Diffusion-Weighted Imaging Abnormalities in Wernicke Encephalopathy

Reversible Cytotoxic Edema?

Kon Chu, MD; Dong-Wha Kang, MD, PhD; Han-Joon Kim, MD; Yong-Seok Lee, MD, PhD; Seong-Ho Park, MD, PhD

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-mediates 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 paramedian 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 paramedian 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

Diffusion-weighted imaging (DWI), first developed by Le Bihan et al., can detect changes in water diffusion associated with cellular dysfunction and can also be used to detect ischemic lesions of the brain within the first few hours. The application of DWI in diagnosing arterial stroke is well established and has been demonstrated by numerous experimental and clinical studies as an early decrease and late increase, or pseudonormalization, of the apparent diffusion coefficient (ADC). It has been well documented that cytotoxic edema related to acute infarction is characterized by markedly decreased diffusion and that the increased interstitial water in vasogenic edema is seen as increased diffusion. Conventional magnetic resonance imaging (MRI) cannot differentiate between vasogenic and cytotoxic edema.

Wernicke encephalopathy (WE) is a disorder of the central nervous system with characteristic neuropathologic changes. The illness results from a deficiency of vitamin B₁ (thiamine hydrochloride). The typical pathologic findings include atrophy of the mamillary bodies; dilatation of the third ventricle and aqueduct; and, microscopically, endothelial swelling in the capillaries, microglial activation, petechial hemorrhage, and necrosis of the periventricular gray matter of the hypothalamus, thalamus, periaqueductal region of the midbrain, floor of the fourth ventricle, and cerebellum. The changes are often reversible with adequate administration of thiamine.

There have been numerous articles concerning the MRI findings of
PATIENTS AND METHODS

DATA ACQUISITION AND ANALYSIS

Patients were examined using a 1.5-T MRI unit (Siemens Horizon; 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 = 0 (SI), where S 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 afebrile 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 hysterec-

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.

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 maps for researching the pathogenesis of the edema in WE.
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 $545 \times 10^{-6}\text{mm}^2/\text{s}$.

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 $612 \times 10^{-6}\text{mm}^2/\text{s}$. 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. 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. 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. The characteristic features of neuronal death in PTD are consistent with those of excitotoxic cell death triggered by glutamate. Zimitat and...
Nixon suggested a unifying hypothesis for the glutamate 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. Failure to maintain cellular electrolyte homeostasis could activate selling-induced anion transporters on glial cell plasma membranes and the release of intracellular glutamate. 

Increases in extracellular fluid glutamate concentration and disruption of the glutamate/glutamine cycle could also result from failure of glutamate transporters on glial cells. As vitamin B1 deficiency progresses and 2-oxo-glutarate 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. 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.

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 arterial infarction, status epilepticus, 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 ischaemic cascade of cell death. In status epilepticus, the main mechanisms are neuronal hyperexcitability and the excessive release of excitatory amino acids, such as glutamate. 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 al. reported ADC changes over time after permanent middle cerebral artery occlusion. They suggested the following ADC values: (1) at less than 450 × 10−6 mm²/s, severe ischemia and irreversible damage occur; (2) at greater than 550 × 10−6 mm²/s, infarction does not occur; and (3) at 450 to 550 × 10−6 mm²/s, the damage is potentially reversible. 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.

Corresponding author and reprints: Seong-Ho Park, MD, PhD, Department of Neurology, Seoul Boramae Municipal Hospital, 395, Shindaebang 2-Dong, Dongjak-Gu, Seoul 156-012, Korea (e-mail: nrps@brm.or.kr).

REFERENCES


