The absence of mammillary body lesions for early differentiation of biotin-thiamine-responsive basal ganglia disease from Wernicke's encephalopathy

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Short Report

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Abstract

Purpose

Primary and secondary conditions that cause thiamine deficiency can result in similar symptoms in children, including acute episodes of encephalopathy and bilateral symmetrical brain lesions. In this study, we investigated the role of mammillary body (MB) involvement in SLC19A3-BTBGD patients and the differentiation between BTBGD and Wernicke's encephalopathy based on Magnetic Resonance Imaging (MRI) findings.

Methods

We conducted a retrospective study of 90 patients with genetically confirmed BTBGD. Two certified neuroradiologists independently reviewed the brain MRI scans, focusing on the involvement or sparing of specific regions such as the mesencephalon, cerebellum, caudate nuclei, globus pallidi, putamina, thalami, cortical and subcortical regions, MBs, and deep white matter.

Results

Clinically, all patients developed acute/subacute encephalopathy triggered by nonspecific febrile illnesses or mild trauma. MRI scans showed bilateral caudate lesions, putamen lesions, cortical-subcortical areas of the cerebral hemispheres, ventromedial region of the thalamus, cerebellar lesions, brainstem lesions, periaqueductal region, spinal cord lesions, and lesions in the globus pallidus. However, none of the patients had any mammillary lesions.

Conclusion

We found no MB involvement in 90 patients with BTBGD caused by the same homozygous variant of SLC19A3. Differentiating between BTBGD and Wernicke's encephalopathy based on MRI findings is critical for clinical decisions about treatment, prognosis, and genetic counselling. This study provides a crucial point in ruling out Wernicke's encephalopathy, especially in adults, and favouring BTBGD before the results of genetic testing are available. MRI is of utmost importance in the diagnosis and differentiation of these conditions.

Introduction

Primary and secondary conditions that cause thiamine deficiency can result in similar symptoms in children, including acute episodes of encephalopathy and bilateral symmetrical brain lesions [1–3]. Undiagnosed and untreated thiamine deficiency can be fatal or lead to severe sequelae [1–3]. Wernicke’s encephalopathy, which results from thiamine deficiency, is characterized by low serum thiamine levels and is treated with thiamine supplementation [3, 4]. In contrast, biotin-thiamine-responsive basal ganglia disease (BTBGD) is an inherited autosomal recessive disorder caused by SLC19A3 gene variants that encode a second thiamine transporter (hTHTR2). Unlike Wernicke’s encephalopathy, serum thiamine

levels are typically normal in BTBGD. However, free thiamine levels in the cerebrospinal fluid are low, indicating a central nervous system thiamine deficiency [1, 2]. Treatment involves supplementation with higher doses of thiamine and biotin to improve neurological symptoms [1, 2].

In the acute phase, the clinical presentations of both conditions can overlap, making a diagnosis challenging. However, early diagnosis is crucial for initiating appropriate treatment and preventing severe sequelae. Neuroimaging findings, particularly magnetic resonance imaging (MRI) results, can aid in differentiating between Wernicke's encephalopathy and BTBGD, even before genetic test results are available [1–4]. This differentiation helps guide the diagnostic workup, optimize treatment, and enables family counseling.

Mammillary body (MB) involvement is a common finding in thiamine deficiency and several other neurological conditions in children, including perinatal asphyxia, stroke, craniopharyngiomas, epilepsy, multiple sclerosis, and a few metabolic diseases, such as Alexander disease and biotinidase deficiency [5]. Further investigation of MB involvement in BTBGD could provide valuable insights into the pathophysiology and clinical presentation of the disease.

In this study, we aimed to investigate the role of MB in patients with SLC19A3-BTBGD. Accurate differentiation between SLC19A3-related diseases and Wernicke's encephalopathy is crucial for determining appropriate treatment strategies, predicting prognosis, and providing genetic counseling to patients and families. In this context, our study can provide important insights and contribute to the development of evidence-based clinical guidelines for managing thiamine-related conditions.

Methods

We conducted a retrospective study to investigate the clinical and neuroimaging characteristics of 90 patients with genetically confirmed BTBGD. All patients met the criteria for the classical form of the disease and had the same homozygous variant, NM_025243.4 (*SLC19A3*): c.1264A > G (p.Thr422Ala). This study was approved by the Ethics Committee of our institution (IRB: 943/2019).

Brain MRI scans were independently reviewed by two certified neuroradiologists. They focused on the involvement or sparing of specific regions such as the mesencephalon, cerebellum, caudate nuclei, globus pallidi, putamina, thalami, cortical and subcortical regions, MBs, and deep white matter. All patients underwent MRI using a 1.5T machine with the following protocol: sagittal spin-echo T1WI, axial and coronal FSE T2WI, axial FLAIR, axial spin-echo T1WI, and axial DWI/ADC. Postgadolinium axial and coronal sequences were performed in 80 cases.

