



# Clinical Features, Diagnosis and Treatment of Children's Wernicke's Encephalopathy

Yinsen Song, Yinghui Zhang, PengBo Guo, Lili Ge, Bo Zhang, Lei Liu, Jingui Kong, Chongfen Chen, Shuying Luo\*

## ABSTRACT

To explore the clinical features, diagnosis, and treatment of Wernicke's encephalopathy (WE) in children and raise awareness of the disease. Summarize the clinical manifestations, diagnosis, and treatment characteristics of a WE case in a child patient with severe sepsis as the first manifestation and review the literatures of children cases reported at home and abroad in recent years. Children's WE often have no specific clinical manifestations, so the misdiagnosis rate is high. The MRI features of the brain show signs of symmetric abnormalities in bilateral mammillary body, basal ganglia, and cerebral periaqueductal area, etc. The characteristic brain MRI abnormal signal combined with rapid response after clinical thiamine treatment is helpful for clinical diagnosis. Early and timely supplementation of large doses of thiamine resulted in rapid improvement of neurological abnormalities in most cases with good prognosis.

**Key Words:** Wernicke's Encephalopathy (WE), Children, Severe Sepsis

**DOI Number:** 10.14704/nq.2018.16.5.1356

**NeuroQuantology 2018; 16(5):35-38**

## Introduction

Wernicke's encephalopathy (WE) is an acute encephalopathic syndrome. Children case is rarely seen at present and often misdiagnosed due to atypical clinical manifestations. If it cannot be diagnosed or treated in time, it can cause death or severe neurological sequelae. If it is identified in time and treated with VitB1, the symptoms can be quickly relieved and the prognosis is good (Sechi and Serra, 2007). According to foreign reports, incidence of in-patient children cases (from retrospective autopsy data) is 0.5%-3%, among which only 15% of the children patients were diagnosed before they were born. Pediatrics do not have statistics yet. Typical adult WE patients have triple symptoms: psychiatric symptoms (such as confusion, coma, and even convulsions, etc.); ocular symptoms (such as ophthalmoplegia, nystagmus, blepharoptosis, etc.) and ataxia. Some

children patients have symptoms such as hypothermia and aphonia. In acute-outbreak period, MRI or CT abnormalities are helpful in the diagnosis (Nishida *et al.*, 2009). MRI often shows intracerebral bilateral mammillary body, tectum, aqueduct III, IV periventricular white matter abnormal signals (T1W is low signal, T2W is high signal change). In foreign reports, the median age of pediatric patients was (11±6.5) years, the symptoms were quite atypical, only 30% of patients had the typical triple symptoms, and misdiagnosis rate is very high. Children patients often visit the emergency department first, so emergency doctors must have sufficient knowledge and high vigilance for this disease. Before the attack of this disease, the patients often have basic diseases, such as malignant tumor patients with long-term chemotherapy, patients who had

**Corresponding author:** Shuying Luo

**Address:** Children's Hospital Affiliated to Zhengzhou University (Henan Key Laboratory of Childhood Genetic Metabolism), Zhengzhou 450018, China

**e-mail** ✉ df13607670608@163.com

**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Received:** 28 March 2018; **Accepted:** 19 April 2018



operation of gastrointestinal diseases, patients who suffered long-term frequent vomiting, patients who had long-term intravenous nutrition and had not supplemented VitB1 timely, some children patients with excessive glucose ratio in their nutritional ingredient, besides, severe infection can induce this disease (Cooke *et al.*, 2006). Patients with the above-mentioned diseases should undergo MRI in order to assist in diagnosis once consciousness changes occur. VitB1 storage in the human body is only 30-50 mg. When patients with above disease do not eat well and VitB1 is not supplemented in time, VitB1 stored in the body will be depleted within 2-3 weeks. In the absence of VitB1, pyruvate cannot enter the tricarboxylic acid cycle, leading to elevated blood lactate. Metabolic abnormalities can also lead to changes in the body's osmotic gradient, causing periventricular nerve cell cytotoxic edema that resulting in neuronal necrosis and irreversible brain damage. This article reported one children patient case, who appeared consciousness disorder with convulsions due to severe infection, after anti-infection, anti-convulsions and other treatment, the symptoms did not improve, MRI examination showed above specific changes, then after treatment with VitB1, the symptoms significantly improved, and the patient was healed. Currently there is no uniform standard for the therapeutic dose of VitB1, and the Pediatrics can use 100 mg/d intramuscular injection. In conclusion, children's WE lacks of typical triple symptoms, the prognosis of the disease is determined by the doctor's timely identification of suspected cases and timely brain MRI or CT examinations (Basit *et al.*, 2011). When there are abnormal signal changes around the aqueduct, the tectum, and the mammillary body, it should be considered as the identification evidence of WE. On September 5, 2017, our hospital had received one children WE case, the child patient had WE symptoms caused by pneumonia and sepsis, the clinical features were analyzed and relevant literatures were reviewed in order to increase the awareness of this disease and to provide assistance for the timely identification and reasonable treatment.

