

MRI of recurrent isolated cerebral Whipple's disease

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ABSTRACT

Whipple's disease is a rare systemic bacterial infection, characterized predominantly by gastrointestinal symptoms. Neurological symptoms are frequent in the course of the disease; however, a purely neurological presentation is uncommon. Diagnosis is confirmed with biopsy and polymerase chain reaction studies. Magnetic resonance imaging (MRI) findings vary, most commonly showing increased signal intensity on T2-weighted images. Contrast-enhanced images and diffusion-weighted imaging are useful to demonstrate meningeal enhancement and any accompanying infarcts. Brain biopsy is often performed, and MRI is crucial to guide the biopsy. Cerebral Whipple's disease is a long-lasting infection requiring long-term follow-up of these patients. MRI should be performed to detect any potential recurrence. We present a case of recurrent isolated cerebral Whipple's disease in a 68-year-old man with atypical presentation and MRI findings.

Key words: • Whipple disease • magnetic resonance imaging • central nervous system

Whipple's disease is a serious illness that may affect all organ systems, resulting in various and extensive clinical features, caused by an infection with *Tropheryma whippelii*. The most frequent and predominant manifestations result from small intestinal involvement; however, musculoskeletal, cardiovascular, and central nervous systems (CNS) are often involved. The usual presenting complaints include weight loss, malabsorptive diarrhea, recurrent non-deforming polyarthritis, and persistent low-grade fever. Cutaneous hyperpigmentation and lymphadenopathy are other signs of the disease. CNS involvement is not rare, observed in 20–40% of the cases; however, isolated cerebral involvement is not frequent (1).

We present a case of isolated cerebral Whipple's disease with an atypical acute onset and atypical magnetic resonance imaging (MRI) findings, including the examinations on admission and follow-up.

Case report

A 68-year-old man was admitted to our hospital with acute onset of high fever, severe nausea, and headache for 12 hours. His past medical history revealed no cerebral event but was positive for benign prostatic hyperplasia and coronary artery disease for which he had bypass surgery 10 years earlier. Abdominal sonography performed three years previously for complaint of abdominal pain had showed no specific findings except for cholelithiasis and simple renal cysts. Endoscopy and endoscopic biopsy performed at that time had revealed mild chronic gastritis.

On admission, the patient was confused, with a fever of 39°C. Neurological examination revealed neck stiffness, dysarthric speech, and paraplegia. In a few hours, he became uncooperative and had generalized seizures. His eyes were open spontaneously, he had stereotypic movements, and he had no response to verbal stimuli. The complete blood count showed a leucocyte count of 8380/mm³ with 83% polymorphonuclear leucocytes. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were high. The urine and oropharynx cultures were negative. A lumbar puncture was performed, revealing mature lymphocytes and monocytes with no significant bacteria. Polymerase chain reaction (PCR) for Cytomegalovirus, *Herpes simplex* virus, Varicella-Zoster virus, and Epstein-Barr virus, VDRL, and serum tests for Brucella, tuberculosis, and HIV antigens were negative. Radiographs of the thorax and abdominal ultrasound were unremarkable.

On the third day of hospitalization, an MRI study was performed on a 1.5 T unit (Siemens Symphony, Erlangen, Germany) including T1-weighted (TR/TE/NEX/slice thickness, 500–580/13–15/2/5), T2-weighted (TR/TE/NEX/slice thickness, 4100–5160/99–103/2/5), FLAIR (TR/TE/NEX/slice thickness, 9000–1000/105–140/2/5), gradient-echo (TR/TE/NEX/slice thickness, 500–580/13–15/2/5), contrast-enhanced and diffu-

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Received 8 April 2008; revision requested 5 June 2008; revision received 16 June 2008; accepted 14 July 2008.

