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MR Imaging of Nonalcoholic Wernicke Encephalopathy: A Follow-Up Study

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Summary: We investigated the correlation of MR imaging features with the pathological evolution and prognosis of nonalcoholic Wernicke encephalopathy. A retrospective review and analysis was conducted of 6 cases of nonalcoholic Wernicke encephalopathy, consisting of MR imaging features, clinical characteristics, and outcomes after thiamine administration. One patient died, 1 patient entered a persistent vegetative state, and the others recovered fully from Wernicke encephalopathy within 2 weeks to 1 year after thiamine administration.

Typical MR imaging showed areas of increased T2-weighted and fluid-attenuated inversion recovery (FLAIR) signals symmetrically surrounding the aqueduct and the third ventricle, at the floor of fourth ventricle, in the medial thalami, and in the capita of caudate nuclei. Two patients presenting without coma showed increased T2-weighted and FLAIR signals of the periaqueductal area only. All 4 patients presenting with coma showed increased T2-weighted and FLAIR signals symmetrically in the medial thalami and in the capita of caudate nuclei. Of the 4 patients with coma, 2 patients with deep coma showed increased T2-weighted and FLAIR signals in the medial thalami and caudate nuclei as well as in the frontal and parietal cortices. According to the follow-up results, increased T2-weighted and FLAIR signals in the 4 patients without cortical damage decreased in intensity, consistent with clinical recovery within 2 weeks to 1 year. The patient in a persistent vegetative state exhibited progressive atrophy of the whole brain during the 2 years of the follow-up study. MR imaging is helpful not only to diagnose acute nonalcoholic Wernicke encephalopathy but also to evaluate the pathologic evolution and prognosis of the disorder.

Wernicke encephalopathy is a neurologic disorder caused by thiamine deficiency. Most patients with Wernicke encephalopathy have a background of alcohol abuse. During the acute phase of Wernicke encephalopathy, typical pathologic findings include variable degrees of necrosis, vascular proliferation, astroglial and microglial proliferation, and petechial hemorrhages in the medial thalami, mammillary bodies, periaqueduct, floor of the fourth ventricle, and superior vermis (1). Being consistent with pathologic

features, MR imaging findings include atrophy of the mammillary bodies and cerebellar vermis, as well as increased T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging signals in the periaqueduct area and bilateral medial thalami (2–5). Correspondingly, the clinical findings of Wernicke encephalopathy include neuroophthalmologic manifestations, ataxia, hypomnesia, and global confusion. However, most of these data originated from studies of alcoholic Wernicke encephalopathy. Nonalcoholic Wernicke encephalopathy has been reported only in isolated cases (6–8). The aim of our study was to investigate the correlation of MR imaging features with clinical characteristics and to compare known pathologic information with the pathologic evolution and prognosis in patients with acute nonalcoholic Wernicke encephalopathy on follow-up examinations.

Case Reports

Six patients, 3 women and 3 men, with an average age of 33.0 years (16–56 years), were enrolled. No patients had a history of alcohol abuse but all had a history of acute pancreatitis (1 patient with acute gallstone pancreatitis, 1 with acute pancreatitis secondary to nodular panniculitis, and the others with idiopathic pancreatitis). Before the onset of Wernicke encephalopathy, all of them underwent a course of therapeutic fasting and received total parenteral nutrition without thiamine supplements (ranging from 16 to 34 days). Initial neurologic presentations, which included drowsiness (5/6), apathy (5/6), vertigo (4/6), mild mental confusion (4/6), unilateral or bilateral abducent palsy (2/6), memory retardation (2/6), and ataxia (2/6), appeared generally within 14–27 days after fasting. MR imaging was immediately conducted when acute Wernicke encephalopathy was clinically suspected, within 3–10 days after the occurrence of initial neurologic presentations. At this time, there were 2/6 patients with deep coma, 2/6 patients with mild coma, and 2/6 patients with drowsiness (Table).

The patients were immediately administered 100 mg of intravenous thiamine when Wernicke encephalopathy was suspected and, thereafter, 100 mg per day for 5–15 consecutive days intravenously or intramuscularly. All patients were followed up for 1–2 years, with the exception of 1 patient who died, and were administered 150 mg of fursultiamin per day via the gastrointestinal tract during follow-up.

