

Magnetic Resonance Imaging of Whipple's Disease Confined to the CNS

Presenting with Multiple Intracerebral Mass Lesions

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Abstract- We report a patient diagnosed with Whipple's disease (WD) who presented only with neurological symptoms. Neuroimaging (MRI) showed lesions with marked mass effect similar to infiltrative tumors, which were hypersignal on long TR and hyposignal on short TR images, located in several areas of the brain. In serial controls, lesions resolved with gliosis and atrophic changes as well as migration of active infiltrative-like lesions to new areas. MR findings of the brain WD are discussed, which confirmed by stereotactic brain biopsy. Familiarity with the range of possible MR imaging appearances of WD enables the radiologist to place WD more effectively on the differential diagnosis which motivates the clinician to consider both the diagnosis and early initiation of treatment; so, this may significantly impact outcome. Moreover, repeated MR investigations may serve as a valuable method to evaluate efficacy of treatment and long term follow-up of WD involving the CNS.

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Introduction

The Whipple's disease (WD) is a rare, systemic infectious disease caused by the bacterium *Tropheryma whipplei*. First described by George Hoyt Whipple (1) in 1907 and commonly is considered a gastrointestinal disorder, WD primarily causes malabsorption but may affect any part of the body including the heart, lungs, brain, joints, skin, and the eyes. Weight loss, diarrhea, joint pain, and arthritis are common presenting symptoms, but the presentation can be highly variable, and approximately 15% of patients do not have these classic signs and symptoms (2). 10–40% of people with WD have problems related to involvement of the brain, and rarely the disease is confined to the nervous system; the symptoms relate to the part of the brain that is affected. The most common problems are dementia, memory loss, confusion and decreased level of consciousness. Weakness and poor coordination of part of the body, headaches, seizures, as well as a number of more uncommon neurological features, are present in

some patients (3,4). The CNS WD is a subset of a rare disease (5). Our understanding of head MR imaging findings is based only on case reports; thus, each new case imaged with modern equipment has the potential to expand our knowledge significantly as long as the diagnosis has been carefully established. Here, we describe a patient with a variety of neurological signs and symptoms where stereotactic biopsy facilitated the diagnosis of cerebral WD and reviewed the MR imaging finding of this disease. We also evaluated the role of MR imaging appearances of WD for initial evaluation and long term follow up of WD involving the CNS.

Case Report

A 30-year-old woman was admitted with a 5-month history of suddenly occurred memory loss, confusion, vertigo, numbness and paresis of right side upper and lower limbs. First MRI of the brain with axial and sagittal T1, axial FLAIR, coronal T2 sequences on a 1.5 Tesla magnet and also axial diffusion sequence revealed

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hypersignal area on T2 weighted spin-echo and FLAIR sequences in white matter of left temporo-parietal region, splenium and posterior portion of body of corpus callosum, left peduncle cerebri and extended toward

right side (Figures, 1A and 1B). There was no enhancement after intravenous (IV) contrast injection. Diffusion-weighted images (DWI) showed some areas of restricted diffusion in the lesions (Figure, 1C).

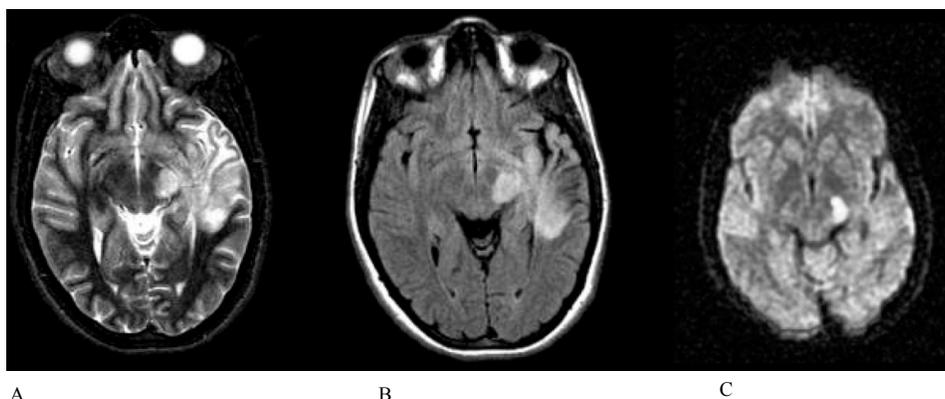


Figure 1. MR images with hypersignal area in white matter of left temporo-parietal region, splenium, corpus callosum and left peduncle cerebri. Axial STIR image (A); axial FLAIR image (B); DW image with some restricted diffusion areas of the lesions (C)

