Japanese Journal of Radiology (2020) 38:809–820
https://doi.org/10.1007/s11604-020-00989-3

INVITED REVIEW

Comprehensive review of Wernicke encephalopathy: pathophysiology, clinical symptoms and imaging findings

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Received: 9 April 2020 / Accepted: 29 April 2020 / Published online: 10 May 2020

Abstract

Wernicke's encephalopathy (WE) is a severe and life-threatening illness resulting from vitamin B1 (thiamine) deficiency. The prevalence of WE has been estimated from 0.4 to 2.8%. If not treated properly, severe neurologic disorders such as Korsakoff psychosis and even death may occur. The classical triad of clinical symptoms (abnormal mental state, ataxia, and ophthalmoplegia) is found in only 16–33% of patients on initial examination. The originally described underlying condition of WE is alcoholism, but it accounts for about 50% of causes of WE. Nonalcoholic patients are also affected by WE and likely to present symptoms and radiological imaging findings different from patients with alcoholism, which further complicates the diagnosis of WE. Being familiar with predisposing causes, symptoms and radiological imaging findings of WE is important for radiologists and clinicians when making the diagnosis to start immediate treatment. This review discusses pathophysiologies, underlying causes, clinical symptoms, imaging findings and their mimics.

Keywords Wernicke encephalopathy · Thiamine · Cytotoxic and vasogenic edema · MRI · Complications

Introduction

Wernicke's encephalopathy (WE) is known as a severe and life-threatening illness resulting from vitamin B1 (thiamine) deficiency. The prevalence of WE in the general population has been estimated from 0.4 to 2.8% [1–7]. If not treated properly, severe neurologic disorders such as Korsakoff psychosis and even death may ensue. The classical triad of clinical symptoms (mental status change, ataxia, and oculomotor abnormality) are found in only 16–33% of patients on initial examination [1, 5, 7]. The originally described underlying condition of WE is alcoholism, but it accounts for about 50% of the current causes of WE [4]. Therefore, nonalcoholic patients are also affected by WE and are likely to present with clinical symptoms and imaging findings different from those of patients with alcoholism [7–9].

Pathophysiologically, thiamine deficiency causes dysfunction of the Krebs cycle (tricarboxylic acid, TCA cycle) and the pentose phosphate pathway with consequent development of brain cytotoxic edema and vasogenic edema [5, 10]. Magnetic resonance imaging (MRI) typically shows abnormal intensity alteration in bilaterally symmetrical lesions in the paraventricular regions of the thalamus, hypothalamus, mammillary bodies, periaqueductal region and floor of the fourth ventricle [6]**.** MRI also shows unusual sites of brain lesions such as the putamen, caudate, splenium of the corpus callosum, dorsal medulla, pons, red nucleus, substantia nigra of the midbrain, cranial nerve nucleus, vermis, dentate nucleus, paravermian region of the cerebellum, fornix and pre- and postcentral gyri**.** It is important for radiologists and clinicians to be familiar with the pathophysiology, underlying conditions, symptoms and usual and unusual imaging findings of WE, especially when making the diagnosis to start immediate treatment.

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Metabolic pathway of thiamine (Fig. 1)

Thiamine is a key vitamin in the maintenance of membrane integrity and osmotic gradients across cell membranes and is stored in body tissues predominantly as thiamine diphosphate (TDP). TDP participates in energy production as an essential cofactor for several enzymes in the TCA cycle and pentose phosphate pathways [5, 6]. The TCA cycle is a metabolic pathway that represents a key part of aerobic respiration. It involves a series of chemical reactions occurring in the mitochondria, which leads to the oxidation of acetate derived from carbohydrates, fatty acids, and amino acids into carbon dioxide, producing chemical energy in the form of adenosine triphosphate (ATP). The pentose phosphate pathway, a cytosolic process, generates pentoses, which are essential for the nucleic acid synthesis and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), which is necessary for several anabolic processes. NADPH also helps to scavenge free radicals during oxidative stress [5, 6].

Pathophysiology of cytotoxic edema and vasogenic edema in WE (Fig. 2)

Thiamine deficiency causes depletion of intracellular TDP, leading to a decreased activity of the TCA cycle and pentose phosphate pathways. Consequently, cellular energy (ATP) depletion and reduction of DNA/RNA and NADPH synthesis ensues, which results in low resistance to oxidative stress. Moreover, there is an accumulation of toxic intermediate metabolic products such as lactate, alanine and glutamate, reduced cellular pH in cells, and disruption of the homeostasis of cellular electrolytes, which results in cytotoxic edema.

As for vasogenic edema, the blood–brain barrier (BBB) has a key role. The BBB is composed of capillary endothelial cells (ECs), mesenchymal-like cells pericytes, and astrocytes terminal processes, known as endfeet, which is essential for the formation and maintenance of the BBB by providing secreted factors that lead to strong tight junctions. BBB dysfunction occurs when astrocytes are damaged by ATP depletion, oxidative stress, pH reduction and secondary excitotoxicity by excessive glutamate concentration in the synaptic clefts [6, 10–13].

Symptoms and related lesions

WE is an acute neurologic disorder resulting from thiamine deficiency and characterized by a clinical triad of confusion, oculomotor abnormalities, and ataxia. Mental status changes are the most common symptom of WE and occur in 34–82% of patients confirmed with postmortem neuropathology [14]. These mental changes include confusion, spatial disorientation, dizziness, drowsiness, apathy, cognitive impairment with disturbance in memory and inability to concentrate. Such symptoms may derive from the involvement of the reticular system at the level of the midline thalamic nuclei or mammillary bodies [5]. The second common clinical