MR imaging with a (Signa) 1.5T MR scanner (GE Healthcare, Milwaukee, WI) consisted of T1-weighted (TR/TE, 500/9), T2-weighted (TR/effective TE, 4000/99), and FLAIR (TR/effective TE, 10,002/148) images. The follow-up imaging was performed once every 3 months.

Results

During the acute stage of Wernicke encephalopathy, increased signal intensities on T2-weighted and

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Patients with pathologic MR imaging in acute nonalcoholic Wernicke's encephalopathy

Patient No./ Sex/Age (y)	Duration* (d)	Conscious State [†]	Duration of Thiamine Therapy and Follow-ups	Initial MR Imaging
1/M/56	7	Deep coma	15 d (died)	T2W and FLAIR increased signals symmetrically in periaqueductal area, floor of fourth ventricle, periventricle region of third ventricle, medial thalami, capita of caudate nuclei, and frontal and parietal cortices
2/M/27	5	Mild coma	2 y	T2W and FLAIR increased signals symmetrically in periaqueductal area, floor of fourth ventricle, periventricle region of third ventricle, medial thalami, and capita of caudate nuclei (Fig 4)
3/F/47	10	Deep coma	2 y	T2W and FLAIR increased signals symmetrically in periaqueductal area, floor of fourth ventricle, periventricle region of third ventricle, medial thalami, capita of caudate nuclei, frontal and parietal cortices (Fig 3)
4/M/16	3	Drowsiness	1 y	T2W and FLAIR increased signals in periaqueductal area
5/F/19	5	Drowsiness	1 y	T2W and FLAIR increased signals in periaqueductal area (Fig 1)
6/F/26	5	Mild coma	1 y	T2W and FLAIR increased signals symmetrically in periaqueductal area, floor of fourth ventricle, periventricle region of third ventricle, medial thalami, and capita of caudate nuclei (Fig 2)

Note.—FLAIR indicates fluid-attenuated inversion recovery.

*From initial neurologic presentation to initial MR imaging.

[†]At initial MR imaging.

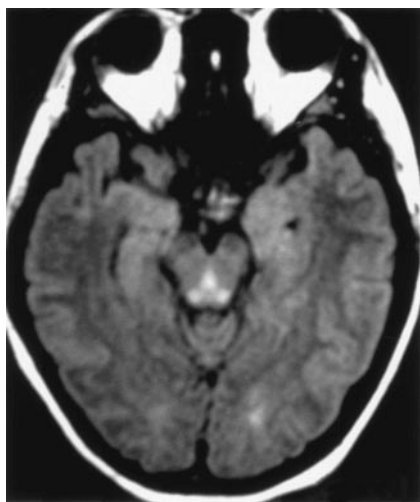


Fig 1. Patient 5. Axial FLAIR MR image shows increased signal intensity in periaqueductal area.

FLAIR images in the periaqueductal area were observed in all 6 patients (Fig 1). Four patients with coma exhibited high T2-weighted and FLAIR signal intensities in the regions of the medial thalami, the capita of the caudate nuclei, the floor of fourth ventricle, and that surrounding the third ventricle (Fig 2). Of the 4 patients with coma, 2 patients with deep coma exhibited high T2-weighted and FLAIR signal intensities not only in the frontal and parietal cortices but also in the bilateral medial thalami and the capita of the caudate nuclei (Fig 3). None of the patients

had atrophy of the cerebellar vermis and mammillary bodies.

Follow-up imaging showed that the 2 patients with deep coma who had high T2-weighted and FLAIR signal intensities in the frontal and parietal cortices had very bad prognoses: 1 patient died 15 days after initial neurological presentations appeared and one entered a persistent vegetative state with her brain showing progressive atrophy during the 2 years of the follow-up. After thiamine administration, the high T2-weighted and FLAIR signal intensities of the other patients without cortical lesions decreased gradually, concomitant with clinical recovery (Fig 4). They recovered fully from Wernicke encephalopathy within 1 year (ranging from 14 days to 1 year).

