Whipple's disease confined to the brain: a case studied clinically and pathologically

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SUMMARY A 40 year old man developed seizures, intermittent fever, and progressive dementia ending in coma and death after four years. The cerebrospinal fluid showed variable pleocytosis and occasional elevation of protein. The necropsy revealed many lesions characteristic of Whipple's disease confined to the grey matter of the brain. The pathological changes were studied with the light and electron microscope. The findings permitted an understanding of the temporal sequence of changes in the lesions. Involvement of the brain in this condition is rare, but the disease is treatable and the diagnosis can be made by brain biopsy.

After Whipple's definition of the disease in 1907, only 15 cases of this condition were reported over a period of 43 years (Hendrix et al., 1950). From 1950 until 1970, the number of cases in the literature increased to 114 (Maizel et al., 1970), and by now it is much larger. We found 21 published cases in which the characteristic lesions of the disease were present in the brain in addition to the other organs and tissues (see Discussion). The purpose of this communication is to report a case which is unique in that both the symptoms and the pathological changes were confined to the brain. Another aim is to present some interesting features of the pathology.

Case report

HISTORY
This patient was well until May 1970 when, at the age of 40 years, he developed severe headaches for three days followed by major motor seizures. Admitted to hospital, he was found to have a left extensor plantar response. Studies including EEG, lumbar puncture, and right carotid arteriogram, were negative. He was discharged on diphenylhydantoin 300 mg a day, but continued having seizures with olfactory aura, lips smacking, and right hand shaking. In July 1970 he was readmitted to the same institution. A lumbar puncture showed clear cerebrospinal fluid under normal pressure, containing 160 erythrocytes, seven polymorphonuclear leucocytes, and 45 lymphocytes/mm³, protein 0.68 g/l, and sugar 2.9 mmol/l (52 mg/dl). A left carotid arteriogram and a pneumonencephalogram were indicative of a left anterior temporal space-occupying lesion. The seizures were controlled on diphenylhydantoin and primidone and he was discharged. Because of headache and confusion, in December 1970 he was readmitted. On examination he had decreased attention span, poor recent memory, and swollen optic discs with fresh haemorrhages. The lumbar puncture revealed clear cerebrospinal fluid under a pressure of 180 mmH₂O, containing 950 erythrocytes, six polymorphonuclear leucocytes, and 25 lymphocytes/mm³, protein 0.16 g/l, and sugar 3.8 mmol/l (68 mg/dl). Arteriography revealed apparent increase in size of the temporal lobe mass which led to surgical resection of the anterior portion of the left temporal lobe. Pathologically, the specimen was found to contain multiple lesions interpreted to represent a granulomatous encephalitis of unknown type. He was maintained on anticonvulsant medications, chlorpromazine and methylprednisolone.

In March 1971 he was transferred to the Boston Veterans Administration Hospital. The general physical examination was normal. Spontaneously he uttered occasional short sentences. When addressed, he looked at the examiner, but did not answer or perform any requested tasks. There was paratonic rigidity in all the limbs, suck, snout, and grasp reflexes, and bilateral extensor plantar

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responses. The EEG showed bilateral theta and delta slow wave activity. The brain scan revealed diffusely increased uptake of isotope in both Sylvian regions. He developed daily temperature elevations with occasional spikes to 39°C. Repeated blood cultures, tests for collagen vascular disease and serum VDRL were negative. Urine cultures at various times showed either *Pseudomonas, Klebsiella* or *Proteus*. He was treated sequentially with ampicillin 2 g for 20 days, tetracycline 1 g for seven days, gentamycin 180 mg for 36 days, and cephalaxin 1 g for 14 days. The lumbar puncture revealed clear colourless spinal fluid under a pressure of 170 mmH₂O containing 190 erythrocytes, eight polymorphonuclear leucocytes, seven lymphocytes, protein 1.08 g/l, gamma globulin 6%, and glucose 3.6 mmol/l (64 mg/dl). The Indian ink preparations, cultures, and cytology of the spinal fluid were all negative for organisms. Repeated lumbar puncture one month later showed an opening pressure of 290 mmH₂O, clear colourless spinal fluid containing no cells, protein 0.83 g/l, and glucose 2.8 mmol/l (50 mg/dl). The cultures and cytology were again negative. The patient showed fluctuations in his neurological status and was eventually discharged on anticonvulsants and dexamethasone 12 mg/day.

