Neuroendocrinology Letters Volume 43 No. 7-8 2022
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

Wernicke encephalopathy with extensive cortical lesions combined with diffuse large B-cell lymphoma

Yuxue Feng[1*], Xia Long[1*] Xiaofeng Li[1]

1 Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, 400010, China.
* These two authors contributed equally to this work.

Correspondence to: Xiaofeng Li, MD, PhD
Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, 400010, China
tel: +86 17815183569, e-mail: lixfcq@cqmu.edu.cn

Submitted: 2022-06-17 Accepted: 2022-12-15 Published online: 2022-12-15

Key words: **Wernicke encephalopathy; Thiamine deficiency; Magnetic Resonance Imaging; Extensive cortical lesions; Diffuse large B-cell lymphoma; Case report**

Neuroendocrinol Lett 2022; **43**(7-8):361–365 **PMID:** 36720123 NEL437822C03

Abstract

Wernicke encephalopathy (WE) is an acute or subacute neurologic disorder resulting from thiamine deficiency. A Magnetic Resonance Imaging (MRI) test is useful in addition to the clinical manifestation, which is the main basis for the diagnosis. Typical MRI findings include areas surrounding the aqueduct and third ventricle, as well as those in the medial thalamus, dorsal medulla, tectal plate, and mamillary bodies. We reported a case of WE with extensive cortical lesions. The beneficial effects of thiamine supplementation and low dosage of glucocorticoid did not sustain after discharge. Eventually, we found that the condition he had was brought on by gastric diffuse large B-cell lymphoma. Thiamine supplements combined with glucocorticoids may be a good administration regimen. The etiology of WE is frequently disregarded. In individuals with WE, it is essential to take the underlying illness into account. Malignancy, especially gastrointestinal tract cancer, should be considered. A good administration regimen may include glucocorticoids and thiamine supplements.

Abbreviations:

AMPA	- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BCL	- B-cell lymphoma
bid	- twice a day
CASPR	- Contactin-associated Protein-like
CD	- Cluster of differentiation
CDR	- Clinical Dementia Rating
CDX-2	- Caudal Type Homeobox 2
CEA	- Carcinoma Embryonic Antigen
CK	- Creatine Kinase
DWI	- diffusion-weighted imaging
EMA	- Epithelial Membrane Antigen
FLAIR	- fluid-attenuated inversion recovery
GABAB	- gamma aminobutyric acid-B
HE	- hematoxylin-eosin
IM	- intramuscular
IV	- intravenous
LCK	- Lymphocyte-specific Protein Tyrosine Kinase
LGI	- Leucine-rich Glioma Inactivated
MBP	- Myelin Basic Protein
mg	- milligram
MMSE	- Mini-Mental State Examination
MoCA	- Montreal Cognitive Assessment scale
MOG	- Myelin Oligodendrocyte Glycoprotein
MRI	- Magnetic Resonance Imaging
MUM-1	- Multiple myeloma oncogene-1
NMDA	- N-methyl-D-aspartate
NMO	- Neuromyelitis Optica
qd	- once a day
TPP	- thiamine pyrophosphate
WE	- Wernicke Encephalopathy

INTRODUCTION

Wernicke encephalopathy (WE) is a neurologic complication of acute or subacute thiamine (Vitamin B1) deficiency. It happens in the setting of decreased intake, increased requirement, or a greater loss of thiamine. The majority of affected patients were alcoholic; however, non-alcoholic causes were reported in 20% to 50% of all cases, such as hyperemesis gravidarum, post-gastrointestinal surgery, cancer, etc (Sechi & Serra 2007; Seo *et al.* 2017) . The classic clinical triad consists of encephalopathy, oculomotor dysfunction, and gait ataxia. Although clinical manifestations are the main basis for the diagnosis of WE, Magnetic Resonance Imaging (MRI) is now the most valuable method to confirm it. Typical MRI findings include areas surrounding the aqueduct and third ventricle, as well as those in the medial thalamus, dorsal medulla, tectal plate, and mamillary bodies (Silva AR 2022). However, cerebral cortical involvement in WE is not unusual. Herein, we reported one case of WE with extensive cortical lesions combined with diffuse large B-cell lymphoma; it should be noted that the patient had WE prior to receiving the cancer diagnosis.