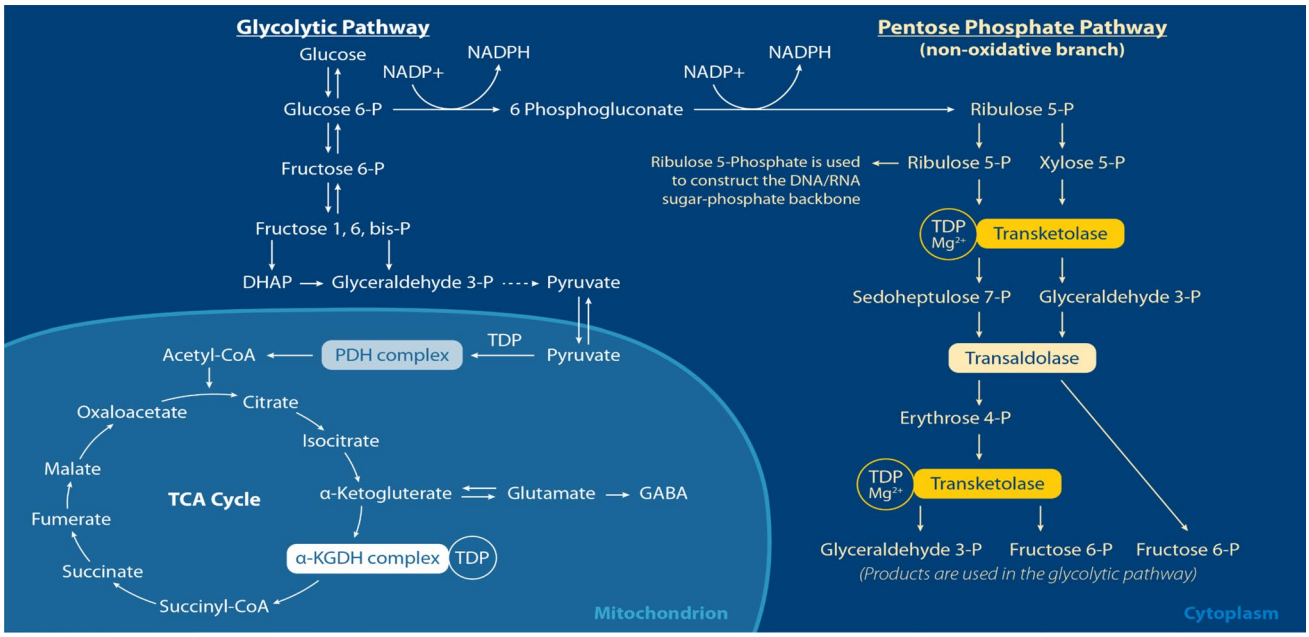

Fig. 1 Metabolic pathway related to thiamine

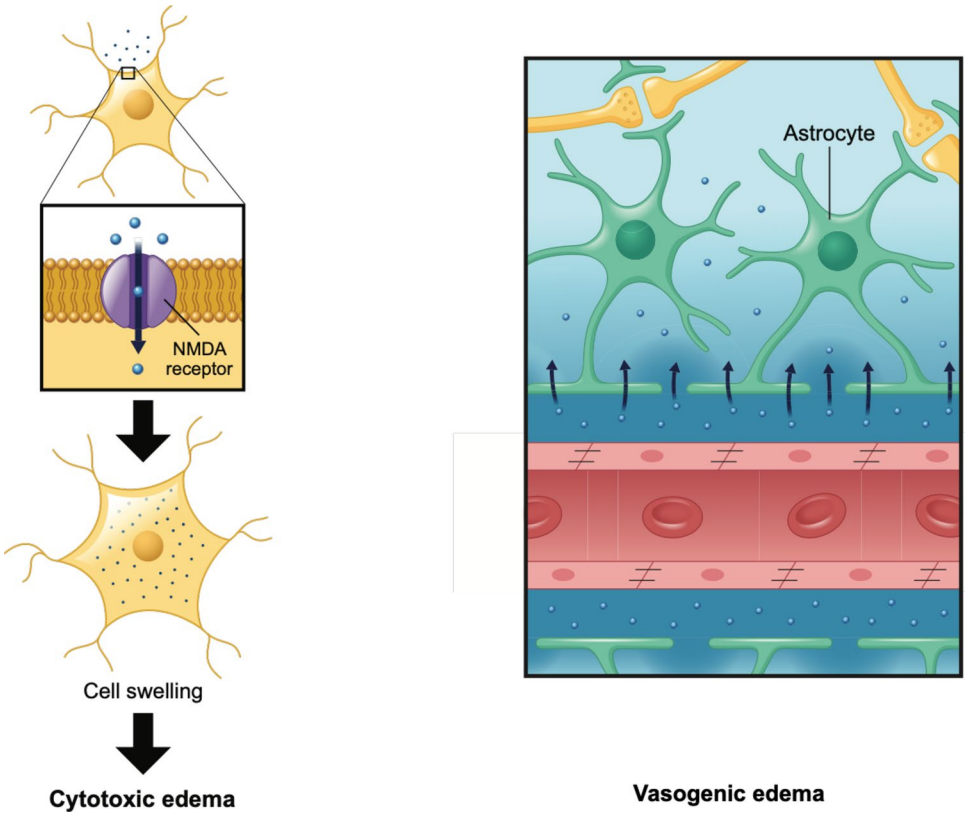

Fig. 2 Cytotoxic edema and vasogenic edema

manifestation is oculomotor abnormality. Complete ophthalmoplegia occurs rarely, while the most common ocular abnormality is nystagmus, usually horizontal. Other ophthalmic alterations involve bilateral decreased visual acuity, diplopia, bilateral abducens palsy and other ocular muscle or conjugate-gaze palsies. These clinical manifestations result from lesions of the pontine tegmentum including the abducens and oculomotor nuclei [6]. The presentation of gait ataxia can range from mild gait abnormality to a complete inability to stand. It results from the involvement of the cerebellar vermis and vestibular dysfunction. Unusual manifestations of WE include hypothermia/hyperthermia due to the involvement of the posterior hypothalamus, deafness, and epileptic seizures [6].

WE can lead to irreversible brain damage that can cause death in up to 20% of cases or Korsakoff syndrome in 85% of survivors [6]. Patients with untreated WE develop Korsakoff syndrome, a form of anterograde and retrograde amnesia with confabulation, related to lesions in the dorsal thalamus and mammillary bodies [5].

Thiamine deficiency can also present other clinical manifestations such as dry beriberi (neuropathy), wet beriberi (neuropathy with high-output congestive heart failure), and gastrointestinal beriberi (abdominal pain, vomiting, and lactic acidosis) [6, 15]. High-output congestive heart failure, although far less common than neuropathy, can present with tachycardia, dyspnea, and electrocardiographic abnormalities. Neuropathic beriberi is a sensorimotor peripheral neuropathy that often involves the lower extremities. It is painful and could result from a deficiency of other vitamins such as pyridoxine and pantothenic acid. Notably, patients receiving total parenteral nutrition can present with components of all forms of vitamin B1 deficiency syndromes.

