Diffusion-Weighted Imaging Abnormalities in Wernicke Encephalopathy

Reversible Cytotoxic Edema?

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Background: Wernicke encephalopathy (WE) is a metabolic disorder of the central nervous system resulting from vitamin B1 deficiency. The exact mechanisms underlying the pathogenesis of the lesions in WE are not completely understood. Vitamin B1 deficiency is associated with intracellular and extracellular edema by glutamate-N-methyl-D-aspartate receptor–mediated excitotoxicity. Conventional magnetic resonance imaging (MRI) cannot differentiate the types of edema. Diffusion-weighted imaging (DWI) has been reported to detect early ischemic damage (cytotoxic edema) as bright areas of high signal intensity (SI) and vasogenic edema as areas of heterogeneous SI.

Objectives: To describe the DWI findings and to characterize the types of edema in WE using DWI.

Setting: Tertiary referral center.

Design and Methods: Two patients with WE underwent DWI and conventional MRI with gadolinium enhancement. Wernicke encephalopathy was diagnosed with salient conventional MRI findings (high SIs in the paravermal thalamus, periaqueductal gray matter, and mamillary bodies) and typical clinical history and symptoms. Apparent diffusion coefficient (ADC) values were measured in abnormal lesions by visual inspection of DWIs and T2-weighted echo planar images.

Results: T2-weighted and fluid-attenuated inversion recovery MRIs showed high SIs in the bilateral paravermal thalamus, mamillary bodies, and periaqueductal gray matter. The DWIs showed bright high SI in the corresponding lesions, and ADC values were decreased (patient 1: 512–545 × 10⁻⁶ mm²/s; patient 2: 576–612 × 10⁻⁶ mm²/s). The ADC decrease and the DWI high SI were normalized in 2 weeks with administration of thiamine hydrochloride.

Conclusions: Abnormalities on DWI and ADC decrease became normalized with adequate therapy. The MRI abnormalities in WE might be owing to the “reversible cytotoxic edema” caused by vitamin B1 deficiency.

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PATIENTS AND METHODS

DATA ACQUISITION AND ANALYSIS

Patients were examined using a 1.5-T MRI unit (Signa Horizon; General Electric Medical Systems, Milwaukee, Wis) with echoplanar imaging capability. A fast spin-echo, T2-weighted images (repetition time/echo time, 4200/112 ms; field of view, 21 × 21 cm; matrix, 256 × 192; and slice thickness, 5 mm with a 1.5-mm gap) were obtained. Diffusion-weighted imaging was obtained in the transverse plane using single-shot echoplanar imaging (repetition time/echo time, 6500/125 ms; field of view, 24 × 24 cm; matrix, 128 × 128; slice thickness, 5 mm with a 2.5-mm gap; and 2 b values, 0 and 1000 s/mm²). The diffusion gradients were applied along 3 axes (x, y, and z) simultaneously. The ADC was calculated based on the Stejskal-Tanner equation⁹ as the negative slope of the linear regression line best fitting the points for b vs ln (SI), where SI is the signal intensity from the region of interest within the images acquired at each b value. Performing this calculation on a pixel-by-pixel basis created ADC maps. The respective ADC values are described. Normal ADC values of the parenchyma and white matter range from 0.78 to 0.91 × 10⁻³ mm²/s (K.C. and D.-W.K., unpublished data, 2000). Regions of interest were carefully drawn in the abnormal areas on calculated average ADC maps and in normal-appearing areas with variable sizes. Small circular regions of interest of 9 to 25 mm² were centered on areas with abnormal signal on the DWIs or T2-weighted images to calculate mean ADC values. Regions of interest were selected using T2-weighted echo-planar images of the same acquisition as the DWIs (ie, images generated from the diffusion sequence with diffusion sensitivity b=0) to avoid errors in regions of interest selection due to spatial distortion problems causing discrepancies between DWIs and conventional MRIs. The analysis of images and ADC values was performed by expert neuroradiologists (Kee-Hyun Chang, MD, PhD, Department of Radiology, Seoul National University Hospital) and neurologists (K.C. and D.-W.K.). Perfusion-weighted MRI was not performed.

PATIENT 1

A 61-year-old woman was admitted to the hospital for altered consciousness. Before admission, nausea, recurrent vomiting, abdominal pain, and swelling developed gradually for 2 months. Because of the recurrent vomiting, she did not eat her meals regularly and followed a light liquid diet during the past 2 months. One month before hospital admission, she visited the local clinic, and mild paralytic ileus was noted. Four days before admission, altered consciousness and confusion developed. She spoke incomprehensible words to her family and could not stand without assistance. Her level of consciousness declined, and on the day of hospital admission she was comatose. The patient was afibrile and afebrile. She had a history of ischemic stroke in the left anterior cerebral artery territory 1 year previously; however, she had since enjoyed good health. She had hypertension for 2 years and took her medications before the incident. She had undergone hysterectomy 3 years previously.

In the emergency department she did not respond to painful stimuli. Vital signs, electrocardiographic evidence, and laboratory findings, including arterial blood gas values, were normal. Neurologic examination revealed complete ophthalmoplegia and a slightly rigid neck. Brain MRI, including DWI, and gadolinium enhancement were performed on the second hospital day (Figure 1). With the help of MRI findings, WE was strongly suspected, and 200 mg of thiamine was given daily via intravenous and oral routes. On the fourth hospital day she regained consciousness, and the ophthalmoplegia started to improve. On the seventh hospital day she became alert and could communicate with her family. On hospital day 10, the ophthalmoplegia completely resolved, and mild confusion was noted. On hospital day 14, follow-up MRI (Figure 2) showed complete resolution of the previous high SIs. However, moderate confabulation, attentional deficit, and gait ataxia remained on hospital day 60.