Low-grade brain tumors (diffuse astrocytoma) and other tumoral lesions like gliomatosis cerebri were considered in the differential diagnosis. She underwent stereotactic needle biopsy from temporal lobe of the brain. First histologic findings were compatible with reactive changes of brain tissue. Four months later the second control MRI showed same lesions which were involved the previously noted areas with the tiny enhanced foci in the background of the lesion after administration of the IV contrast. The enhancement areas were seen just in some boundary regions of lesions as a faint rim of enhancement. Some gliosis atrophic changes were appeared, however active tumoral like infiltrations are migrated to new areas. The lesions

involved both white (WM) and gray matter (GM), and the resultant mass effect changes were considerable. The lesion was more compatible with slow growing and self-improved disease based on images. In this time, the previously prepared paraffin blocks of the brain tissue were evaluated by another pathologist. H&E and Periodic acid-Schiff Diastase (PAS-D) stain slides from the biopsied tissue following features showed: fragments of normal brain cortex and white matter, fragments with large sheets of foamy histiocytes and perivascular lymphocytic infiltration in some areas. The PAS stain showed weak to modest PAS positivity in macrophages with diastase resistant PAS (Figures, 2A, and 2B).

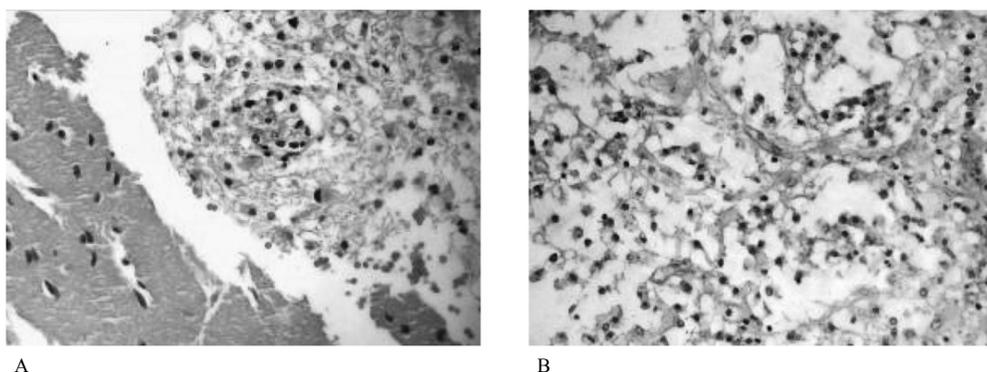


Figure 2. H&E and Periodic acid-Schiff diastase (PAS-D) stain of the biopsied tissue; fragments of normal brain cortex and white matter, fragments with large sheets of foamy histiocytes and perivascular lymphocytic infiltration in some areas (A); weak to modest PAS positivity in macrophages is obvious with diastase resistant PAS (B)

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These histologic features suggested WD as the most probable diagnosis in this patient. She had no prior history of WD with involvement of the brain or any other organs. Broad spectrum antibiotic therapy was initiated. During six months, follow up after the diagnosis, the third and fourth control MR Images of the brain were taken. Improvement was noted in left temporal lobe lesion with secondary atrophy and gliosis. But the lesion was migrated to the posterior aspect of the left temporal lobe as well as adjacent parietal and corpus callosum. The lesion was also extended to the right temporo-parietal lobes via corpus callosum. Mass effect

was noted at newly involved areas (Figure, 3A) which were completely normal on previous MR images (Figure, 3B), but subsiding of lesion with atrophy and gliosis was noticeable at older ones (Figure, 3C). In acute areas, the lesions were combined with mass effect and vasogenic edema was detected in older areas (Figure, 3D, and 3E). According to the migratory and self-improved pattern of the disease along with gliosis and atrophic changes, the possibility of slow growing progressive infectious and inflammatory disease would be corroborated.