Underlying conditions and diseases (Table 1)

The most common condition of WE is alcoholism, which accounts for 50% of WE [4]. However, there are many other conditions related to WE such as unbalanced nutrition, chemotherapy, gastrointestinal surgery, GI fistula, hyperemesis gravidarum, fasting/starvation, gastrointestinal disease, AIDS, dialysis, parenteral nutrition, psychiatric disease with anorexia, infection, and thyroid disease. Compared with alcoholic patients with WE, nonalcoholic patients with WE are more likely to present with oculomotor abnormalities and less frequent cerebellar signs [16]. In nonalcoholic patients, WE commonly presents with mental status changes without other symptoms and the diagnosis is often delayed or missed [17]. Although WE is generally considered to be a disease of an adult, it can also occur in the pediatric population. The cases of infants and children have been reported

Table 1 Underlying conditions and diseases of Wernicke encephalopathy

Causes	Mechanisms of thiamine deficiency
Alcoholism	Low uptake of thiamine Low thiamine absorption rate at the mucosal level Impaired thiamine utilization
GI procedure/starvation	Low uptake of thiamine
Hyperemesis gravidarum	Low uptake of thiamine Increased demands of pregnancy and depleted thiamine stores Loss of thiamine
Chemotherapy	Low uptake of thiamine Decreased thiamine availability Inactivation of thiamine or enzymes of the intermediate carbohydrate metabolism Cachexia
Hyperthyroidism	Raised thiamine metabolism
Infectious and inflammatory diseases	Low uptake of thiamine Raised thiamine metabolism Inhibition of intestinal thiamine uptake
Genetic diseases	Inactivation of thiamine transporter

secondary to inadequate dietary intake or excessive intake of isotonic drink. Inadequate dietary intake may be due to maternal thiamine deficiency during breastfeeding or excessive dietary restriction for conditions such as atopic dermatitis or gluten sensitivity.

Identified mechanisms through which alcoholism may contribute to thiamine deficiency include inadequate nutritional intake, decreased absorption of thiamine from the gastrointestinal tract, reduced uptake into cells and impaired utilization of thiamine in the cells. Acute alcohol exposure interferes with the absorption of thiamine from the gastrointestinal tract due to deactivation of the enzyme thiamine diphosphokinase (TPK), which promotes the absorption of thiamine from the gastrointestinal tract. Cellular utilization of thiamine can be affected in different ways by chronic alcohol use. Once thiamine is imported into the cells, it is first converted into phosphorylated thiamine (ThDP) by the addition of two phosphate groups. ThDP then binds to the thiamine-dependent enzymes, which requires the presence of magnesium. Chronic alcohol consumption frequently leads to magnesium deficiency which contributes to an inadequate functioning of the thiamine-enzyme complex, which leads to the symptoms resembling those of thiamine deficiency [18].

As to the mechanism related to gastrointestinal procedures and fasting and starvation, low uptake of thiamine is responsible for thiamine deficiency. Patients with hyperemesis gravidarum suffer from poor nutritional intake, increased thiamine demands from pregnancy and depleted thiamine stores. Hyperemesis also leads to lowered thiamine levels [19, 20]. Patients treated with chemotherapy might suffer from thiamine deficiency due to low uptake and decreased availability of thiamine. Some chemotherapy agents such as 5-fluorouracil (5-FU), fedratinib (a Janus kinase inhibitor), erbulozole and ifosfamide interfere with thiamine function and enzymes of the intermediate carbohydrate metabolism, which results in cachexia, a multifactorial syndrome characterized by poor nutritional status, systemic inflammation, and muscle wasting [21–24]. Hyperthyroidism also causes thiamine deficiency through hypermetabolism with increased demand of thiamine [25]. The hypermetabolic state may precipitate WE in a patient whose thiamine stores are depleted secondary to prolonged starvation. Infectious and inflammatory diseases may similarly precipitate thiamine deficiency [26, 27].

Genetic mutation of thiamine-transporter is another cause of thiamine deficiency. Biotin-responsive basal ganglia disease, which is known as thiamine metabolism dysfunction syndrome-2 is caused by mutations in the SLC19A3 gene encoding human thiamine transporter 2, which affects the absorption of thiamine and other vitamins in the intestine [28, 29].

Diagnosis and treatment

The diagnosis of WE is a clinical diagnosis. In this regard, the best approach for a correct diagnosis is high clinical suspicion. Clinicians should consider the WE diagnosis if the patient has unbalanced nutrition, subacute or chronic diseases with increased metabolism, or altered food ingestion or absorption, even if patients show only one component of the classic triad. About 19% of patients have none of the symptoms of the classic triad at WE presentation, although usually one or more symptoms appear later in the course of the disease [7]. Some nonalcoholic WE patients, however, exhibit atypical manifestations, which makes the diagnosis difficult. In fact, neuropathological studies indicate that many cases of WE may not be diagnosed in life [18].

The clinical criteria from 2010 European Federation of Neurological Societies (EFNS) guidelines significantly improved the identification of patients with alcoholism related to WE. The clinical diagnosis of WE in alcoholics requires two of the following: (1) nutritional deficiency and a history of an alcohol use disorder, or any other deficiency states, (2) oculomotor abnormalities, (3) equilibrium disorders, and (4) either an altered mental state or mild memory impairment. It is reasonable to apply the same criteria to non-alcoholic patients [3]. Using these criteria, clinical diagnosis of WE, either alone or with Korsakoff's syndrome, can be achieved with 85% of sensitivity [3].

The presumptive diagnosis of WE can be confirmed by determining blood thiamine concentrations or by measuring the red blood cell transketolase activity. However, these measurements are limited by a lack of specificity and technical difficulty [6, 7].

The mainstay of WE treatment is the administration of thiamine in a timely fashion. Diagnostic confirmation is often difficult and delayed and, therefore, a high degree of clinical suspicion and recognition of predisposing conditions should prompt the clinician to initiate treatment at the earliest opportunity. This practice is based on the assumption that thiamine is inexpensive and safe, and its quick administration has been reported to prevent progression of WE to irreversible deficits including Korsakoff syndrome. EFNS guidelines recommend an intravenous infusion of thiamine, 200 mg diluted with 100 mL of normal saline or 5% dextrose, given over 30 min [1]. The European Federation recommends dosing thiamine 3 times daily in cases of WE [15]. In WE patients with gene mutation of thiamine-transporter, biotin therapy in addition to thiamine helps to improve their symptoms [28, 29].

