

# Whipple Limbic Encephalitis

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**Objective:** To describe a relapse of Whipple disease revealed by isolated limbic encephalitis with no other signs of systemic involvement.

**Design:** Case report.

**Setting:** University Hospital of Strasbourg, Strasbourg, France.

**Patient:** A 41-year-old patient.

**Main Outcome Measures:** Cognitive functions and results of cerebrospinal fluid analysis and brain magnetic resonance imaging.

**Results:** A 41-year-old patient was hospitalized for headache associated with anterograde amnesia and temporospatial disorientation. Whipple disease with systemic manifestations was diagnosed 4 years previously and insufficiently

treated. The neuropsychological evaluation showed impaired episodic memory and executive functions. Analysis of the cerebrospinal fluid showed increased lymphocytes and a positive *Tropheryma whipplei* polymerase chain reaction result. Cerebral magnetic resonance imaging revealed a typical pattern of limbic encephalitis with an intense signal in the amygdalae and hippocampi. The outcome under antibiotic treatment was marked by partial improvement of the cognitive disorders, disappearance of the positive *T whipplei* polymerase chain reaction result in cerebrospinal fluid, and a clear decrease of inflammation on brain magnetic resonance imaging.

**Conclusions:** Whipple disease can present as limbic encephalitis. Few cases have been previously described in the literature. Such diagnosis is of importance because of the specific treatment.

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**W**HIPPLE DISEASE IS A systemic bacterial infection due to *Tropheryma whipplei*. Its clinical manifestations generally include diarrhea, preceded in most cases by articular symptoms.<sup>1</sup> Involvement of the central nervous system is possible, often being polymorphous but rarely isolated.<sup>2</sup>

Limbic encephalitis (LE) is related to inflammation of the medial temporal lobe. Subacute amnesia is the main clinical symptom and can be associated with seizures and psychiatric symptoms such as depression or personality change. The main etiologies of LE are paraneoplastic,<sup>3</sup> autoimmune,<sup>4</sup> and viral, particularly herpetic LE. Excluding neurosyphilis,<sup>5</sup> very few bacterial infections are responsible for LE.

We report 1 case of a relapse of Whipple disease revealed by isolated LE with no other signs of systemic involvement.

## REPORT OF A CASE

A 41-year-old patient was hospitalized urgently for headache associated with major anterograde amnesia. These symptoms had developed progressively over

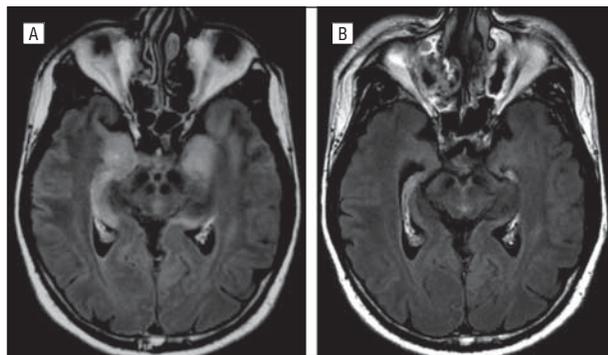
several months. There was no fever, change in the general state of health, or diarrhea.

The patient was followed up for Whipple disease revealed 4 years earlier by migratory polyarthralgia, episodes of fever, and intermittent diarrhea. The diagnosis had been confirmed by a duodenal biopsy specimen that had shown inflammatory lesions containing macrophages with inclusions positive for periodic acid-Schiff. Results of the *T whipplei* polymerase chain reaction (PCR) assay on the duodenal biopsy specimen were, however, negative. A course of antibiotics with a third-generation cephalosporin and cotrimoxazole had been prescribed for 15 months, but this treatment had not been maintained by the patient.

On hospital admission, the physical neurological examination was normal without meningeal syndrome. Conversely, a neuropsychological evaluation confirmed the presence of important disorders of the verbal and visual memory. On the Free and Cued Selective Reminding Test<sup>6</sup> for verbal episodic memory, the patient had a score of 8 of 16 words for immediate recall (<5th percentile) and scores of 1 of 16 for free recall and 2 of 16 for total recall (<5th percentile). In the visual object recognition memory test

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**Figure.** Axial T2-weighted fluid-attenuated inversion recovery brain magnetic resonance imaging. A, At the acute phase, showing an intense signal in the amygdalae and hippocampi. B, One year later, showing mild atrophy of the amygdalae and hippocampi.

