

A Neuropathologic Study of Whipple's Disease

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Summary. A patient with Whipple's disease developed massive and irreversible CNS involvement after a drug-induced intestinal remission. The multifocal brain lesions were apparent grossly with the heaviest concentration being noted in rhinencephalon, diencephalon, and mesencephalon. This patient exhibited progressive neurologic deterioration, although viable organisms could not be identified in the brain at autopsy. Astrocytes, pericytes, and choroid plexus cells attempted to dispose of the organism, in addition to the traditionally implicated microglial and ependymal cell.

Key words: Pre-senile dementia — Infection — Hydrocephalus — Ataxia

Microscopic involvement of the central nervous system (CNS) in Whipple's disease is well documented (Sieracki et al., 1960; Lampert et al., 1962), but infection severe enough to be reflected in grossly detectable brain lesions has been encountered only rarely (Romanul et al., 1977). It has become obvious that neurologic dysfunction in Whipple's disease may exist without apparent intestinal involvement or after a drug-induced intestinal remission (Silbert et al., 1976; Knox et al., 1976; Romanul et al., 1977; Feurle et al., 1979). Neuropathologic proof of CNS infection in such cases has been limited (Silbert et al., 1976; Romanul et al., 1977; Feurle et al., 1979). We have recently examined a patient with a long history of treated Whipple's disease, who developed neurologic disease during an intestinal remission. The gross and microscopic features of the present case provide conclusive proof that CNS involvement in Whipple's disease can be diffuse, severe and irreversible, even when the intestinal disease has been eradicated.

Materials and Methods

Case Report

A 58-year-old white male had a 20-year history of relapsing intestinal Whipple's disease which had responded to treatment with 1 g of

tetracycline daily and steroids. The patient took his medications sporadically. His intestinal symptomatology went into permanent remission 6 years prior to his death. About 6 months after his final intestinal remission, he presented with his first signs of nervous system involvement in the form of "falling". Over the next 5 years he developed a variety of clinical symptoms: frontal headache, urinary incontinence, intermittent disorientation, loss of recent memory, depression, and paranoia. Neurologic signs consisted of diffuse hyperreflexia, equivocal right Babinski response, hypalgesia of V-1 on the right and a slightly ataxic gait. Several episodes of chills and fever were recorded, but frequent blood and spinal fluid cultures (lumbar theca and shunt) were negative. A diagnosis of communicating hydrocephalus was made during the first year of his neurologic disease and numerous shunts and shunt revisions were performed with a variable clinical response. A brain biopsy from the right frontal lobe obtained during his last shunt revision was non-diagnostic. Unfortunately, only superficial cortex was submitted. One year before his death there was a further loss of memory and he developed diminished hearing bilaterally, increasing spasticity and gait disturbance, and hyponatremia secondary to inappropriate secretion of antidiuretic hormone (ADH). His terminal admission was necessary because of fever (103.6°), loss of consciousness and shock secondary to dehydration. Computer assisted tomographic (CT) scan and tapping of the shunt system revealed that his shunt was working effectively. Cultures of the CSF were negative. He subsequently had three grand mal seizures and died.

Family history was provocative in that a brother developed adult-onset ataxia due to an ill-defined PAS-positive neuronal storage disease (perhaps Kuf's form of ceroid-lipofuscinosis); a sister had been diagnosed clinically as alcoholic or nutritional Wernicke-Korsakoff syndrome (no autopsy); and a son is ataxic and currently is considered to be a probable case of multiple sclerosis.

Autopsy revealed pulmonary emboli, emphysema, and a few weakly positive, periodic acid-Schiff (PAS) macrophages in jejunal submucosa and mesenteric lymph nodes, which were consistent with inactive intestinal Whipple's disease.

Routine sections of formalin-fixed brain were embedded in paraffin and stained with hematoxylin and eosin (H & E), diastase-periodic acid-Schiff (D-PAS), Gomori's methenamine silver, and phosphotungstic acid-hematoxylin (PTAH). Sections of frontal cortex, amygdala, hippocampus, midbrain, and pons were also treated with Brown-Brenn and acid-fast stains.

Selected 1–3 mm pieces of formalin-fixed frontal cortex, hippocampus, periaqueductal gray, and tegmentum of midbrain and pons were postfixed in 2% unbuffered osmium tetroxide and processed routinely for electron microscopy. Finally, specific areas were removed from the paraffin blocks, deparaffinized in xylene, rehydrated, and then processed for electron microscopy.