Thiamine administration can improve symptoms, especially if administered promptly. Mental status change and acute encephalopathy often gradually recede, but residual neurologic deficits are common and persistent. Mild neurocognitive symptoms such as apathy, drowsiness, and confusion respond well to treatment. Memory and learning deficits, on the other hand, show poor recovery, and unfortunately, many patients are left with permanent residual Korsakoff amnesia. Delayed recovery is seen in equilibrium disorders such as gait ataxia. Some patients experience complete recovery, although most WE patients have residual gait disturbances. Oculomotor abnormalities respond well to treatment. The response to thiamine administration on oculomotor abnormalities is quite predictable and constant. Delay or failure of recover should alert physicians to consider alternative diagnoses. In most cases, horizontal and vertical gaze palsies and ptosis recover completely within days to weeks. Although horizontal nystagmus shows dramatic recovery soon after treatment with thiamine, it can persist for months in up to 60% of the patients. In patients with chronic dementia, fine horizontal nystagmus and gait abnormalities can be clues to alcohol-related etiology [15].

Imaging studies of WE and the role of MR imaging sequences

In terms of imaging studies, computed tomography (CT) can show areas of reduced attenuation density at the periaqueductal grey matter and the medial portion of thalami but, in most cases, CT findings are negative in the acute phase of WE. MRI has a low sensitivity of only 53% but high specificity of 93% for the diagnosis of WE, thus MRI is currently considered the most valuable method to confirm the diagnosis [7]. T2-weighted images can identify the lesions as hyperintensities more sensitively than CT, but fluid-attenuated inversion recovery (FLAIR) can further increase the sensitivity of MRI and lower the false-negative rate. On FLAIR, CSF appears dark by eliminating the normal hyperintensity of free water, but edematous tissues remain bright. The FLAIR sequence is particularly sensitive to detect edematous lesions near the ventricles when compared with conventional T2-weighted images [30] [31] (Fig. 3).

Diffusion-weighted imaging (DWI) with quantitative measurement of the apparent diffusion coefficient (ADC) can help the detection of edematous tissue. DWI is a sensitive method for identification of edematous lesions early in the course of WE and has the advantage of distinguishing between cytotoxic and vasogenic edema. Cytotoxic edematous lesions show hyperintensity on DWI with low ADC values (restricted diffusion of water molecules), whereas vasogenic edematous lesions show hyperintensity on DWI with high ADC values (unrestricted or high water diffusion) in the affected regions [32]. The absence of MR signal-intensity alterations, however, does not exclude the diagnosis of WE (Figs. 4, 5).

Contrast-enhanced T1-weighted images point out areas with disrupted blood–brain barrier and enhancement can be seen in about 50% of WE cases [6, 33] (Fig. 6). Strong enhancement of the mammillary bodies, for instance, can be the only sign of the disease and is more frequent in chronic alcoholics [34] (Fig. 7).

MR spectroscopy studies have reported low N-acetylaspartate/creatine ratio (NAA/Cr), suggestive of neuronal metabolic impairment, and an abnormal lactate peak, suggesting anaerobic glycolysis [35]. The low NAA/Cr has been reported to improve in parallel with clinical improvement following thiamine therapy in some cases [35]. Animal models of WE have indicated that utilizing of MRI and MRS might be helpful in tracking the brain damage and treatment responses [36].

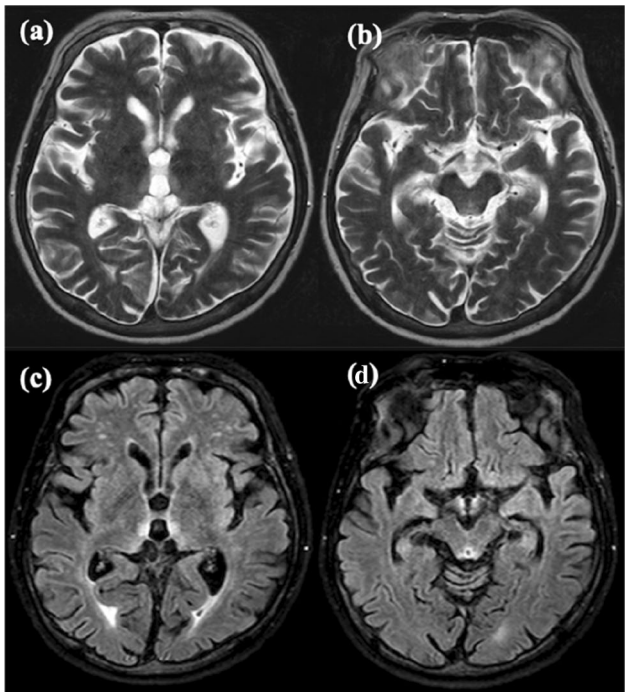

Fig. 3 Typical MRI findings of Wernicke Encephalopathy. A 55-year-old alcoholic man presented with a 2-day history of confusion, ataxia and nystagmus. **a**, **b** T2-weighted images show bilateral and symmetric hyperintensity in the medial thalami, hypothalamus, mammillary bodies, periaqueductal area, and tectal plate. **c**, **d** FLAIR images demonstrate hyperintensity in the same lesions more conspicuously than T2-weighted images

MR imaging typically shows T2, FLAIR and DWI hyperintensity in bilaterally symmetrical lesions of the paraventricular regions of the thalamus, the hypothalamus, the mammillary bodies, the periaqueductal region, and the floor of the fourth ventricle. Importantly, this typical pattern of lesions on MRI is observed in only 58% of patients [7, 37]. MRI also shows unusual sites of lesions including the putamen, caudate, splenium of the corpus callosum, dorsal medulla, pons, red nucleus, substantia nigra of the midbrain, cranial nerve nucleus (VI, VII, VIII, XII), vermis, dentate nucleus, paravermian region of the cerebellum, fornix and pre- and postcentral gyri. These unusual MRI findings are almost always found in association with the typical imaging findings [6, 8, 10] (Fig. 8).

A study on alcoholic and nonalcoholic patients with WE showed symmetric lesions of the medial thalami and of the periventricular region of the third ventricle (80%), the periaqueductal area (59%), the mammillary bodies (45%), the tectal plate (36%), the cranial nerve nuclei (18%), periventricular gray matter located anterior to the fourth ventricle (7%), the cerebellum (5%) the vermis (4%), the dentate nuclei (1.8%), the pre- and postcentral cortex (1.8%) [9]. Among these patients, 63% showed contrast enhancement of the mammillary bodies, the tectal plate, the thalamus, the periaqueductal area, and the cranial nerve nuclei. Gadolinium enhancement was seen more frequently in alcoholic WE than in nonalcohol WE, and the cranial nerve nucleus involvement was seen more frequently in nonalcohol WE than in alcohol WE [9] (Fig. 9). The latter cited study hypothesized that alcohol may contribute to increased BBB permeability. To date, it remains unclear why the cranial nerve nucleus involvement represents a distinctive pattern in nonalcoholic patients. MRI findings of patients with thiamine metabolism dysfunction syndrome 2 show abnormal signal intensity in the caudate nuclei and putamen as well as in the medial thalamus and periaqueductal region [28, 29]. Cerebellar involvement on imaging is rare but autopsy studies have demonstrated that the superior vermis is affected in one-third of patients with WE [7, 38]. One research study reported a case of hemorrhagic focus in the head of the right caudate of a patient with WE [39] (Fig. 10). According to the literature, the presence of lesions of the caudate nuclei, frequently observed in patients in a comatose state, is a sign of severity. Cortical involvement indicates irreversible damage and poor prognosis [8, 40] (Figs. 10, 11) and signal abnormalities of the paramedian thalamic nuclei and contrast enhancement of the mammillary bodies may be a predictor of poor recovery from memory impairment and altered mental state in case of WE [37]. In pediatric patients,

