Neuroimaging Findings in Acute Wernicke's Encephalopathy: Review of the Literature

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OBJECTIVE. Wernicke's encephalopathy is an acute neurological syndrome resulting from thiamine (vitamin B1) deficiency. Early recognition is important because timely thiamine supplementation can reverse the clinical features of the disease. The aim of this article is to provide an update on the typical and atypical neuroimaging findings of the acute phase of the disease.

CONCLUSION. Wernicke's encephalopathy is characterized by a quite distinct pattern of MR alterations, which include symmetrical alterations in the thalami, mamillary bodies, tectal plate, and periaqueductal area, but atypical alterations may also been seen. A thorough knowledge of the neuroimaging findings of Wernicke's encephalopathy will assist in arriving at an early diagnosis, thus reducing the morbidity and mortality associated with this disease.

Wernicke's encephalopathy (WE) is an acute neurologic disorder resulting from thiamine (vitamin B1) deficiency. WE was first described by Carl Wernicke [1] in 1881 as "superior acute hemorrhagic poliencephalitis" in two men with alcoholism and in a woman affected by pyloric stenosis, whereas the association of WE with thiamine deficiency was first suspected in the 1940s [2]. The exact prevalence and incidence of WE are unknown, but necroscopy studies performed in adults have revealed incidence rates ranging from 0.5% over a 5-year period in Norway to 2.8% over a 9-year period in Australia [3–7]. A review of pediatric WE cases revealed that the frequency of WE in children appears to be broadly similar to that reported in adults [8]. Autopsy studies have consistently shown that the diagnosis of WE is often made only postmortem, particularly when patients present with atypical clinical manifestations [3–7, 9]. For instance, in patients with alcoholism and AIDS, WE diagnosis is missed in as many as 75–80% of all patients [10].

Traditionally, the clinical diagnosis of WE rests on the classical triad consisting of ocular signs, altered consciousness, and ataxia, already described by Wernicke [1] in his original article. Ocular signs associated with WE include nystagmus, bilateral lateral rectus palsies, and conjugate gaze palsies reflecting involvement of the oculomotor, abducens, and vestibular cranial nerves nuclei. However, subsequent studies have revealed that this triad occurs in only 16–38% of all patients with WE, which explains at least in part why WE is often clinically underdiagnosed [3, 11, 12]. In view of the poor diagnostic performance of the classical triad, new classification criteria have been proposed. These criteria require two of four items including dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and an altered mental state or mild memory impairment [13].

The pathogenesis of WE is thought to be related to thiamine deficiency, and, conversely, the prognosis of WE critically depends on the time of onset of thiamine supplementation [3]. Thiamine is needed by the cell membranes to sustain osmotic gradients but is also involved in glucose metabolism and in neurotransmitter synthesis. For healthy individuals, the daily thiamine requirement, which depends on the carbohydrate intake, is in the range between 1 and 2 mg. Because the body's reserves of thiamine are only 30–50 mg, the reserves would be completely depleted in 4–6 weeks in the absence of thiamine intake.

Many clinical conditions can impair the correct absorption of an adequate amount of thiamine, including chronic alcohol abuse [5, 14], gastrointestinal surgery [15–17], prolonged vomiting, chemotherapy, systemic

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infectious and noninfectious diseases, and dietary unbalance [12]. Alcoholism does not directly cause thiamine deficiency, although it may induce such deficiency because of its frequent association with malnourishment. More specifically, the low thiamine absorption rate at the mucosal level, the impaired hepatic function, and the alcohol-related raised thiamine metabolism together may lead to the development of chronic thiamine deficiency [14]. Thiamine-deficient membranes are unable to maintain osmotic gradients, which results in the swelling of intra- and extracellular spaces. Pathologic features are represented by edema, spongy degeneration of the neuropil, neuron sparing, swelling of capillary endothelial cells, and extravasation of RBCs [18].

In WE, the blood–brain barrier is defective in the periventricular regions, in which there is a high rate of thiamine-related glucose and oxidative metabolism [19]. MRI usually shows symmetric signal intensity alterations in the thalami, mamillary bodies, tectal plate, and periaqueductal area [12]. Signal intensity alterations in the cerebellum, cerebellar vermis, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium, and cerebral cortex represent atypical MRI findings [12, 18, 20–34] (Fig. 1 and Table 1). Atypical MRI findings are always found in association with the classical neuroradiological presentation. In the acute setting of WE, the cytotoxic edema can appear on both CT and MR images as symmetric hypodensity [35] and signal intensity alterations [12], respectively.

