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The role of MRI in the prognosis of Wernicke's encephalopathy

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Abstract

Background and Purpose
Wernicke's encephalopathy (WE) is a severe acute disorder related to thiamine deficiency. This study was aimed at revealing the relationship between clinical and imaging findings and WE recovery.

Methods
We retrospectively reviewed 34 cases of WE diagnosed between 2003 and 2020 (median 57 years, 14 females) at two academic institutions. WE cases were divided into 2 groups with symptomatic recovery within 4 weeks (group 1) or later (group 2). The lesion sites were divided into typical and atypical sites (total sites defined as when either typical or atypical sites were involved). Clinical and MRI features were compared between them as appropriate.

Results
WE patients were divided into group 1 (19 cases, median age 57, 10 females) and group 2 (15 cases, median 57 years, 4 females). Regarding clinical features, only cerebellar ataxia was more often observed in group 1 than in group 2. Regarding MR imaging features, signal abnormality on T2-weighted image (WI)/fluid-attenuated inversion recovery (FLAIR) was more often observed in atypical sites between group 1 and 2 (1/19 vs 7/15; P=0.01). There were significant differences between group 1 and 2 regarding the presence of both of vasogenic edema and cytotoxic edema in total sites (4/11 vs 11/15; P=0.005, 1/19 vs 6/15; P=0.03), with a significant difference in the presence of vasogenic edema in typical sites (4/19 vs 10/15; P=0.01).

Conclusion
The early recovered group showed a lower incidence of T2WI/FLAIR abnormality in atypical sites and diffusion signal abnormality in total or typical sites with a lower incidence of cerebellar ataxia.

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Introduction

Wernicke's encephalopathy (WE) is an acute neurologic disorder caused by thiamine deficiency with prevalence of 0.4–2.8% in the general population.[1-7] If not appropriately treated, WE can lead to Korsakoff syndrome or death. The classical triad of clinical symptoms includes mental status change, ataxia, and oculomotor abnormalities, and the most common cause of thiamine deficiency is alcoholism, accounting for about 50% of WE cases.[6] There have been other reported causes of WE such as hyperemesis gravidarum, fasting, hemodialysis, uremia, hyperalimentation, and gastric surgery. Moreover, the classic triad of symptoms are found in only 16-33% of WE patients on initial examination, and about 19 % of patients have none of the classic triad, making the diagnosis of WE challenging.[8,9]

Magnetic resonance imaging (MRI) is currently considered the standard imaging modality to confirm a diagnosis of Wernicke's encephalopathy. MRI has a sensitivity of only 53% but has a high specificity of 93%.[10,11] Typical imaging findings of WE can be seen as symmetrical signal abnormalities in the periventricular regions of the thalamus, hypothalamus, mammillary bodies, periaqueductal region and floor of the fourth ventricle. Additionally, MRI findings can be seen in the paravermian region of the cerebellum, dorsal medulla, pons, cranial nerve nucleus (CNN), red nucleus, dentate nucleus, putamen, caudate nucleus, fornix, splenium of the corpus callosum and pre- and postcentral gyri.[12,13,14] The abovementioned lesions can show hyperintensity on T2-weighted image (WI) and fluid-attenuated inversion recovery (FLAIR) with or without contrast enhancement or abnormal signal on diffusion-weighted imaging.

The prognosis of patients with WE can vary, depending on the time of onset of thiamine supplementation, the degree of thiamine deficiency, and the underlying condition of the patient.[8] Typically, recovery from the ophthalmoplegia is complete after a few hours, except

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for a residual fine, horizontal nystagmus in 60% of patients. Recovery from ataxia often occurs after a period of a few days, although in some cases is incomplete.[15,16] The changes in mental status tends to improve after 2–3 weeks of therapy.[15,16] Prior studies have shown that poor prognosis is related to the underlying etiology of WE and location of the lesions,[17] but the relationship between the prognosis and clinical and MR imaging features has not been fully revealed. Clinically, it is of importance for both clinicians and radiologists to recognize the prognosis of patients with WE for clinical management. Persistent symptoms, permanent Korsakoff syndrome, or death occur even after appropriate treatment, and these conditions can be defined as poor prognosis.[7]

Therefore, the aim of this study was to investigate clinical and MRI features relating to the clinical outcome of WE.

Methods

Study population

This international multicenter retrospective study was approved by each center's institutional review board, and informed consent was waived.

We retrospectively reviewed 34 cases of Wernicke's encephalopathy (median age, 57 years; age range, 19-86 years; 14 females) with available MR imaging at WE diagnosis from April 2003 to October 2020 in 2 academic centers. All consecutive cases of Wernicke's Encephalopathy during the study period were reviewed (29 and 5 patients collected respectively from each institution). The diagnosis of WE was determined with consensus by radiology and neurology departments based on imaging and clinical features. Clinical follow-up was performed and assessed by the neurology department at each institution. Based

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on this assessment, the cohort was divided into 2 groups: patients' whose neurologic symptoms resolved or returned back to baseline within 4 weeks after the diagnosis (group 1) and patients' whose neurologic symptoms persisted 4 weeks after the diagnosis or who developed Korsakoff syndrome or died during follow-up (group 2). All patients were treated with intravenous infusion of 500-1000 mg of thiamine after the diagnosis of WE.

Patient demographics

Patient demographics were obtained from the electronic medical records and included the following information: sex, age, symptoms at the diagnosis, cause of thiamine deficiency (alcohol, a history of gastric surgery, malnutrition), history of malignancy and chemotherapy, and time to recovery after thiamine administration.