Published online 21 October 2009
DOI 10.4261/1305-3825.DIR.1830-08.1

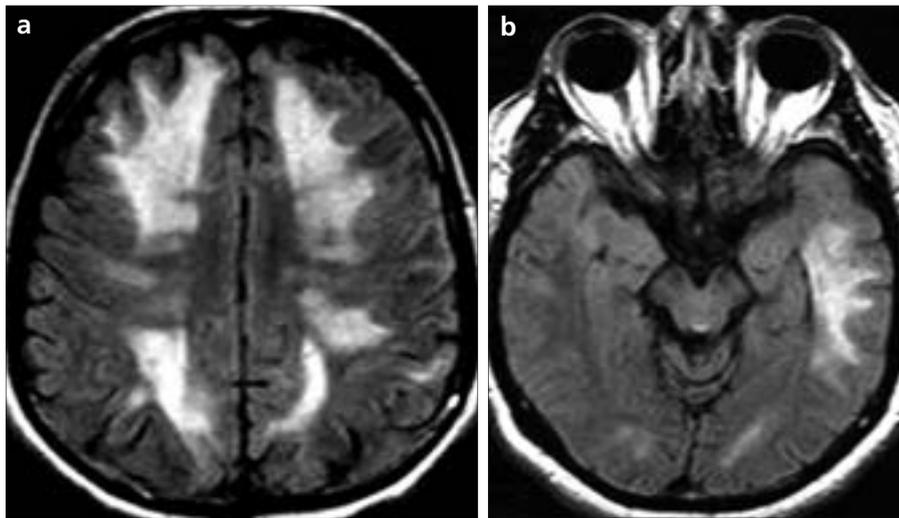


Figure 1. a, b. Initial cranial MRI examination. Axial FLAIR images of the frontal, parietal and temporal lobes show diffuse hyperintensity.

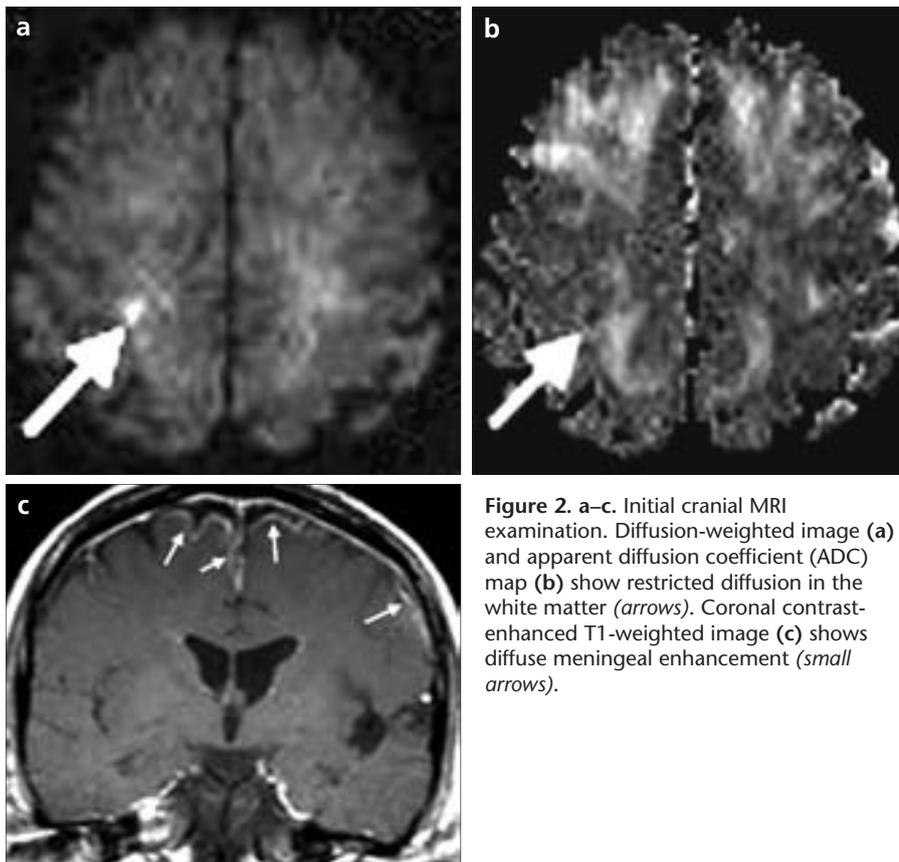


Figure 2. a–c. Initial cranial MRI examination. Diffusion-weighted image (a) and apparent diffusion coefficient (ADC) map (b) show restricted diffusion in the white matter (arrows). Coronal contrast-enhanced T1-weighted image (c) shows diffuse meningeal enhancement (small arrows).