(DMS48),<sup>7</sup> the patient was deficient, with only 64% correct answers. The Mini-Mental State Examination score was 19 (temporal orientation, 2 of 5; spatial orientation, 2 of 5; attention, 3 of 5; and recall, 0 of 3). There were also disorders of the working memory (backward digit span) and executive functions with an inhibition defect in the go/no go test (error rate of 4 of 40) and defective mental flexibility (error rate of 23 of 40 in the opposing orders test). The Wechsler Adult Intelligence Scale score likewise showed a retardation of the rate of processing of information (<5th percentile). The Rey-Osterrieth complex figure copy was normal.<sup>8</sup> The major and predominant effect on the episodic memory was in favor of involvement of the Papez circuit, especially the areas of the medial temporal lobes, while the rest of the cognitive evaluation pointed to involvement of the frontal lobes and, notably, orbitofrontal areas.

The immunological profile (antinuclear antibodies, polynuclear neutrophil anticytoplasmic antibodies, and antiendomysium antibodies) was negative. Immunological tests for intraneuronal antibodies, by immunohistochemistry and immunoblot including anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2, anti-Ta, and Ma1, were unremarkable. Results of *Legionella*, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and Lyme disease serologies were likewise negative and levels of vitamins B<sub>1</sub>, B<sub>6</sub>, B<sub>9</sub>, and B<sub>12</sub> were normal. Analysis of the cerebrospinal fluid (CSF) revealed 335 leukocytes/mm<sup>3</sup> with 99% lymphocytes, and results of *T. whipplei* PCR targeting a 191 base pair-specific fragment of the 16S ribosomal DNA were positive on 2 different aliquots of CSF. The specificity was confirmed by direct sequencing of the amplified DNA fragment showing 100% similarity with *T. whipplei* DNA only. Results of PCR for *Herpesviridae* (including herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus, cytomegalovirus, and human herpesvirus 6) were negative. Results of the *T. whipplei* PCR assay were negative on a duodenal biopsy specimen.

Brain magnetic resonance imaging showed diffuse gadolinium enhancement of the leptomeninges and hyperintensity in both the medial temporal lobes and amygdalae on T2 and fluid-attenuated inversion recovery sequences and present to a lesser degree in the insular and frontobasal regions, evoking the diagnosis of meningoencephalitis with limbic involvement (**Figure, A**).

The electroencephalogram displayed a well-organized cycle of wake and sleep and there was no ictal or interictal pattern. Ophthalmologic examination of the eye revealed the existence of left posterior hyalitis with discrete retinal hemorrhage, possibly evoking the presence of Whipple disease uveitis.

Treatment with a third-generation cephalosporin, trimethoprim-sulfamethoxazole, doxycycline, and hydroxychloroquine was initiated for a period of 2 years. Corticotherapy at a dose of 30 mg/d was administered for 6 weeks.

The evolution was marked by a very clear regression of the cognitive disorders with correct inhibition (no error on the go/no go test), a normal mental flexibility (2 errors on the opposing order test), and normal speed of information processing (normal Wechsler Adult Intelligence Scale score). The Mini-Mental State Examination score was 25 (temporal orientation, 4 of 5; attention, 3 of 5; and recall, 1 of 3). The disturbance of working memory remained unchanged. The episodic memory partially improved, with maximal scores of 11 words of 16 for immediate recall, 1 of 16 for free recall, and 4 of 16 for total recall on the Free and Cued Selective Reminding Test at 3 months and 4 of 16 for free recall and 11 of 16 for total recall at 1 year. On the DMS48 visual recognition test, the patient displayed great improvement and gave 94% and 98% correct answers at 3 months and 1 year, respectively. A new search of *T. whipplei* by PCR in CSF was negative after 1 month of treatment. Follow-up brain magnetic resonance imaging performed after 3 months and 1 year showed a diminution of the internal temporal hypersignal (**Figure, B**). Conversely, an atrophy of the hippocampus appeared with persistence of a discrete uptake of contrast in the right temporal uncus and at the base of the third ventricle.