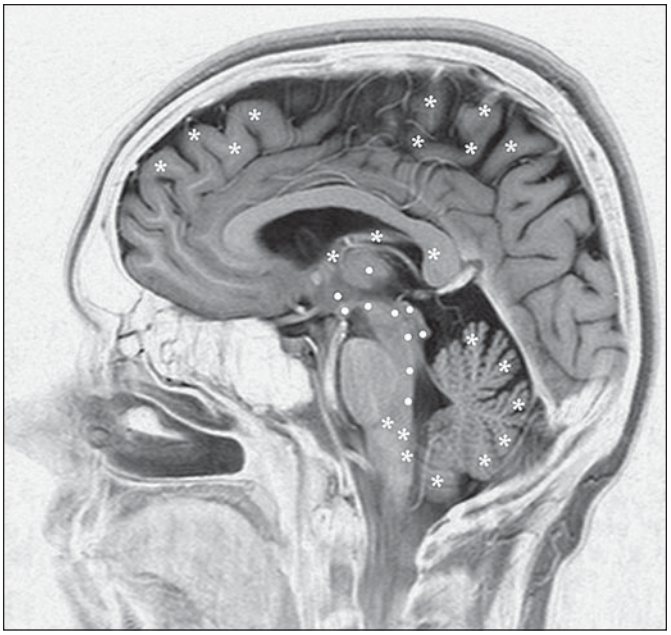


Fig. 1—Midsagittal T2-weighted MR image with gray-scale inversion in healthy 37-year-old man shows schematic representation of anatomic regions typically (*circles*) and infrequently (*asterisks*) affected by Wernicke's encephalopathy. Note that caudate capita and dentate nuclei are not seen in this view.

CT Findings

In the acute setting of WE, the sensitivity of the brain CT (Figs. 2A and 2B) is low compared with MRI. Antunez et al. [35] reported low-density alterations along the third ventricle walls in only two of 15 (13%) patients affected by WE during the acute phase of the disease. Those authors did not find any alteration in the periaqueductal area. The study protocol included 8-mm-thick slices parallel to the orbitomeatal plane. Antunez et al. concluded that CT is not useful in the diagnosis of WE. However, although no studies have formally investigated the role of CT perfusion protocols in comparison with MRI, we hypothesize that the application of such protocols might improve the diagnostic accuracy of CT in detecting WE. Recently, a patient affected by WE showing CT hypodensity of the fornices was described as an atypical case [36]. To our knowledge, there are no reports on the capacity of CT to show one of the most distinctive neuroradiological findings of WE—that is, cytotoxic edema of the mamillary bodies.

MRI Findings

Reversible cytotoxic edema is considered the most distinctive lesion of WE, and it is easily shown on MR images. Typical findings are represented by symmetric alterations in the thalami, mamillary bodies, tectal plate, and periaqueductal area. High-signal-intensity alterations on long-TR spin-echo images are the most frequent pathologic findings seen on MRI compared with low-signal-intensity alterations on short-TR spin-echo images (88% vs 31%, respectively) [12]. Among seven patients affected by WE with evidence of pathologic MRI findings, only two had low-signal-intensity alterations on short-TR images. On the contrary, four patients showed high-signal-intensity alterations on long-TR images and four showed contrast enhancement [37]. Brain images of alcoholic patients with WE during the acute phase of the disease may differ from those of nonalcoholic patients. In fact, in patients with alcoholism, atrophy of the mamillary bodies, infratentorial regions, supratentorial cortex, and corpus callosum may be found in association with the alterations typical of WE [35, 38]. In contrast, signal intensity alterations in nonalcoholic patients likely represent the first thiamine-related metabolic breakdown. For these reasons, no atrophy is found in nonalcoholic patients during the acute phase of the disease or at follow-up [12, 26].