CASE PRESENTATION

We admitted a 67-year-old patient with progressive ataxia for 50 days. He had a 30-year history of alcohol abuse (200 ml/d) (Baijiu, Chinese liquor). However, he had abstained from alcohol for a year. During hospitalization, he complained of metamorphopsia symptoms and altered mental status. A neurologic examination indicated mental status abnormalities (impaired spatial orientation, impaired retrograde memory, and acalculia), oculomotor dysfunction (limited right eye abduction), ataxia (dysdiadochokinesia, heel-to-shin test positive bilaterally). The cognitive rating scale was scored as follows: Mini-Mental State Examination (MMSE): 24 scores; Montreal Cognitive Assessment scale (MoCA): 18 scores; Clinical Dementia Rating (CDR): 0.5 scores. These laboratory results were obtained: ① Low levels of Vitamin B (Vitamin B_1: 50.46 nmol/L; Vitamin B_2: 180.10 ug/L, Vitamin B_{12}: 174.91 pg/mL). ② Routine and biochemical tests on the cerebrospinal fluid were regular. Cerebrospinal fluid smear and culture tests were negative. ③ Antibodies related to autoimmune or demyelinating diseases were negative in cerebrospinal fluid: N-methyl-D-aspartate (NMDA) antibody (-), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 (AMPA1) antibody (-), AMPA2 antibody (-), Leucine-rich Glioma Inactivated 1 (LGI1) antibody (-), Contactin-associated Protein-like 2 (CASPR2) antibody (-), anti-gamma aminobutyric acid-B (anti-GABAB) antibody (-), anti- Neuromyelitis Optica (anti-NMO) antibody (-), anti- Myelin Basic Protein (anti-MBP) antibody (-), anti- Myelin Oligodendrocyte Glycoprotein (anti-MOG) antibody (-). Brain MRI revealed increased T2 and fluid-attenuated inversion recovery (FLAIR) signals, decreased T1 signals, and slightly increased diffusion-weighted imaging (DWI) and contrast-enhancement signals. It also showed abnormalities throughout the periaqueductal, diffuse white matters of cortices (frontal, temporal, parietal, and occipital lobes), pons and knees of corpus callosum (Fig. 1).

The patient was treated with 200 milligram (mg) of thiamine (IM, intramuscular) twice a day (bid) and 10 mg of dexamethasone (IV, intravenous) once a day (qd). Ten days later, his symptoms of metamorphopsia