Discussion

Thiamine, a water-soluble essential vitamin obtained from the diet, is an important cofactor for 3 key enzymes involved in both the Krebs and pentose-phosphate cycle: α -ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex, and transketolase. It is also essential in maintaining osmotic gradients across cell membranes. Thiamine deficiency leads to impaired cerebral energy metabolism, focal lactic acidosis, *N*-methyl-D-aspartate receptor-mediated excitotoxicity, blood-brain-barrier breakdown, and decreased osmotic gradients across cell membranes (5–6, 9). This pathophysiologic abnormality is prone to occur in the periventricle and periaqueductal regions in which thiamine-related glucose and ox-

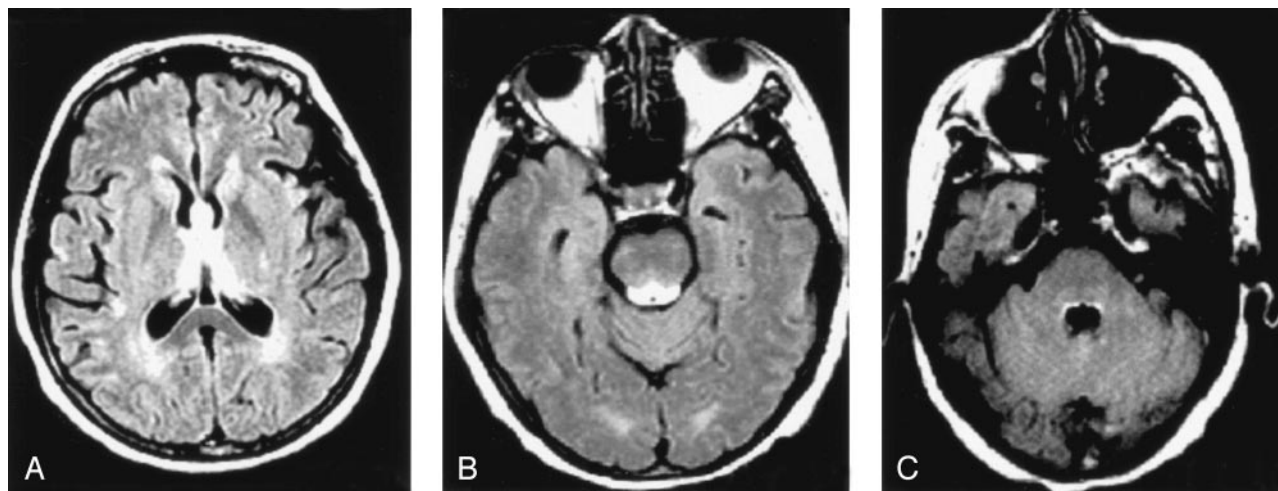


FIG 2. Patient 6. Axial FLAIR MR images show increased signal intensity symmetrically within the medial thalami and the capita of caudate nuclei (A), periaqueductal area (B), and the floor of fourth ventricle (C).

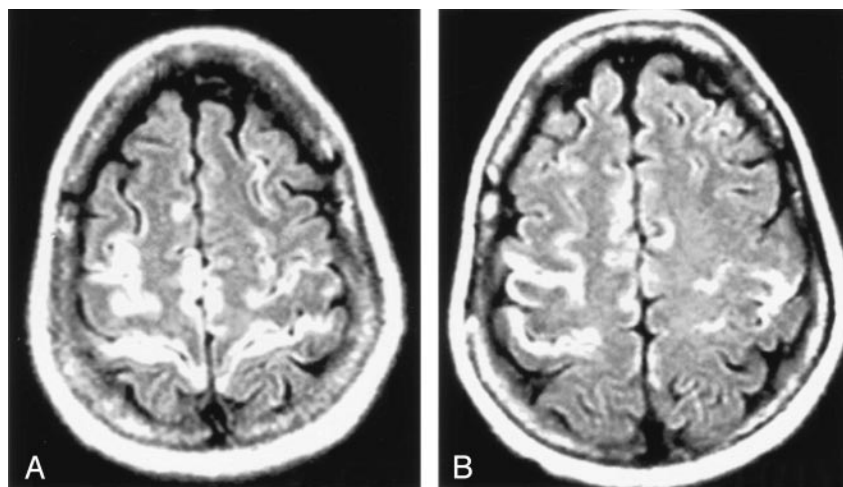


FIG 3. Patient 3. Axial FLAIR MR images show symmetric increased signal intensity in the frontal and parietal cortices.