Typical MRI Findings

The anatomic regions most frequently involved by MRI in WE are the medial thalami and the periventricular regions of the third ventricle [12] (Figs. 2C–2F and 3). These findings may be explained by the maintenance of cellular osmotic gradients that are strictly related to the concentration of thiamine levels in these areas [19]. Alterations in the median thalami and periventricular regions of the third ventricle are almost always found in association with other typical alterations of the disease [12, 38]. Rarely, these alterations represent the only findings of WE, as previously described, to our knowledge, in just two reports in the English-language scientific literature [12, 39]. If isolated symptoms such as altered consciousness are present, the differential diagnosis of alterations of the medial thalami should include ischemia in the artery of Percheron and deep cerebral vein thrombosis [40–42]. Primary acute disseminated encephalomyelitis, cytomegalovirus encephalitis, primary cerebral lymphoma, variant Creutzfeldt-Jakob disease, influenza A virus infection, and West Nile virus meningoencephalitis represent other disorders that should be considered in the differential diagnosis in the presence of symmetric medial thalamic lesions [43–49].

Usually, the differential diagnosis of symmetric thalamic alterations in WE is easy

TABLE 1: Atypical MRI Findings of Acute Wernicke's Encephalopathy

Areas Affected	Reference Study																
	[34] (*n* = 1 NA)	[20] (*n* = 1 NA)	[28] (*n* = 1 NA)	[63] (*n* = 1 NA)	[29] (*n* = 2 NA)	[27] (*n* = 1 NA)	[31] (*n* = 1 NA)	[32] (*n* = 1 NA)	[23] (*n* = 1 NA)	[33] (*n* = 1 NA)	[22] (*n* = 1 A)	[36] (*n* = 1 NA)	[38] (*n* = 1 A)	[12] (*n* = 13 A, 13 NA)	[21] (*n* = 1 NA)	[26] (*n* = 12 NA)
Abducens nuclei		●				●										
Caudate nuclei			●													■ □
Cerebellum/vermis		●		●					●		●		●	●	●	● ○
Cortex																
Dentate nuclei		●					●		●						●	
Facial nuclei		●				●									●	
Fornices	●											●				
Frontal cortex			●						●							
Hypoglossal nuclei														○	●	
Medulla oblongata									●							
Motor strip					●					●						
Parietal cortex			●						●							
Pontine tegmentum									●							
Pre- and postcentral cortex						●										
Precentral gyri	●															
Putamina			●													
Red nuclei		●					●									
Splenium							●	●								
Thalami			●		○											
Vestibular nuclei		●				●									●	

Note—Atypical findings are always associated with typical findings. Solid circles (●) indicate areas involved in one patient. Additional patients (when case reports involved more than one patient) are identified with open circles (○), solid squares (■), and open squares (□). A = alcoholic patients, NA = nonalcoholic patients.

because such alterations are almost always found in association with other classical neuroradiological signs represented by symmetric alterations in the thalami, mamillary bodies, tectal plate, and periaqueductal area [12, 39]. Signal intensity alterations and contrast enhancement in mamillary bodies are seen significantly more often in alcoholic patients [12]. Furthermore, contrast enhancement of the mamillary bodies may be the only sign of WE [12, 50]. This phenomenon has also been described in a pediatric patient who also showed signal intensity alterations of the medial thalami and periaqueductal gray matter [51] and may be similar to the well-known "fogging effect" [52] or to the increased detection of small lesions with contrast-enhanced T1-weighted images compared with T2-weighted images [53]. These findings support the indication to administer gadolinium-based contrast material when no signs of WE are found on unenhanced MR images. Movement artifacts are frequently seen in acute WE imaging studies, especially if changes in consciousness are present; however, in our experience, movement artifacts do not significantly affect the diagnostic accuracy [12].

Atypical MRI Findings

Atypical MRI findings are represented by symmetric alterations of the cerebellum, vermis of cerebellum, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium, and cerebral cortex [12, 18, 20–34] (Figs. 3 and 4). Cerebellar signal intensity alterations are rare in WE, but they have been reported in patients both with and without alcoholism. Cerebellar alterations are reversible and invariably associated with other typical findings; however, cerebellar alterations have also been associated with atypical findings [12, 20–22, 24]. Pathologic studies have shown a higher prevalence of cerebellar involvement compared with that observed in imaging studies. In fact, the cerebellum has been reported to be involved in more than half of WE cases [54].