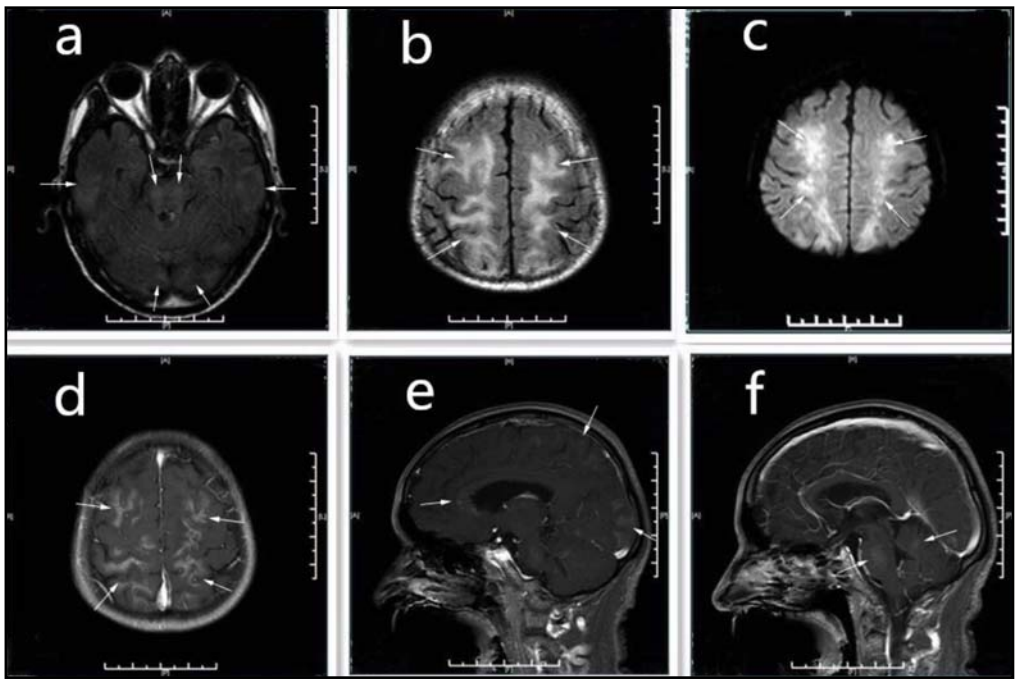

Fig. 1. Initial brain Magnetic Resonance Imaging (MRI) findings include the following:
a) hyperintensity signals in bilateral temporo-occipital cortices and pons (FLAIR, fluid-attenuated inversion recovery);
b-c) hyperintensity signals in bilateral frontoparietal cortices [b-FLAIR, c-DWI (diffusion-weighted imaging)];
d) gadolinium enhancement in the white matters of bilateral frontoparietal cortices;
e) gadolinium enhancement in the corpus callosum knee, occipital lobes, and parietal lobes;
f) gadolinium enhancement in the pons and cerebellum.

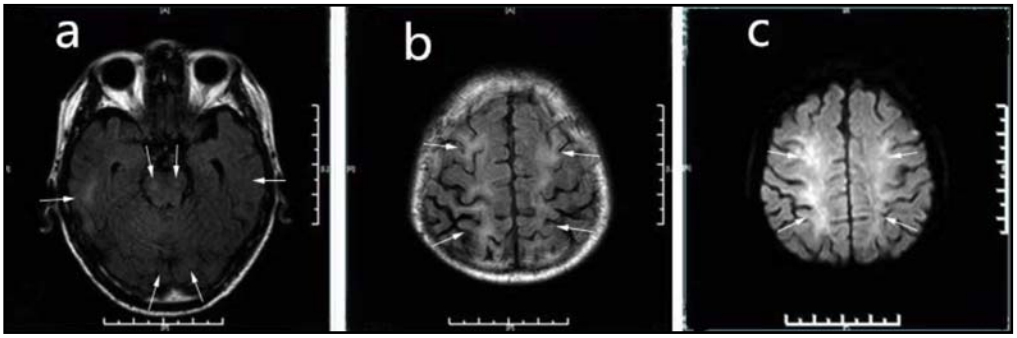

Fig. 2. IAfter treatment, the following abnormal signals were reduced on brain Magnetic Resonance Imaging (MRI): a. abnormal hyperintensity signals in the bilateral temporo-occipital cortices and pons reduced (FLAIR, fluid-attenuated inversion recovery); b-c. abnormal hyperintensity signals in the bilateral frontoparietal cortices reduced [both FLAIR (b) and DWI(c) (diffusion-weighted imaging)].

and ataxia improved obviously. Twenty days later, he was able to walk on his own and successfully complete the graphic drawing and connection test, earning an MMSE score of 27 and a MoCA score of 24, respectively. Reduced lesions were visible in T2, FLAIR, and DWI sequences after a review of brain MRI images (Fig. 2). He was discharged with the instruction to administer Vitamin B_1 intramuscularly.