In October 1973 he was readmitted to the Boston VA Hospital because of seizures, incontinence, and deterioration of gait. The general physical examination was unremarkable. His speech was paraphasic and meaningless. He did not seem to understand spoken or written language and did not follow commands. The optic discs were pale but the rest of the cranial nerves were normal. The motor power was good, the deep tendon reflexes symmetrical, and the plantar responses were tonic flexor. Pain was perceived throughout. An EEG showed diffuse theta and delta slow activity with occasional right mid-temporal sharp activity. The lumbar puncture revealed clear colourless cerebrospinal fluid containing three erythrocytes, 12 polymorphonuclear leucocytes, and two lymphocytes/mm³, protein 0.33 g/l, gamma globulin 13%, and glucose 3.7 mmol/l (66 mg/dl). Indian ink preparations, cultures, cytology, and VDRL were all negative. A three vessels arteriogram and pneumoencephalogram disclosed no abnormalities. He gradually became mute and less alert, but then improved again.

Repeat lumbar puncture six weeks later showed clear colourless spinal fluid under a pressure of 220 mmH₂O, containing 120 polymorphonuclear leucocytes/mm³, protein 0.48 g/l, and glucose 3.6 mmol/l (65 mg/dl). Indian ink preparations and cultures were again negative. He was observed to have a generalised seizure with turning of the head and eyes to the right. A repeated pneumoencephalogram showed slight enlargement of the ventricles. The patient developed nystagmus on gaze to the left and the plantar responses became extensor. Cisternal puncture revealed clear cerebrospinal fluid under a pressure of 275 mmH₂O, containing one erythrocyte, two lymphocytes, protein 0.55 g/l, and glucose 2.8 mmol/l (50 mg/dl). Cultures grew alpha *Streptococcus* in thioglycolate broth only. A ventriculo-atrial shunt was inserted. He gradually became less responsive and lapsed into coma. The pupils were 6 mm, equal and reactive to light. There were no decerebration signs on painful stimulation. He died on 22 March 1974.

PATHOLOGICAL FINDINGS

At necropsy no abnormalities were seen with the naked eye in any visera except for petechial haemorrhages in the stomach. The microscopic study of the organs was also entirely negative except for superficial erosions of the stomach mucosa and mild terminal bronchopneumonia. Careful attention to the intestines, peripheral and mesenteric lymph nodes, heart, pericardium, liver, and spleen with the use of special stains including PAS and methenamine silver failed to demonstrate any lesions.

The brain weighed 1750 g. A patent ventriculo-atrial shunt was in place. The amputation of the tip of the left temporal lobe was evident. The brain was diffusely swollen with flattening of the gyri and mild moulding against the tentorial edge but no other abnormalities were visible on its surface. When the sectioning was carried out after fixation in formalin, a most unusual picture became evident. The entire cerebral cortical ribbon was studded with an extraordinary number of minute lesions (Fig. 1). These were roughly circular or oval, measuring on the average 2 mm in diameter. In places the lesions were confluent. They were recognisable by a chalky yellowish-white colour which was most intense at the periphery of each lesion, outlining it like a ring. Less numerous lesions of this type were present in the caudate nucleus and putamen, and a few could be seen in the thalamus and in the cerebellar cortex. The white matter was entirely free of lesions. None were visible in the brain stem or the spinal cord. Granular ependymitis was present throughout the ventricular system.

Many blocks of tissue were processed in paraffin and the sections stained with haematoxylin and eosin (H and E), luxol fast blue, cresyl violet, phosphotungstic acid haematoxylin (PTAH),
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Fig. 1 Lesions in the parietal cortex. ×2.

Masson trichrome, periodic acid Schiff (PAS), methenamine silver, and Gram stain.

Some sections of the cerebral cortex showed a multitude of lesions many of which were confluent (Fig. 2). Three types of lesions could be distinguished. The first, which was most frequent, consisted of a massive aggregate of macrophages containing material which stained faintly blue with H and E but was brilliantly red with PAS (Fig. 3) and intensely black with methenamine silver (Fig. 2). In most lesions two zones of macrophages could be distinguished from the standpoint of the tinctorial properties of their content. In the macrophages located at the periphery of the lesions Gram positive organisms could be seen and the staining with PAS was finely stippled and only moderate in intensity (Fig. 3). In the centrally located macrophages no organisms were visible on Gram stain and the staining with PAS was in coarser clumps and very intense. Some lesions contained bundles of collagen inside them and the brain tissue immediately around the lesions had reactive and hypertrophic astrocytes. An occasional lesion had a larger blood vessel in its

Fig. 2 Lesions in the frontal cortex. Methenamine silver stain. ×4.
centre (Fig. 3). Perivascular lymphocytes were seen in a few lesions and occasionally in an apparently unaffected area of the brain.