idation metabolism is abundant. Thus, Wernicke encephalopathy has characteristic pathologic and MR imaging alterations symmetrically distributed in the perimidine of brain. Corresponding to morphologic abnormalities, ophthalmoplegia and ataxia ensue from the involvement of the pontine and mesencephalic tegmentum; hypomnesia and global confusion are related to damage within the thalami and possibly to damage to the mammillary bodies (6, 10–11). Most researchers have obtained the previously mentioned features from studying alcoholic Wernicke encephalopathy.

Nonalcoholic Wernicke encephalopathy is an uncommon disorder of the central nervous system. To our knowledge, the studies that investigate MR imaging features and the evolution of the process are very limited. Recently, a small number of isolated case studies showed that typical MR imaging findings are similar in alcoholic and nonalcoholic patients with Wernicke encephalopathy, but the atrophy of the cerebellar vermis and mammillary bodies differs between the 2 (7–8, 12). This difference may be due to the following factors: (1) Cerebellar vermis and mammillary bodies are susceptible to thiamine deficiency

in alcoholic patients; (2) The alcoholic patients might have had previous attacks, and MR imaging findings in the acute phase were contaminated by previous injury. MR imaging studies among nonalcoholic patients likely represented the evolution of pathologic findings in the first attack of Wernicke encephalopathy because of the absence of previous Wernicke encephalopathy attacks (1, 6).

Our study confirmed these results. All patients did not present with atrophy of the cerebellar vermis and mammillary bodies. Increased T2-weighted and FLAIR signal intensities in the regions of the periaqueduct, periventricle, and medial thalami were the main features. The analysis combining clinical manifestations with MR imaging features showed that the patients without coma exhibited only periaqueductal damage (Fig 1) and all patients with coma presented with the lesions of the bilateral medial thalami and the capita of the caudate nuclei in the acute phase of nonalcoholic Wernicke encephalopathy (Fig 2). Our results show that lesions of the bilateral medial thalami are related to the degree of conscious disturbance in acute Wernicke encephalopathy, which is consistent with the clinical observation that damage of the

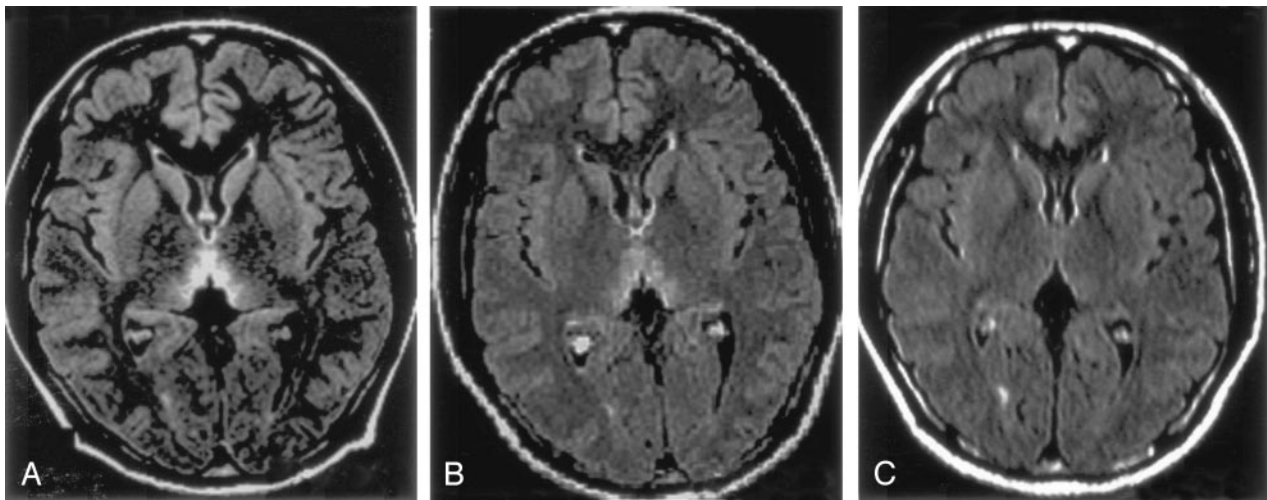


FIG 4. Patient 2. Axial MR images show symmetric FLAIR increased signal intensity within the medial thalami and capita of caudate nuclei in the acute phase (A), high signal intensity decreased 6 months after administration of thiamine (B), and normal signal intensity 1 year after treatment (C).