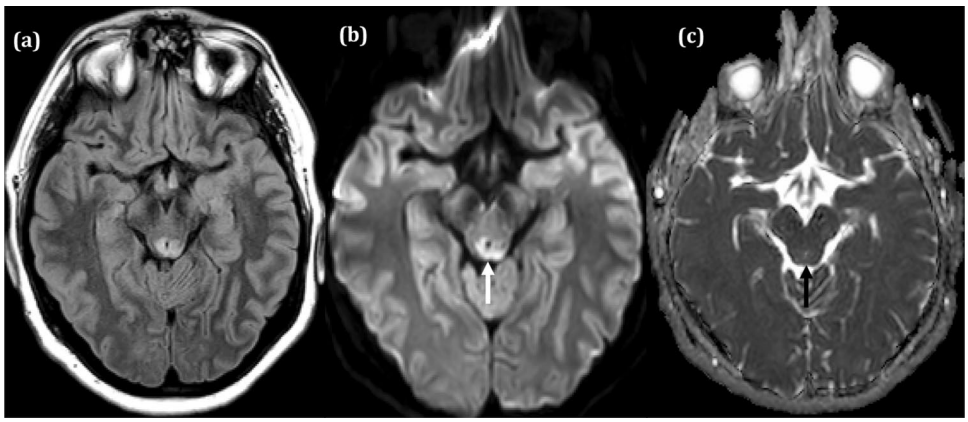

Fig. 4 Vasogenic edema in Wernicke encephalopathy due to unbalanced diet. A 28-year-old nonalcoholic male with an unbalanced diet presented with apathy for 3 weeks. **a** FLAIR image shows hyperintensity in the tectal plate, the periaqueductal area, the bilateral hypothalamus and the mammillary bodies. **b**, **c** DWI shows hyperintensity in the tectal plate with increased ADC value, suggesting vasogemic edema (arrows)

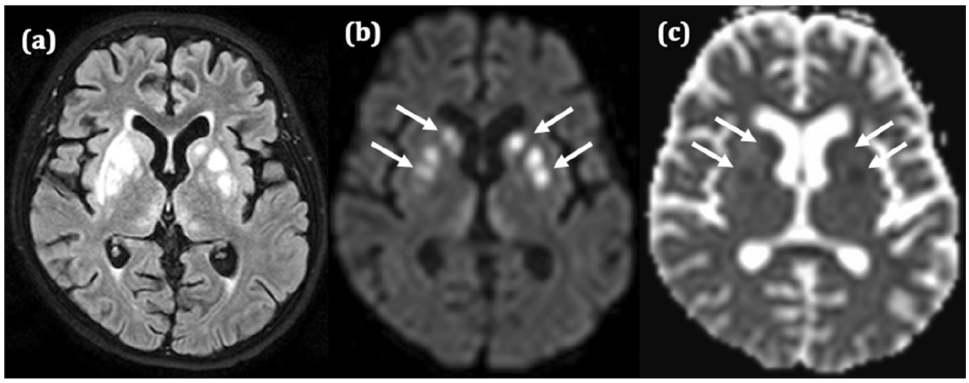

Fig. 5 Cytotoxic edema in Wernicke encephalopathy after chemotherapy. A 8-year-old female with a history of acute lymphocytic leukemia treated with chemotherapy including cyclophosphamide presented with coma. **a** FLAIR image shows hyperintensity in the bilateral striatum, bilateral medial thalami and mammillary bodies. **b**, **c** DWI/ADC show diffusion restriction in the bilateral putamina and caudates, suggesting cytotoxic edema (arrows)

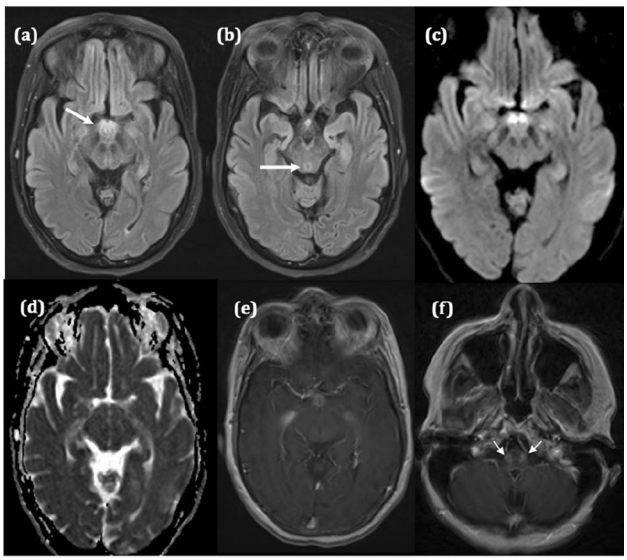

Fig. 6 Wernicke encephalopathy in septic shock. A 58-year-old female presented with mental status changes, malaise, nausea and vomiting. She was diagnosed with severe colitis, which resulted in septic shock. **a**, **b** FLAIR hyperintensity is seen in the bilateral hypothalamus and mammillary bodies (arrows). **c**, **d** DWI/ADC suggest vasogenic edema in the bilateral hypothalamus. **e**, **f** Postcontrast T1-weighted images demonstrate enhancement in the bilateral hypothalamus and olivary nuclei (small arrows)

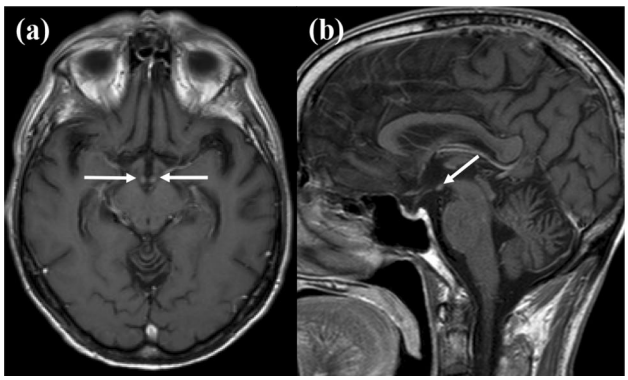

Fig. 7 Wernicke encephalopathy in Diabetic Ketoacidosis. A 54-year-old alcoholic patient with hyperglycemia, diabetes and ketoacidosis presented with mental status changes. **a**, **b** Symmetric abnormal enhancement in the mammillary bodies are demonstrated (arrows). FLAIR images show no signal intensity alteration (not shown)

abnormal intensity alteration is often observed in the basal ganglia with a characteristic involvement of the putamen, probably due to the high thiamine-dependent metabolism of these areas in children [41, 42] (Fig. 5).

