Journal of the Neurological Sciences 379 (2017) 324–326

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Thiamine deficiency in metronidazole-induced encephalopathy: A metabolic correlation?

Keywords:
Metronidazole-induced encephalopathy
Thiamine deficiency
Wernicke encephalopathy
Metronidazole
Metronidazole neurotoxicity
Thiamine

Abbreviations:
MIE
Topic:
metronidazole-induced encephalopathy
WE
Topic:
Wernicke encephalopathy

Dear Editor,

Metronidazole, an antimicrobial drug, can induce central nervous system dysfunction such as cerebellar ataxia, external ophthalmoplegia, seizures, or alterations in mental status referred to as "metronidazole-induced encephalopathy" (MIE). The diagnosis of MIE depends upon clinical course, specific radiological findings, the exclusion of other differential diagnoses, and the confirmation of significant improvement after metronidazole cassation [1,2]. Importantly, the signal abnormalities of the dentate nucleus on magnetic resonance imaging (MRI) are considered as one of the most characteristic features of MIE [1,2]. Although the mechanism of metronidazole neurotoxicity is not yet fully understood, various hypotheses have been proposed, including the inhibition of thiamine pyrophosphorylation as a thiamine analog [3], the inhibition of neuronal protein synthesis via binding to RNA [4], or the oxidization of neurotransmitters producing semiquinone radicals which are neurotoxic [5].

The potential role of metronidazole as an antagonist of thiamine in catabolism implies the possible association between underling pathological mechanisms in MIE and thiamine deficiency [6]. Indeed, some cases of Wernicke encephalopathy (WE) can show similar clinical symptoms and radiological findings as MIE, and it is not always easy to distinguish MIE from WE. However, in earlier literature, there is limited evidence to support the potential correlation between blood thiamine levels and MIE development. Here we report a case of a 76-year-old man with MIE who simultaneously presented with significant thiamine deficiency.

A 76-year-old man was admitted to our hospital and treated with oral metronidazole (1500 mg per day) and ciprofloxacin (400 mg per day) for osteomyelitis due to diabetic gangrene of his toe. He had used insulin daily because of type 2 diabetes mellitus, and his blood sugar control was fair with an HbA1c of 6.3%. On day 13 of metronidazole treatment, he successfully underwent surgery to remove his fifth toe on the left side. He had been taking a sufficient daily hospital diet, with daily total energy of 1600 kcal and protein of 60 g, respectively. On day 33 of metronidazole treatment, he developed depression and a reduced appetite. Over the next few days, symptoms of nausea and dizziness emerged.

On day 41, he developed dysarthria and ataxia, both of which rapidly worsened. He was soon referred for neurological consultation, and neurological examinations revealed gaze-evoked nystagmus, external ophthalmoplegia, dysarthria, limb and truncal ataxia, but no significant altered mental status or memory disturbance were observed. He could not even sit still due to ataxia. Laboratory tests were mostly within normal limits, except for the lowered level of blood thiamine at 17 ng/mL (lower limit of normal = 20 ng/mL), which became evident later in the clinical course. Brain MRI revealed symmetrical hyperintensities in the dentate nuclei, tectal plate, and periaqueductal area on fluid-attenuated inversion recovery (FLAIR) images (Fig. 1: A, B), but there were no abnormal findings on diffusion-weighted imaging. We immediately started the intravenous administration of high-dose thiamine (1000 mg per day) from day 41, suspecting a diagnosis of WE at first. Oral metronidazole was also discontinued from day 43. The total dose of oral metronidazole given to this patient was 66 g, and symptoms started to improve from day 42. Around day 50, he had made a significant recovery and was able to walk unaided again.

Four months later, follow-up brain MRI was performed, revealing the disappearance of the abnormal intensities which were previously seen in the dentate nuclei and tectal plate (Fig. 1: C, D). There was no recurrence of symptoms, and eventually we diagnosed the patient with MIE and not WE based particularly upon the specific radiological findings.

Our case with MIE demonstrated two clinically unique points. First, thiamine deficiency is likely to have made a significant pathological contribution to his neurological symptoms because of his too fast recovery, given that he had MIE alone. Second, his blood thiamine level was reduced despite sufficient dietary intake and a lack of malabsorption. These features could create a potential pitfall in the treatment for MIE, suggesting the need for routine measurement and supplementation of thiamine in patients suspected of having MIE.

The diagnosis of MIE in our case appeared to be certain, because of the typical clinical symptoms as MIE [1,2,8], timing of disease onset, total dose of metronidazole administered and, especially, the bilateral dentate nuclei lesions on MRI that are specific to MIE [1,2]. Although these lesions have also been reported in some earlier published case reports as "atypical WE cases" [7,8], these cases can rather be considered as MIE due to the use of metronidazole [9]. In addition, this case demonstrated no abnormal findings in the mammillary bodies or thalami, where normally abnormalities would be frequently seen in WE [10]. While lesions seen in both of WE and MIE reflect either vasogenic or cytotoxic edema of the brain [8], the cause of the difference in the lesion distribution between MIE and WE is not well understood. The metronidazole's neurotoxicity to cerebellar inhibitory neuromodulation

