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Brief Communications

Chronic Migraine Responding to Intravenous Thiamine: A Report of Two Cases

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Background.—Migraine is a risk factor for thiamine deficiency and Wernicke's encephalopathy (WE). WE is a highly underdiagnosed condition. The misdiagnosis is associated more with early or mild WE. The interrelation between migraine and thiamine deficiency is unknown

Case reports.—Here, we report two female patients with chronic migraine. During examinations, we also noted clinical signs pertinent with a diagnosis of WE. Both patients had low blood thiamine level. Intravenous thiamine supplementation led to the improvement of both WE and associated headaches.

Discussion.—Nausea, vomiting, and anorexia of migraine may lead to mild to moderate thiamine deficiency and WE. Review of the literature suggests that WE in early or subclinical form will have nonspecific symptoms that may include frequent headache, nausea, vomiting, and anorexia. So, WE in the early stage may simulate migrainous features and this will further aggravate thiamine deficiency and a vicious cycle may be formed, and that will progressively increase the chronicity of headaches and other features. Breaking of this cycle by thiamine supplementation might be a promising therapy in a subset of patients with chronic migraine.

Conclusion.—Thiamine deficiency due to nausea, vomiting and anorexia of migraine may further aggravate migraine like headaches in cyclical pattern.

Key words: chronic migraine, Wernicke's encephalopathy, thiamine

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INTRODUCTION

Migraine is considered a risk factor for thiamine deficiency and Wernicke's encephalopathy (WE). However, the literature is silent regarding the prevalence and clinical features associated with thiamine deficiency in migraine patients.[1] WE is highly underdiagnosed condition. The clinical diagnosis of WE is missed in over 80% of cases.[2] The very high rate of incorrect diagnosis of WE is partly due to its protean manifestations and partly due to not recognizing clinical symptoms and signs.[3] Early detection of subclinical thiamine deficiency is more

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difficult, as symptoms may be vague and nonspecific.[1–3]

Herein, we report two patients with chronic migraine who had mild WE with thiamine deficiency. Thiamine supplementation led to the improvement in both WE and associated headaches. We also speculate the interrelation between headaches and thiamine. Written informed consent was taken from both patients for publication of this report. The study did not require approval by the Institute Ethic Committee as per the local regulations for retrospective observations.

Case Reports.—*Case 1.*—A 32-year-old female had a history of migraine of more than 10 years. Her migraine attacks gradually increased in frequency and became chronic (>15 days headache per month) one year ago. However, for the last 4-5 months, she had daily and almost continuous headaches. The continuous headache was described as mild, holocephalic, and pressing-type. Over it, she had episodes of moderate to severe exacerbations. The exacerbations occurred 3-5 times per week and used to persist for about 4-24 hours. Migrainous features (nausea, vomiting, photophobia, and phonophobia) were reported in about 50% of the exacerbations. However, nausea (with anorexia) was felt even without headache exacerbations and it was present almost daily for the last 6-8 weeks. She lost 3-4 kg weight over a few months.

Besides the headache, she had frequent attacks of dizziness, vertigo, imbalance (feeling of swaying while walking), feeling fatigue, and disturbed sleep for about 2-3 months. There was no history of alcohol or substance abuse.

The patient was subjected to multiple extensive medical examinations, investigation, and therapeutic trials by various physicians. However, no physical and laboratory abnormality was ever noted by any physician.

She received a number of drugs as preventive measures over the months (amitriptyline, dothiepin, sodium valproate, topiramate, propranolol, etc), but did not have any significant reduction in attack frequency or headache days. She used to take paracetamol or naproxen, or diclofenac for severe acute attacks (8-10 times in a month), and these abortive drugs used to reduce the intensity of headache exacerbations. The drug history was not suggestive of medication overuse headache (MOH)

She consulted us for the most recent attack/exacerbation of headache that had been occurring for the previous 4-5 days. Physical and neurological examinations revealed: Mini Mental Status Examination (MMSE) −26 (impaired recall and serial sevens), gaze-evoked nystagmus intentional tremor, positive heel-shin test, and impaired tandem walk.