A second type of lesion was much smaller and was not visible grossly. Microscopically, it was found in the thalamus and throughout the tegmentum of the brain stem. With H and E it appeared simply as a pleomorphic microglial nodule but with PAS it had the staining characteristics of the peripheral macrophages of the large lesions (Fig. 4). With bacterial stains it contained Gram positive organisms.

A third type of lesion was seen very rarely in the cerebral cortex and in the basal ganglia. It consisted of an area of shrinkage and astrocytic scarring of the tissue comparable in size to that of a medium size or large lesion of the first type.

The leptomeninges showed a light infiltration with lymphocytes and occasional macrophages filled with PAS positive material. There was striking granular ependymitis. Most of the ependymal cells contained PAS positive material which was also present in macrophages shedding into the ventricular system (Fig. 5).
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Discussion

Whipple (1907) characterised the disease pathologically to consist of accumulations of macrophages filled with lipidin the mucosa of the small intestine and in the mesenteric lymph nodes. Subsequently the disease was shown to affect many other tissues and organs (Sieracki, 1958; Sieracki and Fine, 1959). The content of the macrophages was found to stain with a unique brilliance with PAS (Black-Schaffer, 1949), to be finely granular.
(Sieracki, 1958; Sieracki and Fine, 1959), and to stain also very intensely with methenamine silver (Chears and Ashworth, 1961; Yardley and Hendrix, 1961). Using the Levaditi method, Whipple (1907) demonstrated rod bodies in the intestinal lesions and thought that these might be microorganisms which could conceivably cause the disease. Recently by electron microscopy the macrophages were shown to contain bacilli in intact form as well as in various stages of degradation into membrane-like structures derived from bacterial walls and responsible for the strong PAS staining (Chears and Ashworth, 1961; Yardley and Hendrix, 1961; Kurtz et al., 1962; Kent et al., 1963; Trier et al., 1965). Antibiotic therapy resulted in improvement of the gastrointestinal symptoms (Paulley, 1952; England et al., 1960; Kent et al., 1963; Ashworth et al., 1964; Trier et al., 1965) and of the pathological changes in the small intestine (Kent et al., 1963; Ashworth et al., 1964; Trier et al., 1965). A number of bacteria were cultured from the lesions or from the blood,
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including atypical alpha streptococci (Charache et al., 1966; Knox et al., 1968; Clany et al., 1975), brucella (Kok et al., 1964), aerobic (Kent et al., 1963; Dybkaer and Kok, 1965) and anaerobic (Caravati et al., 1963; Prevot and Morel, 1964; Greenberger et al., 1971) corynebacteria and haemophilus (Kok et al., 1964; Kjaerheim et al., 1966). The aetiological role of any of these organisms remains to be proven, although a bacterial participation in the disease is firmly established by both the electron microscope findings and by the response of the disease to antibiotic therapy. It has been suggested that the action of the microorganisms in this condition may occur on a background of defective immunological mechanisms (Maxwell et al., 1968; Groll et al., 1972; Martin et al., 1972; Cochran et al., 1973).

The brain can be affected occasionally by the disease. The lesions in the central nervous system are identical to those in the small intestine both with the light (Sieracki et al., 1960) and the electron microscope (Groodt-Lassell and Martin, 1969; Schochet and Lampert, 1969). There are 21 cases in the literature in which the brain was found to contain the lesions at necropsy (Rutishauser and Borer, 1960; Sieracki et al., 1960; Krücke and Stochdorph, 1962; Lampert et al., 1962; Badenoch et al., 1963; Smith et al., 1965; Schwartzová et al., 1967; Groodt-Lassell and Martin, 1969; Minauf and Stochdorph, 1969; Schochet and Lampert, 1969; Stoupe1 et al., 1969; Switz et al., 1969; Kodousek and Kojecki, 1971; Janota, 1974; Kitamura, 1975; Silbert et al., 1976). In two of these (Rutishauser and Borer, 1960; Janota, 1974) the examination of the important organs was not available but the patients had clinical evidence of systemic involvement. All the other patients had systemic symptoms and pathological changes in many organs and tissues. The present case is unique in that both the symptoms and the pathological changes were confined to the brain.