http://dx.doi.org/10.1016/j.jns.2017.06.042

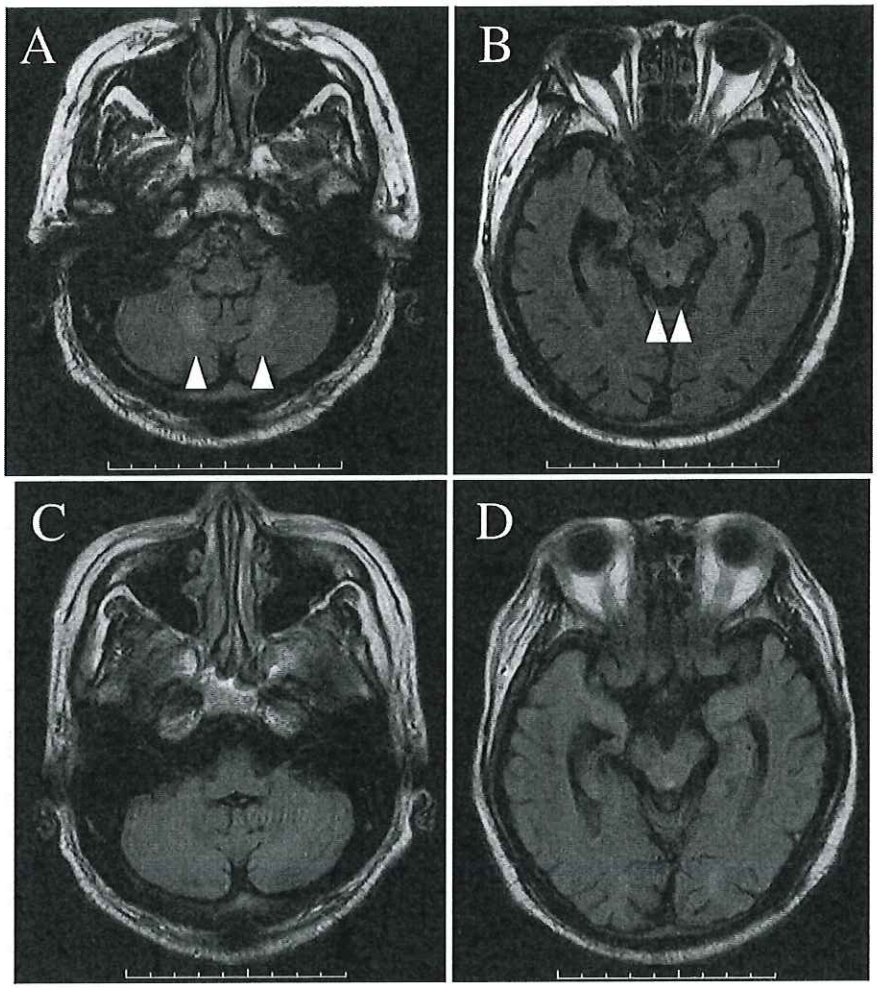

Fig. 1. Brain magnetic resonance imaging revealed symmetrical hyperintensities in the dentate nuclei, tectal plate, and periaqueductal area on fluid-attenuated inversion recovery images (A, B; indicated with white arrowheads). There were no abnormal findings in the mammillary bodies or thalami. Follow-up brain magnetic resonance imaging was performed four months after treatment and revealed that the abnormal signals previously seen had disappeared (C, D). Note that the hyperintensity in the midbrain aqueduct (D) was due to an artifact associated with the flow of cerebrospinal fluid.

may be the possible underlying pathology of cerebellar involvement in MIE [8], while the high activity in the thiamine-dependent glucose metabolism is considered as the cause of lesion tendency to distribute to periventricular areas in WE.

In this particular case, apart from the primary diagnosis of MIE, we suspected the pathogenic involvement of thiamine deficiency in the neurological disturbances. The recovery of symptoms was swiftly achieved from the very next day after initiating thiamine administration, which would be too fast for MIE alone [1,2]. In addition, oral metronidazole administration had been continued even on the first day when significant recovery was clearly evident.

Thiamine deficiency occurred despite sufficient dietary intake and the lack of apparent malabsorption, and our patient's background of chronic toe infection would not be enough to induce thiamine deficiency. Metronidazole itself may act as an effective inhibitor of thiamine during catabolism due to the structural similarity of these two molecules [3]. Thus, the use of metronidazole may have reinforced thiamine deficiency.

On the contrary, although the direct mechanism of metronidazole neurotoxicity is not yet fully understood, several proposed mechanisms have been put forward and relate to disturbances in neuronal function [4,5]. It is possible that coexisting thiamine deficiency can be one of the causes of MIE. Collectively, these observations suggest the existence of a pathological correlation between the underling mechanisms of MIE and thiamine deficiency, as suggested in earlier literature [6].

In conclusion, we would like to suggest that the routine measurement and supplementation of thiamine may be helpful when treating patients suspected of having MIE, particularly owing to the potential pathological correlation between thiamine deficiency and metronidazole neurotoxicity.

Conflicts of interest

The authors have no conflict of interest to disclose.

Ethical approval

This work was performed in accordance with the ethical standards laid down in the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Acknowledgment

This study received no funds. The authors thank Ms. Yamamoto for collecting clinical information and for her technical assistance (Department of Clinical Nutrition, Toranomon Hospital).

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Dosuke Iwadate
Kenichiro Sato*
Mami Kanzaki
Chinatsu Komiyama
Department of Neurology, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, Tokyo, Japan
*Corresponding author at: Department of Neurology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan.
E-mail address: kenisatou-tky@umin.ac.jp.

Chizuru Watanabe
Department of Endocrinology and Metabolism, Toranomon Hospital, Japan

Tomoaki Eguchi
Department of Plastic Surgery, Toranomon Hospital, Japan

Yoshikazu Uesaka
Department of Neurology, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, Tokyo, Japan

12 May 2017