PATIENT 2

A 73-year-old man was admitted to the hospital because of gait disturbance and diplopia. Nausea, vomiting, and poor oral intake developed 3 weeks before admission. Because of the severe nausea, he could not eat his meals regularly, and he ate a light fluid diet. Two weeks before hospital admission, gait disturbance and diplopia developed, and he could not walk without assistance. The symptoms progressed, and mental confusion developed 1 week before hospital admission. He had had rectal cancer and had undergone hemicolectomy with colostomy 5 years earlier. Vital signs, electrocardiographic evidence, and laboratory findings, including arterial blood gas values, were normal. In the emergency department, neurologic examination showed confused mentality, left-sided sixth nerve palsy, and bilateral limb ataxia. Magnetic resonance imaging, including T1-weighted, T2-weighted, and FLAIR images, was performed with DWI on the first hospital day. The diagnosis of WE was made using the typical clinical manifestations and MRI findings, and 200 mg of thiamine was given intravenously daily. The ataxia and ophthalmoplegia started to resolve on hospital day 2, and on the fifth hospital day, confused mentality and the previously described symptoms completely resolved. However, mild confusion developed on the seventh hospital day, and the symptoms persisted on hospital day 30.

WE. These findings are summarized as high signal intensities (SIs) on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRIs in the involved areas, such as the thalamus, hypothalamus, periaqueductal gray matter and cerebellum, and gadolinium-enhancing lesions, indicating blood-brain barrier breakdown. However, DWI findings have not yet been reported in WE, to our knowledge. We report DWI findings and the analysis of ADC maps for researching the pathogenesis of the edema in WE.

RESULTS

For patient 1, T2-weighted and FLAIR MRI performed on hospital day 2 showed high SIs in the paramedian thalamus, periaqueductal gray matter, and mamillary
bodies bilaterally (Figure 1A-B). Diffusion-weighted imaging performed on the same day showed the high SIs in the corresponding regions (Figure 1C-D). The corresponding apparent diffusion coefficient values of the lesions range from 512 to 545 × 10⁻⁶ mm²/s.

For patient 2, T2-weighted and FLAIR MRI performed on the first hospital day showed high SIs on the bilateral paramedian thalamus and periaqueductal gray matter (data not shown). Diffusion-weighted imaging performed on the same day showed high SIs on the corresponding areas, and the ADC values ranged from 576 to 612 × 10⁻⁶ mm²/s. On follow-up DWI, FLAIR images performed on hospital day 10 showed normal results.

Our patients had WE. The triad of WE symptoms—confusion, ophthalmoplegia, and gait ataxia—and the typical MRI findings developed during the prolonged fasting and recurrent vomiting. The neurologic deficits with MRI abnormalities were improved by administration of thiamine. Findings from DWI in our patients include reversible high SI in the bilateral paramedian thalamus and periaqueductal gray matter with decreased ADC values. The findings suggest that the MRI abnormalities of WE are caused by the cytotoxic edema and can be reversed with adequate treatment.

The exact mechanisms underlying the pathogenesis of the lesions in WE are incompletely understood. Vitamin B₁ is required as a coenzyme at intermediate points in carbohydrate metabolism and is important in maintaining osmotic gradients across cell membranes.¹⁹ Thus, vitamin B₁ deficiency is associated with intracellular and extracellular edema. The edema can progress to cellular proliferation, demyelination, and petechial hemorrhage, leading to cellular degeneration. Glutamate-N-methyl-D-aspartate (NMDA) receptor–mediated excitotoxicity has been proposed as a cause of neuronal cell death in pyrithiamine-induced thiamine deficiency (PTD) (the animal model of human WE) in rats on the basis of findings from histologic studies, microdialysis, and enzymatic studies.²⁰-²³ Decreased activity of the thiamine-dependent enzyme 2-oxoglutarate dehydrogenase is associated with the onset of neurologic signs and the progress of vitamin B₁ deficiency and could lead to the accumulation of glutamate in the brain.²⁴-²⁶ The characteristic features of neuronal death in PTD are consistent with those of excitotoxic cell death triggered by glutamate.²¹,²⁷,²⁸ The strongest evidence in support of a glutamateNMDA receptor–mediated process in PTD is that MK 801 (a glutamateNMDA receptor antagonist) administered to PTD rats blocked the localized increases in extracellular glutamate concentration in the brain and also significantly attenuated neuronal cell death.²³,²⁹ Zimitat and
Nixon\textsuperscript{30} suggested a unifying hypothesis for the glutamate\textsubscript{NMDA} receptor–mediated process in PTD rats. A decrease in 2-oxo-glutarate dehydrogenase activity could lead to the accumulation of intracellular glutamate and could adversely affect cellular energy levels in the PTD rat brain, limiting the function of adenosine triphosphate–dependent pumps of neurons or glial cells.\textsuperscript{31} Failure to maintain cellular electrolyte homeostasis could activate sodium–calcium–dependent pumps of neurons or glial cells.\textsuperscript{31} Abnormalities on DWI in our patients indicate that MRI abnormalities in WE might be due to cytotoxic edema caused by vitamin B\textsubscript{1} deficiency. Our findings suggest that DWI can be used as a tool in researching the pathogenesis of WE and in predicting the outcome of tissue with adequate treatment.

Abnormalities on DWI in our patients indicate that MRI abnormalities in WE might be due to cytotoxic edema caused by vitamin B\textsubscript{1} deficiency. Our findings suggest that DWI can be used as a tool in researching the pathogenesis of WE and in predicting the outcome of tissue with adequate treatment.

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