MR imaging acquisition

MR imaging examinations in all cases were performed during the acute symptomatic phase of WE with multiple scanners including the following: 1T (n=2 Panorama HFO, Philips; n=1 GENESIS SIGNA, GE); 1.5T scanner (n=10 Achieva, Philips Healthcare; n=4 Intera, Philips Healthcare; n=1 Optima, GE ; n=4 GENESIS SIGNA, GE; n=4 SIGNA EXCITE, GE); 3Tscanner (n=4 Ingenia, Philips Healthcare; n=1 Achieva, Philips Healthcare; n=1 Magnetom Vida, Siemens; n=1 Skyra, Siemens). Reviewed sequences included axial T2WI, axial FLAIR, axial T1WI, axial post-contrast T1WI, and diffusion-weighted imaging (DWI). MR imaging was performed with contrast for 25 patients. The initial MR imaging at the time of diagnosis was evaluated.

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MR imaging features

Two board-certified radiologists with 8 and 9 years of experience interpreted all MR imaging sequences with consensus. They were aware of the diagnosis, but were blinded to the clinical information. Both radiologists evaluated T2WI, FLAIR, DWI, and post-contrast T1WI (if available) in the following sites: typical sites (thalamus, periaqueductal area, periventricular region of the third ventricle, mamillary bodies, hypothalamus, tectal plate), atypical sites (cerebellum, medulla, corpus callosum, pre- and postcentral gyri, basal ganglia, olive nuclei, cranial nerve nuclei (CNN)(VI, VII, VIII, XII).

The presence of hyperintensity on T2WI/FLAIR, vasogenic edema (high signal on DWI and ADC) or cytotoxic edema (high signal on DWI and low signal on ADC), and enhancement was recorded as binary variables, and each binary variable was compared between the 2 groups in three patterns: in total sites (abnormal signal involving either typical or atypical sites), in the typical sites, and in the atypical sites. Each site was considered positive when a signal abnormality was identified in at least one anatomical region.

Statistical analysis

Continuous variables, such as age, were compared using the Mann-Whitney U test. The categorical values of clinical features (sex, neurological symptoms, and cause of thiamine deficiency) were compared between the 2 groups using the Fischer exact test. Regarding MRI features, binary variables of presence of hyperintensity on T2WI/FLAIR, presence of vasogenic edema (high signal on DWI and ADC) or cytotoxic edema (high signal on DWI and low signal on ADC), and presence of enhancement were compared between the 2 groups using the Fischer exact test.

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All statistical calculations were conducted using R software (version 4.1.1; R Core Team, Vienna, Austria). Variables with p-values of <.05 were considered statistically significant.

Result

Patient demographics

Table 1 summarizes overall patients' clinical information, including sex and age, cause of thiamine deficiency, presence of clinical symptoms, and time to recovery after thiamine administration.

Group 1, which consisted of patients who recovered within 4 weeks (n=19; median age, 57; 10 female) showed history of alcohol abuse (13 cases), malnutrition (2 cases), gastric surgery (4 cases), and malignancy (1 case: gastric cancer).

Group 2, patients with delayed recovery or irreversible symptoms (n=15; median age, 55; 4 females) had a history of alcohol abuse (6 cases), malnutrition (6 cases), gastric surgery (2 cases), and malignancy (2 cases: gastric cancer, breast cancer). There was no history of chemotherapy. Four patients died from complications of WE such as Korsakoff syndrome and heart failure.

There was no significant difference in sex (female/male, 10/9 versus 4/11; P = 0.17), age (median, 57 versus 55; P = 0.26), cause of thiamine deficiency (presence of alcohol abuse, 13/19 versus 6/15; P = 0.17, presence of malnutrition, 2/19 versus 6/15; P = 0.10, or presence of gastric surgery, 4/19 versus 2/15; P = 0.67).

Neurological features

The most frequent neurologic symptom at the time of diagnosis of WE was altered mental status (22/34 total, 12/19 group 1 versus 10/15 group 2; P = 1). 18 patients showed abnormality of eye movement (18/34 total; 9/19 group 1 versus 9/15 group 2; P = 0.51), 16

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patients showed cerebellar ataxia (16/34 total; 13/19 group 1 versus 3/15 group 2; P = 0.007). Cerebellar ataxia was significantly more common in early recovered group.

As for atypical symptoms, there was no significant difference in presence of other neurologic symptoms between the 2 groups (15/19; early recovered 12/15; delayed recovered; P = 1.0). Additional symptoms included speech impairment, sensory abnormality, abnormal tongue movement, seizure, fatigue.

The median and range of time to recovery after thiamine administration was as follows: 7 days (1-21) in group 1, 40 days (28-90) in group 2.

MR imaging features

Table **2** summarizes the results of MR imaging features between groups 1 and 2.

All 34 patients underwent MR imaging. MR imaging was performed with contrast for 25 patients (14 patients in the early recovered Group 1, and 11 patients in the delayed recovered Group 2).

T2WI/FLAIR

There was no significant difference between group 1 and group 2 in the presence of signal alteration in total sites nor in typical sites (in total sites 16/19 vs 14/15; P = 0.61, in typical sites 16/19 vs 13/15; P = 1.0). There was a significant difference between group 1 and group 2 (1/19 vs 7/15; P=0.01) in atypical sites. Table 3 shows the frequency of signal alterations on T2WI/FLAIR in each region.

DWI

There were significant differences in the presence of both of vasogenic edema and cytotoxic edema in total sites (vasogenic edema, 4/19 versus 11/15; P = 0.005, cytotoxic edema, 1/19

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versus 6/15; P = 0.03). There was also a significant difference in the presence of vasogenic edema in typical sites (4/19 versus 10/15; P = 0.01). Otherwise, there was no significant difference in the remaining analyzed MR imaging features. Details regarding vasogenic edema and cytotoxic edema were shown in Table 4.