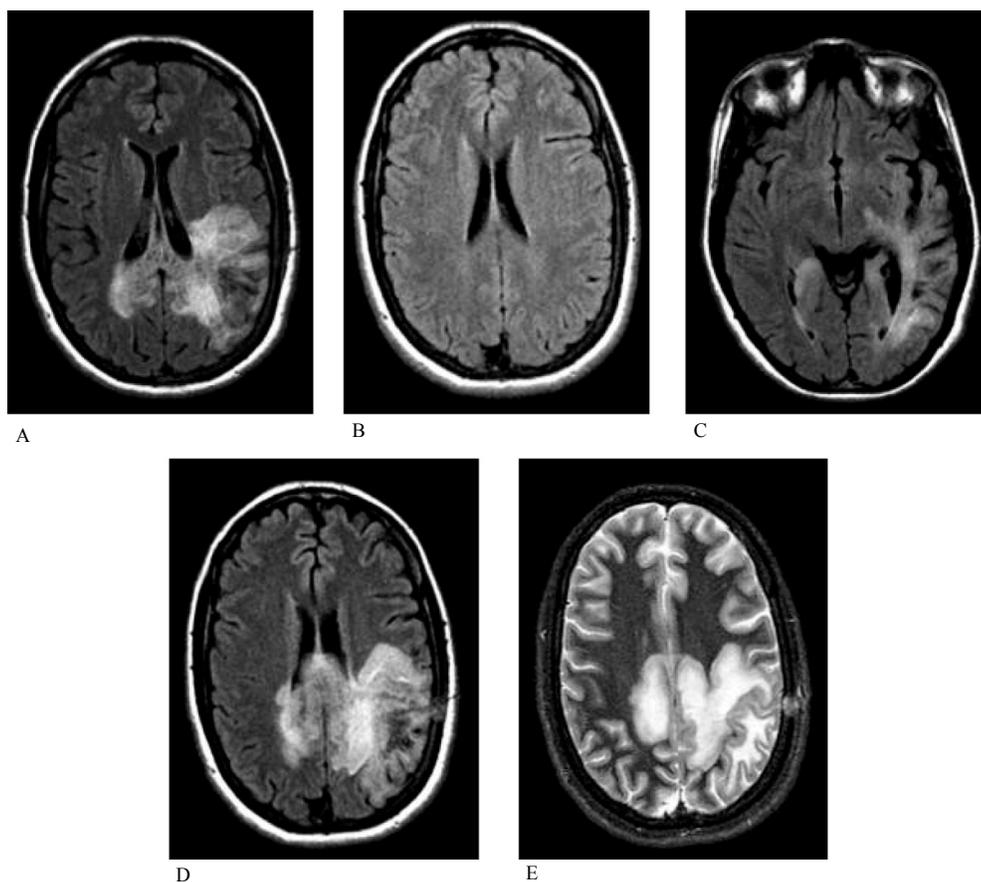


Figure 3. Follow-up MR images after five months in comparison with previous MR images. The lesion was also extended to the right temporo-parietal lobes via corpus callosum. Axial FLAIR, mass effect was noted at newly involved areas (A); comparing to previous axial FLAIR images (B); Axial FLAIR, subsiding of lesion with atrophy and gliosis which is noticeable at older areas (C); the lesions were combined with mass effect in acute areas (D); in older areas vasogenic edema was detected (E)

Discussion

The WD is a rare, chronic, and systemic illness characterized predominantly by intestinal involvement but including a variety of other organs, especially the

lymphatic system, heart, and CNS (6). It occurs predominantly in middle-aged individuals (mean age at diagnosis around 50 years) and is about 8 times more frequent in men. The nervous system may be involved in around 10–43% of patients with multisystem WD. There

is no pathognomonic pattern for radiologic involvement of WD, though most imaging findings correlate with pathologic studies showing predominant involvement of the basilar telencephalon, thalamus, hypothalamus, quadrigeminal plate, and periaqueductal gray matter (7). The reason, *Tropheryma whippelii* is trophic to the gray matter in these regions, is not understood. Furthermore, the exact pathophysiology is poorly understood, though it is suspected that damage is caused by direct bacterial replication, more so than the associated host's immune response to inflammatory damage (8). Gross pathologic findings of the CNS include generalized atrophy, scattered granulomas in the gray matter of the cerebral and cerebellar cortex, the periventricular gray matter, and the gray matter around the aqueduct (9).

The CT scan can be normal, regardless of the clinical features, or can reveal focalized lesions, which can be hypo or hyperdense, contrast-enhanced or not, and with or without mass effect (10). Imaging techniques do not reveal any specific findings; however, MRI is superior to other techniques for the detection of small lesions (11). Unfortunately, the abnormalities on MRI are not specific to every patient. Review of the literature shows a wide array of MR appearances and clinical presentations in WD ranging from similar midline abnormalities as presented here to nodular parenchymal lesions or leptomeningeal enhancement to stroke-like presentations of focal tumor-like lesions (12, 13). Multiple mass lesions have rarely been described. They

usually appear hypointense on T1-weighted images and hyperintense on T2-weighted images and enhance after infusion of contrast media (14). However, a small number of patients have normal-appearing MR images (15).