bilateral medial thalami by other factors (such as anoxia, ischemia, and inflammation) leads to various conscious disturbances (13). We found that fewer patients with nonalcoholic Wernicke encephalopathy exhibit the typical triad of ophthalmoplegia, ataxia, and global confusion seen in patients with alcoholic Wernicke encephalopathy because unreasonable glucocorticosteroid and/or intravenous glucose were used as therapeutic measures without thiamine supplement. These therapeutic measures accelerate the consumption of insufficient thiamine and deteriorate the situation of the patients.

A few authors have reported an atypical MR imaging presentation of Wernicke encephalopathy. Bae et al (14) reported a patient with bacterial meningitis and brain abscess accompanied by acute Wernicke encephalopathy because of persistent vomiting. MR imaging exhibited atypical lesions of the symmetric bilateral red nuclei and cerebellar dentate nuclei in addition to injuries of the periaqueductal area and bilateral medial thalami (14). We have not observed these atypical lesions in our patients. Recently, a few authors with isolated case studies reported increased T2-weighted and FLAIR signal intensities in the capita of the caudate nuclei and frontal and parietal cortices as uncommon presentations (15–17). However, all patients with coma in our study exhibited abnormal signs of the capita of the caudate nuclei. This finding shows that lesions of the caudate nuclei might be one of the marks of pathologic evolution, like the medial thalami in the acute phase of Wernicke encephalopathy, but these lesions are an uncommon presentation. It is possible that lesions of the caudate nuclei are less commonly reported in the literature because the cases reported have milder states of illness (4, 12). The capita of the caudate nuclei may be prone to damage during thiamine deficiency because it is in deep gray matter adjacent to lateral ventricle, like the medial thalami. In addition, 2 patients with cortical damage in our study had a

very bad prognosis: one died and another entered a persistent vegetative state.

These results differ from the cases that have previously been reported: Doss et al (15) reported one patient who presented with seizures and showed changes of Wernicke encephalopathy on diffusion-weighted MR imaging with involvement of the motor strip. She had a rapid recovery after thiamine administration, except for residual gait ataxia and substantial long-term psychiatric sequelae. We think the cortical involvement of this patient cannot rule out anoxic damage because of status epilepticus. D'Aprile et al (16) reported a 13-year-old girl with leukemia and Wernicke encephalopathy. During the second cycle of chemotherapy, she was diagnosed with acute Wernicke encephalopathy after persistent nausea and vomiting (we do not know how many days the patient vomited). T2-weighted images showed high-signal-intensity lesions bilaterally and symmetrically in the thalami, putamina, caudate nuclei, and frontal and parietal cortices. This patient improved and the abnormalities on MR imaging disappeared after intravenous thiamine administration and chemotherapy interruption. Because the authors did not indicate the duration of total parental nutrition without thiamine supplement and putamen lesions are very rare in acute Wernicke encephalopathy, we think there is not sufficient reason to diagnose this case as Wernicke encephalopathy, and the authors did not rule out the possibility of toxic encephalopathy by chemotherapeutic drugs. In our study, 6 patients did not undergo the previously mentioned factors. We have reason to believe that their pathologic features were caused only by thiamine deficiency and reflected a real evolution of acute Wernicke encephalopathy.

Conclusion

MR imaging is helpful not only to diagnose acute nonalcoholic Wernicke encephalopathy but also to

evaluate the pathologic evolution and prognosis of the disorder. The involvement of the caudate nucleus and cortex is not an uncommon presentation but rather the sign of pathologic evolution. The disorder may be remediable if only the periaqueductal area, thalamus, and caudate nucleus are involved. However, cortical damage may be indicative of irreversible damage and poor prognosis.

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