Post-contrast T1WI

MR imaging with contrast was performed in 25 patients (14 in early recovery and 11 in delayed recovery). Among these patients, 8 patients showed contrast enhancement (4/14 in early recovery, 4/11 in delayed recovery). The anatomic structures that most frequently enhanced were the mamillary bodies (5 patients, 20%), followed by the medulla and olivary nuclei (3 patients, 12%), and the tectal plate, hypothalamus, and CNN (one patient each, 4%). The other sites had no contrast enhancement. There was no significant difference between group 1 and 2 in any sites (in total sites 4/14 vs 4/11; P = 1, in typical sites 3/14 vs 3/11; P = 1.0, in atypical sites 1/14 vs 2/11; P = 0.57). Table 5 summarizes the post-contrast evaluation.

Representative cases are shown in Fig. 1–3.

Discussion

Our study aimed to assess clinical and MRI features relating to the clinical outcome of WE by dividing WE into 2 groups: group 1 with recovery within 4 weeks following the diagnosis of WE and group 2 with unfavorable outcomes.

Our clinical data showed that age, sex, cause of thiamine deficiency, history of malignancy, and history of chemotherapy did not significantly associate with prognosis of WE. Regarding neurologic symptoms, cerebellar ataxia was significantly more often seen in the early recovered group than in the delayed recovered group (13/19 versus 3/15). It is known that

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recovery from ataxia often occurs a few days after WE treatment.[15,16] This result may be because our study constituted a heterogeneous population including varying basis of patients' underlying disease or because we were not able to reflect the severity of the symptoms in the analysis, resulting in more cases with milder symptoms included in the early recovered group and more cases with severe symptoms in the delayed recovery group. In previous studies, loss of equilibrium with incoordination of gait and trunk ataxia affected about 23% of WE patients.[15,18] In our study, 16 patients showed cerebellar ataxia (16/34, 47%), twice the previously reported rate. The cause of this is unclear, possibly related to variation in underlying etiology of our patient population, as severity of alcohol abuse and other underrecognized clinical characteristics could potentially affect this discrepancy.

Regarding MRI features, there was no significant difference between the early recovered group and the delayed recovered group in the presence of high intensity in total sites and in typical sites on T2WI/FLAIR. However, the delayed recovered patients were more likely to show T2WI/FLAIR alterations in the atypical sites than the early recovered group. A previous study showed that consciousness level had a positive correlation with involvement of atypical areas (cerebral cortex, ninth CNN, corpus callosum, basal ganglia, and cerebellum).[17] In addition to this correlation between clinical and imaging features, T2WI/FLAIR signal alteration in atypical areas could be potentially used as an imaging prognostic biomarker for the patient's assessment. The frequency of alteration in atypical sites has been reported as uncommon,[7] but it is postulated that signal change in an atypical site could be a manifestation of greater severity of disease in WE.

Vasogenic edema and cytotoxic edema in typical or atypical sites were seen more frequently in the delayed recovered group than in the early recovered group. High intensity on DWI has been previously reported to reflect reversible vasogenic and/or cytotoxic edema, and can represent underlying vulnerability of patients to severe thiamine deficiency. Conventionally,

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T2WI and FLAIR are used for the diagnosis of WE, as variability regarding the presence of increased diffusion signal, and heterogeneity in associated ADC values, has resulted in a lack of clarity regarding the clinical utility of this sequence. As well as T2WI/FLAIR signal alteration in atypical areas, the presence of vasogenic and/or cytotoxic edema on DWI could potentially provide additional prognostic information, which can help clinicians to decide whether a patient with WE can recover from the symptom faster or not or to consider more intensive intervention such as early rehabilitation as well as standard thiamine infusion dose when patients are suspected to show delayed recovery from the symptoms.

In a previous study, contrast enhancement was present in 63% patients (26/41).[19] In our study, contrast enhancement was observed in fewer patients (32%, 8/25) than previously stated and showed no significant difference in typical, atypical or total sites between the 2 groups. However, enhancement of mamillary bodies was the only finding in 2 cases in our study, suggesting adding postcontrast T1WI sequence could be beneficial, as stated in the previous reports.[19] Future studies with larger WE population evaluating the severity of signal alteration on each MRI sequences would provide more promising parameters to suggest WE prognosis.

Our study has several limitations. First, this is a retrospective design with a relatively small population for a longer period. Second, infusion of thiamine ranged from 500-1000 mg and MR imaging protocol were not equal throughout the 18-year period and between centers. Also, we included multiple scanners (1T to 3T). These factors could influence our results. Third, assessment of restricted diffusion was performed on the basis of visual assessment, as imaging examinations were obtained across multiple vendors with various parameters and magnetic field strengths. Finally, not all patients had post-contrast T1WI, resulting in a smaller available cohort in the evaluation of lesional enhancement.

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In conclusion, a lower incidence of T2WI/FLAIR abnormality in atypical sites and diffusion signal abnormality in total or typical sites with a lower incidence of cerebellar ataxia were observed in the early recovered group than in the group with unfavorable prognosis, suggesting that distribution of T2WI/FLAIR hyperintensities and careful analysis of the DWI sequence could be potentially used as a prognostic value in WE patients. Future studies with more patients are required to justify our study.

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Tables

Table 1: Patient demographics

	Early recovered	Delayed recovered	P value
No. of patients	19	15	NA
Sex (female/all)	53%	27%	0.17
Age (year)	57 (23-79)	55 (19-86)	0.26
Alcohol (yes/all)	68%	40%	0.17
Malnutrition (yes/all)	11%	40%	0.10
Gastric surgery (yes/all)	21%	13%	0.67
History of malignancy (yes/all)	5%	13%	0.57
History of chemotherapy (yes/all)	0%	0%	NA
Altered mental status (yes/all)	63%	67%	1
Abnormal of eye movement (yes/all)	47%	60%	0.51
Cerebellar ataxia (yes/all)	68%	20%	0.007
Presence of symptoms other than classic triad (yes/all)	79%	80%	1.0
Time to recovery after thiamine administration (day)	7 (1-21)	40 (28-96)*	NA

Note–NA, not applicable. Values of age and time to recovery after thiamine administration are described as median (interquartile range). *Four patients passed away, and the time to recovery for these cases represents days from starting thiamine administration to death.