He was readmitted a few months after being discharged due to persistent and recurring ataxia. Only taking Vitamin B_1 orally at home aggravated his symptoms. He was treated with the previous therapy (200 mg of Vitamin B_1 IM bid and 10 mg of dexamethasone IV qd). Considering the possibility of gastrointestinal malabsorption, the patient underwent a barium meal examination. The result showed a shadow in the lesser curvature of the gastric antrum, indicating a malignant ulcer. Furthermore, an antrum ulcer with multiple enlarged lymph nodes was found by abdominal contrast-enhanced Computed Tomography. The ulcer was finally determined to be a non-Hodgkin's lymphoma by gastroscopy and biopsy (Fig. 3 and 4). The tissue's immunohistochemistry outcomes: Lymphocyte-specific Protein Tyrosine Kinase (LCK) (-) Creatine Kinase (CK) (-) CK7 (-) CK20 (-) Carcinoma Embryonic Antigen (CEA) (-) Epithelial Membrane Antigen (EMA) (-) Villin (-) Caudal Type Homeobox 2 (CDX-2) (-) Ki-67 (+++) 90% CerbB-2 (-) P53 (+) Cluster of differentiation 3(CD3) (-) CD20 (+++) CD79α (++) B-cell lymphoma (BCL-2) (-) CD10 (+) BCL-6 (++) CD2 (+) Multiple myeloma oncogene-1 (MUM-1) (scattered in +). The cytology of his bone marrow revealed a proliferative phase. After consulting with the hematologist, we confirmed the diagnosis: diffuse large B-cell lymphoma, stage III, and group A. Unfortunately, the patient declined additional testing and care for private reasons. One year later, we followed up with the patient by telephone. His symptoms were far worse than they had been.

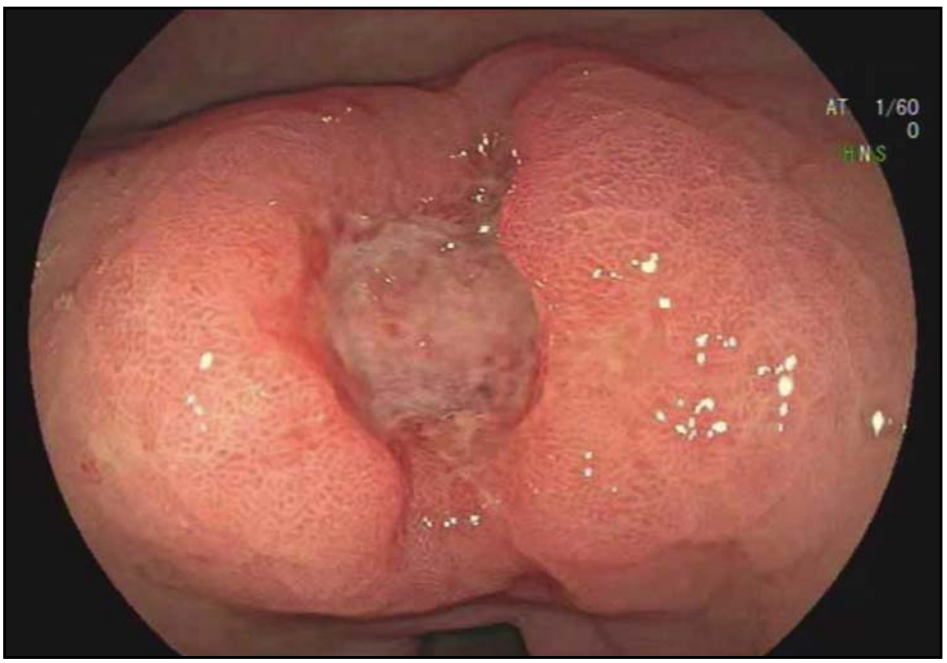

Fig. 3. Lesions under gastroscopy: an ulcer 1.5cm in diameter, covered in white moss, congested and swollen gastric mucosa.