sion-weighted images (TR/TE/NEX/slice thickness, 10,000/139/3/5) with diffusion gradients in the x, y, z planes. Images were evaluated by two radiologists on a workstation (Leonardo, Siemens, Forchheim, Germany). On FLAIR and T2-weighted images, there was diffuse hyperintensity bilaterally in the frontal, and parietal lobes, and in the lat-

eral part of the left temporal lobe (Fig. 1). The hypothalamus, medial areas of temporal lobes, and pons were preserved. Gradient-echo sequence showed small foci of chronic hemorrhage, most prominent in the frontal and parietal lobes. In the frontal and parietal lobes, there were small areas of restriction on diffusion-weighted images and appar-

ent diffusion coefficient (ADC) maps (Fig. 2a, b). Contrast-enhanced images showed no parenchymal enhancement; however, diffuse meningeal enhancement was evident (Fig. 2c).

A brain biopsy was performed two days after the MRI study, revealing macrophage infiltration, most commonly in the perivascular areas, staining with periodic acid-Schiff stain (Fig. 3). PCR of cerebrospinal fluid was not diagnostic. Endoscopic biopsy specimens obtained from the stomach and the duodenum after the brain biopsy did not show any finding suggestive of Whipple's disease.

With the histological diagnosis of cerebral Whipple's disease, high dose ceftriaxone and cotrimoxazole was started. The patient recovered, and was better-oriented three weeks after admission. One month after the initial examination MRI was repeated, revealing regression of the high signal intensities in the frontal, parietal, and temporal lobes (Fig. 4a, b). On this MRI, meningeal enhancement was absent; however, small foci of enhancement were seen in the periventricular white matter, associated with the previously infarcted areas, and consistent with the subacute phase of the infarct (Fig. 4c). Oral cotrimoxazole was continued. One year after the initial presentation, the patient was admitted to the hospital again with confusion. An MRI examination was performed on the same day, revealing an increase in the hyperintensities in the frontal, parietal, and left temporal lobes (Fig. 5a, b). Images obtained after administration of intravenous contrast showed no enhancement (Fig. 5c). No acute infarction or hemorrhage was found.

The patient recovered spontaneously, and continued with antibiotic therapy. Clinical follow-up in the next year was normal.

Discussion

Whipple's disease is a relapsing systemic illness characterized by migratory polyarthralgias, chronic diarrhea, weight loss, and fever. Central nervous system involvement in association with systemic disease is not rare; moreover, cerebral Whipple's disease may occur without evidence of gastrointestinal infection (2).

Neurologic manifestations vary widely; the most common clinical findings (in decreasing order) are su-

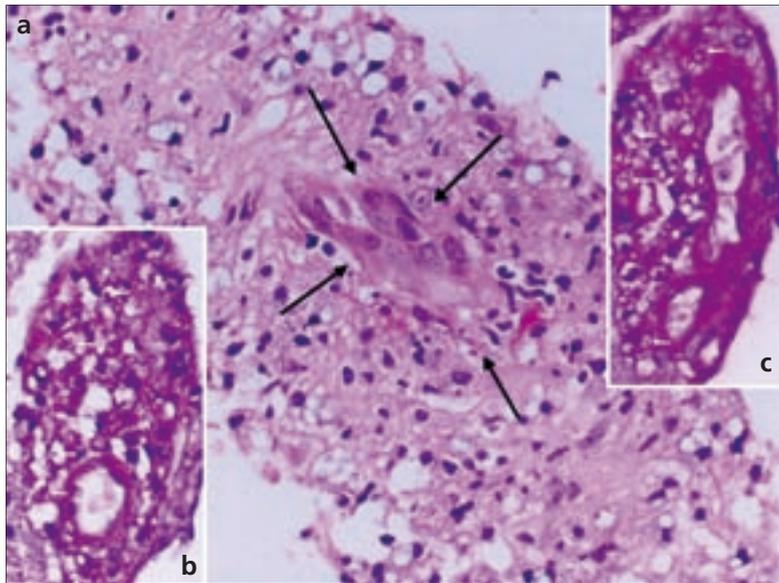


Figure 3. a–c. Histopathologic images. Perivascular macrophage infiltration around the minimally reactive endothelial cells of the vessel (*large black arrows, a*) in the brain parenchyma. Note the PAS-positive (*b*) and diastase-resistant (*c*) microorganisms (*small white arrows*).

