

A 52-YEAR-OLD MAN WITH MYOCLONIC JERKS

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CLINICAL HISTORY

A 52-year-old man with an unremarkable clinical history started to complain of daily somnolence, unusual irritability and some memory lapses. A few months later, he had fever and developed confusion with myoclonic jerks of the left limbs. Upon admission a diagnosis of encephalitis was made. MRI FLAIR images (Figure 1a) showed cortical and sub-cortical abnormal signal intensity in parasagittal posterior frontal and anterior parietal regions, compatible with ischemic damage in watershed areas. On coronal T1-weighted image (insert in Figure 1a) cortex was hyperintense for petechial hemorrhage. Multivoxel proton magnetic resonance spectroscopy (¹H-MRS) demonstrated lactic acid in the lesions. The CSF showed 10 white cells/mL with normal protein and glucose. He was treated with antibiotics, acyclovir, steroids and immunoglobulins and improved so much that he was discharged to a rehabilitation facility. The patient could play chess and walk around with the help of a walking frame.

Two months later he again had fever with confusion and inappropriate mood. His myoclonic jerks and weakness was now bilateral. He had decreased alertness and was not able to walk or stand. MRI showed additional lesions in other cerebral regions. Axial FLAIR (Figure 1b) images demonstrated acute ischemic stroke in the right temporo-parietal area and in right parietal region at the vertex (insert in Figure 1b). DWI showed a marked hyperintensity due to cytotoxic edema. A small ischemic area was present in the right pulvinar (arrowhead in Figure 1b). A total body CT scan showed liver cirrhosis with left pleural effusion. The patient was

treated again with antibiotics, acyclovir and antiepileptics without any improvement and a flaccid tetra paresis with muscular atrophy and areflexia developed in few weeks.

The patient was then admitted to our institution with indication for brain biopsy. He was alert, in bad general condition and with fecal incontinence. He responded with vocalization and grimacing to painful stimuli. Hypotonic tetraplegia, diffuse muscle atrophy and areflexia were present with hypotonia more evident in the left limbs. An EMG study provided evidence of a severe axonal sensory-motor polyneuropathy. An EEG showed low voltage activity unresponsive to stimuli as in the alpha-coma condition. Brain MRI demonstrated large gliotic areas and cortex atrophy in the frontal and parietal regions and in the right temporo-parietal area as the result of ischemic strokes, and did not show additional lesions.

MICROSCOPIC FINDINGS

An open biopsy of posterior right temporal lobe was performed and showed severe neuronal loss, neuropil vacuolization (Figure 1c) striking gliosis with numerous reactive astrocytes by GFAP (Figure 1d) and marked microglial activation. Mild lymphomonocytic perivascular infiltrates were present in the cerebral cortex, subcortical white matter and leptomeninges by CD45 and CD68. Myelin showed pallor but no areas of demyelination. Some macrophages harboring periodic acid–Schiff (PAS)-positive, diastase-resistant material in the cytoplasm were observed in the thickened leptomeninges (Figure 1e) as well as in the neuropil (Figure 1f). **What is your diagnosis?**

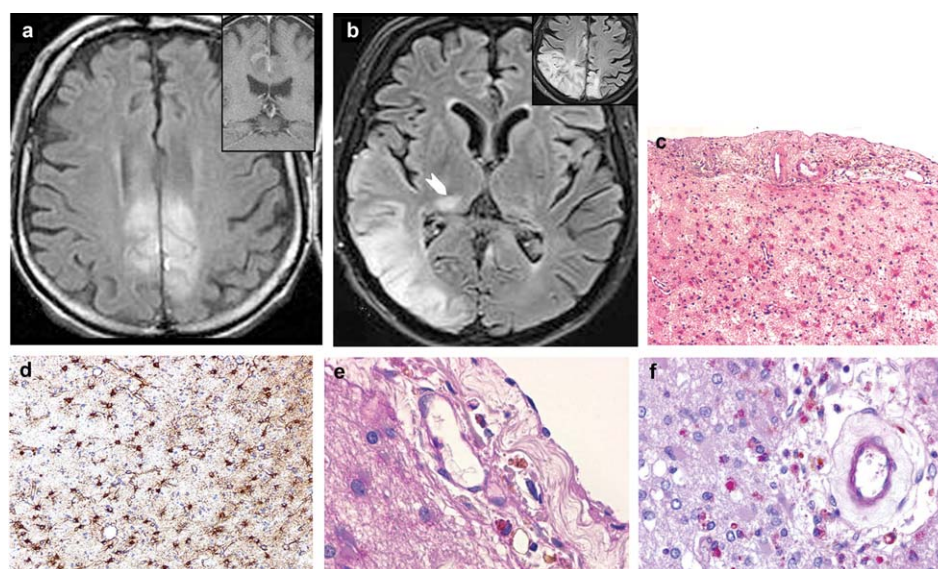


Figure 1.

