Gastrointestinal Beriberi as a prodrome of non-alcoholic Wernicke’s encephalopathy: a study of an emerging nutritional deficiency disorder from Kashmir, India

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ABSTRACT

Background: Gastrointestinal manifestations of thiamine deficiency have not been well described in literature. Authors aimed to study the symptoms of gastrointestinal beriberi in a cohort of patients of non-alcoholic Wernicke’s encephalopathy and review the relevant literature.

Methods: In a retrospective analysis, case records of 52 patients diagnosed with non-alcoholic Wernicke’s encephalopathy were analyzed for the nature of gastrointestinal symptoms, their duration, severity and associated findings, investigations and response to treatment. The available literature on gastrointestinal symptoms in thiamine deficiency disorders and gastrointestinal beriberi was reviewed.

Results: Gastrointestinal symptoms were found in 46 of the 52 patients. The most common gastrointestinal symptom in our patients was recurrent vomiting in 42 patients. Eight patients had water brash. Ten patients had epigastric pain and 10 patients had anorexia. Based on the nature and severity of symptoms, patients were evaluated for their symptoms using endoscopy, ultrasonography, amylase and lactate levels, and routine laboratory studies and the results were normal in the majority of patients. Gastrointestinal symptoms settled in all the patients after receiving intravenous thiamine. On reviewing the literature multiple studies were found to have reported prominent gastrointestinal symptoms in patients of Wernicke’s encephalopathy and other thiamine deficiency related disorders. However, the definition of gastrointestinal beriberi is not clearly stated.

Conclusions: Gastrointestinal symptoms were prominent prodromal manifestations in our cohort of Wernicke’s encephalopathy and have also been amply reported in literature. Presence of gastrointestinal symptoms in individuals predisposed to thiamine deficiency without alternative explanation should be enough to label a patient as gastrointestinal beriberi. The study highlights the importance of recognizing gastrointestinal beriberi as a distinct syndrome that may precede the development of Wernicke’s encephalopathy.

Keywords: Gastrointestinal beriberi, Thiamine deficiency, Wernicke’s encephalopathy
neuropathy, gastrointestinal symptoms and ophthalmoplegia co-occur. The entity of gastrointestinal beriberi is relatively new and has been added in the previous decade only. The classical description given is that of abdominal pain, vomiting and lactic acidosis in a person with a predisposition for developing thiamine deficiency. Gastrointestinal beriberi is a recognized term but has been poorly described in literature.

In the past, plentiful studies have reported gastrointestinal symptoms in various forms of thiamine deficiency most notably in Wernicke’s encephalopathy. However in these studies, the symptoms are mentioned as ancillary manifestations with stress being given on the symptoms defining the illness under consideration or on the radiological findings.

The likelihood that gastrointestinal symptoms can be the early or only manifestations of thiamine deficiency has not been acknowledged. Authors argue that gastrointestinal symptoms may be an early presentation of thiamine deficiency and a prodrome for neurological manifestations especially Wernicke’s encephalopathy. The study describes gastrointestinal symptoms in patients of Wernicke encephalopathy.

METHODS

In a retrospective analysis, 52 patients diagnosed with non-alcoholic Wernicke’s encephalopathy over a period of 5 years at a tertiary care centre from December 2011 to December 2016 were reviewed for their gastrointestinal symptoms.

The diagnosis of Wernicke’s encephalopathy was made using the criteria recommended by European federation of neurological societies (EFNS) guidelines 2010 originally proposed by Caine et al. The diagnosis requires two of the following four signs: dietary deficiencies, cerebellar dysfunction, eye signs and either an altered mental state or mild memory impairment.

The data was reviewed for the nature of gastrointestinal symptoms, their duration, dietary history, associated findings, investigations, treatment and outcome. All the patients received thiamine initially intravenously for about 5 to 10 days followed by oral therapy. The available literature on gastrointestinal beriberi and gastrointestinal manifestations of thiamine deficiency was reviewed using Pub Med search. Studies where alternative cause of vomiting or gastrointestinal symptoms was stated were excluded.

Statistical analysis

The statistical analysis was performed using SPSS version 20 software. Categorical variables were compared employing nonparametric tests (chi-square, Fischer exact test) whereas continuous variables were compared by using student’s t test.

RESULTS

The mean age of the patients was 50.38 years (range 23 to 80 years). Male to female ratio was 2:3. The mean duration of hospital stay was 8.9 days (range 05 to 20 days). All the patients had history of consuming polished rice as their main staple diet which is washed once to three times before cooking. Besides, the patients also had history of consuming green tea on a daily basis. No patient had history of alcohol intake.

