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AJNR Am J Neuroradiol 1996, 17 (8) 1589-1591

<http://www.ajnr.org/content/17/8/1589>

This information is current as of April 18, 2024.

Whipple Disease Confined to the Central Nervous System in Childhood

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Summary: In a case of pediatric Whipple disease confined to the central nervous system, white matter lesions initially appeared as areas of very low signal intensity on T1-weighted MR images and as areas of hyperintensity on proton density-weighted and T2-weighted images, and showed slight peripheral enhancement on delayed contrast-enhanced T1-weighted images. On MR studies obtained 3 and 6 months after antibiotic therapy, the lesions had decreased in size and no longer enhanced. They became progressively less hypointense on T1-weighted images and less hyperintense on T2-weighted images.

Index terms: Brain, infection; Children, diseases

Whipple disease is a systemic subacute or chronic illness long known to be associated with a persistent intracellular gram-positive bacillus (1). Few patients have central nervous system (CNS) involvement with a severe prognosis that includes mental deterioration and brain stem or hypothalamic dysfunction (2).

Case History

A 4-year-old boy with previously normal neurologic development suddenly exhibited such behavioral changes as aggressiveness, inappropriate emotional reactions, and decreased mental functioning. On admission, findings at physical examination were negative and neurologic tests revealed only slight pyramidal signs. Results of routine blood, urine, and cerebrospinal fluid examinations were negative. An electroencephalogram showed mild perturbation in the posterior portions of the brain bilaterally.

Magnetic resonance (MR) studies of the brain disclosed multiple round or oval lesions in both supratentorial and infratentorial white matter, appearing as areas of very low signal intensity on T1-weighted images (Fig 1A) and as areas of hyperintensity on proton density-weighted and T2-weighted images (Fig 1B). Almost no perilesional edema was observed, and a slight peripheral enhancement

in several of the lesions was seen on the delayed contrast-enhanced T1-weighted images (Fig 1A).

Because an infectious disorder was strongly suspected, parenteral broad-spectrum antibiotics were prescribed; however, antibiotic therapy was unsuccessful. As a result of worsening mental status, we performed a stereotactic brain biopsy under MR imaging control. Microscopic examination revealed typical intramacrophagic periodic acid-Schiff-positive and salivary diastase-resistant bacillary inclusions, which established the diagnosis of Whipple disease. Since results of twice-repeated endoscopic jejunal biopsies were negative, and no clinical manifestations other than mental regression were observed, the disease process was considered to be confined strictly to the CNS.

A parenteral regimen combining chloramphenicol and trimethoprim-sulfamethoxazole was started and continued for 2 weeks, followed by oral monotherapy with the latter for 18 months. Improvement in mental status was noted within a few days. Normal speech was recovered at 10 weeks and a sufficiently normalized social behavior allowed school reintegration at 3 months, with progressive recovery of the former level of performance.

Follow-up MR examinations at 3 and 6 months (Fig 1C) showed a progressive decrease in the size of the lesions, and no further enhancement was observed. Moreover, the lesions became progressively less hyperintense on the T2-weighted images and less hypointense on the T1-weighted images. These changes were highly suggestive of either a mild increase in protein content within necrotic lesions or a secondary gliosis within previously necrotic areas.

Additional follow-up studies at 12 and 18 months showed no further modifications in brain status.

Discussion

Whipple disease is a systemic infectious disease of middle age that often remains clinically confined to one system, with the gastrointesti-

Received August 1, 1995; accepted after revision November 27.

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AJNR 17:1589-1591, Sep 1996 0195-6108/96/1708-1589 © American Society of Neuroradiology

