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PICTORIAL ESSAY

Underdiagnosed Wernicke's Encephalopathy in Children: Spectrum of Imaging Findings in Three Local Cases

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INTRODUCTION

Although vitamin B1 deficiency is increasingly being recognised in ill adults, Wernicke's encephalopathy (WE) remains underrecognised in children. We present three local cases of paediatric WE observed over a 2-year period.

Importantly, WE was not considered a primary differential diagnosis at initial presentation. This article aims to raise awareness of paediatric WE since time from recognition to thiamine replacement determines prognosis and mortality. We also illustrate some of its magnetic resonance imaging (MRI) findings to promote early radiological detection of the disease.

CASE REPORTS

Three patients with WE, aged between 12 and 17 years, are described. All three patients were prescribed total parenteral nutrition (TPN) prior to development of WE. All were examined with MRI. In all cases, diagnosis was confirmed by symptom regression, serum transketolase increase, and/or improved MRI findings following thiamine administration. Details of these three cases are illustrated in the Table.

Case 1

A 12-year-old boy was undergoing chemotherapy for osteosarcoma. One week prior to presentation, he was started on TPN due to recurrent severe vomiting. He then developed confusion and athetoid movements. Computed tomography revealed subtle hypodensity in bilateral thalami (Figure 1). MRI revealed symmetrical T2 hyperintensity and restricted diffusion at the dorsomedial thalami (Figure 2). After the possibility of WE was raised, he was given high doses of thiamine (>1000 mg daily) and slowly resumed oral feeding. Clinically, the child regained his usual functional and neurological status with no residual neurological deficits. Follow-up MRI 6 months later showed resolution of the thalamic signal abnormalities (Figure 3).

Case 2

A 17-year-old girl was undergoing chemotherapy for osteosarcoma. She presented insidiously with dullness

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Table. Case summary.

	Case 1	Case 2	Case 3
Age, y	12	17	12
Sex	Male	Female	Male
Underlying illness	Osteosarcoma on chemotherapy	Osteosarcoma on chemotherapy	Haemolytic uraemic syndrome
Presentation	Confusion, athetoid movements	Dullness, flaccid tones	Lethargy, unsteady gait, vertical nystagmus
Duration of total parenteral nutrition prior to presentation	1 week	2 months	Episodic with various lengths over 3 years
Magnetic resonance imaging findings	Dorsomedial thalamic T2 hyperintensity and restricted diffusion	T2 hyperintensity and restricted diffusion at mammillary bodies, thalami, and PAG; cerebral cortex involvement; contrast enhancement in mammillary bodies	Cerebral atrophy, especially at PAG
Laboratory findings (post thiamine replacement)	Increased TKS and normal TPP effect	Normal TKS and TPP effect	Increased TKS and decreased TPP effect
Outcome	Complete resolution of symptoms	Improved mental status but limited motor control	Resolved gait and gaze disturbance; underperforming in life

Abbreviations: PAG = periaqueductal grey matter; TKS = transketolase; TPP = thiamine diphosphate.