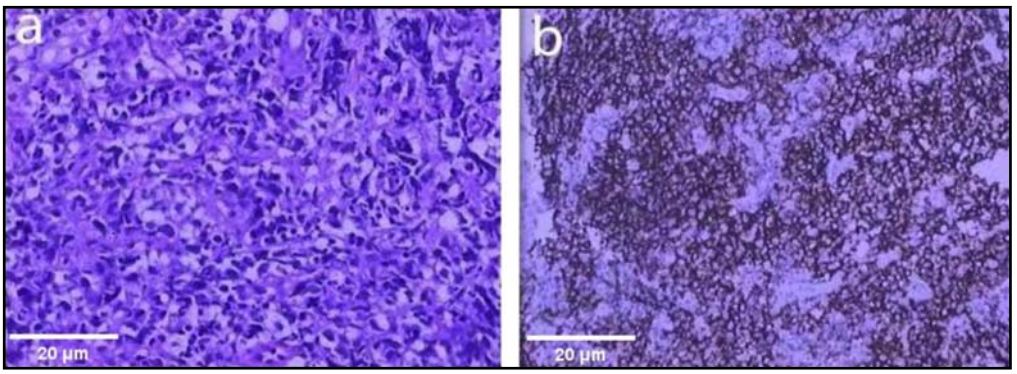

Fig. 4. The biopsy of the gastric antrum ulcer (400X): a) HE (hematoxylin-eosin) staining showed that different types of large diffuse lymphocytes replaced normal tissues; b) Immunohistochemistry showed strong CD20 (+++) (Cluster of differentiation) staining.

This report was carried out following the recommendations of The Second Affiliated Hospital of Chongqing Medical University. The procedure discussed in this report was basically standard clinical treatment rather than a component of a research study. The subject provided written, fully informed consent to publish of his clinical information in accordance with the Helsinki Declaration.

DISCUSSION

Thiamine is a precursor of thiamine pyrophosphate (TPP), a cofactor for critical enzymes involved in energy metabolism (Isenberg-Grzeda *et al.* 2012). Therefore, the deficiency of thiamine may inhibit metabolism in brain regions with high metabolic requirements, leading to WE.

WE is most frequently associated with chronic alcoholism. Additionally, it happens in patients with hyperemesis gravidarum (increased loss of thiamine), post-gastrointestinal surgery (decreased intake), and malignancy (increasing demand), such as gastric cancer, malignant lymphoma, and leukemia (Kudru *et al.* 2014). This situation may be caused by a thiamine shortage brought on by the consumption of tumor cells and malabsorption, according to certain theories. Hematologic malignancy cells proliferate rapidly. Moreover, the situation was rendered worse by the comparatively large amounts of thiamine-dependent enzymes found in leukocytes (H C van Zaanen 1992). The total amount of thiamine in the body is about 30 mg, and its half-life is 9 to18 days (Chandrakumar *et al.* 2018). Thiamine is mainly absorbed in the duodenum and proximal small intestine (Zheng 2015). However, the region of stomach and duodenal mucosa for thiamine absorption may be reduced in patients with gastric cancer and after partial gastrectomy (Şen *et al.* 2022; Zheng 2015). It is important to take into account the likelihood of gastrointestinal tract cancer in clinical WE cases without ongoing alcoholism (such in our case), protracted vomiting, and poor oral intake. It is worth noting that WE is a common complication of chemotherapy (Kudru *et al.* 2014; Seo *et al.* 2017; Onishi *et al.* 2021). Therefore, prophylactical administration of thiamine is essential for oncotherapy.