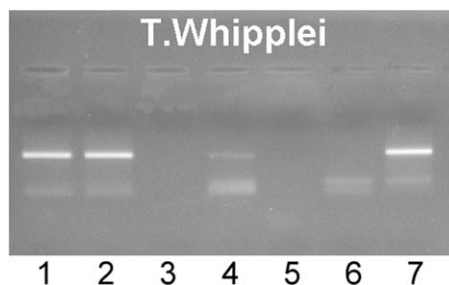


Figure 2.

DIAGNOSIS

Cerebral Whipple's disease

Even if they were scanty, the presence of PAS-positive, diastase-resistant material in macrophages suggested to explore the possibility of cerebral Whipple's disease. PCR for *Tropheryma whipplei* (*T. whipplei*) DNA was carried out following a previously reported procedure (3) on cerebral biopsy specimens, both on frozen material and on tissue obtained from histological sections from formalin-fixed, paraffin-embedded blocks. The PCR was positive for *T. whipplei* DNA both on frozen specimen and on material obtained from histological sections (Figure 2, lanes 1–4: present case; lane 1: frozen tissue; lane 2: frozen tissue diluted 1:10; lane 3: fixed tissue; lane 4: fixed tissue diluted 1:10; 5: buffer; 6: negative control; 7: positive control). In the latter, the positivity was fainter and detectable only after 10-fold dilution.

CLINICAL HISTORY (ADDITIONAL INFORMATION)

After the biopsy, the general conditions of the patient worsened, for diarrhea and anemia. A test for *Clostridium difficile* was positive. The patient was transferred to a general medical ward and Vancomycin was started with improvement of the diarrhea. An esophago-gastroduodenoscopy was performed with a duodenal biopsy which was normal. PCR for *T. whipplei* DNA in intestinal specimens was negative. When the diagnosis of cerebral Whipple's disease could be established, sulfamethoxazol + trimetoprim were changed to ceftriaxone. Despite this the neurological conditions of the patient worsened, he became less reactive, myoclonic jerks became continuous and were not improved by infusion of levetiracetam or midazolam. An EEG showed low amplitude generalized slowing in the delta range but there was no correlation with the jerks. Forty days after the biopsy, the patient was transferred to a long-term care facility near home. At discharge he was in a state of coma with occasional grimacing or eye opening when stimulated, he had severe tetraparesis and persistent jerks of his right face and right arm. He died a month later in a condition of generalized wasting. Autopsy was not performed.

DISCUSSION

Whipple's disease is a rare, chronic inflammatory, multi-systemic disease caused by the Gram-positive, ubiquitous, environmental bacterium *T. whipplei*, large numbers of which accumulate within macrophages in the affected tissues. The disorder present with prominent and frequent but not invariable gastrointestinal involvement (2). *T. whipplei* cannot be cultured by traditional methods, so the diagnosis is based on typical histological lesions and identification of the causative organism that can be achieved by PCR.

Neurologic signs of Whipple disease are protean and isolated neurologic symptoms due to *T. whipplei* without histologic evidence of intestinal involvement rarely occur and present further complexity (1, 4).

Our patient had a purely neurological presentation and involvement restricted to the central nervous system indicated by non-contributory medical history in particular without any diarrhea or weight loss before the onset of neurological symptoms and confirmed by histology and PCR analysis of intestinal biopsy.

The patient who we presented emphasizes the importance of cerebral biopsy and the need to consider Whipple disease in cases with atypical subacute meningoencephalitis even in the absence of gastrointestinal involvement. Actually, the diagnosis should be considered incidental since PAS stain was carried out with the aim to rule out PAS positive neuronal inclusions as some neurons showed the presence of nuclei displaced at the periphery of the perikaryon. Following the detection of PAS positive macrophages infiltrates in the leptomeninges, even if sparse and scarce, Whipple disease was suspected and specific PCR was performed with positive results.

Brain MRI showed multiple cerebral ischemic lesions that occur in characteristic locations, at the junction of the distal fields of two main arterial territories, like watershed infarcts. Our patient therefore represents a rare case of cerebral Whipple disease presenting with stroke-like symptoms (3), and a unique case with border-zone infarcts. The pathogenesis of this type of cerebral infarctions remains debated, probably precipitated by a hemodynamic impairment associated to a microembolic etiology. Isolated cortical border-zone infarcts, as seen in this case report might be embolic in nature. Microemboli from the heart or from atherosclerotic plaques or from fibrotic artery may propagate preferentially to cortical border zones, which have lower perfusion than other areas and, thus, a scarce ability to wash out these emboli. It is noteworthy that in Whipple disease endocarditis is reported and could have represented a source of microemboli (2).

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