Clinical history and physical examinations were suggestive of chronic migraine with Wernicke's encephalopathy. Injection thiamine was started immediately and the patient was subjected to various investigations. MRI of the brain was reported normal. The whole blood thiamine level was 15.4 ng/mL (range 25-75). CSF analysis did not reveal any abnormality. Routine biochemical parameters were normal.

Thiamine was started at the dose of 500 mg (dissolved in 100 mL normal saline) intravenously (IV) over 60 minutes, three times per day. Surprisingly, there was marked improvement in the headache intensity within 12 hours (after the second dose of thiamine). The headache subsided completely in 24 hours. Impaired tandem walk also improved within 24 hours. Thiamine was continued at the same dose (500 mg IV 8 hourly) for another 2 days. The dose was reduced on the 4th day to 200 mg IV 8 hourly for another 2 days. There was just a mild headache attack for a few hours on day 4. MMSE of patients returned to normal on the 5th day. Mild nystagmus was noted on day 5. The patient was put on oral thiamine (100 mg two times daily). She had been receiving flunarizine (10 mg daily). We asked her to continue flunarizine. Oral sumatriptan was advised for an acute migraine attack. The patient had only three headache attacks over the next 6 weeks. Continuous background headache almost disappeared. There was no nystagmus at this time. Dizziness, vertigo, and disturbed sleep also improved markedly.

Case 2.—A 27-year-old female reported episodic migraine without aura since the age of 15 years. Her headaches were infrequent until 2 years prior to presentation (2-3 attacks per year).

However, the frequency of headaches gradually increased and she had almost daily headaches for the last 7-8 months. She identified two types of headaches. There was a continuous mild to moderate headache for the most of the time of the day for 7-8 months. In addition, she had superimposed severe attacks. The continuous headache was nonpulsatile, mild to moderate in intensity, and maximally felt on both sides of frontal areas. She could manage her routine activities with such background activities. The exacerbations were described as holocephalic, severe and throbbing in quality. The usual duration of the exacerbations was 6 to 12 hours and used to occur 2-3 times in a week. The exacerbations were associated with significant nausea, vomiting, photophobia, and phonophobia in most of the attacks. In fact, the patient had chronic nausea that got aggravated during exacerbation of headaches. With nausea, she also had anorexia and lost 3-4 kg weight over 4-5 months. In addition to headaches, she developed many other symptoms: frequent irritability, episodic vertigo, disturbed sleep, and occasional imbalance while walking. There was no history of alcohol or substance abuse.

She received a number of prophylactic drugs (amitriptyline, topiramate, and propranolol) recently; however, her headache frequency largely remained unchanged. She was advised to take a naproxen and sumatriptan combination for severe attack. This combination was used to lower the intensity of severe attacks (rarely a complete improvement). The drug history was not suggestive of associated MOH.

Physical and neurological examinations revealed: MMSE −27 (impaired serial sevens), gaze-evoked nystagmus, and impaired tandem walk. The patient fulfilled the criteria for chronic migraine (without MOH). A suspicion of Wernicke's encephalopathy was also felt. Injection thiamine was started immediately in a similar regimen as with the previous case (500 mg IV 8 hourly) and the patient was subjected to various investigations. MRI of the brain did not reveal any abnormality. Whole blood thiamine was low (17.5 ng/mL).

The patient noted improvement in her background headache within 12 hours and it subsided in 36 hours. Her chronic nausea and impaired tandem walk also improved over the next 48 hours. MMSE returned to normal on the 4th day. Mild nystagmus was still present at the time of discharge (day 5). She was discharged to take oral thiamine (100 mg three times daily) only. Naproxen was given for acute migraine attack.

Follow-up was done after 2 months. Continuous background headache had almost disappeared. The patient had on average one headache attack per week (a typical migraine attack). There was no nystagmus. Irritability, vertigo, and disturbed sleep also subsided completely. No adverse effect was noted because of the drug.