Out of the 52 patients, 46 patients were found to have gastrointestinal symptoms. In all patients, the gastrointestinal symptoms preceded the development of Wernicke encephalopathy. The most common gastrointestinal symptom in our patients was recurrent vomiting in 42 patients. The vomiting was described by the patients as low volume, non-projectile, and usually associated with nausea and water brash. The frequency was irregular ranging multiple bouts a day to no episodes for many days. Three patients had nausea only. Ten patients had anorexia. Also, ten patients had associated epigastric pain along with vomiting. The average duration of symptoms before the onset of Wernicke’s encephalopathy was 27.2 days with the length being as short as two days and as long as 90 days. 09 patients had duration of more than 45 days and 05 patients had symptoms of 03 days or less (Table 1).

Table 1: Gastrointestinal symptoms in the patients of nonalcoholic Wernicke’s encephalopathy (n= 46).

| Symptom                  | Number of patients (%) |
|--------------------------|------------------------|
| Nausea and vomiting      | 42 (84)                |
| Nausea only              | 03 (06)                |
| Abdominal pain           | 10 (20)                |
| Water brash              | 08 (16)                |
| Anorexia                 | 10 (20)                |

Based on the nature and severity of symptoms, 21 patients underwent an upper gastrointestinal endoscopy in which 12 had a normal study while 08 had endoscopic lesions out of whom 06 had gastritis and two had healed duodenal ulcer. Twenty-three patients underwent an abdominal ultrasonography, 16 had normal study, while in 7 it was abnormal. Out of these 7 patients, 1 had chronic liver disease and 6 had gallstones among which only 2 had features of acute cholecystitis. Out of the 10 patients with abdominal pain associated with vomiting, two had acute cholecystitis; two had gastritis while in six no cause of pain was found. Serum amylase was normal in all of these 10 cases. Lactate levels were done in 12 patients before receiving thiamine, 04 had raised levels out of which only 01 had acidosis. Estimation of levels of serum thiamine was not done in any patient due to non-availability of reagents. Brain imaging was done in 33 patients; CT was done in 21 patients and was normal in 18 patients while 02 patients had medial thalamic hyper densities and 1 had few subcortical hypodensities.
Twenty patients underwent an MRI, 04 had normal MRI, while in the rest it was abnormal. The most common findings were medial thalamic hyperintensities in 11 patients followed by periaqueductal hyperintensities in 09 patients and tectal hyperintensities in 03 patients.

All patients were treated with intravenous thiamine in doses of 300 mg to 600 mg per day for 05 to 10 days followed by oral tablets of 100 to 300 mg per day. Intravenous thiamine was given as an infusion 2 to 3 times a day. Forty one of 45 patients had complete improvement in their gastrointestinal symptoms during hospital stay while 4 had partial improvement. At the time of discharge the only residual gastrointestinal symptom was anorexia in 04 patients.

**DISCUSSION**

Gastrointestinal beriberi was first described as a clinical syndrome in 2004 when Donnino et al, reported two patients with gastrointestinal symptoms and lactic acidosis who responded completely to thiamine therapy. The author argued that early observations of gastrointestinal symptoms of thiamine deficiency were not translated into a syndrome, so the recognition of this clinical entity was delayed. Authors further substantiate the idea of recognizing gastrointestinal Beriberi as a separate clinical disorder and try to elucidate the various manifestations of this syndrome and clarify the case definitions. No study has analyzed in detail the possible gastrointestinal manifestations of thiamine deficiency and their relation to other forms of this nutritional disorder. The syndrome can be a prodromal manifestation of Wernicke’s encephalopathy or may occur in isolation. In both the case however, diagnosis requires a high index of suspicion since gastrointestinal symptoms are often considered nonspecific both by the patients and the clinicians.

Vomiting was the most prominent symptom in our patients. Vomiting has been described both as a cause and a manifestation of thiamine deficiency. Recurrent vomiting as a cause of thiamine deficiency has received much attention and has been well described in literature. However in many of the published cases, ascribing vomiting as a cause of thiamine deficiency, the authors are not clear as to whether vomiting has precipitated thiamine deficiency or else it was possibly the GI symptom of the disease. The causality can be wrongly attributed if the investigator has not kept in mind the GI manifestations of Beriberi. The fact that vomiting can be an initial manifestation of this multi-facet disease has not received attention even though the syndrome and symptoms of gastrointestinal beriberi have been described more than 12 years before. Many studies on Wernicke’s encephalopathy have reported gastrointestinal symptoms especially vomiting in all the studied patients while others have reported them in the majority. Prakash S et al, suggested that gastrointestinal Beriberi may be a former fruste of Wernicke's encephalopathy.

Most of our patients did not have any identifiable cause for vomiting. Also, in a substantial number of patients the duration of symptoms was short and episodes of vomiting infrequent which are insufficient to deplete the body’s thiamine stores. In majority of patients with abdominal pain also, no plausible reason for pain was found. The imaging findings on CT scan or MRI of brain were related to Wernicke’s encephalopathy and no patient had any intracranial lesion as a cause of vomiting. Consequently, we infer that nausea, vomiting and abdominal pain were mainly initial symptoms of thiamine deficiency in our patients as there was no alternative explanation for them and these GI symptoms are well known in thiamine deficiency.