Repeated MR investigations in this patient showed different extent and degree of signal alteration at various stages of the disease, indicating different stages in the inflammatory process and different degrees of edema. During acute phase both the GM and WM which combined with mass effect were involved, but during the recovery period, first, the GM showed improvement and then vasogenic-edema-like changes were seen in the WM (Figure, 4A). Very small contrast enhancement foci in the background of the lesion may be attributable to a focal disruption of the blood-brain barrier; the combination of that enhancement with signal intensity changes on T1-images might indicate a progression of the inflammation. In the present study, these enhancements mostly were seen in expanding periphery of the lesions. Another finding in current patient with brain involvement was some striated lines extending from cortex to the ventricle which could be secondary to mark atrophic changes and perivascular space dilatation that occurs in different stage of the disease (Figure, 3A). There was also some small cystic degeneration at corpus callosum (Figure, 4B). On DW images, it seems that the restriction confined only to the active lesions, especially in the expanding area of the injured tissues (Figure, 1C).

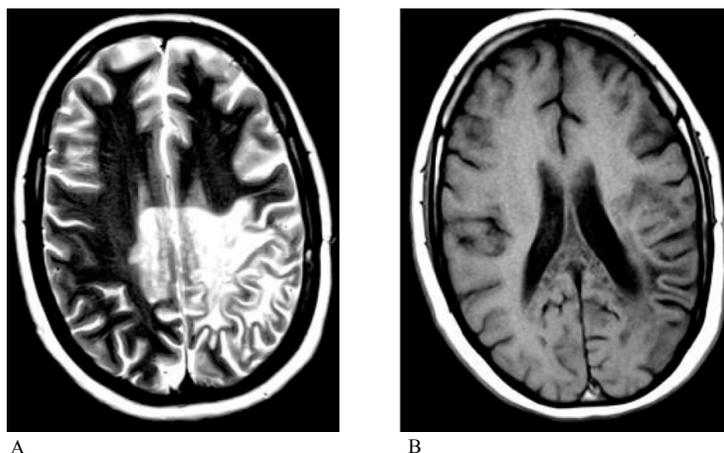


Figure 4. Repeated MR images six months after initial admission. Axial T2 WI during acute phase of the lesion, both the GM and WM which combined with mass effect were involved but over the recovery period, first the GM showed improvement and then vasogenic-edema-like changes were seen in the WM (A); axial T1WI with some small cystic degeneration at corpus callosum (B)

The diagnosis of WD involving solely the nervous system remains difficult. Mostly it is based on a combination of various neurological symptoms and the

evidence of PAS-positive macrophages detected in cerebro-spinal fluid. The CNS WD consists of multiple small circular or oval lesions, measuring an average of

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two mm in diameter, disseminated throughout the gray matter and characterized by the accumulation of macrophages, staining very intensely with periodic acid-Schiff stain, as shown in postmortem studies (7) or in brain biopsied specimens as described in this case (Figure 2).

Differentiating the cerebral involvement of WD, which presents as multiple or focal mass lesions is important. In the differential diagnosis of those lesions, glioma was the first consideration. However, because of the fact that the clinical and neuroimaging findings are nonspecific, there are various diseases other than neoplasms in the differential diagnosis, such as parasitic infections (e.g. cysticercosis and toxoplasmosis), unusual mycobacterial and fungal infections, metabolic disorders, vasculitis, or autoimmune demyelinating disease (11, 12). As mentioned previously MRI findings of corpus callosum associated with cerebral WD are also not specific and can mimic other diseases including tumoral diseases like lymphoma and glioma, inflammatory-demyelinating events, vascular processes, traumatic injuries, endocrine and metabolic causes (16). But repeated MRI of the brain which indicates the coincident of atrophic and acute lesions simultaneously could be a valuable diagnostic indicator of brain WD using MR images. However, the radiologist should know the different imaging features of the various diseases in order to establish the correct differential diagnosis. So, it is crucial a good clinical context to establish an accurate diagnosis and an early treatment to reduce mortality.

Here, we reported a WD involving brain in a woman based on the MR features and signal characteristics, which is relatively rare in female. However, in the present patient, as mentioned above the different parts of the brain could be involved, particularly with regard to the various phases of the disease. Only approximately 1000 cases of all types of WD have been reported (5), and our understanding of brain MR imaging is based only on case reports; thus, each new case imaged with modern equipment has the potential to expand our understanding significantly as long as the diagnosis has been carefully established. The main MRI diagnostic findings in current patient were encephalomalacia in chronic lesions of WM and mass effect in acute lesions as hypersignal areas simultaneously in FLAIR sequences. Simultaneous incident of atrophic and acute lesions was one of the valuable diagnostic indicators of brain WD using MR images in this patient. Understanding wide range of possible MR imaging appearances of WD enables the radiologist to consider

WD in the differential diagnosis more effectively and thus spurs the clinician to consider both the diagnosis and early initiation of treatment, which may significantly impact outcome.

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