DISCUSSION

These two cases fulfilled the ICHD-3β criteria for chronic migraine without MOH. In parallel, patients fulfilled the Caine criteria of WE. A diagnosis of WE could be made if two of the following were present: (i) history suggestive of nutritional deficiencies; (ii) ocular abnormality; (iii) cerebellar dysfunctions; and (iv) cognitive impairment.[1,4] Both patients fulfilled all four features. We noted a history suggestive of nutritional imbalance (persistent anorexia, vomiting, anorexia, and weight loss), ocular abnormality (nystagmus), cerebellar dysfunctions (impaired tandem walk, positive heel-shin test, and intentional tremor), and cognitive impairment (impaired MMSE). In addition, serum thiamine levels were low in both cases. A response to thiamine further reinforces the diagnosis of WE.

Thiamine supplementation led to the improvement of headache in both cases. The continuous background headache subsided almost completely in both cases. The frequency of exacerbations (or attacks of severe headaches) also reduced markedly. In case 1, intravenous thiamine even led to the cessation of ongoing headache exacerbations. Both patients received oral thiamine for another 6-8 weeks (case 1 also received flunarizine). There was a marked reduction in the frequency of headache attacks. The improvement was also noted in other associated symptoms (dizziness, vertigo, irritability, and disturbed sleep). There was a temporal relation between thiamine supplementation and headache improvement. Moreover, previous treatment with various drugs in the past did not produce any

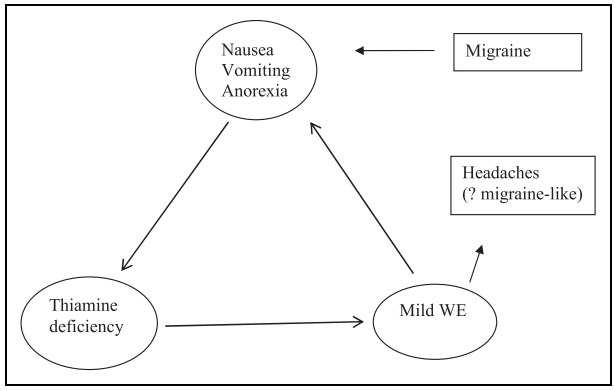

Fig. 1.—A possible interrelation among migraine headaches, nausea/vomiting, and Wernicke's' encephalopathy (WE).

significant improvement in overall frequency of the headache attack/days. Therefore, we speculate that thiamine was pivotal in relieving the headaches.

INTERRELATION BETWEEN THIAMINE AND HEADACHE (OR MIGRAINE)

Recurrent vomiting because of migraine attacks is considered as a risk factor for WE (thiamine deficiency). Refusal of food (because of the persistent nausea or anorexia associated with migraine) is also considered a risk factor for WE.[1,4] However, the literature is silent regarding the prevalence of WE in migraineures.

WE is a highly underdiagnosed condition. Diagnosis may be overlooked even with a classical presentation in 75-80% of patients with alcoholism and 94% of patients without alcoholism.[1,3,5] Therefore, WE with subtle and nonspecific symptoms and signs could be easily unnoticed.[1,2]

Articles on WE mention *"frequent headaches"* as one of the accompanying features of early or mild WE.[1,3] However, according to our literature search, thiamine deficiency as a cause of headache has not been mentioned in any major book on "Headache," headache classification system, any study, or even in a case report.

Besides headache, WE in mild or early stages may cause nausea, vomiting, and anorexia.[4,6] Nausea, vomiting, anorexia, and headaches of WE may simulate an attack of migraine. In a migraine patient, any such symptom would be considered as an attack of migraine and no other diagnosis could be entertained here. However, a vicious circle could be formed here (Fig. 1). Nausea, vomiting, or anorexia in patients with migraine would lower thiamine level and low thiamine level would further exacerbate nausea, vomiting, anorexia, and headaches. So, there could be progressively increased frequency of the headaches (and other associated features) because of this cycle. Reed et al as a part of the AMPP Study noted that persistent frequent nausea is common (43.7%) among persons with episodic migraine.[7] They further noted that progression of episodic migraine to chronic migraine was two times more in patients having nausea compared with those with no or low frequency nausea. We speculate that a subset of patients in Reed's observations could be related to the vicious cycle initiated by nausea of migraine (nausea → thiamine deficiency → nausea → thiamine deficiency → headaches).