Results

The study included 90 patients with *SLC19A3* mutations, with a mean age of approximately 5 years (range, 9 months to 15 years), of whom 37 had been previously reported [1, 2, 6].

Clinical presentation included acute/subacute encephalopathy triggered by nonspecific febrile illnesses or mild trauma, with confusion, slurred speech, seizures, and difficulty swallowing, and external ophthalmoplegia occasionally.. If left untreated, these symptoms could progress to a coma or even death, as observed in 4 patients. Seizures (focal or generalized tonic-clonic) occurred in 70% of the patients.

MRI scans revealed bilateral caudate lesions (n = 81; 90%), putamen lesions (n = 87; 96,7%), cortical-subcortical areas of the cerebral hemispheres (n = 60; 66,7%), ventromedial region of the thalamus (n = 60; 66,7%), cerebellar lesions (n = 45; 50%), brainstem lesions (n = 30; 33%), periaqueductal region (n = 30; 33%), spinal cord lesions (n = 18; 20%), and lesions in the globus pallidus (n = 10; 11%). Acute MRIs revealed swelling, but none of the patients had any mammillary lesions.

Discussion

We conducted a study of 90 patients with BTBGD caused by the same homozygous variant of *SLC19A3* and found no involvement of MB. This finding is critical in differentiating BTBGD from Wernicke encephalopathy, especially in adults, before genetic testing results are available.

Neuroimaging, especially MRI, is essential in this differentiation. In Wernicke's encephalopathy, MRI typically shows edema in at least three of the following neuroanatomical locations: the MB, the tectal plate, the medial thalami, and the peri-aqueductal area, with a characteristic butterfly-like appearance on coronal scans [3, 4]. Atypical findings such as bilateral striatal, cerebellar, cortical, cranial nerve nuclei, and red nuclei signal changes, have also been reported in nonalcoholic and pediatric patients [3, 4]. However in BTBGD, MRI often reveals bilateral symmetrical lesions in the basal ganglia, mainly in the caudate heads and putamen, in addition to white matter involvement at the gray-white matter junction, thalami, cerebellum, and brainstem. During the acute phase, the affected regions of the brain display edema and swelling [1, 2].

The MB are small but important structures in the brain that play a role in supporting recollective memory. Various pediatric conditions can affect the MB, resulting in signal alterations and/or atrophy on MRI [5]. Thiamine deficiency, ischemia, acute injury caused by tumors or hydrocephalus, and deafferentation due to pathology in the Papez circuit are the most common causes of MB damage [5]. Thiamine deficiency is the most prevalent condition associated with MB disease, affecting 17–58% of patients [4].

Experimental and neuropathological studies support the findings of MB sparing in *SLC19A3*-related BTBGD [7, 8]. This absence of MB involvement is evident on MRI, and in combination with the absence of predisposing factors for Wernicke’s encephalopathy such as altered thiamine intake resulting from vomiting due to conditions like anorexia nervosa, hyperemesis, and gastrointestinal obstruction, or absorption problems resulting from chronic gastrointestinal disorders and bariatric surgery, as well as the presence of consanguinity or similar cases in the family, are important indicators for considering inherited thiamine transporter defects as a possible cause of the disease. Early identification of these clues can lead to optimized treatment in the early stages of the disease.

In conclusion, this retrospective study aimed to investigate the role of mammillary body (MB) involvement in patients with SLC19A3-BTBGD. The study included 90 patients with genetically confirmed BTBGD, all of whom had the same homozygous variant of SLC19A3. The study found no involvement of MB in these patients, which is critical in differentiating BTBGD from Wernicke encephalopathy, especially in adults, before genetic testing results are available. Neuroimaging, especially MRI, is essential in this differentiation, and this study contributes to the development of evidence-based clinical guidelines for managing thiamine-related conditions.

Declarations

Conflict of interest

None

Disclosure

The authors report no relevant disclosures.

Author contribution

Hanin Alsini**:** Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data.

Brahim Tabarki: Drafting/revision of the article for content, including medical writing for content; study concept or design; and analysis or interpretation of data.

Raid Hommady: Major role in the acquisition of data.

Rawan Alsafh : Major role in the acquisition of data.

Zeeshan Asmat: Analyzing or interpretation of the data and reviewing the manuscript.

Wejdan Hakami: Analyzing or interpretation of the data and reviewing the manuscript.

Majid Alfadhel: Analyzing or interpretation of the data and reviewing the manuscript.

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