pranuclear ophthalmoplegia, confusion and dementia, psychiatric signs, myoclonic signs, seizures, hypothalamic involvement, cerebellar signs, cranial nerve involvement, peripheral neuropathies, and spinal cord involvement (3). Most commonly involved anatomic locations in the brain are basal parts of the telencephalon, hypothalamic nuclei, thalamus, periaqueductal gray matter, and tectum pontis (4). Gross pathologic findings of the CNS include generalized atrophy, scattered granulomas in the gray matter of the cerebral and cerebellar cortex, the periventricular gray matter, and the gray matter around the aqueduct (5). Imaging techniques do not reveal any specific findings; however, MRI is superior to other techniques for the detection of small lesions (6).

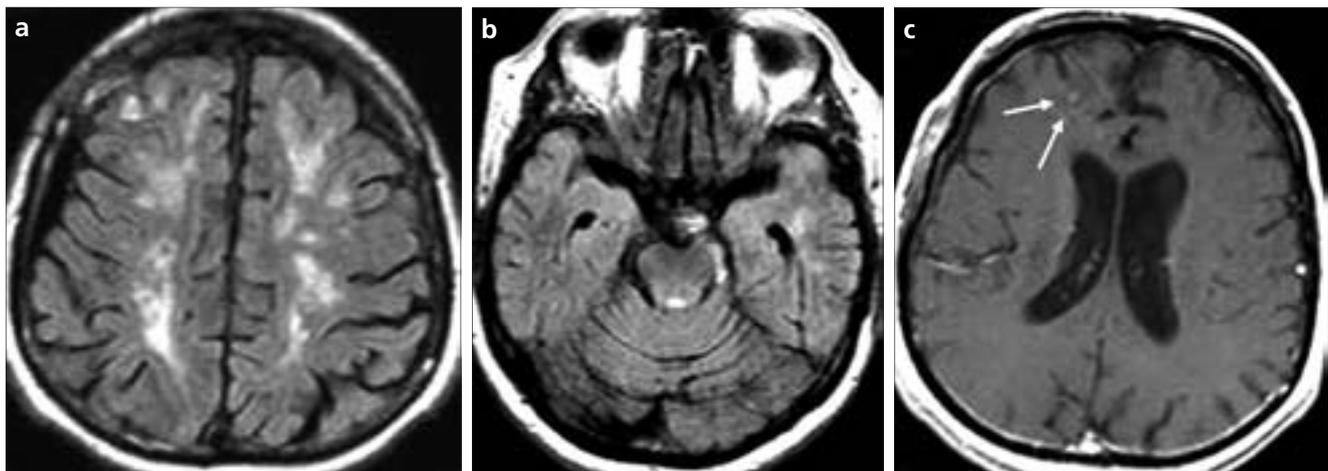


Figure 4. a–c. Follow-up MRI examination. Axial FLAIR images of the frontal, parietal, and temporal lobes (*a, b*) show regression of the lesions. Contrast-enhanced axial T1-weighted image (*c*) shows no meningeal enhancement; however, parenchymal enhancement at the areas of the infarcts is seen (*arrows*).