Eating disorders, especially anorexia nervosa (extreme dieting) and bulimia nervosa, are also considered a risk factor for thiamine deficiency and WE.[8] In one study, 38% patients with anorexia nervosa had low serum thiamine.[9] Review of the literature demonstrates increased prevalence of headaches and migraine in patients with anorexia nervosa.[10] Thiamine, again, could be a contributing factor here.

Besides headaches, patients with chronic migraine have many other clinical features, such as: fatigue, irritability, abdominal discomfort, dizziness, disturbed sleep, poor attention.[11,12] These features are all reported with early or mild WE.[1,6] Therefore, we speculate that a subset of chronic migraine patients might have these symptoms because of mild to moderate thiamine deficiency.

WE is classically described in alcoholic patients. However, it may occur in nonalcoholic patients. It is said that the body's reserves of thiamine is sufficient only for up to 18 days. So, it is suggested that any condition that causes unbalanced nutrition only for 2-3 weeks may lead to WE.[1,3] In an individual with marginal stores of thiamine, WE may occur even after a few days of unbalanced nutrition.[1,3] Migraine patients, especially with frequent attacks, are always at the risk of unbalanced nutrition because of frequent nausea/vomiting and anorexia.[1] In turn, they are at the risk for thiamine deficiency or WE. However, total avoidance of foods (or complete starvation) is not common in migraine patients. Therefore, complete depletion of thiamine would not be so common. The possibility of mild to moderate thiamine deficiency is more likely. With mild to moderate deficiency, there could be only nonspecific features (headache, others), and full-blown WE would be very rare.

Alcohol, Headache, and Thiamine: Any Relation?—Alcohol is considered as the most common cause of thiamine deficiency. Therefore, in this regard, it would be interesting to know the interrelations among alcohol, headache, and thiamine: The ICHD recognizes two types of headache related to alcohol ingestion: the "immediate alcohol-induced headache" (IAIH) and the "delayed alcohol-induced headache" (DAIH). Delayed alcohol-induced headache is one of the most common types of secondary headache.[13] Besides, alcohol precipitates a number of primary headaches including migraine and cluster headache. A few studies have shown that patients with migraine consume less alcohol than the general population. It is explained that migraineurs avoid drinking alcohol as alcohol triggers headache attacks.[14] However, many conflicting observations have also been reported.[15,16] The interrelation between headaches may vary with age, sex, associated smoking habit, type and amount of drinks, pattern or frequency of drinking habits, associated stress, and so forth.[15,16] Therefore, the effects of alcohol on headaches seem to be multifactorial, and thiamine deficiency could be one of the factors. It could be interesting to evaluate the serum thiamine level in these patients.

Pathophysiology: postmortem examinations in patients who died of WE have shown neuropathological abnormalities, mainly in the periaqueductal grey matter, the mammillary bodies, and medial thalamus.[1] The same regions of the brain are also involved in migraine patients.[17] With such similarity in the structures involved in both conditions, we speculate that a subset of patients with thiamine deficiency may have migraine-like headaches (headaches, nausea, and vomiting). Mid-brain periaqueductal gray matter (PAG) is considered as a center of a powerful descending antinociceptive neural network.[18] PAG is one of the main centers involved in both WE and migraine.

Limitations.—A possibility of unrecognized selection bias and recall bias exist. Moreover, findings noted in the case reports cannot be generalized. Besides these limitations, we cannot rule out the possibility of other causes for the patients' current problems as full laboratory investigations were not done.

