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 parietal 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 parietal 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.

Arch Neurol. 2002;59:123-127
PATIENTS AND METHODS

DATA ACQUISITION AND ANALYSIS

Patients were examined using a 1.5-T MRI unit (Signa Horizon, Echospeed; General Electric Medical Systems, Milwaukee, Wis) with echoplanar imaging capability. 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 equation 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 she ate 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 afebrile and apanic. 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 ophthomoplegia 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 confabulation 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 confabulation developed on the seventh hospital day, and the symptoms persisted on hospital day 30.

For patient 1, T2-weighted and FLAIR MRI performed on hospital day 2 showed high SIs in the paramedian thalamus, periaqueductal gray matter, and mammillary maps for researching the pathogenesis of the edema in WE.

RESULTS
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 ADC values in the corresponding areas were low (512-545 × 10⁻⁶ mm²/s). Gadolinium enhancement showed no abnormalities. T1-weighted MRI and MRI angiography showed normal results. In the 2-week follow-up DWI and T2-weighted images (Figure 2), the hyperintensities previously seen on DWI were reversed, and the ADC values were also normalized (876-940 × 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.

**COMMENT**

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-oxo-glutarate 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.²¹⁻²³,²⁷,²⁸ 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.²³,²⁸ Zimitat and
Nixon30 suggested a unifying hypothesis for the glutamate$_{NMDA}$ receptor–mediated process in PTD rats. A decrease in 2-oxo-glutamate 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.31 Failure to maintain cellular electrolyte homeostasis could activate selling-induced anion transporters on glial cell plasma membranes and the release of intracellular glutamate.32 Increases in extracellular fluid glutamate concentration and disruption of the glutamate/glutamine cycle could also result from failure of glutamate transporters on glial cells.33 As vitamin B$_6$ deficiency progresses and 2-oxo-glutamate dehydrogenase activity and cellular energy reserves further decline, the extracellular fluid glutamate concentration in affected brain structures could increase, as has been measured in the thalamus of PTD rats.22,23 Increased extracellular fluid concentrations of glutamate would lead to glutamate$_{NMDA}$ receptor stimulation and thus increased expression of Fos proteins, which would eventually cause cell death.30

High SIs on DWI and decreased ADC values indicate the presence of cytotoxic edema, which conventional MRI cannot differentiate. Cytotoxic edema, presented as high SI on DWI, can occur in various situations, such as acute atherosclerotic infarction,1–9 status epilepticus,30,34 and WE. The initial triggering factors leading to cytotoxic edema may also vary according to the main conditions; however, the subsequent results may become similar, leading to cell death. In arterial ischemia, the cessation of blood flow can cause the initiation of ischemic cascade of cell death. In status epilepticus, the main mechanisms are neuronal hyperexcitability and the excessive release of excitatory amino acids, such as glutamate.35 In WE, the main triggering mechanism may be the excitotoxicity caused by the nutritional deficit (thiamine), affecting glucose metabolism, leading to glutamate$_{NMDA}$ receptor–mediated excitotoxicity. Questions about the reversibility of affected tissue might arise. The high SIs on DWI do not always indicate irreversibility but the presence of “tissue at risk.” Dardzinski et al36 reported ADC changes over time after permanent middle cerebral artery occlusion. They suggested the following ADC values: (1) at less than 450 × 10$^{-6}$ mm$^2$/s, severe ischemia and irreversible damage occur; (2) at greater than 550 × 10$^{-6}$ mm$^2$/s, infarction does not occur; and (3) at 450 to 550 × 10$^{-6}$ mm$^2$/s, the damage is potentially reversible. Our ADC results (patient 1: 512-545 × 10$^{-6}$ mm$^2$/s; patient 2: 576-612 × 10$^{-6}$ mm$^2$/s) corresponded well with those of the previous studies. With adequate treatment, the DWI abnormalities in WE might be reversible, similar to the cells in the ischemic penumbra.36–38

Abnormalities on DWI in our patients indicate that MRI abnormalities in WE might be due to cytotoxic edema caused by vitamin B$_6$ 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.

Accepted for publication August 28, 2001.

Author Contributions: Study concept and design (Drs Chu, Kang, Kim, Lee, and Park); acquisition of data (Drs Chu, Kang, Kim, Lee, and Park); analysis and interpretation of data (Drs Chu, Kang, Kim, and Park); drafting of the manuscript (Drs Chu, Kang, Kim, Lee, and Park); critical revision of the manuscript for important intellectual content (Drs Chu, Kang, Kim, Lee, and Park); statistical expertise (Dr Kim); obtained funding (Dr Kim); administrative, technical, and material support (Drs Chu, Kang, Kim, and Park); and study supervision (Drs Kim and Lee).

This work was supported by the clinical research fund of Seoul Boramae Municipal Hospital, Seoul, Korea. We thank Yon-Jae Chung, BSc(Pharm), MS, for her editorial assistance.

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