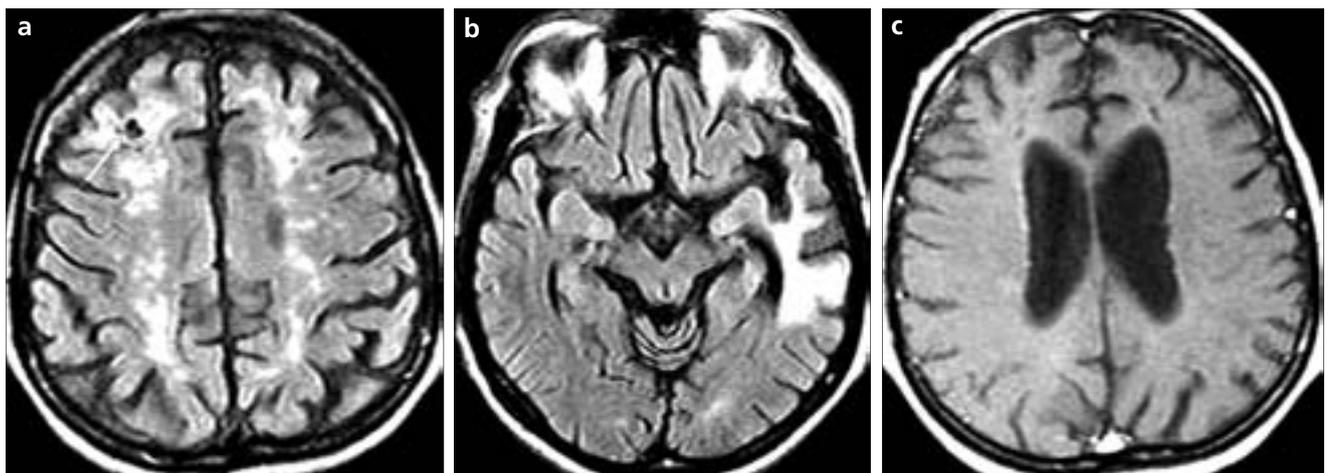


Figure 5. a–c. MRI examination at the time of second admission. The hyperintensities on axial FLAIR images (*a, b*) are increased, compared with the previous study. There is a small focus of chronic infarct (*arrow, a*). On contrast-enhanced axial T1-weighted image (*c*), there is no meningeal or parenchymal enhancement.

Our patient had diffuse lesions in the frontal, parietal, and temporal lobes, predominantly in the white matter, with the preservation of the hypothalamus, basal ganglia, pons, and medial temporal lobes. The hyperintensities were nonspecific, and might be related to edema. Given the history of severe coronary artery disease, chronic ischemic gliosis is also a possible cause of hyperintensities in the periventricular white matter. There were focal areas of restricted diffusion in the frontal and parietal lobes, consistent with acute infarcts. Infarcts have been described previously, but their frequency is unclear, which may be associated with arteriolar fibrosis and thickening or emboli (7). Systemic inflammation affecting the expression of complement, coagulation, and the fibrinolytic cascade, which increases the thrombotic risk in the brain, is also suggested as a factor in the occurrence of acute infarct (8). Systemic inflammation and the tendency to a thrombotic event might have contributed to the infarction process; moreover, the meningeal enhancement showing the meninx involvement might also be associated with small infarcts in our patient, as described previously (7). The pathological examination also confirmed this, showing intense perivascular inflammation. The prompt response to antibiotic treatment together with the clinical presentation might have led to the diagnosis of meningitis; however, the small focal infarcts could not have been predicted without MRI.

Whipple's disease may present in various forms on MRI; no specific finding is described. The clinical presentation of our patient is atypical for Whipple's disease, with such an acute onset and no symptoms related to the gastrointestinal system. The MRI findings were associated with infection and infarction, but no specific diagnosis

could be made, therefore brain biopsy was crucial in this patient. However, MRI was useful to show the infarcts on diffusion-weighted images, to guide the biopsy, and for follow-up. Follow-up MRI showed good correlation with the clinical recovery, and also was diagnostic for the recurrence of disease at the time of the patient's second admission. Magnetic resonance spectroscopy can also be performed, which may aid in early diagnosis and treatment by showing increased choline and decreased n-acetylaspartate and creatine levels (9). In a case study, the use of positron emission tomography (PET) is reported, by helping in the preoperative differentiation of inflammatory from neoplastic lesions, based on the uptake pattern of amino acid tracer (10).

Differentiating the cerebral involvement of Whipple's disease, which presents as multiple or focal mass lesions is important. There are a few case reports of presentation with a solitary mass, which is rare. In the differential diagnosis of those lesions, glioma was the first consideration. However, due to the fact that the clinical and neuroimaging findings are nonspecific, there are various diseases other than neoplasms in the differential diagnosis, such as parasitic infections (e.g. cysticercosis and toxoplasmosis), unusual mycobacterial and fungal infections, metabolic disorders, vasculitis, or autoimmune demyelinating disease (11–13).

In conclusion, symptoms related to the CNS may be the sole presentation of Whipple's disease, and these symptoms may be atypical. In case of an unexplained clinical presentation and negative laboratory findings, MRI with contrast-enhanced and diffusion-weighted images must be performed for baseline study, for follow-up, and as a guide for biopsy.

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