Patents fulfilled the Caine criteria and had a low thiamine level. However, the presence of MRI abnormality typical of WE could have been more reinforcing. MRI abnormalities are an important diagnostic feature for WE. However, the sensitivity of MR imaging is relatively low (53%) even with classical WE.[1] There is no study correlating MRI changes with mild to moderate WE. We presume that neuroimaging abnormalities could not be that common in patients with mild or early WE as found with severe WE.

There was a temporal relationship between thiamine supplementation and improvement in the patients. However, as this is a 2-patient case report, we cannot draw that conclusion with confidence. Some prospective observation is required.

CONCLUSION

Nausea and anorexia of migraine may lead to mild to moderate thiamine deficiency that will further aggravate nausea and vomiting in the cyclical pattern. As mild to moderate thiamine deficiency may cause frequent headaches, there will be increasing chronicity of migraine or headache attacks. Breaking of this cycle by thiamine supplementation might be a promising therapy in a subset of patients with chronic migraine.

We hope these case reports and our speculation on the interrelation between thiamine nausea and headaches may serve as a catalyst for further investigations to clarify the issue.

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REFERENCES

1. Sechi G, Serra A. Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. *Lancet Neurol.* 2007;6:442-455.
2. Isenberg-Grzeda E, Kutner HE, Nicolson SE. Wernicke-Korsakoff-syndrome: Under-recognized and under-treated. *Psychosomatics.* 2012;53:507-516.
3. Sechi GP, Serra A, Pirastru MI, et al. Relationship between diet and Wernicke's encephalopathy. In: Watkins SV, ed. *Nutrition Research Advances*. New York: Nova Science; 2007:47-80.
4. Thomson A, Guerrini I, Marshall E. Wernicke's encephalopathy: Role of thiamine. *Pract Gastroenterol.* 2009;75S:21-30.
5. Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *Eur J Neurol.* 2010;17:1408-1418.
6. Thomson AD, Cook CH, Guerrini I, Sheedy D, Harper C, Marshall EJ. Wernicke's encephalopathy: 'Plus ça change, plus c'est la même chose. *Alcohol Alcohol.* 2008;43:180-186.
7. Reed ML, Fanning KM, Serrano D, Buse DC, Lipton RB. Persistent frequent nausea is associated with progression to chronic migraine: AMPP study results. *Headache.* 2015;55:76-78.
8. Saad L, Silva LF, Banzato CE, Dantas CR, Garcia C Jr. Anorexia nervosa and Wernicke-Korsakoff syndrome: A case report. *J Med Case Rep.* 2010;4:217.
9. Winston AP, Jamieson CP, Madira W, Gatward NM, Palmer RL. Prevalence of thiamin deficiency in anorexia nervosa. *Int J Eat Disord.* 2000;28:451-454.
10. Ostuzzi R, D'Andrea G, Francesconi F, Musco F. Eating disorders and headache: Coincidence or consequence? *Neurol Sci.* 2008;29:83-87.
11. Katsarava Z, Buse DC, Manack AN, Lipton R. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep.* 2012;16:86-92.
12. Burshtein R, Burshtein A, Burshtein J, Rosen N. Are episodic and chronic migraine one disease or two? *Curr Pain Headache Rep.* 2015;19:53.
13. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition. *Cephalalgia.* 2013;33:629-808.
14. Panconesi A, Bartolozzi ML, Mugnai S, Guidi L. Alcohol as a dietary trigger of primary headaches: What triggering site could be compatible? *Neurol Sci.* 2012;33:S203-205.
15. Dueland A. Headache and alcohol. *Headache.* 2015;55:1045-1049.
16. Panconesi A, Bartolozzi ML, Guidi L. Alcohol and migraine: What should we tell patients? *Curr Pain Headache Rep.* 2011;15:177-184.
17. Goadsby PJ. Pathophysiology of migraine. *Ann Indian Acad Neurol.* 2012;15(Suppl. 1):15-22.
18. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: Cause or the burden of illness? *Headache.* 2001;41:62937.