The neuropathological findings in our case are remarkable from several points of view. In the typical lesion of the first type (Fig. 3) the peripheral rim of macrophages contained Gram positive organisms, moderately intense PAS staining material, and many bacilli demonstrable by electron microscopy. By contrast, the more centrally located macrophages had no organisms on Gram stain, their content stained intensely with PAS and ultrastructurally had no demonstrable bacteria, being filled only with empty bacterial ‘ghost’ and membranous structure. These differences lead us to conclude that the peripheral portion of the lesion is more recent while the central part is old. It is in this older part which contains only degraded bacteria that the staining with PAS is most intense. This finding supports the view that the brilliant staining of the macrophages with PAS is due to the degraded packed bacterial membrane remnants. Correlating the gross and the microscopic findings in the lesions of the first type, we conclude that the yellowish-white ring outlining the lesion on naked eye inspection of the brain (Fig. 1) is due to the different content of the peripherally located macrophages.

The second type of lesion (Fig. 4) is also of considerable interest since with H and E it appeared only as a pleomorphic microglial nodule while with PAS it showed the typical staining and with the Gram method had demonstrable organisms. We interpret these to be early small lesions which do not yet contain macrophages in the form of compound granular cells. It is important to know that such lesions exist since if they are the only ones present in a biopsy or a section of brain, the nature of the process will not be recognised unless the PAS stain is used.

The third type of lesion, which was rare, consisted of minute scars which must represent lesions which have healed either spontaneously or as a result of antibiotic therapy.

Reviewing the clinical manifestations of the reported cases of Whipple’s disease with verified cerebral pathology, the patients first developed systemic symptoms such as diarrhoea, arthritis, fever, malaise, and lymphadenopathy. In some cases the presence of a systemic disease was readily apparent, while in others there were only mild symptoms such as arthralgia which seemed nonspecific. The neurological manifestations followed the systemic ones by months or years. The picture was that of progressive dementia with rather inconspicuous pyramidal or extrapyramidal signs, ending in an akinetic mute state and eventual coma over a period of a few months to seven years (Krücke and Stochdorph, 1962; Lampert et al., 1962; Badenoch et al., 1963; Smith et al., 1965; Schwartzová et al., 1967; Minauf and Stochdorph, 1969; Silbert et al., 1976). Several patients had disorders of eye movements (Lampert et al., 1962; Badenoch et al., 1963; Smith et al., 1965; Minauf and Stochdorph 1969; Stoupel et al., 1969) and seizures or myoclonus (Lampert et al., 1962; Smith et al., 1965; Minauf and Stochdorph, 1969; Stoupel et al., 1969). One patient had papilloedema (Lampert et al., 1962). Two cases were not noted to have neurological symptoms or signs in spite of the presence of
lesions in the brain (Sieracki et al., 1960). Our patient was unique in several respects. He did not have preceding systemic symptoms. He began having seizures, underwent mental changes, and developed evidence of a space-occupying lesion. Subsequently, he continued to deteriorate mentally over a period of four years ending in coma. Fever was present intermittently throughout his illness.

The cerebrospinal fluid findings in the cases reported in the literature were given in six instances (Lampert et al., 1962; Badenoch et al., 1963; Minauf and Stochdorph, 1969; Stoupel et al., 1969; Switz et al., 1969; Silbert et al., 1976). They ranged from normal to elevated pressure, no erythrocytes, 0-3 polymorphonuclear leucocytes, and 0-420 lymphocytes/mm³. The protein ranged from 0.21-0.85 g/l being elevated in only two cases (Switz et al., 1969; Silbert et al., 1976), in spite of the pleocytosis present in the other cases. The sugar content was always normal. In our patient the cerebrospinal fluid pressure was usually normal but on a few occasions was elevated. It contained 0-950 erythrocytes, 0-120 polymorphonuclear leucocytes, and 0-45 lymphocytes/mm³. The protein ranged from 0.23-1.08 g/l and the sugar content was never decreased.

From the above considerations it is apparent that the diagnosis of Whipple's disease of the brain may be extremely difficult when the symptoms occur without the systemic manifestations of the disorder. The clinical picture of the cerebral involvement is rather non-specific and similar to that of vasculitis and other subacute or chronic encephalopathies. When the systemic manifestations are lacking, a brain biopsy may be diagnostic if the PAS stain is used. The examination of a spinal fluid cell block with the electron microscope may be of some help.

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