#### COMMENT

This relapse of Whipple disease has the particularity that it was revealed by LE. Involvement of the central nervous system is rare in Whipple disease but represents the most serious complication.<sup>9</sup> It occurs during evolution of the disease in 10% to 20% of patients.<sup>10</sup> In 2002, Gerard et al<sup>2</sup> described in a literature review 122 patients with neuro-Whipple disease. Among these individuals, only 21 displayed isolated initial neurological involvement, while the majority had developed other extraneurological manifestations. Neurological symptoms appear especially in patients whose treatment has not included antibiotics able to cross the blood-brain barrier.<sup>11</sup>

The neurological manifestations of Whipple disease are extremely diverse and poorly specific. Cognitive impairment is the most frequent and is detected in 71% of patients with neurological involvement.<sup>12</sup> These disorders affect memory (25% of cases) and orientation (24% of cases) and can even lead to dementia (28% of cases).<sup>2</sup> Oculomasticatory myorhythmia, always associated with vertical supranuclear gaze palsy, is detected in 8% to 20% of patients and has important diagnostic value as it is encountered only in Whipple disease.<sup>2,13</sup>

Brain magnetic resonance imaging shows lesions in 53% of cases.<sup>12</sup> These lesions consist of T2 or T2-

weighted fluid-attenuated inversion recovery hyperintensities, with or without T1 contrast enhancing, located in the medial part of the temporal lobe, hypothalamic region, or pons.<sup>14</sup> Forty-two percent of patients also have mild to moderate atrophy.<sup>12</sup> In our patient, the lesions were localized in the hippocampi and the amygdalae, typical of LE, with clear inflammation (Figure, A). One year later, there was atrophy of these structures (Figure, B). The involvement of the medial temporal lobe was confirmed by cognitive tests that showed impairment of verbal—without improvement by cueing—and visual memory. To our knowledge, in the literature, no case of Whipple disease was described as a “limbic encephalitis.” But we found 10 cases, including ours, with cognitive impairment and brain magnetic resonance imaging described that correspond to such a syndrome.<sup>9,14-21</sup> Cases with necropsy have also demonstrated the frequent involvement of the amygdala and the hippocampus (25%).<sup>22</sup>

Results of CSF PCR analysis have been found to be negative in more than 30% of cases during neurological involvement of Whipple disease.<sup>23,24</sup> Conversely, in some patients, results of the PCR assay remain positive in CSF despite antibiotic treatment and sometimes persist for years, without clinical relapse. This positivity can indicate either the persistence of an infectious agent insufficiently controlled by antibiotics or the persistence of residual DNA from dead organisms, which explains the controversial interest of PCR in therapeutic follow-up.<sup>13</sup> In our patient, results of the PCR assay became negative after 1 month of antibiotic treatment.

Therapeutic recommendations are not based on any controlled trial. The strategy normally proposed is the administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily for 1 to 2 years, but relapse is possible.<sup>11</sup> In neurological forms of the disease, a combination of hydroxychloroquine, cyclines, and sulfadiazine has been proposed,<sup>25</sup> while according to Cooper et al,<sup>26</sup> in the case of neurological relapse while taking trimethoprim-sulfamethoxazole, cefixime can be quite efficacious. Hence, we opted in our case for triple antibiotherapy in association with hydroxychloroquine.

The prognosis in the event of involvement of the central nervous system remains somber, with a mortality of more than 25% at 4 years. One-quarter of the patients have severe sequelae.<sup>27</sup> The evolution of our patient's disease was marked by partial persistence of the amnesia.

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**Author Contributions:** Drs Blanc and Ben Abdelghani equally contributed to this study. *Study concept and design:* Blanc and Sibilia. *Acquisition of data:* Blanc, Ben Abdelghani, Chatelus, Sordet, Gottenberg, and Sibilia. *Analysis and interpretation of data:* Blanc, Schramm, Jaulhac, Gottenberg, and Sibilia. *Drafting of the manuscript:* Blanc, Ben Abdelghani, Schramm, Jaulhac, and Sibilia. *Critical revision of the manuscript for important intellectual content:* Blanc, Chatelus, Sordet, and Gottenberg. *Adminis-*

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