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 B_1_ deficiency. The exact mechanisms underlying the pathogenesis of the lesions in WE are not completely understood. Vitamin B_1_ 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 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 \times 10^{-6} \text{ mm}^2/\text{s}; patient 2: 576-612 \times 10^{-6} \text{ mm}^2/\text{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 B_1_ deficiency.

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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 B_1_ (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 (Signa Horizon, Echospeed; 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 equation\(^1^8\) as the negative slope of the linear regression line best fitting the points for \(b\) vs In (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 afebrile and acyanotic. 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 confusion, 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.

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, periaqueuductal 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, periaqueuductal 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 $512 \times 10^{-6}$ to $545 \times 10^{-6}$ mm$^2$/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 $612 \times 10^{-6}$ mm$^2$/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 B$_1$ is required as a coenzyme at intermediate points in carbohydrate metabolism and is important in maintaining osmotic gradients across cell membranes. 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 $\times 10^{-6}$ mm$^2$/s).

The finding in patient 1 on follow-up DWI and T2-weighted images show complete resolution of the lesions in 2 weeks.
Nixon\textsuperscript{30} suggested a unifying hypothesis for the glutamate\textsubscript{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.\textsuperscript{31} Failure to maintain cellular electrolyte homeostasis could activate selling-induced anion transporters on glial cell plasma membranes and the release of intracellular glutamate.\textsuperscript{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.\textsuperscript{33} As vitamin B\textsubscript{1} 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.\textsuperscript{22,33} Increased extracellular fluid concentrations of glutamate would lead to glutamate\textsubscript{NMDA} receptor stimulation and thus increased expression of Fos proteins, which would eventually cause cell death.\textsuperscript{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 arterial infarction,\textsuperscript{1-9} status epilepticus,\textsuperscript{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.\textsuperscript{35} In WE, the main triggering mechanism may be the excitotoxicity caused by the nutritional deficit (thiamine), affecting glucose metabolism, leading to glutamate\textsubscript{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\textsuperscript{36} reported ADC changes over time after permanent middle cerebral artery occlusion. They suggested the following ADC values: (1) at less than 450×10\textsuperscript{-6} mm\textsuperscript{2}/s, severe ischemia and irreversible damage occur; (2) at greater than 550×10\textsuperscript{-6} mm\textsuperscript{2}/s, infarction does not occur; and (3) at 450 to 550×10\textsuperscript{-6} mm\textsuperscript{2}/s, the damage is potentially reversible. Our ADC results (patient 1: 512-545×10\textsuperscript{-6} mm\textsuperscript{2}/s; patient 2: 576-612×10\textsuperscript{-6} mm\textsuperscript{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.\textsuperscript{36-38}

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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