Results

The brain weighed 1,240 g prior to fixation. It was small and demonstrated slight, diffuse gyral atrophy. Three shunts and their tracts were noted: one right superior-frontal, which was found to terminate in the right fornix at the splenium; one right lateral-frontal which drained the body of the right ventricle; and one right parieto-occipital, which ended in the right posterior horn. There were no cingulate, uncal or tonsillar herniations. Coronal sections of the cerebral hemispheres (especially after prolonged fixation in formalin) revealed multifocal, granular, depressed lesions, which were most prominent at the gray-white junction (Fig. 1) and in periventricular tissue. The centrum semiovale and corpus callosum were essentially unremarkable, except for shunt tracts. The right lateral ventricle was small with marked adhesions in the frontal horn, while the left lateral and third ventricles were dilated. The right foramen of Munro was almost totally occluded by thickened ependyma. A beige ependymal membrane covered the posterior part of the third ventricle with complete obstruction of the anterior end of the aqueduct of Sylvius. Transverse sections of the brainstem revealed that the aqueduct was occluded by firm white tissue throughout its entire length. The superior and inferior portions of the fourth ventricle were about 60% compromised by thickened ependymal tissue (Fig. 2), while its midportion was totally occluded. The periaqueductal tissue was firm and white; the foramina of Luschka were probe patent. Serial sections of spinal cord were grossly unremarkable.

The lesions noted grossly were composed histologically of cell clusters containing weakly hematoxylinophilic macrophages, gliosis, and occasionally collagen. These clusters were often found near small blood vessels. Both PAS and methenamine silver identified two elements: a peripheral one, composed of intensely positive, elongated structures measuring 5–15 μm in length admixed with reactive astrocytes; and a central one, composed of intensely positive (the hematoxylinophilic) macrophages. These two elements were often haphazardly mixed. Occasionally, weakly PAS-positive, foamy macrophages were also present. Brown-Brenn and acid fast stains were consistently negative. Inflammatory cells, usually lymphocytes, were rarely seen, except when the lesions were near the lateral ventricular surface. It was common to find chronic inflammation, multinucleated giant cell reaction and ependymal granulations in the periventricular lesions. Ependymal granulations were most severe at the inferior margin of the septum pellucidum adjacent to the right foramen of Munro and in the inferior portion of the right anterior horn. The shunt tracts demonstrated circumferential subacute to cystic

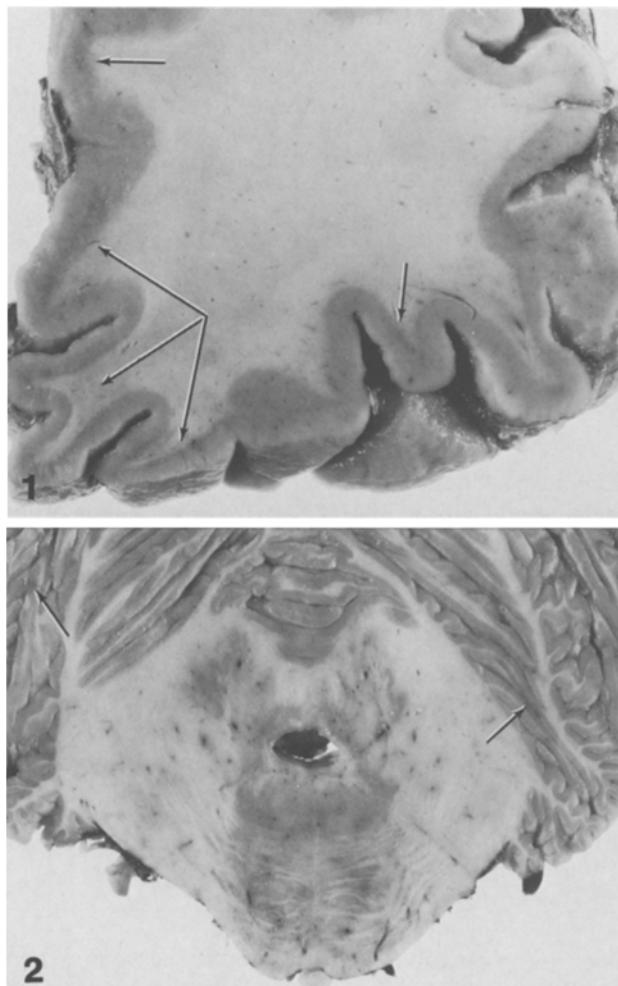


Fig. 1. Dark and granular depressions (arrows) are present at the gray-white junction of the straight and orbital gyri. Magnification $\times 2$

Fig. 2. The inferior portion of the IV ventricle is distorted and contracted by ependymal granulation tissue. Rare foci of discolored cerebellar tissue (arrows) are seen. Magnification $\times 2$

necrosis and gliosis, but very little PAS-positive material.