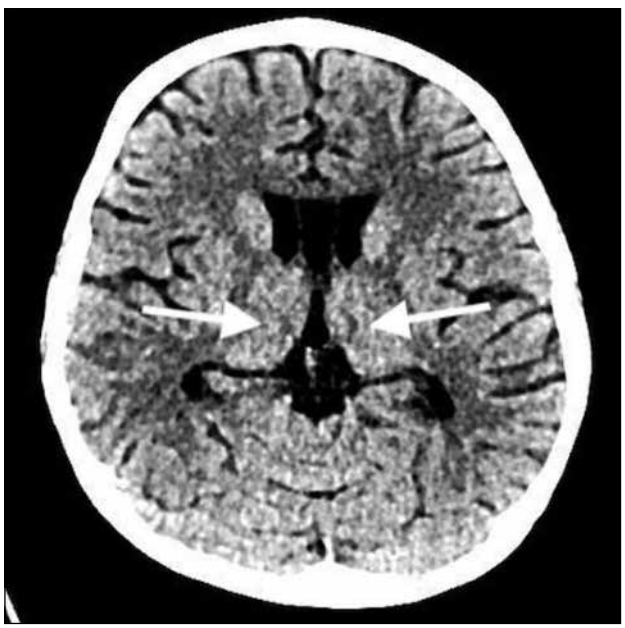

Figure 1. Plain computed tomography in case 1. Non-enhanced computed tomography shows only subtle hypodensity in bilateral thalami (arrows).

and generalised flaccid tone after being on TPN for 2 months due to poor intake. She was admitted in a decorticate posture, had fixated gaze and generalised areflexia. MRI showed T2 hyperintensity and restricted diffusion at mammillary bodies, dorsomedial thalami, periaqueductal grey matter, and around the third ventricle on fluid-attenuated inversion recovery. The mammillary bodies and colliculi showed subtle contrast enhancement. Notably, signal abnormalities were also detected in parts of bilateral cerebral cortices (Figure 4). Thiamine (1500 mg daily) was given and enteral feeding was resumed. Nonetheless despite improvement in mental status, she regained very minimal voluntary motor control and remained bedbound.

Case 3

A 12-year-old boy was on monoclonal antibody therapy for recurrent atypical haemolytic uraemic syndrome. He had experienced bouts of pancreatitis over the years and was put on bowel rest and TPN episodically. He developed lethargy, unsteady gait and vertical nystagmus 1 week after the current episode of TPN. Compared with MRI images 2 years previously, there was generalised cerebral atrophy, with volume loss most significant at bilateral thalami (evidenced by widening of the third ventricle), mammillary bodies, colliculi, and hippocampi (Figure 5). Features and interval changes were highly suggestive of chronic WE. This suspicion was substantiated by interviews with the carer who reported past episodes of abnormal behaviour in the form of disinhibition and limb twitching. He was prescribed thiamine (1000 mg daily) and resumed enteral feeding. His gait disturbance and eye signs soon subsided but he remained underperforming in academic and social aspects.

DISCUSSION

WE is a potentially fatal acute neuropsychiatric disease

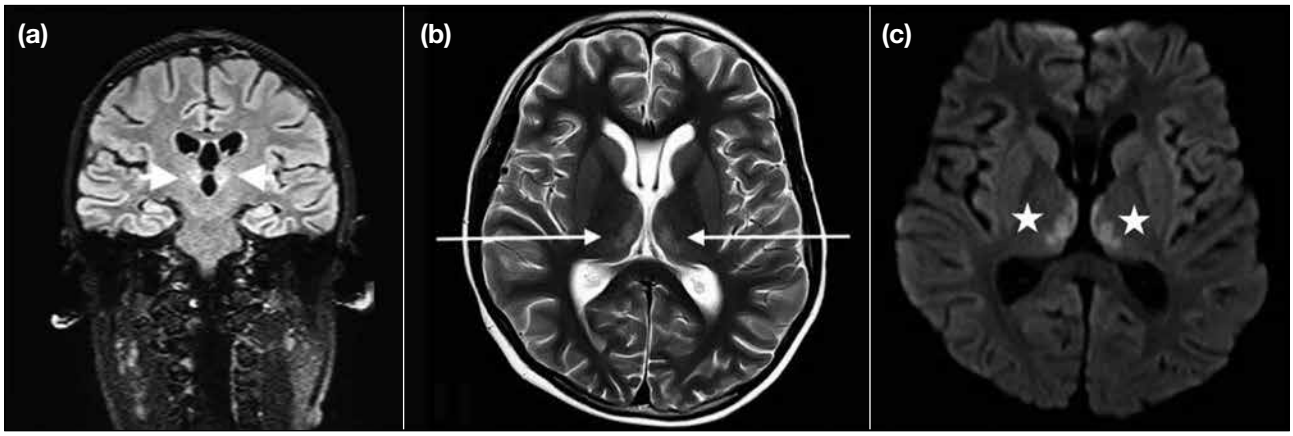

Figure 2. Magnetic resonance imaging in case 1. (a) Fluid-attenuated inversion recovery and (b) T2-weighted sequences showing symmetrical T2 hyperintensity in bilateral thalami (arrows). (c) Diffusion-weighted imaging showing corresponding restricted diffusion (stars).