While the diagnosis of WE is primarily based on clinical presentation, brain MRI is the most effective diagnostic tool. The sensitivity and specificity of MRI are 53% and 93%, respectively (Sechi & Serra 2007). Typical lesions are hypointense on T1, hyperintense on T2 and FLAIR. They are bilaterally symmetrical in the paraventricular regions of the thalamus, mamillary bodies, periaqueductal region, the floor of the fourth ventricle, and midline cerebellum (Seo *et al.* 2017). Atypical MRI findings in WE represent abnormal signals in the cerebellum, pons, splenium, and cerebral cortex (Ha *et al.* 2012). Lesions in our patient were located in both typical periaqueductal areas and atypical areas, including bilateral cortices, pones, and knees of the corpus callosum. In addition, hyperintensity on gadolinium enhancement was observed. Involvement of the cerebral cortex is common. One series of 51 autopsy examinations was conducted in 57% of both acute and chronic WE cases (Liu *et al.* 2006). The frontal and the parietal lobes are the regions of cortical lesions that are most vulnerable (Wu *et al.* 2017). Brain lesions of our patient were far more than limited cortices. Furthermore, extensive cortical impairment might be an indicator of poor prognosis (Wu *et al.* 2017). These manifestations should serve as a reminder that underlying illnesses are likely present as well. Similar reports have been made in the past. After receiving a diagnosis of WE, the gastric cancer was discovered (Jung *et al.* 2010).

WE is a neurological emergency. Any treatment delay can cause permanent neurological damage. For any potential scenario, immediate parenteral thiamine administration is advised. There are no universally accepted guidelines for WE. The European Federation of Neurological Societies suggests administering 200 mg of thiamine intravenously three times each day (Level C) (Galvin *et al.* 2010). The alternative regimen is to administer 500 mg IV thrice day for two days of thiamine, followed by 250 mg IV or IM once daily for additional five days (Thomson & Marshall 2013). Our patient's symptoms and signs significantly improved after receiving 200 mg of intramuscular thiamine twice

a day. Absorption of thiamine is incomplete through the gastrointestinal tract. Therefore, oral administration is not recommended during the acute phase (Boulanger *et al.* 2017). After the parenteral course of treatment is finished, thiamine 100 mg should be taken orally every day (Ghomari *et al.* 2023; Hutcheon 2015). Administration of glucose before thiamine can worsen WE because thiamine requirements depend on metabolic rate. High glucose intake means heavy metabolic state. Thus, administration of glucose must be given after thiamine (Leilani Hernandez 2022). Magnesium supplementation should also be a part of the treatment because magnesium is a cofactor of thiamine-dependent enzymes (Wijnia 2022; Ott & Werneke 2020).

The intriguing part of our treatment was the usage of low-dose dexamethasone (10 mg/d IV). Enhancement of lesions indicated dysfunction of the blood-brain barrier. Cytotoxic edema was represented by the strong signal in the DWI. In accordance with previous literature, we added dexamethasone to repair the blood-brain barrier and lessen edema in the brain's cells (Witt & Sandoval 2014). Fortunately, it had a positive effect on our patient.

CONCLUSION

This report presented the clinical course and neurological recovery in a rare case of WE with extensive cortical lesions caused by gastric lymphoma. Malignancy, especially gastrointestinal tract cancer, is essential to be considered in patients with WE. Last but not least, low-dose dexamethasone may help with WE alleviation.

FUNDING

This research was funded by Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University.