PAS-positive cell clusters in cerebral cortex were situated in the deeper cortical layers and impinged on subcortical white matter. They also were observed in the caudate nucleus, putamen, globus pallidus, hypothalamus, infundibulum, thalamus, hippocampus, amygdala, corpus callosum, centrum semiovale, and septum pellucidum. The cerebral areas with the greatest concentration of PAS-positive cells (hypothalamus, amygdala, and hippocampus) demonstrated an apparent decrease in neuronal perikarya. PAS-positive material was found predominantly in macrophages or microglia but was seen also within reactive astrocytes, ependymal cells, choroid plexus epithelium, and arachnoid granulations. Conclusive demonstration of the

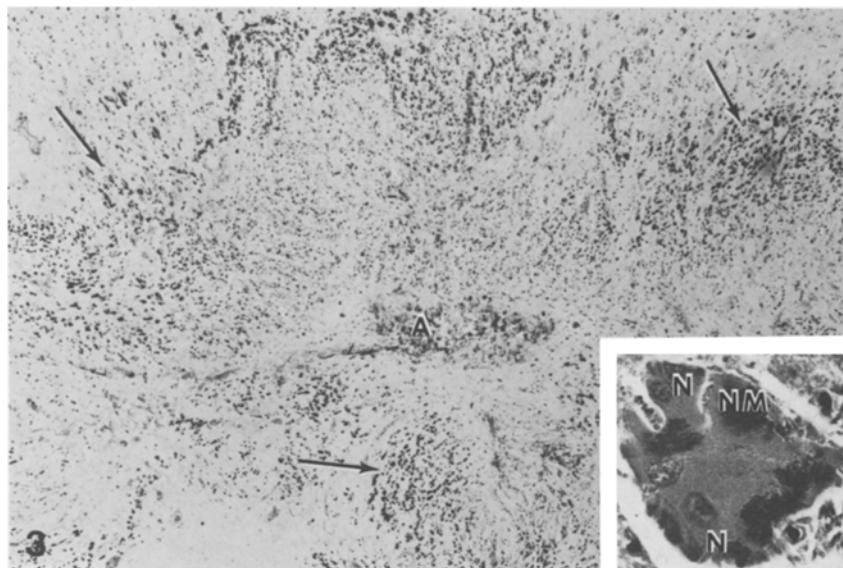


Fig. 3. The aqueduct of Sylvius (A) shows total occlusion by a profuse proliferation of glial tissue studded with positive debris (arrows). Methenamine silver. Magnification $\times 36$. Inset: Locus coeruleus. A multinucleated (N) giant neuron with clumps of neuromelanin (NM). H.-E. Magnification $\times 230$