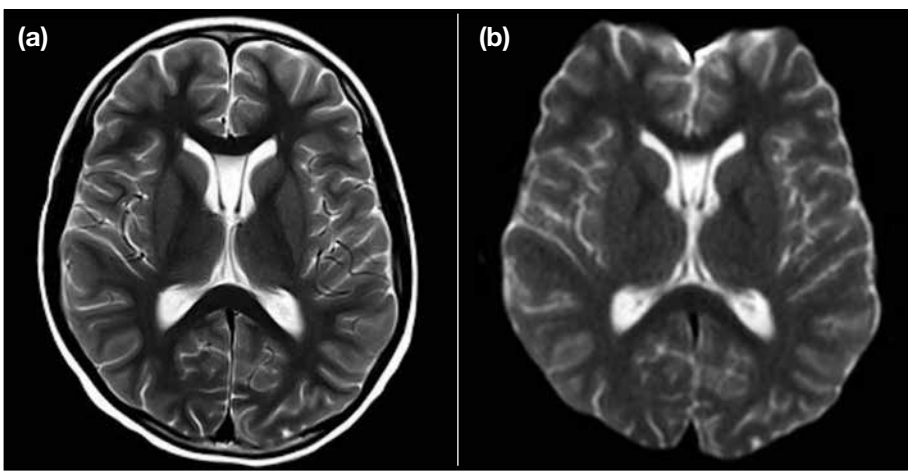

Figure 3. Follow-up magnetic resonance imaging in case 1 after 6 months of presentation. There is resolution of thalamic signal abnormalities on both (a) T2-weighted and (b) diffusion-weighted imaging sequences.

caused by thiamine (vitamin B1) deficiency. Thiamine, in its biologically active form thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain. The body's reserve of thiamine can be readily depleted over 2 to 3 weeks[1] after which brain lesions develop, usually restricted to selective, vulnerable regions with high thiamine content and turnover.

Epidemiology

Although WE is a relatively well-recognised disease entity in alcoholic adults, it remains underrecognised in children. There has been increasing academic and clinical interest in WE in sick children over the last two to three decades, but as many as 58% of paediatric WE cases have been missed at clinical examination and recognised only on autopsy.[2] This lack of awareness of WE in the paediatric patient group may be due to poor clinical familiarity, non-classic presentation, and atypical imaging features.

Thiamine deficiency in childhood is most often associated with cancer.[2] Other recognised causes are prolonged parenteral nutrition without supplementation of thiamine, gastrointestinal surgery, and other systemic diseases.[3] Seear et al[4] reported that as many as four of six children undergoing chemotherapy, and 10 of 80 children receiving intensive care were deficient in thiamine. Such prevalence is much higher than previously believed; therefore, clinical awareness and a low threshold of suspicion are vital.