## Methods

### *Clinical conditions*

Child patient, female, 4 years and 1 month, hospitalized due to "fever, cough for 48 hours, consciousness disorder for 1.5h". Past history: the child has a history of cutaneous pruritus, but no rash, desensitization treatment invalid,

increased severity in the past 3 months. Family history: None. Physical examination: T 40.2°C, P176 beats/min, R40 beats/min, Bp130/63 mm Hg (1mm Hg=0.133 kPa), confusion, Glasgow score (GCS) 3 points, bilateral pupils same size equally round, diameter about 4 mm, slow reflection to light, no sense of resistance to the neck, pharyngeal hyperemia, moist rales heard in the bottom of left lung, no abnormalities in heart or abdomen, slightly increased muscle tension in the limbs, bilateral knee and Achilles tendon active reflexes, negative Kernig sign, negative Brudzinski sign and negative bilateral Babinski sign (Zuccoli and Pipitone, 2009).

### *Assistant examinations*

Blood routine: WBC  $7.93 \times 10^9/L$ , N61.9%, L32.6%, RBC  $4.07 \times 10^{12}/L$ , HB 117 g/L, PLT  $62 \times 10^9/L$ , cRP 30.7 mg/L, Procalcitonin (PCT) 16.5 ng/L. Electrolyte and ESR are normal. PT 12.9s, INR 0.98, APTT 34.6 s, FIB 1.83 g/L, TT 15.5 s, D-D 2.89 mg/L. Electrocardiogram (ECG) showed sinus tachycardia; Chest X-ray shows: left lung inferior lobe shows flaky high-density shadow; sleep EEG shows background wave abnormalities; lumbar puncture measured normal intracranial pressure, cerebrospinal fluid routine and protein quantification were normal (Hazell *et al.*, 2009).

### *Diagnosis and treatment process*

Giving meropenem for anti-infection, using Mannitol for dehydration and antipyretic symptomatic treatment. Frequent convulsions occurred after admission for 12h, with increased muscle tone in the extremities, intermittent diazepam in combination with phenobarbital for sedation, convulsions in the child patient could not be suppressed, and midazolam was given continuously for anticonvulsant and the convulsions relieved. 24 hours after hospital admission, the child patient's body temperature decreased, rales in bottom of left lung decreased. The child patient's consciousness did not improve. GCS remained 3 points. Brain MRI examination: Abnormal signals showed in bilateral basal ganglia, thalamus, medial temporal lobe and dorsal pons. Brain MRI contrast enhancement: no enhancement in the basal ganglia injury area. Blood and urine tandem mass spectrometry screening was normal. "Wernicke's encephalopathy" is suspected and intramuscular injection of thiamine 100 mg/d. After 1d thiamine treatment, the seizures eased and the muscle tension of the limbs decreased, and midazolam



was gradually stopped. GCS score was 7 points (E2V1M4); treatment 2d, the child patient's consciousness was improved, GCS score was 12 points (E4V3M5); treatment 5d, the child patient's consciousness turned clear, and the muscle tension of the limbs was normal, but still in language disorder; after 1-week treatment, changed to oral thiamine 30 mg/d, the child patient's language function gradually recovered; the neurological function was completely restored in 2 and a half months and the rechecked sleep EEG and brain MRI all returned to normal.