The differential diagnosis of symmetric signal intensity alterations of the dentate nuclei, vestibular cranial nerves nuclei, abducens, red nuclei, and splenium include metronidazole-induced encephalopathy [55]. Nonalcoholic patients with WE may show virtually the same MRI features of metronidazole-induced encephalopathy in addition to those typical of WE [20, 21, 31]. Perhaps the conversion of metronidazole to a thiamine analog and its vitamin B1 antagonism may act via metabolic

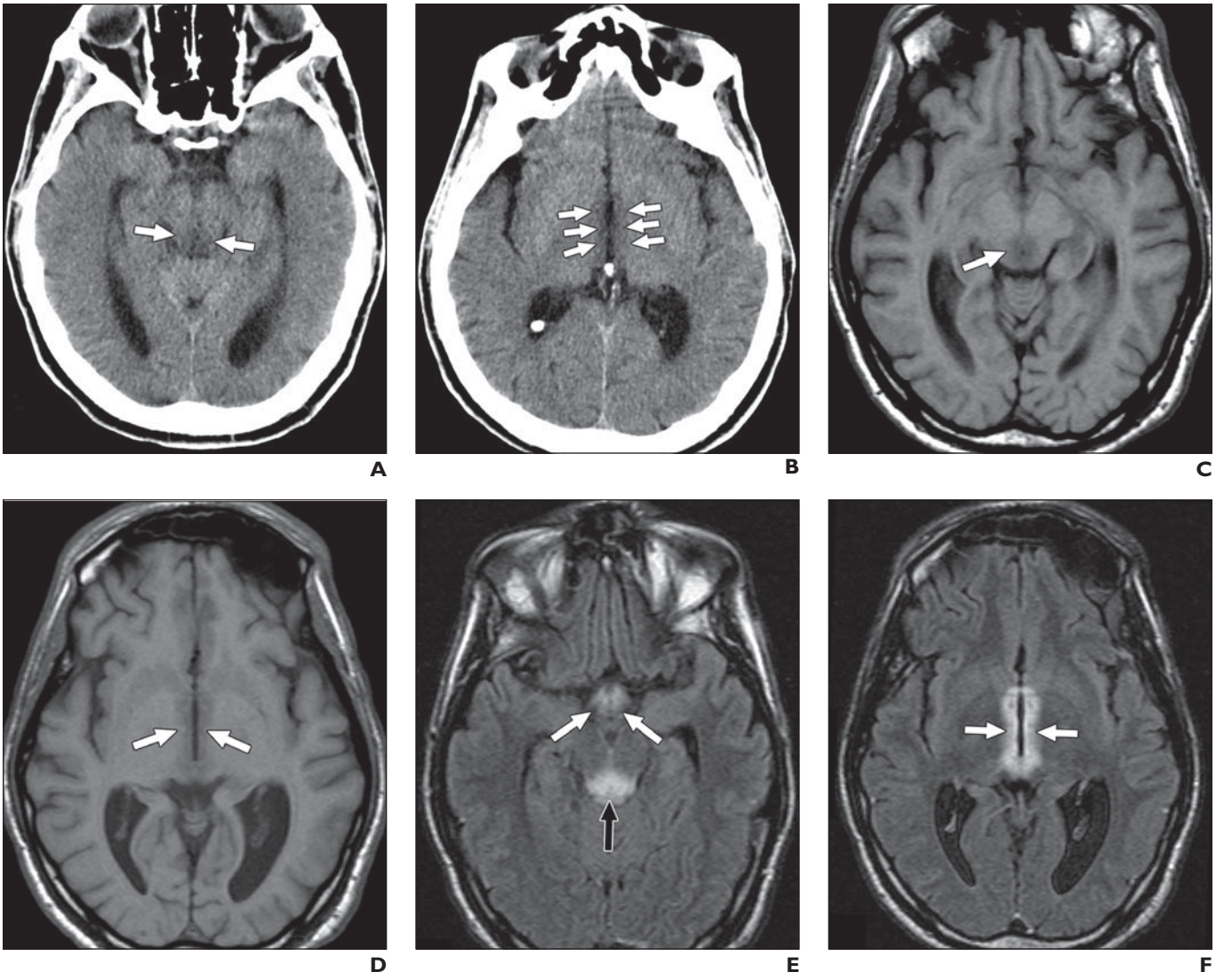


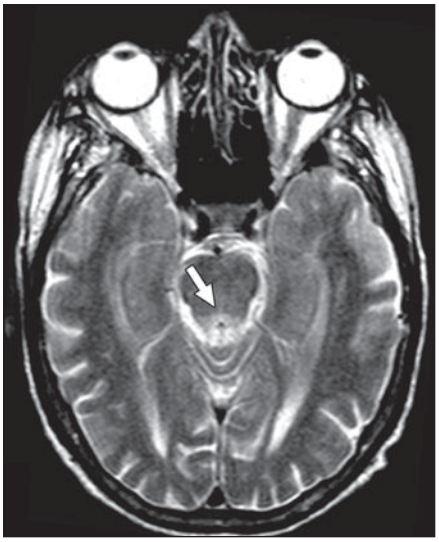
Fig. 2—33-year-old man affected by acute Wernicke's encephalopathy caused by severe malnutrition.
A and **B,** Axial unenhanced CT images show low-density alteration in periaqueductal area (*arrows,* **A**) and mild low-density alterations along third ventricle walls associated with mass effect (*arrows,* **B**).
C and **D,** Axial T1-weighted conventional images show low signal intensity of periaqueductal gray matter (*arrow,* **C**) and periventricular region of third ventricle (*arrows,* **D**).
E and **F,** Axial FLAIR images show signal intensity alterations of mamillary bodies (*white arrows,* **E**), periaqueductal area (*black arrow,* **E**), and periventricular region of third ventricle (*arrows,* **F**).

pathways similar to those operating in WE [56, 57]. Therefore, the differential diagnosis between WE and metronidazole-induced encephalopathy may be difficult in malnourished patients treated with metronidazole.

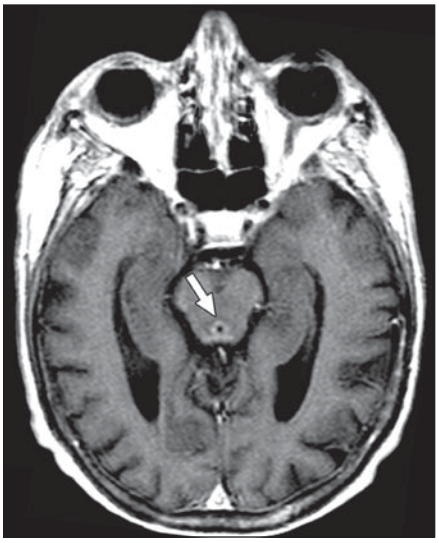