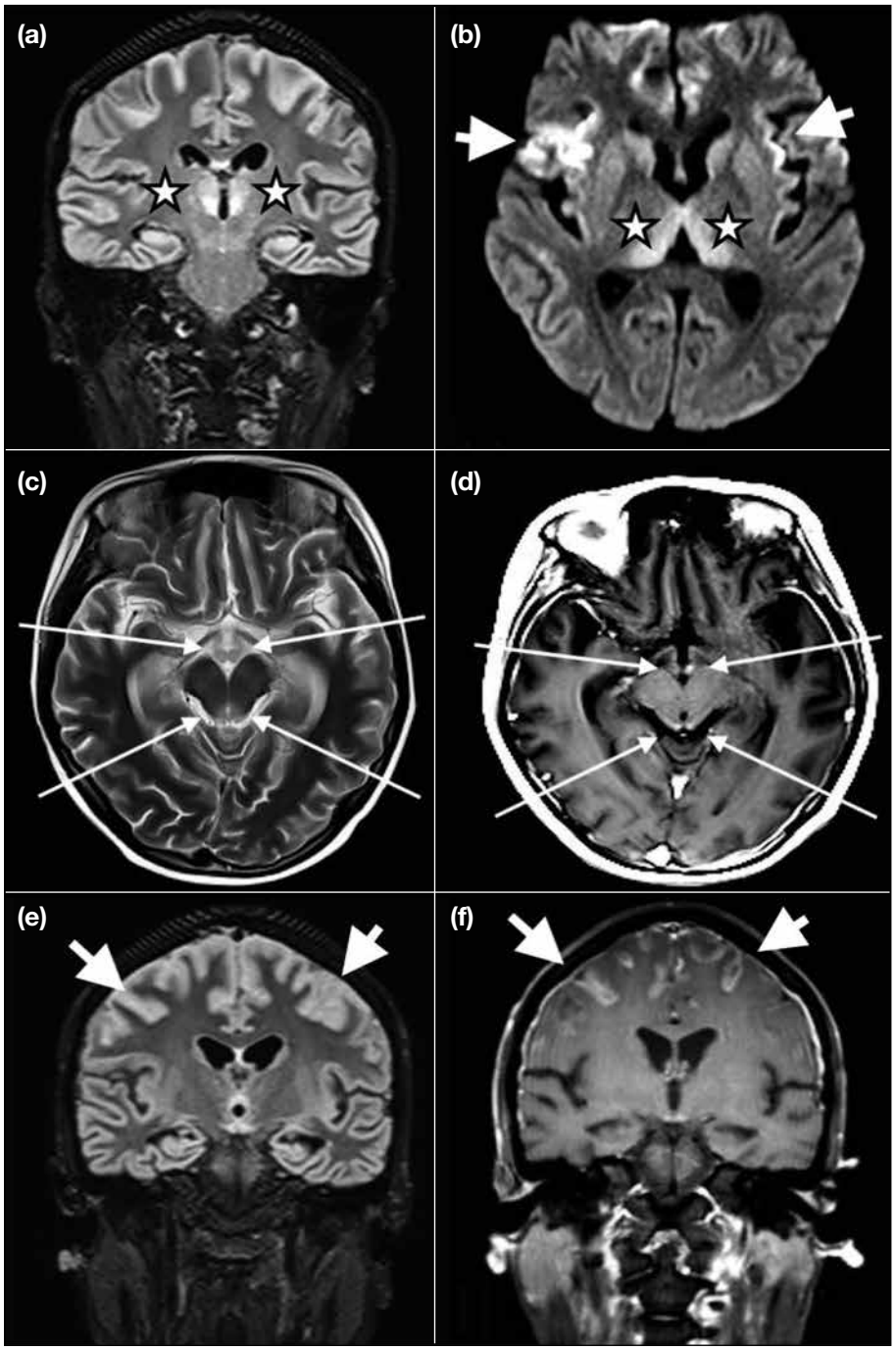

Figure 4. Magnetic resonance imaging of case 2. (a) Fluid-attenuated inversion recovery (FLAIR) shows symmetrical bilateral thalamic hyperintensity and (b) diffusion-weighted imaging (DWI) shows restricted diffusion in corresponding areas (stars), similar to case 1. (c) Mamillary bodies and colliculi show T2 hyperintensity and (d) contrast enhancement (long arrows). Features of cortical involvement (short arrows) imply poorer prognosis; there is (b) restricted diffusion in DWI, (e) gyral oedema in FLAIR, and (f) contrast enhancement.