Complications associated with WE include hepatic encephalopathy, osmotic demyelination syndrome, status epilepticus and posterior reversible encephalopathy syndrome (PRES). Hepatic encephalopathy is a functional and potentially reversible syndrome from any cause or chronic liver disease. Abnormality on T2-weighted images is demonstrated in the cortex, dorsal brain stem and external capsule in the acute phase. The chronic phase is characterized by symmetric T1 hyperintensity in the basal ganglia (more often the globus pallidus) [43, 44]. Osmotic demyelination syndrome is a condition that results from an osmotic insult and demyelination of the basis points (previously known as central pontine myelinolysis) and/or outside of the pons (extrapontine myelinolysis) [45, 46]. The extrapontine lesions are typically seen in the thalami, capsula externa, basal ganglia, lateral geniculate body, cerebellum, and the cerebral cortex (Fig. 12). Status epilepticus is a neurological medical emergency and continues to be associated with significant morbidity and mortality. Excessive extracellular glutamate in the synaptic cleft causes hyperexcitotoxicity mediated by NMDA receptors [7]. PRES is a reversible neurologic syndrome that follows the

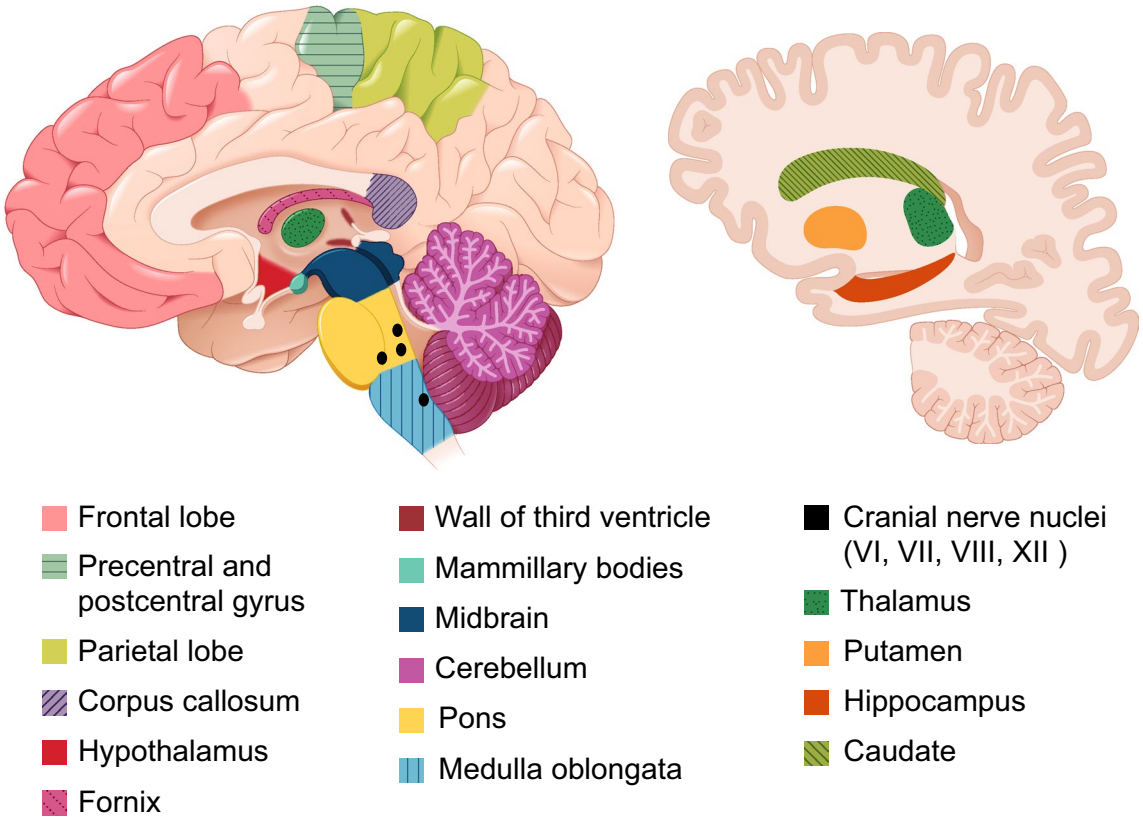

Fig. 8 Distribution of brain lesions in Wernicke encephalopathy

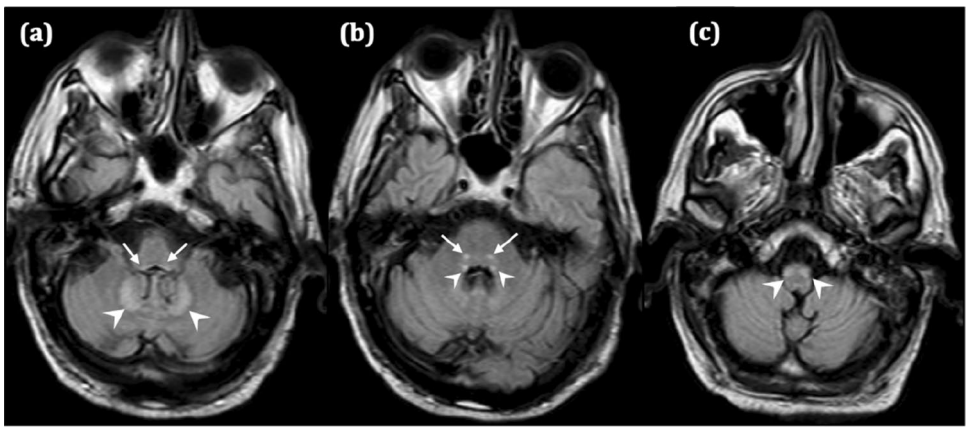

Fig. 9 Wernicke encephalopathy with cranial nerve nucleus involvement. A 57-year-old male with alcoholic cirrhosis presented with acute mental status change and nystagmus. **a** FLAIR image shows hyperintensity in the bilateral abducens nerve nuclei (arrows) and dentate nuclei (arrowheads). **b** More caudal FLAIR image shows hyperintensity in the bilateral facial nerve nuclei (arrows) and vestibular nuclei (arrowheads). **c** More caudal FLAIR image shows hyperintensity in the bilateral olivary nuclei (arrowheads), which results from secondary involvement of the Guillain-Mollaret triangle

failure of the cerebrovascular autoregulatory mechanism, with consequent vasodilatation, hyperperfusion and vasogenic brain edema [47]. The main causes of PRES include hypertension, eclampsia, immunosuppressive medications such as cyclosporine, various antineoplastic agents, severe hypercalcemia, amyloid angiopathy, systemic lupus erythematosus, renal failure as well as alcohol withdrawal [46] (Fig. 13).

