

## Missed Diagnosis

# Whipple's disease with cerebral involvement

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**Summary:** A case of Whipple's disease, initially presenting with abdominal symptoms and later with neurological manifestations, is reported. The diagnosis was not made in life, but on post-mortem examination of the brain. This case emphasizes the importance of early diagnosis and treatment of this uncommon disorder.

### Introduction

Whipple's disease is a manifestation of chronic infection by an unidentified bacterium and most commonly presents with small intestinal dysfunction.<sup>1</sup> Other systems may become involved, including the central nervous system. Characteristically, in such cases, brainstem involvement causes ophthalmoplegia and facial myoclonus,<sup>2</sup> but dementia and cerebral atrophy may occur.<sup>3</sup> Meningitis has also been reported.<sup>4</sup>

### Case report

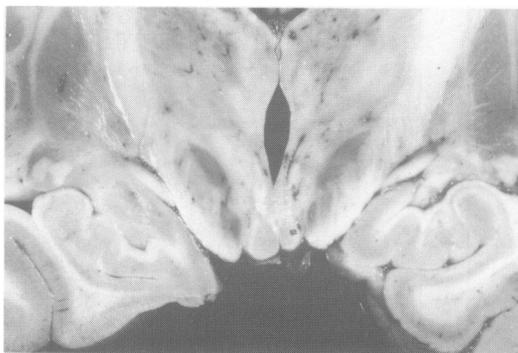
A 41 year old man presented to hospital with a 2- to 3-month history of abdominal pain and slight weight loss. Physical examination at that stage did not reveal any positive findings. Extensive investigations of his gastrointestinal tract, including tests for malabsorption and a small bowel biopsy, revealed no abnormalities.

Subsequently, he underwent laparotomy which showed enlarged lymph nodes in the mesentery. Biopsy of these nodes was performed and they were reported histologically as showing only non-specific reactive changes. A few weeks later he started to behave oddly with poor short term memory and the development of incessant facial twitching, even while he was asleep. Examination showed absent upward and eventually downward gaze. A cranial computerized tomography (CT) scan with and without contrast was normal, as were magnetic resonance imaging (MRI) studies of the brain, visual evoked responses and an electroencephalogram. Cerebrospinal fluid examination showed no

abnormality with a normal protein pattern. Syphilis serology was negative as were auto-antibody and porphyrin screens.

While a second laparotomy was being considered, he developed bronchopneumonia, unresponsive to antibiotic therapy, and died. Post-mortem confirmed bronchopneumonia as the immediate cause of death and showed enlarged mesenteric, para-aortic and coeliac lymph nodes. The brain was submitted for neuropathological examination and showed areas of brownish discoloration of the hypothalamus and related structures (Figure 1), but no other macroscopic abnormality.

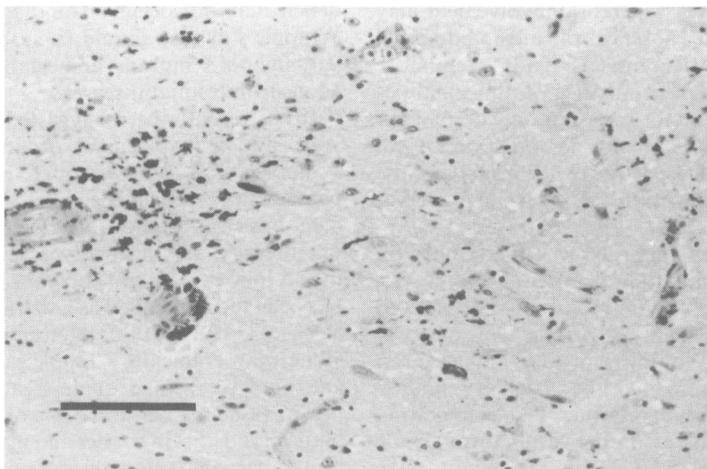
Histological examination showed focal neuronal loss in the hypothalamus, dorsal midbrain and upper pons with aggregates of macrophages present mainly around blood vessels. On haematoxylin and eosin staining these macrophages had abundant, foamy, pale blue cytoplasm, which stained very strongly with the periodic-acid-Schiff (PAS) method (Figure 2). With the latter method,



**Figure 1** Coronal section of the fixed brain shows bilateral ill-defined areas of discoloration in the hypothalamus lateral to the mammillary bodies.