Clinical Presentation

Early detection of subclinical thiamine deficiency is difficult as symptoms in children can be vague and non-specific such as headache, fatigue, irritability, and decline in growth rate.[1] Textbooks describe a classic triad of confusion, ataxia and ophthalmoplegia in only 16% to 21% of adult patients at presentation, with up to 19% having none of these symptoms.[2,5] More consistently though, 82% of WE patients will experience some degree of altered mental status ranging from confusion, sluggishness and apathy to coma and death.[5] Other less common presentations include stupor, hypotension and tachycardia, hypothermia and seizures, all of which can be related to insults to the hypothalami and thalami.[1]

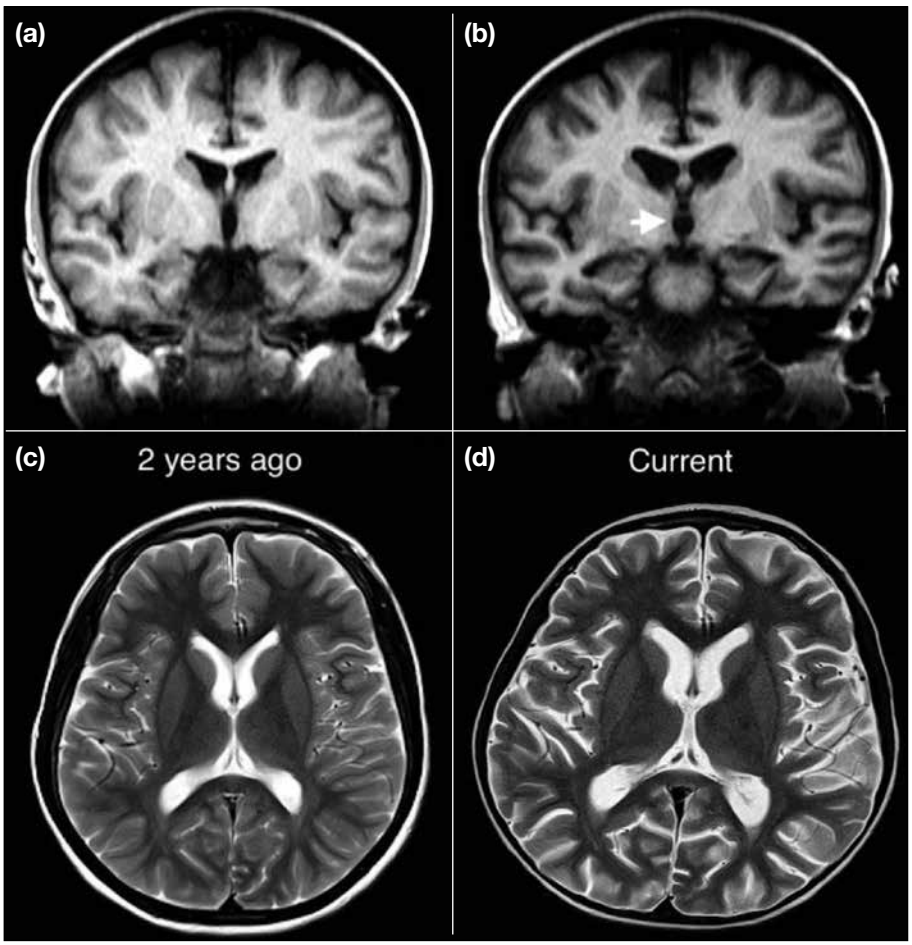

Figure 5. Comparison of magnetic resonance imaging 2 years apart in case 3. Features of chronic Wernicke's encephalopathy evidenced by interval neuronal loss at (b) bilateral thalami (note widening of third ventricle, short arrow) and mammillary bodies (as compared with [a]), as well as (d) generalised cerebral atrophy (note widened sulci and the Sylvian fissure; as compared with [c]).