REFERENCES

1 Boulanger AS, Paquette L, Létourneau G, Richard-Devantoy S (2017). Thiamine et encéphalopathie de Gayet-Wernicke : quelles règles de prescription?"[Wernicke encephalopathy: Guiding thiamine prescription]. Encephale. **43**: 259–267.
2 Chandrakumar A, Bhardwaj A, 'T Jong GW (2018). Review of thiamine deficiency disorders: Wernicke encephalopathy and Korsakoff psychosis. J Basic Clin Physiol Pharmacol. **30**: 153–162.
3 Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone Ma, EFNS (2010). EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. **17**: 1408–1418.
4 Ghomari CF, Misgault B, Diallo AO, Durand H, Bund C, Namer IJ (2023). Sequential Brain Perfusion Findings in a Case of Osmotic Demyelination Syndrome. Clin Nucl Med. **48**: 52–53.
5 H C Van Zaanen JVDL (1992). Thiamine deficiency in hematologic malignant tumors. Cancer. **69**: 1710–1713.
6 Ha ND, Weon YC, Jang JC, Kang BS, Choi SH (2012). Spectrum of MR imaging findings in Wernicke encephalopathy: are atypical areas of involvement only present in nonalcoholic patients? AJNR Am J Neuroradiol. **33**: 1398–1402.
7 Hernandez L, Brockman, Mehta T (2022). Identification of Wernicke Encephalopathy in a Patient Presenting With Altered Mental Status and Dehydration. WMJ. **121**: E10–E14.
8 Hutcheon DA (2015). Malnutrition-induced Wernicke's encephalopathy following a water-only fasting diet. Nutr Clin Pract. **30**: 92–99.
9 Isenberg-Grzeda E, Kutner HE, Nicolson SE (2012). Wernicke-Korsakoff-syndrome: under-recognized and under-treated. Psychosomatics. **53**: 507–516.
10 Jung ES, Kwon O, Lee SH, Lee KB, Kim JH, Yoon SH, et al. (2010). Wernicke's encephalopathy in advanced gastric cancer. Cancer Res Treat. **42**: 77–81.
11 Kudru CU, Nagiri SK, Rao S (2014). Wernicke's encephalopathy in a patient with gastric carcinoma: a diagnosis not to miss. BMJ Case Rep. **2014**.
12 Liu YT, Fuh JL, Lirng JF, Li AF, Ho DM, Wang SJ (2006). Correlation of magnetic resonance images with neuropathology in acute Wernicke's encephalopathy. Clin Neurol Neurosurg. **108**: 682–687.
13 Onishi H, Sato I, Uchida N, Takahashi T, Furuya D, Ebihara YEA (2021). High proportion of thiamine deficiency in referred cancer patients with delirium: a retrospective descriptive study. Eur J Clin Nutr. **75**: 1499–1505.
14 Ott M, Werneke U (2020). Wernicke's encephalopathy — from basic science to clinical practice. Part 1: Understanding the role of thiamine. Ther Adv Psychopharmacol. **10**: 204512532097810.
15 Şen O, Çetin D, Dumanlı G, Türkçapar AG (2022). Nutritional Deficiencies in Morbid Obese Patients Before and After Laparoscopic Sleeve Gastrectomy. Turk J Gastroenterol. **33**: 885–890.
16 Sechi G, Serra A (2007). Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. **6**: 442–455.
17 Seo JH, Kim JH, Sun S, Won HS, Park JW, Ko YH (2017). Wernicke encephalopathy as initial presentation of lymphoma. Korean J Intern Med. **32**: 1112–1114.
18 Silva AR, Almeida-Xavier S, Lopes M, Soares-Fernandes JP, Sousa F, Varanda S (2022). Is there a time window for MRI in Wernicke encephalopathy - a decade of experience from a tertiary hospital. Neurol Sci.
19 Thomson AD, Marshall EJ (2013). BNF recommendations for the treatment of Wernicke's encephalopathy: lost in translation? Alcohol and alcoholism (Oxford, Oxfordshire). **48**: 514–515.
20 Wijnia JW (2022). A Clinician's View of Wernicke-Korsakoff Syndrome. J Clin Med. **11**: 6755.
21 Witt KA, Sandoval KE (2014). Steroids and the blood-brain barrier: therapeutic implications. Adv Pharmacol. **71**: 361–390.
22 Wu L, Jin D, Sun X, Liang L, Huang D, Dong ZEA (2017). Cortical damage in Wernicke's encephalopathy with good prognosis: a report of two cases and literature review. Metab Brain Dis. **32**: 377–384.
23 Zheng L (2015). Wernicke Encephalopathy and Sleeve Gastrectomy A Case and Literature Review. Am J Ther. **0**: 1–4.