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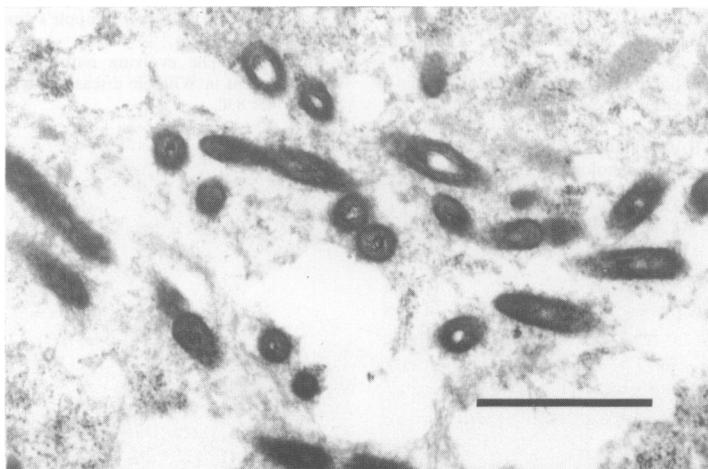
**Figure 2** Numerous macrophages with a granular, strongly PAS-positive cytoplasm are present around blood vessels and within the neurophil in the upper pons. (Bar equals 100  $\mu\text{m}$ .)

the cytoplasm was seen to be laden with rod-shaped structures characteristic of Whipple's disease. These structures were unreactive on staining with a modified Ziehl-Nielsen method.

Electron microscopy was performed on cerebral tissue but showed only degenerate debris among the neurophil. Retrospective review on further sections of the mesenteric lymph node biopsy showed scanty aggregates of similar PAS-positive macrophages within the sinuses. Tissue from paraffin blocks of this node was taken and reprocessed for electron microscopy. Grids were screened on a JEOL transmission electron microscope and a small number of macrophages containing bacterial forms was found (Figure 3).

### Discussion

The clinical findings in this case were in keeping with the diagnosis of gastrointestinal Whipple's disease, although tests for malabsorption are often positive and small bowel biopsy is frequently abnormal in this disorder.<sup>5</sup> The subsequent neurological disease was also typical of cerebral Whipple's disease, with facial myoclonus and gaze palsies.<sup>2</sup> The possibility of Whipple's disease was considered initially, but none of the gastrointestinal investigations provided evidence to support this diagnosis; the reactive changes seen in initial sections of the mesenteric lymph nodes were non-specific.



**Figure 3** Electron microscopy shows a macrophage containing the bacilliform structures characteristic of Whipple's disease in an abdominal lymph node. (Bar equals 1  $\mu\text{m}$ .)

In Whipple's disease, cerebral involvement may be present in the absence of intra-abdominal pathology,<sup>3,6</sup> this diagnosis is made even more difficult by the frequent absence of abnormalities on CT scanning.<sup>7</sup> In our case, not only cranial CT but also MRI was unable to demonstrate a focal lesion, even on retrospective review following the post-mortem localization of sites of cerebral involvement.

The diagnosis in this case was made only on post-mortem examination of the brain. However, review of the lymph nodes biopsied in life showed the presence of scanty PAS-positive material characteristic of Whipple's disease and electron microscopy demonstrated the 'bacillary bodies' characteristic of this condition.<sup>8</sup> The examination of multiple sections at deeper levels through the biopsies with the PAS technique might have enabled earlier diagnosis, although affected macrophages were unusually scanty in the lymph nodes and absent in the small bowel biopsy on post-mortem review. The outcome in this case demonstrates the importance of making the diagnosis of this treatable condition in life. Brain biopsy may be useful for this purpose.<sup>9</sup> Early diagnosis and treatment may arrest the progress of the neurological disease, but recovery of an established neurological

deficit may not occur.<sup>3</sup> The diagnosis of cerebral Whipple's disease should be suspected in patients with mental symptoms and established or suspected gastrointestinal disease.<sup>2</sup>

It has recently been suggested that central nervous system involvement occurs in all cases of Whipple's disease,<sup>10</sup> although only 10–20% of patients may show evidence of this. Such involvement has clear implications for antibiotic therapy; parenterally administered penicillin and streptomycin followed by oral cotrimoxazole for one year has been recommended as a therapeutic regimen in all cases.<sup>10</sup> The use of oral tetracycline or penicillin alone may eradicate Whipple's disease from the gut, but proves inadequate treatment for central nervous system disease because of poor penetration of the blood–brain barrier and may predispose to a central nervous system relapse in otherwise asymptomatic patients.<sup>11</sup>

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