Few published studies exist on selective cranial nerve nuclei involvement, and those have described abducens, facial, vestibular, and hypoglossal nerve nuclei signal intensity alterations only on long-TR images [12, 20, 21]. These changes have always been found in nonalcoholic patients in association with the other typical alterations of the disease. The signal intensity alterations can be reverted by thiamine supplementation similar to those typical of the disease. To date, it remains unclear whether cranial nerve nuclei involvement represents a distinctive pattern in nonalcoholic patients. The presence of cortical lesions in association with coma may indicate a poor prognosis as a consequence of irreversible brain damage, as shown in two patients [26].

Diffusion-Weighted Imaging and Apparent Diffusion Coefficient

There are few data regarding the appearance of WE lesions on diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) transformation during the acute phase of the disease. DWI can detect changes in the diffusion of water molecules and may also show early ischemic changes in brain tissue [58, 59]. WE alterations typically show restricted diffusion, suggestive of cytotoxic edema [60]. However, DWI may show only slightly increased signal intensities within the thalami and periaqueductal area bilaterally but no signal intensity alterations in the other brain regions or no signal intensity abnormalities of the affected brain areas (Figs. 4C and 4D, and Fig. 5B). Thus, DWI may not be sensitive enough to

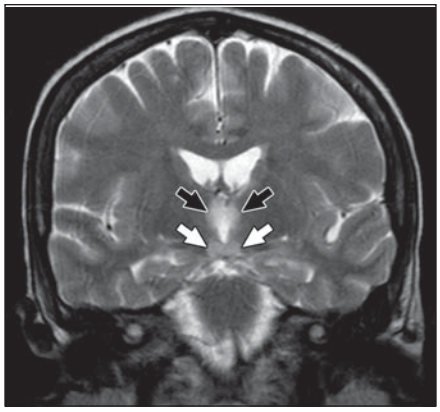


A

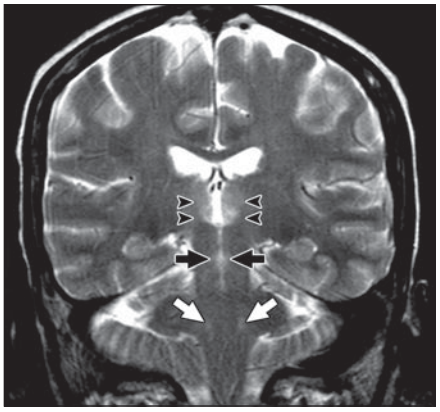


B

Fig. 3—60-year-old woman with history of gastric cancer treated with gastrectomy who presented with changes in consciousness and nystagmus.
A, Axial T2-weighted image shows high signal intensity of both periaqueductal gray matter and quadrigeminal plate (*arrow*).
B, Contrast-enhanced image of affected areas shows characteristic "Ω" shape (*arrow*).