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Table 2: Analysis of MR imaging features

		Early recovered N=19 (14)*	Delayed recovered N=15 (11)*	P value
T2WI/FLAIR	Total sites	84%	93%	0.61
	Typical sites	84%	87%	1.0
	Atypical sites	5.2%	47%	0.01
Vasogenic edema	Total sites	21%	73%	0.005
	Typical sites	21%	67%	0.01
	Atypical sites	0%	20%	0.08
Cytotoxic edema	Total sites	5.2%	40%	0.03
	Typical sites	5.2%	33%	0.07
	Atypical sites	0%	20%	0.08
Post-contrast T1WI	Total sites	29%	36%	1.0
	Typical sites	21%	27%	1.0
	Atypical sites	7.1%	18%	0.57

Note–*Parentheses represent total number of WE patients with post-contrast T1WI. Total sites: either typical sites or atypical sites; Typical sites represent thalamus, periaqueductal area, periventricular region of the third ventricle, mamillary bodies, hypothalamus, and tectal plate. Atypical sites represent cerebellum, medulla, corpus callosum, pre- and postcentral gyri, basal ganglia, olive nuclei, and cranial nerve nuclei (VI, VII, VIII, XII). N = Number of subjects; FLAIR = fluid attenuated inversion recovery; T1WI = T1 weighted image; T2WI = T2 weighted image

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Table 3: Frequency of signal alteration on T2WI/FLAIR

	Typical sites					
	Thal	Periaq	TV	TP	MB	Hypothal
Total N=34	67%	56%	44%	21%	24%	50%
Early recovered N=19	58%	47%	32%	5.2%	16%	37%
Delayed recovered N=15	80%	67%	60%	40%	33%	67%

	Atypical sites						
	Cer	Medu	CC	Pre and post CG	BG	ON	CNN (VI, VII, VIII, XII)
Total N=34	2.9%	5.9%	2.9%	2.9%	8.8%	5.9%	21%
Early recovered N=19	0%	0%	0%	0%	0%	0%	5.3%

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Delayed recovered N=15	6.7%	13%	6.7%	6.7%	20%	13%	40%

Note– FLAIR, fluid attenuated inversion recovery; T1WI, T1-weighted image; T2WI, T2 weighted image; Thal indicates medial thalami; Periaq, periaqueductal gray matter; TV, periventricular region of the third ventricle; TP, tectal plate; MB, mamillary bodies; Hypothal, hypothalamus; Cer, cerebellum; Medu, medulla; CC, corpus callosum; pre and post CG, pre and post central gyri; BG, basal ganglia; ON, olive nuclei; CNN, cranial nerve nuclei; N = Number of subjects

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Table 4: Frequency of signal alteration on diffusion-weighted imaging: Vasogenic edema or Cytotoxic edema

	Typical sites					
	Thal	Periaq	TV	TP	MB	Hypothal
Total N=34	29% (8.8%)	24% (8.8%)	15% (2.9%)	5.9% (8.8%)	8.8% (15%)	18% (8.8%)
Early recovered N=19	16% (5.3%)	11% (5.3%)	0% (0)%%	0% (5.3%)	0% (0%)	5.3% (0%)
Delayed recovered N=15	47% (13%)	40% (13%)	33% (6.7%)	13% (13%)	20% (33%)	26% (20%)

	Atypical sites						
	Cer	Medu	CC	Pre and post CG	BG	ON	CNN (VI, VII, VIII, XII)
Total N=34	2.9% (0%)	2.9% (2.9%)	2.9% (0%)	0% (2.9%)	5.9% (2.9%)	2.9% (2.9%)	5.9% (2.9%)
Early	0%	0%	0%	0%	0%	0%	0%

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recovered N=19	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)
Delayed recovered N=15	6.7% (0%)	6.7% (6.7%)	6.7% (0%)	0% (6.7%)	13% (6.7%)	6.7% (6.7%)	13% (6.7%)

Note–The numbers represent the frequency of DWI signal alteration in each region. Parentheses represent frequency of cytotoxic edema. DWI, diffusion-weighted imaging; Thal, medial thalami; Periaq, periaqueductal gray matter; TV, periventricular region of the third ventricle; TP, tectal plate; MB, mamillary bodies; Hypothal, hypothalamus; Cer, cerebellum; Medu, medulla; CC, corpus callosum; pre and post CG, pre and post central gyri; BG, basal ganglia; ON, olive nuclei; CNN, cranial nerve nuclei; N = Number of subjects

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Table 5: Frequency of signal alteration on post-contrast T1WI

	Typical sites					
	Thal	Periaq	TV	TP	MB	Hypothal
Total N=25	0%	0%	0%	4%	20%	4%
Early recovered N=14	0%	0%	0%	0%	21%	0%
Delayed recovered N=11	0%	0%	0%	9.1%	18%	9.1%

	Atypical sites						
	Cer	Medu	CC	Pre and post CG	BG	ON	CNN (VI, VII, VIII, XII)
Total N=25	0%	12%	0%	0%	0%	12%	4%
Early recovered N=14	0%	7.1%	0%	0%	0%	7.1%	0%
Delayed	0%	18%	0%	0%	0%	18%	9.1%