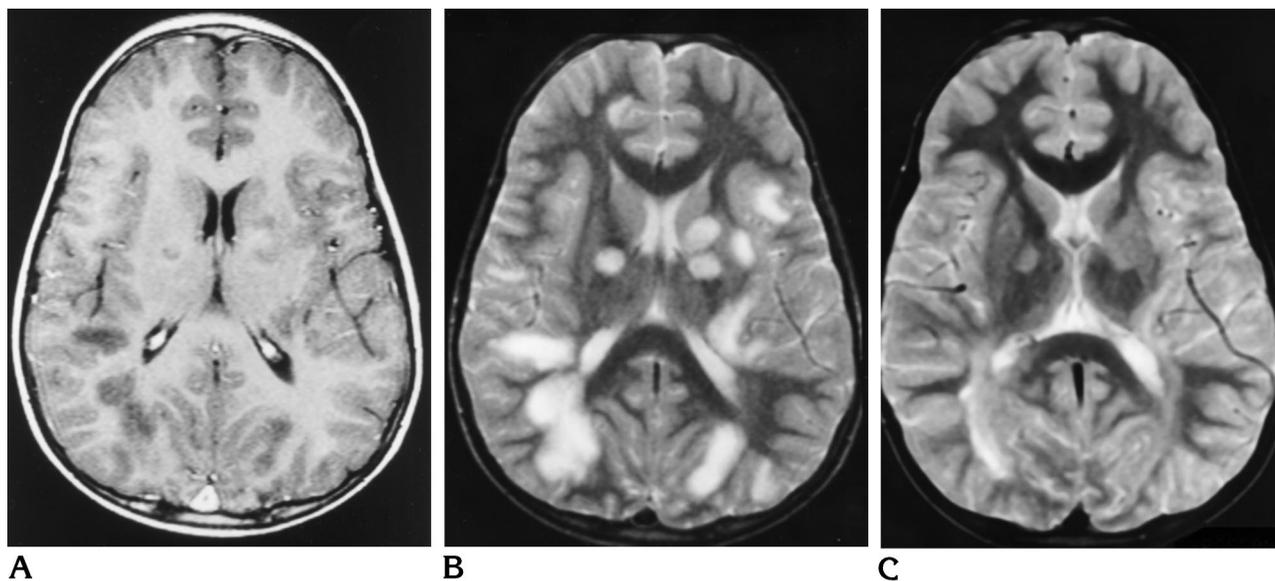


Fig 1. MR findings in a 4-year-old boy with Whipple disease.

A, Contrast-enhanced T1-weighted (440/20/4 [repetition time/echo time/excitations]) spin-echo image obtained on admission shows lesions as deep hypointense areas with irregular peripheral enhancement in a few places.

B, On T2-weighted (2200/90/2) spin-echo image, also obtained at admission and in the same plane as A, lesions appear hyperintense and sharply delineated. Neither perilesional edema nor mass effect is seen.

C, At 6-month follow-up examination, T2-weighted image (same plane and parameters as in B) shows lesions have decreased in size and appear less hyperintense. No atrophy has occurred.

nal tract being by far the most frequently involved (1).

The actual prevalence of the CNS-restricted form of the disease remains controversial, but it is undoubtedly low (2). Some investigators recently postulated that all patients with Whipple disease may have CNS involvement, although only 10% to 20% of them will exhibit clinical, laboratory, or radiologic features consistent with such involvement (3). Pediatric cases of Whipple disease are extremely rare, and their clinical features seem no different from those of the adult form, although scarce data are available (4).

Despite the availability of such high-resolution imaging techniques as computed tomography and MR, only a few cases of *in vivo* and biopsy-proved cerebral Whipple disease have been described, as most lesions consist of microscopic granulomatous foci that are well beyond the resolution range of these techniques. Previous reports have described nonspecific features, such as hyperintense areas on T2-weighted MR images (2, 5) and enhanced areas on T1-weighted images (6, 7), with or without diffuse cerebral atrophy.

The MR pattern of diffuse white matter changes seen in our patient led to a differential

diagnosis that included essentially inflammatory diseases (progressive multifocal leukoencephalopathy, acute disseminated encephalomyelitis, Whipple disease, multiple sclerosis) and neurodegenerative disorders like MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke) or, less probably, lysosomal storage diseases. Other processes, like ischemic or tumoral diseases, were ruled out because of the absence or paucity of mass effect, vascular systematization, and contrast enhancement. Brain biopsy was in this case unavoidable owing to the lack of specific MR features and to the absence of paraclinical data that would allow a firm diagnosis. For this purpose, MR imaging was certainly the most sensitive method for accurately delineating and identifying target lesions for biopsy.

Recovery of normal mental status has to be underlined as an exceedingly rare event in Whipple disease (8). Cerebral involvement usually causes reversible brain stem and hypothalamic dysfunctions due to inflammatory changes and/or mental deterioration resulting from neuronal loss. Rapid and complete reversal of dementia in our patient was probably facilitated by the functional plasticity of the brain during childhood.

Remarkably, clinical and radiologic improvement progressed in parallel during the initial 6-month treatment period. Discrepancy between the clinical course and imaging findings occurred later, when the mental status had normalized but the brain lesions were still visible on MR images, although they were significantly decreased in size (Fig 1C).

In conclusion, this case illustrates an unusual example of restricted brain involvement with Whipple disease. MR imaging provided the most accurate depiction of the lesions, facilitated stereotactic biopsy, and mirrored the clinical improvement during the initial phase of treatment. The potential to completely reverse a rapidly worsening demential syndrome underscores the need to recognize the possibility of Whipple disease in the presence of unexplained (sub)acute mental deterioration in childhood, despite the rarity of the condition.

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