## Discussion

Children's WE is an acute neuropsychiatric syndrome caused by deficiency of thiamine (vitamin B1). Its characteristic "triple signs" are: change of psychiatric state, ocular signs, and ataxia. Only 16% of adult patients can show this "triple signs", the data from children is also roughly similar to it. Children cases reported so far are often associated with improper infant feeding, long-term vomiting and anorexia, immunosuppressant treatment, dialysis treatment, malignant disease, gastrointestinal surgery, etc. Children's WE is often associated with infections (including upper and lower respiratory tract infections, gastrointestinal infections, etc.), so many of the symptoms and signs of infection led to higher misdiagnosis rates. This WE case was caused by pneumonia combined with sepsis, after 48h, patient appeared acute encephalopathy mainly represented in consciousness disorder, studies have shown that thiamin deficiency exists in children with severe sepsis, or it may develop into thiamin deficiency in the acute phase. In those children patients with combined infection/sepsis, the cause of thiamin deficiency might be related to the body's high metabolic state, increased demand for vitamins, and malabsorption of intestinal epithelial cells. Studies have shown that pathogenic *E. coli* can inhibit human isolated intestine epithelial Caoco-2 cells from absorbing the thiamine. This case has pruritus but no skin disease, and the symptom tends to increase, suggesting that there is mild to moderate long-term thiamine deficiency leading to peripheral nerve injury, and when combined with acute infection/sepsis, thiamin deficiency is aggravated, resulting acute children's WE. The high misdiagnosis rate of WE is related to the non-specific clinical manifestations at the time of onset, and the low diagnostic value of routine

clinical examinations (such as the cerebrospinal fluid is often normal, and EEG only shows background abnormalities), especially in emergency situations, consciousness disorder is the only sign of WE. By measuring the serum pyruvate and lactic acid levels and directly measuring erythrocyte phosphothiamine levels, using high performance liquid chromatography for the determination of thiamine levels in whole blood and analysis of erythrocyte transketolase activity, and other laboratory methods are useful in helping the diagnose of thiamin deficiency, however, the former lacks specificity and the latter requires higher technical conditions and experimental time, so it is difficult for clinical use. At present, it is believed that the brain MRI is of most diagnostic value. Although it is reported that its sensitivity is only 53%, its specificity is as high as 93%. The typical performance of MRI is T2, WI long symmetrical signals, which can involve bilateral thalamus, mammillary body, cerebral periaqueductal area, IV ventricle bottom and cerebellar midline area, and other atypical areas including cortical area, corpus callosum and so on. Thiamine and its transformed compounds (phosphothiamine) are required as a coenzyme in many biochemical metabolisms in the brain, such as the metabolism of carbohydrates, lipids and their intermediates, and the synthesis of neurotransmitters (such as glutamine acid,  $\gamma$ -aminobutyric acid, etc.). In the above vulnerable areas, there is a high rate of thiamine metabolism. When in thiamin deficiency, the cell membrane cannot maintain a normal osmotic gradient, which can lead to intracellular and intercellular edema, manifested as nerve fiber edema, cavernous transformation, endothelial cell edema and erythrocytolysis, studies have shown that the cell damage mechanisms involved in thiamin deficiency mainly include oxidative stress, excitatory cytotoxicity, and inflammatory injury, but the relationship between these mechanisms is still unclear. In recent years, several scholars have used diffusion-weighted imaging, fluid attenuated inversion recovery (FLAIR) and contrast-enhanced methods to investigate WE, the results suggested that reversible cytotoxic edema and vasogenic edema are present in acute WE, not acute bleeding. In this case, a typical MRI was performed, but no enhancement was observed in the injury area after contrast enhancement, suggesting that the blood-brain barrier was not damaged and may be cytotoxic edema. In addition, an important help for clinical diagnosis is the rapid reversal of neurological



abnormalities after parenteral administration of large doses of thiamine, especially in children patients. This point is important in the differential diagnosis of emergency patients with coma as the main performance but unable to provide thiamin deficiency susceptibility factors. Diseases that need to be identified include sepsis-associated encephalopathy, paramedian thalamic infarction (basal ganglia top region syndrome), ventriculitis, Miller-Fisher syndrome, etc., because these diseases are not responsive to thiamine supplementation [1]. In this case, after admission, the patient was given anti-infective treatment for 24 hours, the inflammatory index was significantly decreased, but the consciousness disorder was not improved. When large dose of thiamine was given, the consciousness disorder was significantly improved in 24 hours, and combined with typical brain MRI manifestations, therefore, the diagnosis of WE was tenable (Guerrini *et al.*, 2009).