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recovered	
N=11	

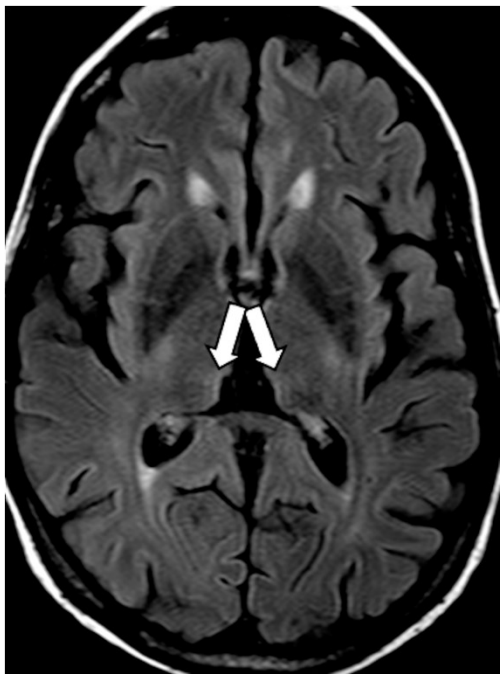
Note: The numbers represent the frequency of post-contrast T1WI signal alteration in each region. T1WI, T1-weighted image; Thal, medial thalami; Periaq, periaqueductal gray matter; TV, periventricular region of the third ventricle; TP, tectal plate; MB, mamillary bodies; Hypothal, hypothalamus; Cer, cerebellum; Medu, medulla; CC, corpus callosum; pre and post CG, pre and post central gyri; BG, basal ganglia; ON, olive nuclei; CNN, cranial nerve nuclei; N = Number of subjects

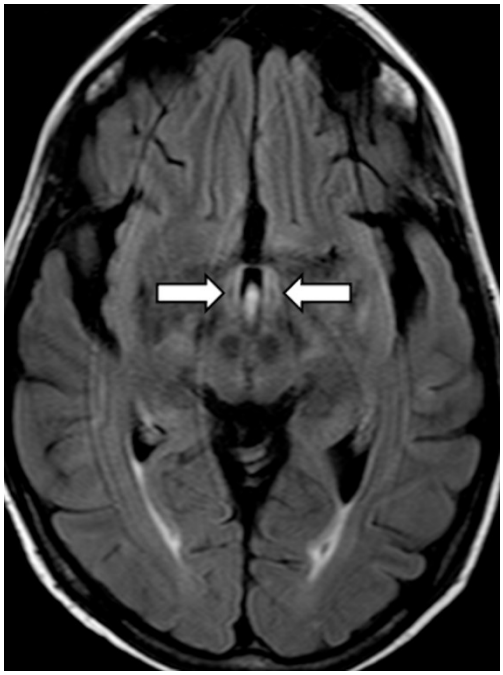
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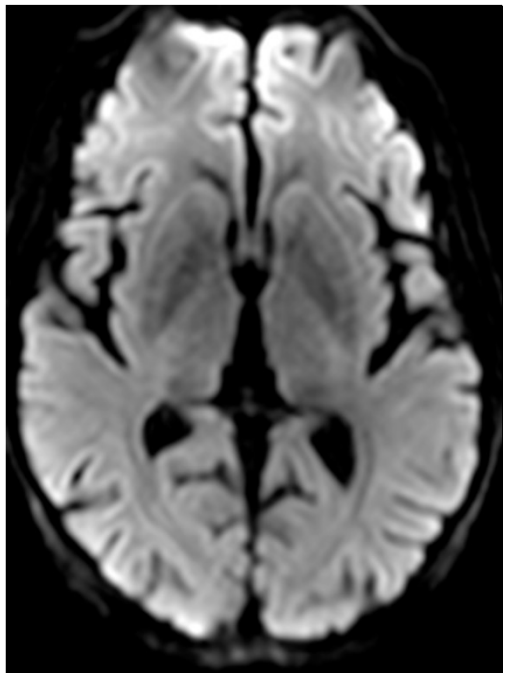
Figures





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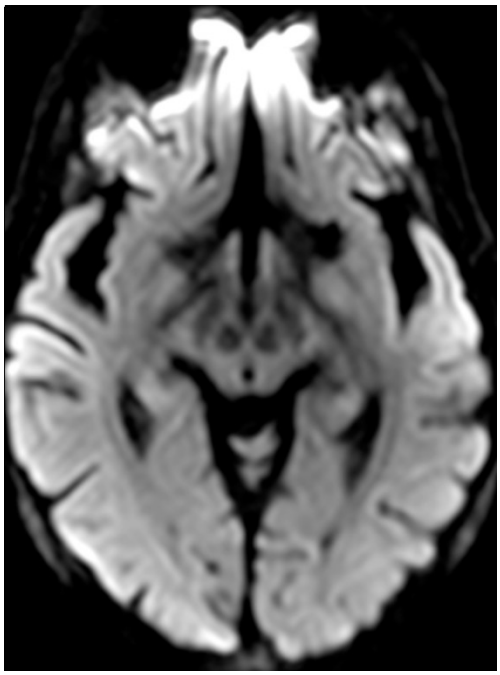