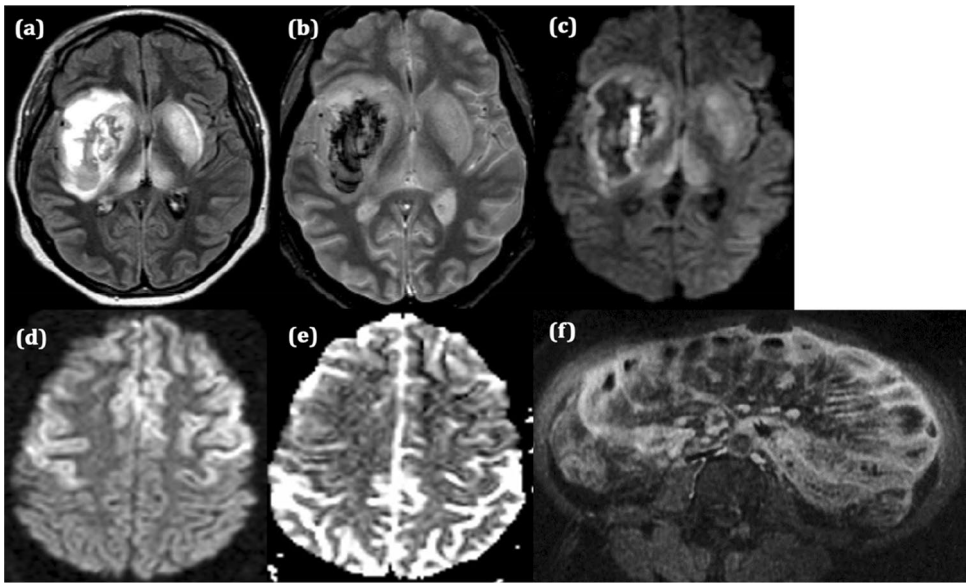

Fig. 10 Wernicke encephalopathy with hemorrhage. A 19-year-old nonalcoholic female presented with a comatose state with a 3-week history of significant abdominal pain, diarrhea, and non-bloody emesis. She was diagnosed with septic shock and disseminated intraabdominal tuberculosis. **a** FLAIR, **b** T2*-weighted image and **c** DWI show abnormal signal intensity in the bilateral thalami and basal ganglia with hemorrhage in the right putamen. **d**, **e** DWI/ADC show diffusion restriction along the cortex of the bilateral frontal lobes. **f** Fat-sat T2-weighted image shows hyperintensity in the intraperitoneal fat tissue. She died despite immediate thiamine infusion

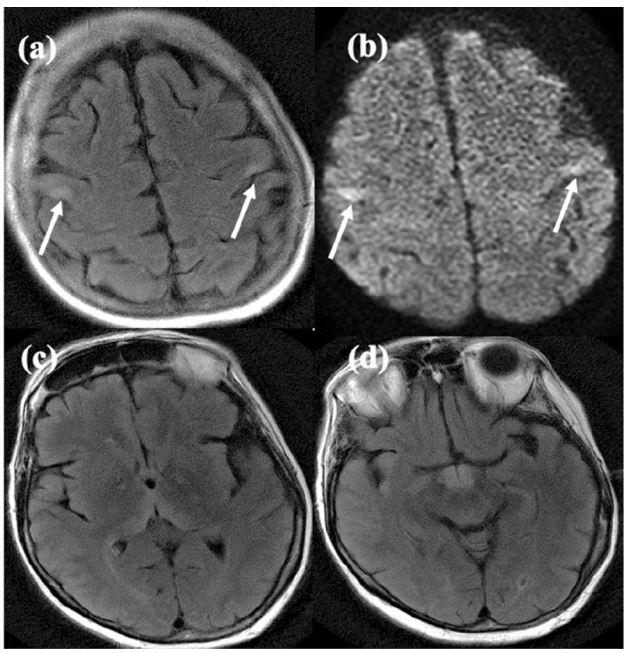

Fig. 11 Wernicke encephalopathy with cortical involvement. A 58-year-old nonalcoholic female with bipolar disorder and fibromyalgia presented with a 1-week history of altered mental status and decreased visual acuity. She did not have enough thiamine in her diet. **a**, **b** FLAIR image shows hyperintensity in bilateral precentral gyri with DWI hyperintensity (arrows). **c**, **d** FLAIR images show hyperintensity in the bilateral thalami, hypothalamus, and mammillary bodies

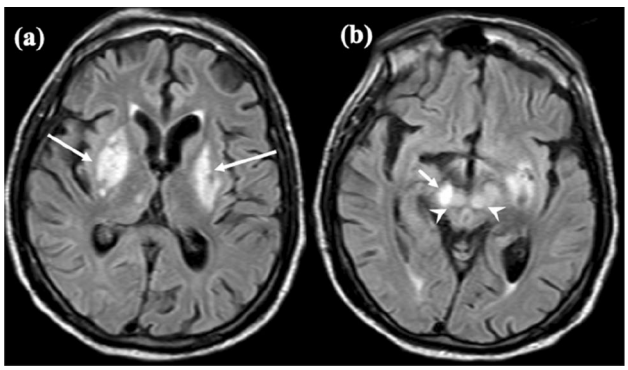

Fig. 12 Wernicke encephalopathy coexistent with osmotic demyelination syndrome. A 57-year-old alcoholic male with cirrhosis presented with a 2-day history of altered mental status. This study was taken after rapid correction of hyponatremia. **a**, **b** Signal alterations on FLAIR images are seen in the bilateral thalami and periaqueductal area from Wernicke encephalopathy. The basal ganglia (arrows), red nuclei (arrowheads) and right substantia nigra (small arrow) of the midbrain are involved from pontine and extrapontine myelinolysis)