A



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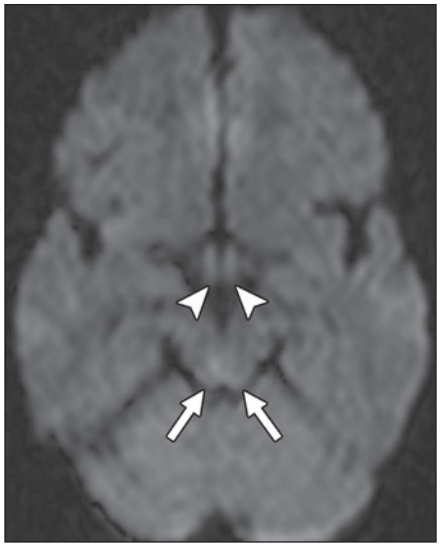

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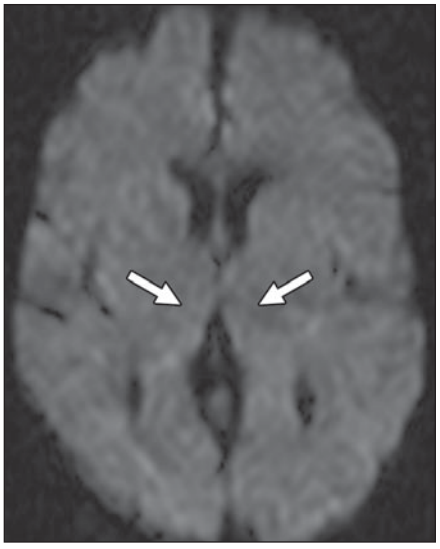

D

Fig. 4—54-year-old woman with chronic myeloid leukemia resistant to imatinib mesylate therapy.
A and **B,** Coronal T2-weighted MR images show signal intensity alterations of periventricular region of third ventricle (*black arrows,* **A**) and mamillary bodies (*white arrows,* **A**). Selective alterations of facial nerve nuclei (*white arrows,* **B**) in association with periaqueductal (*black arrows,* **B**) and thalamic (*arrowheads,* **B**) alterations are also seen.
C, Diffusion-weighted image does not show signal intensity alteration in tectal plate (*arrows*) and mamillary bodies (*arrowheads*).
D, Diffusion-weighted image shows no signs of decreased or increased diffusion in thalami (*arrows*) affected by Wernicke's encephalopathy.

reveal WE lesions [26]. The role of ADC in the diagnosis of WE is unclear because various patterns of decreased, normal, or increased ADC values have been described in WE [22, 60–63].

MR Spectroscopy

We know of only two reports on MR spectroscopy in humans [24, 62]. In one case, the authors showed low levels of *N*-acetylaspartate/creatine in the thalamus and cerebellum and a lactate peak in the cerebellum that did not resolve completely, suggesting tissue necrosis. In the other case, a remarkable lactate increase in the thalami represented the only alteration. This increase was attributed to the presence of anaerobe oxidation and thiamine deficiency worsened by an excessive parenteral dextrose load. To date, MR functional images do not have a clinical prognostic impact.

Discussion

The clinical diagnosis of WE traditionally rests on the presence of the classical triad (ocular signs, altered consciousness, and ataxia) described by Wernicke [1] in his original article. However, this classical clinical triad is found, in fact, in only a minority of WE patients [3, 11, 12]. As a result, WE is often clinically underdiagnosed, particularly when patients present with atypical clinical manifestations or have no history of alcohol intake. New criteria have been proposed in an attempt to capture more effectively the spectrum of WE clinical manifestations [13], but it is unclear how these criteria perform in settings different from that in which they were generated and whether they have found wide acceptance in clinical practice.

