterior brain symmetrically, implying a metabolic disorder, such as MELAS; however, no stratiform necrosis existed on MRI and the negative muscular biopsy results did not support this diagnosis. Therefore, the patient was suspected of having an unusual infection according to the clinical and MRI features. There was no evidence of causative organisms or specific antibodies in the serum or CSF for parasitic, mycobacterial, or fungal infections. Thus, these infectious diseases were effectively ruled out. Indeed, the diagnosis of CNS WD was not established until periodic acid-Schiff (PAS)-positive material in the macrophages was demonstrated from the brain biopsy.

In the CNS, WD lesions which consist of nodular granulomatous polioencephalitis or panencephalitis, most frequently involve the periaqueductal grey matter, thalamus, hypothalamus, hippocampus, cingulate gyrus, basal ganglia, cerebellum, and very rarely, the spinal cord [4,8–12]. Cerebral MRI appears to be the best imaging modality for WD, although the specificity is not very high [13]. Intracerebral lesions in WD appear predominantly as a hyperintensity on T_2 -weighted images. On T_1 -weighted images, the lesions may demonstrate a homogeneous contrast enhancement, a

ring, or patchy enhancement, as in our patient. The lesions may lack a mass effect or be space-occupying, with or without marked perifocal edema.

Serial MRIs of our patient showed several salient features which differed from other WD patients described [10,11]. First, the lesions were localized mostly in the cortical and subcortical regions, with the periaqueductal grey matter spared; the latter area was most frequently involved, as reported in the literature [14]. Second, diffuse lesions involving almost all lobes has been rare in previously reported cases of WD [14]. Diffuse lesions with severe edema produce very high intracranial pressures, which are extremely rare [15]. Lastly, to our knowledge, our patient was the first one with hemorrhage in the lesions of the cerebral cortex, although gastrointestinal bleeding has been reported in WD [16]. Our interpretation of these findings is that, the initial treatment of the patient with methylprednisolone and cyclophosphamide may have facilitated the probable cerebral infection by reducing cell-mediated immunity [17], so that severe diffuse brain damage developed, which accounted for the hemorrhage. After receiving chlormycetin and sulfadiazine, although the high intracranial pressure was under control, the patient still progressed to a decorticate state due to the severe irreversible damage to the brain.

4. Conclusion

Although cerebral WD is an extremely rare disease, it does in fact occur in the Chinese population. Diffuse cortical lesions with hemorrhage can be present in severe cases. Early recognition is critical because misdiagnosis of this potentially treatable disease can lead to irreversible sequelae.

References

- Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal mesenteric lymphatic tissues. Bull Johns Hopkins Hosp 1907;18:382–91.
- [2] Fenollar F, Raoult D. Whipple's disease. Clin Diagn Lab Immunol 2001;8:1–8.
- [3] Yogi T, Hokama A, Kinjo F, Tomiyama R, Koide M, Kishimoto K, et al. Whipple's disease: the first Japanese case diagnosed by electron microscopy and polymerase chain reaction. Intern Med 2004;43:566–70.
- [4] Anderson M. Neurology of Whipple's disease. J Neurol Neurosurg Psychiatry 2000;68:2–5.
- [5] Rossi T, Haghighipour R, Haghighi M, Paolini S, Scarpino O. Cerebral Whipple's disease as a cause of reversible dementia. Clin Neurol Neurosurg 2005;107:258–61.
- [6] Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol 1996;40:561–8.
- [7] Simpson DA, Wishnow R, Gargulinski RB, Pawlak AM. Oculofacial-skeletal myorhythmia in central nervous system Whipple's disease: additional case and review of the literature. Mov Disord 1995;10:195–200.

- [8] Schröter A, Brinkhoff J, Günthner-Lengsfeld T, Suerbaum S, Reiners [1 K, Messmann H, et al. Whipple's disease presenting as an isolated
- lesion of the cervical spinal cord. Eur J Neurol 2005;12:276–9. [9] Knox DL, Green WR, Troncoso JC, Yardley JH, Hsu J, Zee DS.
- [9] Khox DL, Green WK, Honcoso JC, Faddey JH, Fsu J, Zee DS. Cerebral ocular Whipple's disease: a 62-year odyssey from death to diagnosis. Neurology 1995;45:617–25.
- [10] De Coene B, Gilliard C, Indekeu P, Duprez T, Trigaux JP. Whipple's disease confined to the central nervous system. Neuroradiology 1996;38:325–7.
- [11] Duprez TPJ, Grandin CBG, Bonnier C, Thauvoy CW, Gadisseux JF, Dutrieux, et al. Whipple disease confined to the central nervous system in childhood. Am J Neuroradiol 1996;17:1589–91.
- [12] Romanul FCA, Radvany J, Rosales RK. Whipple's disease confined to the brain: a case studied clinically and pathologically. J Neurol Neurosurg Psychiatry 1977;40:901–9.

- [13] Löhr M, Stenzel W, Plum G, Gross WP, Deckert M, Klug N. Whipple disease confined to the central nervous system preseting as a solitary frontal tumor. J Neurosurg 2004;101:336–9.
- [14] Kremer S, Besson G, Bonaz B, Pasquier B, Le Bas JF, Grand S. Diffuse lesions in the CNS revealed by MR imaging in a case of Whipple disease. Am J Neuroradiol 2001;22:493–5.
- [15] Wroe SJ, Pires M, Harding B, Youl BD, Shorvon S. Whipple's disease confined to the CNS presenting with multiple intracerebral mass lesions. J Neurol Neurosurg Psychiatry 1991;54:989–92.
- [16] Feldman M, Price G. Intestinal bleeding in patients with Whipple's disease. Gastroenterology 1989;96:1207–9.
- [17] Cooper GS, Blades EW, Remler BF, Salata RA, Bennert KW, Jacobs GH. Central nervous system Whipple's disease: relapse during therapy with trimethoprim–sulfamethoxazole and remission with cefixime. Gastroenterology 1994;106:782–6.