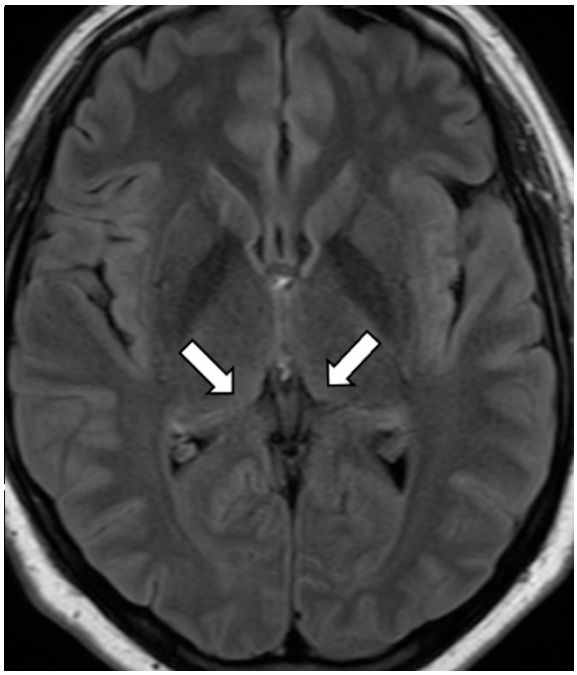
Figure 1

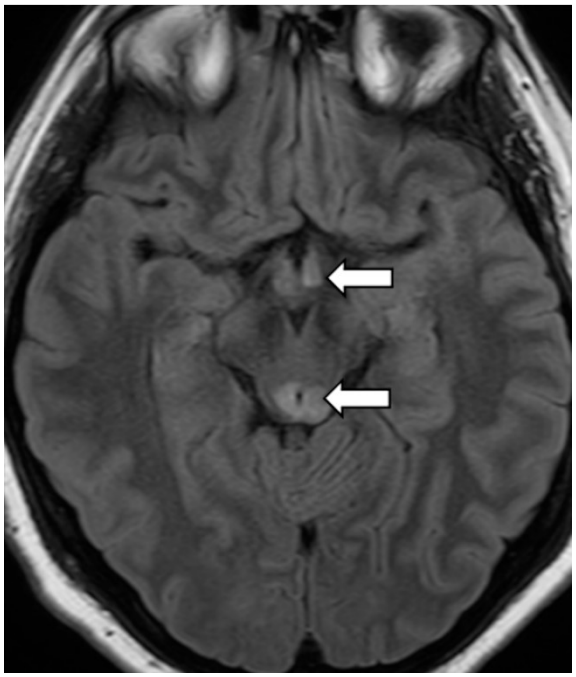
Fig. 1–A 44-year-old female with visual, gait, and speech impairment, with early recovery. She recovered back to normal baseline 2 weeks after starting thiamine infusion. (A, B) Fluid attenuated inversion recovery sequences showed symmetric hyperintensity in the medial

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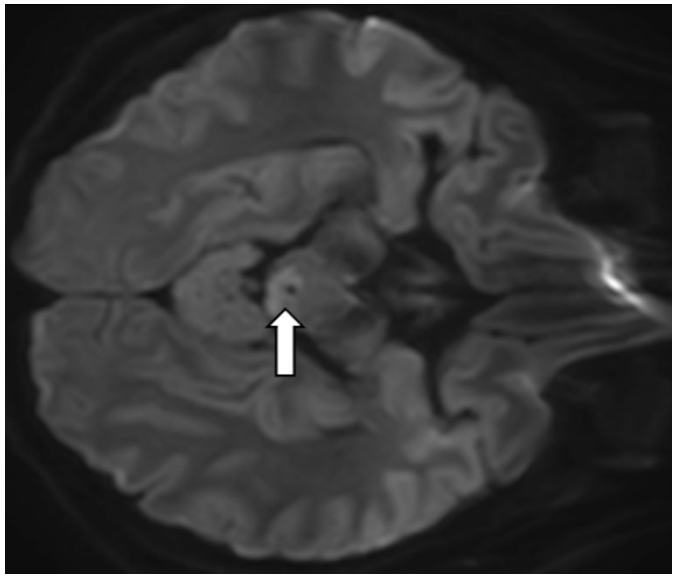
thalami and hypothalamus (arrows). (C, D) Diffusion-weighted imaging sequences did not reveal signal alteration.