Neuroimaging studies are powerful tools in supporting the diagnosis of WE and can also

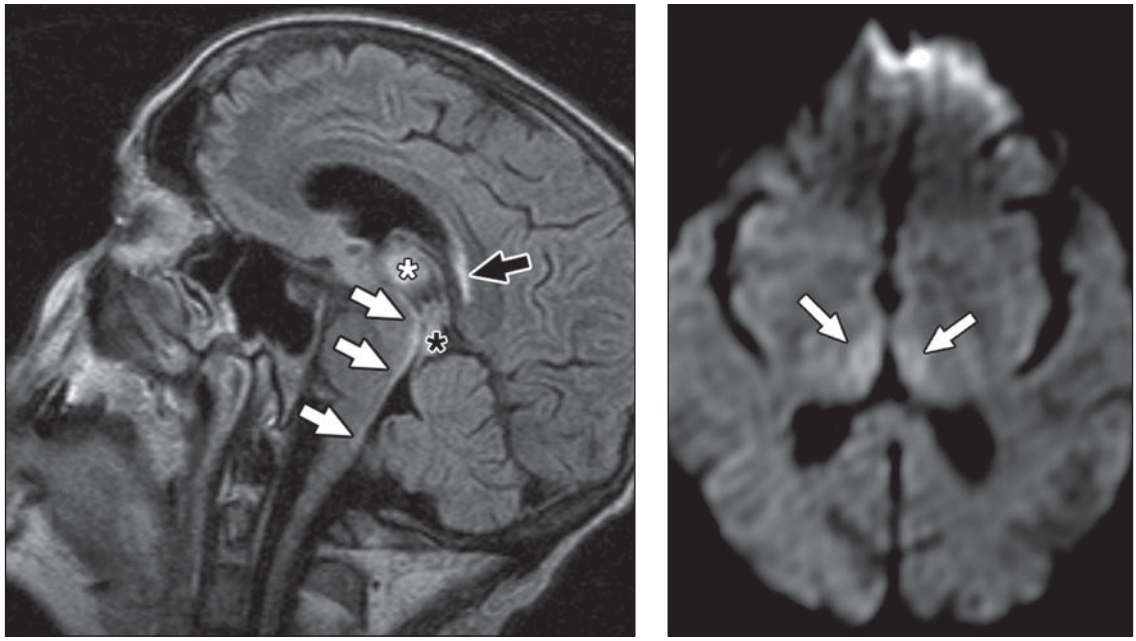

Fig. 5—62-year-old woman admitted to hospital for altered consciousness after 2 weeks of nausea, vomiting, and diarrhea.
A, Sagittal FLAIR image shows extensive signal intensity alteration of mesencephalon, central gray matter, and posterior medulla (*white arrows*). Signal intensity alterations of thalamus (*white asterisk*), tectal plate (*black asterisk*), and corpus callosum (*black arrow*) are seen.
B, Diffusion-weighted image shows areas of restricted diffusion of thalami (*arrows*).

help to distinguish WE from other neurologic disorders, especially in comatose patients. Long-TR MR images are the most sensitive sequences. Symmetric alterations in the thalami, mamillary bodies, tectal plate, and periaqueductal area represent typical lesions of WE, but atypical lesions may also been seen. As we have shown here, atypical changes of WE almost always have been described in nonalcoholic patients and only in association with the typical alterations with the exception of two alcoholic patients showing cerebellar involvement associated with the characteristic findings of the disease [6, 32]. The reasons why specific brain areas are affected by WE are poorly understood, but we speculate that the brain areas characterized by intense thiamine metabolism would be those that appear to be typically involved on MRI. On the other hand, atypical MRI findings of WE, which occur in nonalcoholic patients only, are very similar to those of metronidazole-induced encephalopathy, suggesting that WE and metronidazole-induced encephalopathy may share common metabolic pathways [56, 57]. Because atypical lesions have been reported only in nonalcoholic patients with WE, it would be tempting to surmise that alcohol may have a protective effect on the brain areas that show atypical lesions in WE, although at the present this hypothesis remains a matter of speculation.

Turning to other applications of MRI, the roles of DWI and ADC and of MR spectroscopy are still unclear. Contrast-enhanced MRI is usually not required; however, in patients in whom there is a clinical suspicion of WE but no lesions on unenhanced MR images, gadolinium-based contrast material should always be administered because contrast enhancement of the mamillary bodies may be the only sign of WE [12, 50].

In conclusion, a thorough knowledge of the neuroimaging findings of WE may assist in making an early diagnosis and thus in reducing the morbidity and mortality associated with this disease. Close cooperation between radiologists and physicians is required, particularly when patients present without clear-cut clinical manifestations or with no history of alcohol intake.

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