Imaging Features

Neuroimaging is the most valuable method in diagnosing WE. In all our patients, the radiologist was the first to propose a diagnosis of WE.

A normal computed tomography of the brain cannot exclude WE since changes are subtle or even undetectable. The most useful imaging modality is MRI that has a high specificity of 93% and an acceptable sensitivity of 53%.[6] As demonstrated in our cases, typical MRI findings of acute WE are symmetrical signal intensity alterations (usually in the form of T2 hyperintensity and restricted diffusion as shown in Figure 2) in the dorsomedial thalami, mammillary bodies, tectal plate, and periaqueductal area. Selective involvement of the cerebellum (particularly the vermis), cranial nerve nuclei, red nuclei, cerebellar dentate nuclei, fornix, splenium, and cerebral cortex has been previously described.[7] Interestingly, basal ganglia involvement, which has not been reported in adults, has been observed in up to 55% of paediatric WE patients.[2,3] This finding may be related to the high thiamine-dependent metabolism of nuclear-basal regions in children. Importantly, albeit uncommon, mammillary body contrast enhancement (Figure 4) can be the only sign of WE.[8,9] Cortical involvement in WE (Figure 4) usually implies poorer prognosis, as shown by the inferior outcome in case 2.[10]

In chronic WE, the brain can show necrosis, gliosis, and neuronal loss.[11] As illustrated in case 3 (Figure 5), these changes can be gradual and subtle. Thus, it is salient that a comparison has to be made with prior imaging studies to detect temporal differences. MR spectroscopy, if performed, will reveal the expected lactate doublet and decreased N-acetylaspartate peak at the periaqueductal lesion, reflecting anaerobic metabolism and necrosis.[10]

Blood Tests

Traditionally, blood tests with measurement of serum thiamine, thiamine pyrophosphate effect and

transketolase have been performed to diagnose WE. These tests are now considered inadequate for diagnosis due to their poor sensitivity and specificity.[12] In addition, a normal serum thiamine level does not necessarily exclude the presence of WE.[13] In our cases, serum thiamine was not measured, and transketolase level and thiamine pyrophosphate effect showed varied changes in each case following thiamine replacement (Table).

Imaging Differential Diagnoses

There are other disease entities that can show similar MRI features to WE. These include paramedian thalamic infarction, ventriculoencephalitis, demyelinating disease, Leigh disease, primary cerebral lymphoma, Behçet's disease, variant Creutzfeldt–Jakob disease, other metabolic disturbances, and intoxication. When the clinical history lacks a predisposing factor for thiamine deficiency, or when response to thiamine replacement is unclear, these differential diagnoses should be considered.

Management

Since the timing of thiamine replacement determines outcome, WE is regarded as a medical emergency. In all cases when the disorder is suspected, thiamine therapy should be initiated immediately. There is currently no consensus on thiamine dosage or route of administration for individuals with WE, but high-dose intravenous infusion is common.

A retrospective study by Wrenn et al[14] found no significant allergic reactions in more than 300,000 patients treated with parenteral thiamine. Given its generally safe profile, some institutes advocate administration of prophylactic thiamine supplements to patients with predisposing factors or suggestive neurological symptoms.[15]

CONCLUSION

In this article, we have demonstrated the spectrum of MRI findings of WE. In all three cases, the radiologist was the first to propose WE as a differential diagnosis. We suspect that these cases may just be the tip of the iceberg in terms of the prevalence of malnutrition in children with long-term illnesses, in particular cancers. Further investigations are warranted to reveal the true prevalence of paediatric malnutrition, which is currently presumed rare, in this world city.

In the case of WE, since the time to thiamine replacement determines prognosis, we recommend radiologists maintain a high level of suspicion when imaging children with abnormal behaviour, especially if there is a recent history of parenteral nutrition without thiamine replacement. Awareness of this entity and its findings can facilitate early diagnosis and timely management to improve disease outcome.

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