WE often develops on certain basic conditions, including alcoholism, long-term nutritional imbalance, long-term complete parenteral nutrition, gastrointestinal malignancy, and post-operation, etc. However, there are also case reports that do not meet the above conditions, suggesting genetic susceptibility exists in children with WE. Recent studies have found that in children with WE, there are thymidine transporter-1 (hTHTR-1) and transporter-2 (hTHTR-2) function insufficiency so that it expressed SLC19A2 and SLC19A3 genes. The high expression of SLC19A3 RNA in the thalamus of children with WE can be used as a mechanism to explain the selective injury of the thalamus. From the analysis of the patient's medical history in this case, there is no such susceptibility condition, but there is a peripheral nerve injury performance, suggesting that the child patient's body thiamine level is low, it is speculated that there may be hTHTR function insufficiency. It is generally accepted that large doses of thiamine should be given as soon as possible, which can reverse nerve damage, reduce disability and mortality. After the initial diagnosis of this case, intravenous thiamine was infused at 100 mg/d, consciousness was improved in 24 hours after treatment, consciousness was clear after 5 days of medication, after 1-week medication, it changed to oral 30 mg/d, the treatment was maintained for 2 months, neurological abnormalities completely recovered, brain MRI completely

returned to normal. In conclusion, WE is a neurological emergency. If sufficient thiamine treatment is not given as soon as possible, the nerve injury can develop irreversibility, with high rate in disability and mortality, especially for the children WE group. It is extremely easy to misdiagnose, so timely identification is crucial. The typical brain MRI manifestation has high specificity in the diagnosis of WE, and it is helpful for early diagnosis. In most cases, if enough thiamine treatment is applied in time, it can quickly improve the clinical symptoms, and eventually the disease can be cured.

## References

- Basit S, Elsas T, Kvistad KA, Høsoien LS. Wernicke's encephalopathy because of pancreatitis in a young boy. *Acta Ophthalmologica* 2011; 89(8): e656-57.
- Bentham P, Callaghan R. Thiamine for Wernicke's Korsakoff syndrome in people at risk from alcohol abuse. *Cochrane Database of Systematic Reviews* 2004; 1(1): CD004033.
- Cooke CA, Hicks E, Page AB, Mc Kinstry S. An atypical presentation of Wernicke's encephalopathy in an 11-year-old child. *Eye* 2006; 20(12): 1418-20.
- da Cruz LH, Domingues RC, Vilanova I, Gasparetto EL. MR imaging findings in Wernicke encephalopathy: nonalcoholics may be similar to alcoholics. *American Journal of Neuroradiology* 2010;31(6):E54-55.
- Guerrini I, Thomson AD, Gurling HM. Molecular genetics of alcohol-related brain damage. *Alcohol & Alcoholism* 2008; 44(2):166-70.
- Hazell AS, Butterworth RF. Update of cell damage mechanisms in thiamine deficiency: focus on oxidative stress, excitotoxicity and inflammation. *Alcohol & Alcoholism* 2009; 44(2):141-47.
- Liu YT, Fuh JL, Lirng JF, Li AF, Ho DM, Wang SJ. Correlation of magnetic resonance images with neuropathology in acute Wernicke's encephalopathy. *Clinical Neurology and Neurosurgery* 2006; 108(7):682-87.
- Nishida M, Sato H, Kobayashi N, Morimoto M, Hamaoka K. Wernicke's encephalopathy in a patient with nephrotic syndrome. *European Journal of Pediatrics* 2009; 168(6):731-34.
- Peters TE, Parvin M, Petersen C, Faircloth VC, Levine RL. A case report of Wernicke's encephalopathy in a pediatric patient with anorexia nervosa-restricting type. *Journal of Adolescent Health* 2007; 40(4):376-83.
- Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *The Lancet Neurology* 2007; 6(5):442-55.
- Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: review of the literature. *American Journal of Roentgenology* 2009; 192(2):501-08.
- Zuccoli G, Siddiqui N, Bailey A, Bartoletti SC. Neuroimaging findings in pediatric Wernicke encephalopathy: a review. *Neuroradiology* 2010; 52(6):523-29.