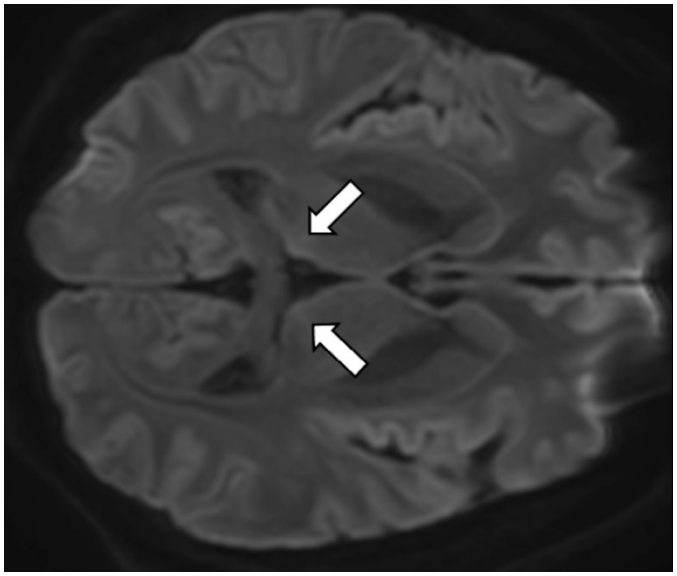




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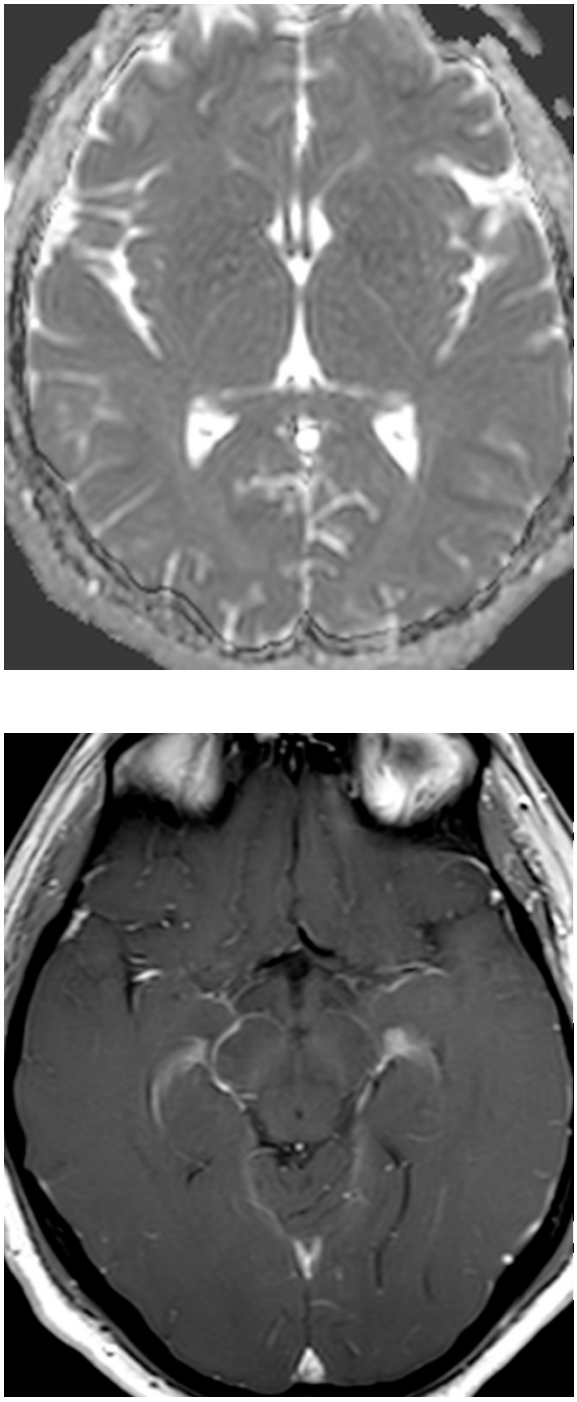


Figure 2

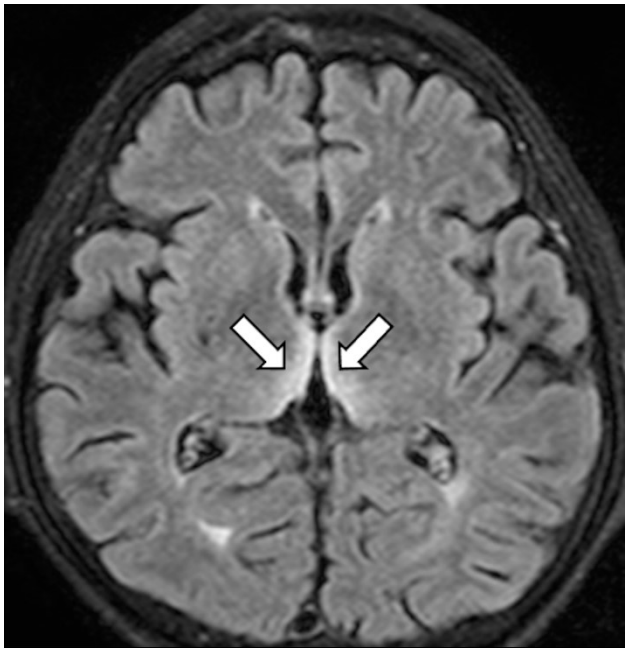
Fig. 2–A 28-year-old male presented with fatigue and showed delayed recovery. He recovered 3 months after starting thiamine infusion.

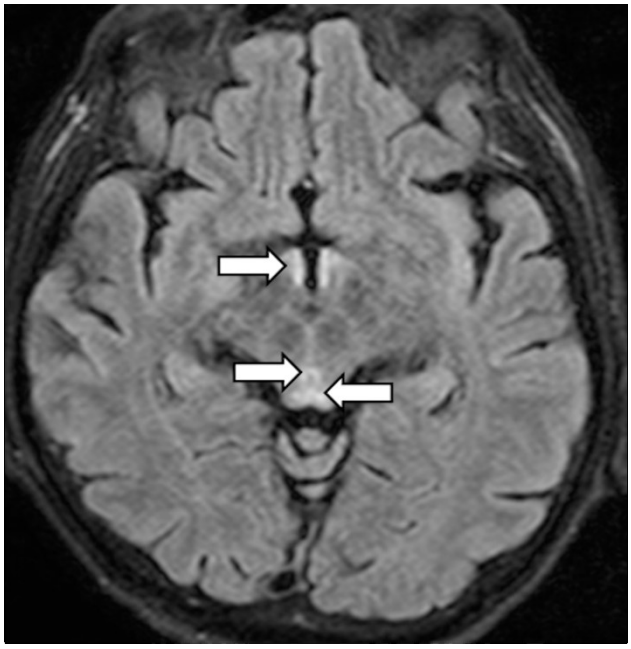
(A, B) Fluid attenuated inversion recovery sequences showed symmetric hyperintensity in the medial thalami, mamillary bodies, periaqueductal gray matter, and tectal plate (arrows). (C,