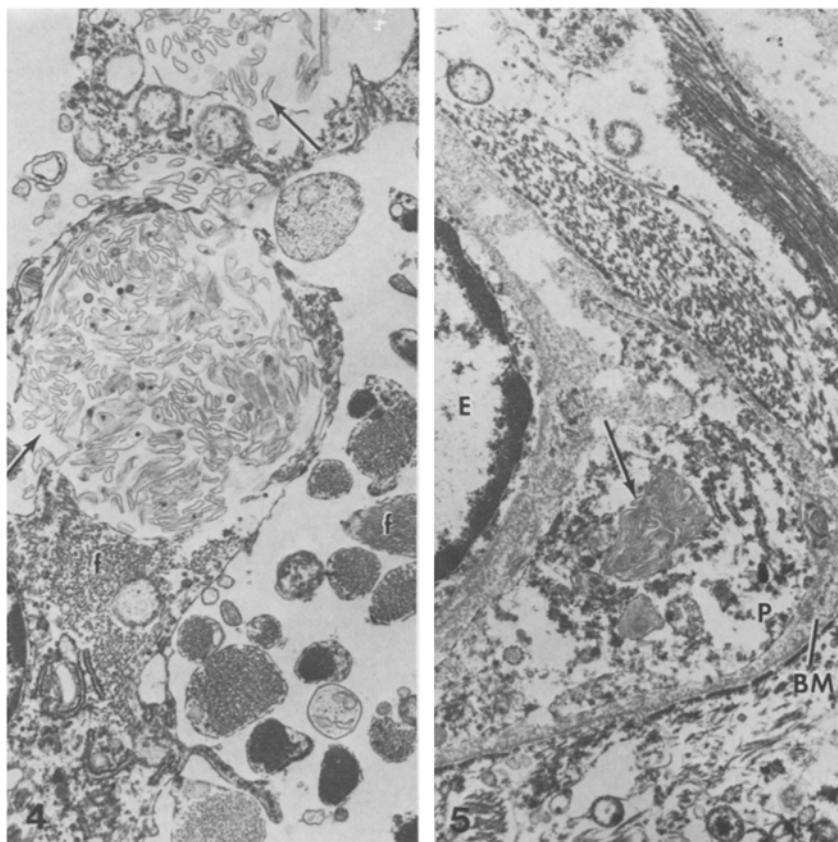


Fig. 4. Partially digested bacterial cell walls (arrows) lie within astrocytes rich in filaments (f). Uranyl acetate-lead citrate. Magnification $\times 9,600$

Fig. 5. Residual bacterial cell wall (arrow) is present in a pericyte (P). The basement membrane (BM) and endothelial cell nucleus (E) are labeled for orientation. Uranyl acetate-lead citrate. Magnification $\times 9,600$

same type of cytoplasmic inclusions in neurons could not be accomplished, even with the electron microscope.

Multiple sections of midbrain and pons confirmed the complete gliotic obstruction of the aqueduct of Sylvius and midportion of fourth ventricle. PAS and methenamine silver stains demonstrated countless positive fragments enmeshed in the obliterative glial

tissue (Fig. 3) and numerous positive cell clusters throughout the tegmentum of midbrain and pons. Smaller numbers of PAS-positive cells were seen in medullary subependymal regions, medial lemniscus, and reticular formation. The basis pontis, inferior medullary olives, and pyramidal tracts were conspicuously spared. One noteworthy and unexpected histologic finding was the presence of multinucleated neu-

rons in the locus coeruleus (Fig. 3, inset). The sections of meninges and spinal roots contained a few PAS-positive deposits, while optic nerves, tract and chiasm, spinal cord, peripheral nerve, and pituitary were essentially unremarkable.

Ultrastructural examination of 20 areas of brain failed to demonstrate morphologically intact microorganisms, but confirmed that the weakly hematoxylinophilic, intensely PAS- and methenaminesilver-positive material in macrophages was identical to partially degraded cell walls of Whipple's bacteria (de Groodt-Lasseel and Martin, 1969; Kitamura, 1975). Astrocytes (Fig. 4) and pericytes (Fig. 5) displayed the same cytoplasmic debris as microglial cells, but less frequently.

Discussion

The present case provides conclusive proof that CNS involvement in Whipple's disease can be a devastating clinical problem even when the intestinal component is well under control. The demonstration of gross CNS lesions such as these is extremely rare and reflects the severity of this patient's neurologic disease; their distribution correlates well with the clinical symptomatology. The sites of predilection: rhinencephalon, diencephalon, and mesencephalon, recapitulate many of the cases reported in the literature (Stoupel et al., 1969; Pallis and Lewis, 1974; Schliep et al., 1979). Proximity to ependyma appears to be a common link between these major sites of involvement. The demonstration of PAS-positive, intracytoplasmic debris within ependymal and choroid plexus cells and of diffuse ependymal damage emphasize the importance of the ventricular system in the dissemination, and perhaps persistence, of disease within the CNS. The severe, obliterative midbrain lesions in the present case probably reflect a combined effect of infection and a complication of shunting (Foltz and Shurtleff, 1966). This case confirms the histologic observations of several investigators (Lampert et al., 1962; Romanul et al., 1977), but fails to document viable or intraneuronal organisms. Although microglial and ependymal cells are the most frequent brain cells to contain remnants of Whipple's bacteria, we also find them within astrocytes, pericytes, and choroid plexus cells.

In addition to the demonstration of gross lesions, the most important point to be learned from the present case is that CNS damage in treated Whipple's disease can be irreparable, either because of neuronal loss or because of the magnitude of the infection. This study provides a pathologic substrate for the clinical observation that neurologic responses to therapy are slower and less predictable than those in other organs (Bayless

and Knox, 1979). No viable, or morphologically intact, organisms could be found after an exhaustive search. We assume that the severity and persistence of CNS disease in the present case was due to delay in instituting, or failure in maintaining, appropriate therapy and to a defect in the brain's ability to dispose of the organisms. These two deficiencies would permit the accumulation of insurmountable numbers of bacteria and bacterial debris. We agree that cortical biopsy can be a definitive diagnostic test (Finelli et al., 1977; Romanul et al., 1977). The anatomic distribution of the lesions, however, emphasizes that brain biopsies should be at least full cortical thickness and should be multiple, if false negative results are to be minimized.

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