Differential diagnosis

As for the differential diagnosis on MRI, diseases presenting with bilaterally symmetric lesions in the medial thalami should be included such as deep cerebral venous thrombosis, paramedian thalamic syndrome, top-of-the-basilar syndrome, Japanese encephalitis, atypical Creutzfeldt-Jakob

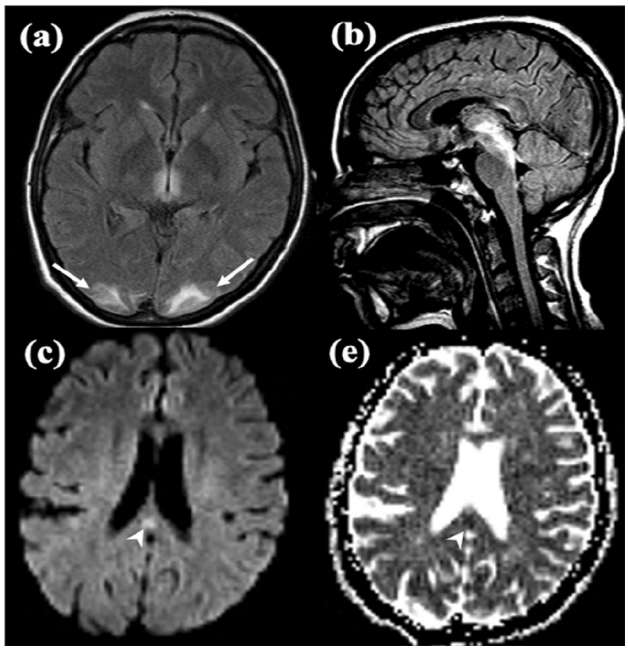

Fig. 13 Wernicke encephalopathy coexistent with posterior reversible encephalopathy syndrome. A 28-year-old female with hyperemesis gravidarum presented with visual loss and nystagmus. **a** Axial FLAIR image and **b** Sagittal FLAIR image show symmetric hyperintense lesions in the bilateral medial thalami and periaqueductal area, consisting with Wernicke encephalopathy, while hyperintensity in the bilateral occipital lobes suggests posterior reversible encephalopathy syndrome (PRES) (arrows). **c**, **d** DWI/ADC show restriction in the splenium of corpus callosum (cytotoxic edema) (arrowheads)

disease and influenza A virus infection (Fig. 14) [6, 37]. All these diseases can be differentiated from WE from their clinical characteristics and other MR imaging findings such as symmetric signal intensity change in the mammillary bodies, tectal plate, and periaqueductal area in classical WE.

The differential diagnosis of symmetric signal-intensity alterations of the dentate nuclei, cranial nerves nuclei, red nuclei, and splenium should include metronidazole-induced encephalopathy (MIE). Metronidazole is thought

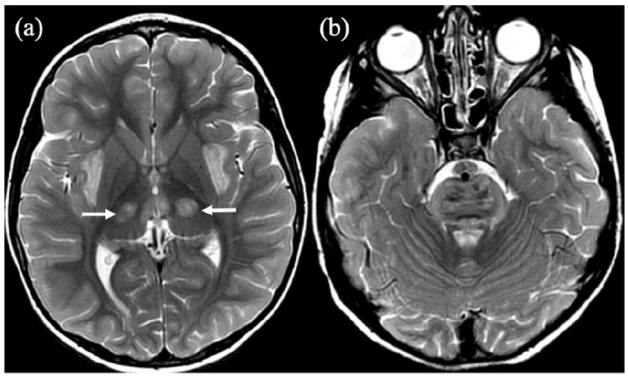

Fig. 14 Influenza virus-associated encephalopathy. A 5-year-old male with influenza A infection presented with acute decline in neurological function. **a**, **b** T2-weighted images show hyperintensity in the bilateral thalami (arrows), external capsular areas, and basis pontis

to penetrate CSF and the central nervous system and can produce cerebellar dysfunction. Metronidazole neurotoxicity may be mediated by the impairment of vitamin B1 action through its conversion to a thiamine analog and consequent vitamin B1 antagonism. On MRI, MIE can mimic WE presenting with bilaterally symmetric hyperintense lesions in cerebellar dentate nuclei, midbrain, dorsal pons, medulla, corpus callosum, and cerebral white matter with similar symptoms to those produced by acute WE (Fig. 15). Therefore, the differential diagnosis may be difficult in the case of the malnourished patients treated with metronidazole [9]. MR imaging follow-up should be done after an effective thiamine treatment or discontinuation of metronidazole in conjunction with the resolution of clinical symptoms.

Conclusion

This review covered epidemiology, pathophysiology, underlying causes and conditions, symptoms and imaging findings of Wernicke encephalopathy. Being familiar with all of the

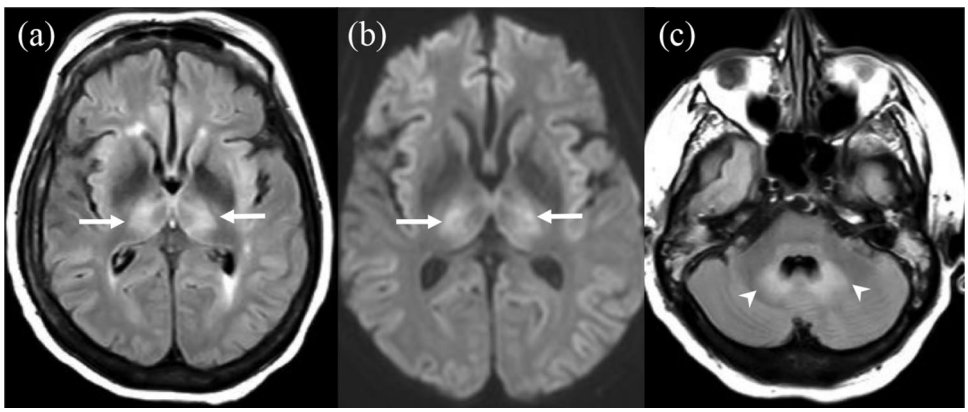

Fig. 15 Metronidazole-induced encephalopathy. A 56-year-old female with colitis treated by metronidazole presented with altered mental status. **a** FLAIR image and **b** DWI show hyperintensity in the bilateral thalami (arrows). **c** FLAIR image shows abnormal intensity alteration in the dentate nuclei (arrowheads)

above is important for radiologists and clinicians alike when making the diagnosis of WE to start immediate treatment.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

Informed consent The requirement for informed consent for study participation was waived.

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