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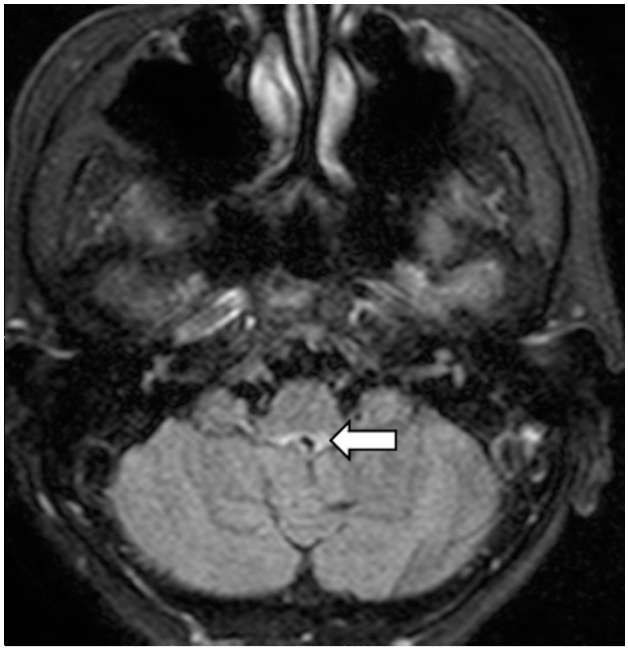
D) Diffusion-weighted imaging sequences showed hyperintensity in the medial thalami and tectal plate, without (E) Apparent diffusion coefficient alteration, suggesting vasogenic edema. (F) Postcontrast T1-weighted image showed no enhancement.

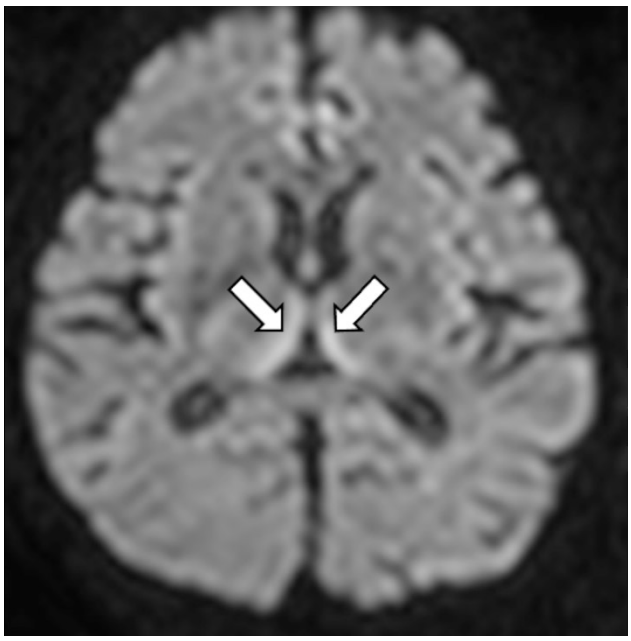




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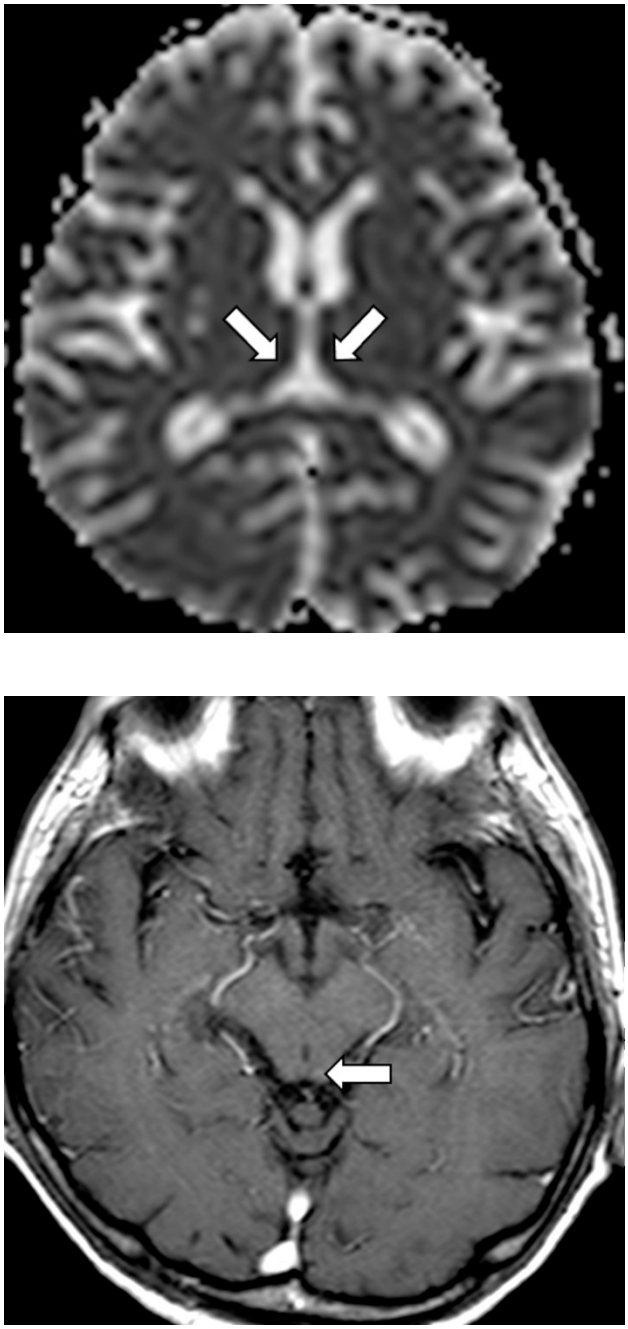


Figure 3

Fig. 3–A 58-year-old male with altered mental status, nystagmus, ophthalmoparesis, swallowing dysfunction, and visual impairment. He showed delayed recovery. (A,B,C) Fluid attenuated inversion recovery sequences showed symmetric hyperintensity in the medial thalami , mamillary bodies, periaqueductal gray matter, tectal plate and the medial vestibular nuclei (arrows). (D) Diffusion-weighted imaging sequences showed hyperintensity in the

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medial thalami with (E) Apparent diffusion coefficient alteration suggesting cytotoxic edema (arrows). (F) Postcontrast T1-weighted image showed contrast enhancement in the tectal plate (arrow).

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