In the 1940s, many researchers studied the effects of induced thiamine deficiency in humans. Majority of the participants in these experiments reported nausea, vomiting, and abdominal pain as major symptoms. At that time, the likelihood that these symptoms could represent a manifestation of beriberi was not considered. On reviewing the literature, it was found that since 1990, multiple studies have reported gastrointestinal symptoms in patients of Wernicke’s encephalopathy and other thiamine deficiency related disorders (Table 2). Yet again the possibility of a gastrointestinal syndrome has not been considered in majority of these studies.

In a total of 21 studies reviewed, 06 had gastrointestinal symptoms in all the patients, 06 had in more than 50% while 09 had in less than 50% patients. In most of these studies (19/21) nausea and vomiting were the most common symptoms. Whether gastrointestinal symptoms preceded the neurological symptoms or occurred simultaneously has not been clearly stated in these studies.

Present study has also shown prominence of GI symptoms in patients of Wernicke’s encephalopathy. However, the percentage of patients showing these symptoms especially vomiting was much higher in our series. The reason may be that our patients were non-alcoholic, and nausea and vomiting have been seen to be more common in non-alcoholic Authors as compared to alcoholic authors. Other reason may be a genetic difference in the initial manifestations of thiamine deficiency. Studies have reported that thiamine deficiency mainly manifests as wet beriberi in oriental people and dry beriberi in Europeans. A similar reason may apply to gastrointestinal Beriberi. These gastrointestinal symptoms preceded the development of Wernicke’s encephalopathy in our patients by days, weeks and even months. The possible explanation may be that the gastrointestinal system perhaps gets involved early in thiamine deficiency before affecting the nervous system. Also, the manifestations of thiamine deficiency can progress from involvement of one system to another. Else patients can present simultaneously with involvement of multiple systems. Chaves et al, reported occurrence of polyneuropathy and Wernicke-Korsakoff
syndrome together in a group of patients admitted in a bariatric unit.38

Elevation of lactate was documented in only four of our patients out of which one had acidosis. Lactic acidosis has been reported to occur in patients with thiamine deficiency Madl et al, reported prolonged lactic acidosis in two chronically ill patients with limited nutritional intake developing due to thiamine deficiency.39 Amrein et al, reported a case of isolated severe lactic acidosis reversed by thiamine within 24 hours.40 Qureshi et al, reported thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants.33 Also studies have found an inverse relationship between thiamine levels and lactate levels in critically ill patients.41,42 Lactic acidosis may thus suggest the severity of thiamine deficiency or it may itself be a separate syndromic manifestation that sometimes overlaps or follows the other systemic manifestations of this disease. Lactic acidosis thus occurs in a proportion of cases with thiamine deficiency and is not specific to gastrointestinal beriberi as proposed by Donnino et al.3

Table 2: Gastrointestinal symptoms reported in various studies on Wernicke's encephalopathy and other thiamine deficiency disorders.

| Authors                  | Syndromic diagnosis               | Total number of patients | Number of patients with GI symptoms | Predominant GI symptom            |
|--------------------------|----------------------------------|--------------------------|-------------------------------------|-----------------------------------|
| Gallucci et al3          | Wernicke’s encephalopathy        | 05                       | 05                                  | Nausea and vomiting               |
| Naidoo et al6            | Wernicke’s encephalopathy        | 17                       | 08                                  | Nausea and vomiting               |
| Vege et al7              | Non-alcoholic Wernicke’s encephalopathy | 04                       | 01                                  | Nausea and vomiting               |
| McGready et al8          | Thiamine deficiency              | 48                       | 07                                  | Loss of appetite                  |
| Merkin-Zaborsky H et al19 | Non-alcoholic Wernicke’s encephalopathy | 03                       | 02                                  | Nausea and vomiting               |
| Park et al23             | Non-alcoholic Wernicke’s encephalopathy | 03                       | 02                                  | Nausea and vomiting               |
| Ogershok et al24         | Non-alcoholic Wernicke’s encephalopathy | 06                       | 03                                  | Nausea and vomiting               |
| Weidauer et al16         | Non-alcoholic Wernicke’s encephalopathy | 01                       | 01                                  | Nausea and vomiting               |
| Chen et al25             | Beriberi                        | 104                      | 20 (minimum)                       | Loss of appetite                  |
| Halavaara et al19        | Wernicke’s encephalopathy        | 05                       | 03                                  | Nausea and vomiting               |
| Fattal-Valevski et al26  | Thiamine deficiency              | 09                       | 09                                  | Vomiting, abdominal pain          |
| Zhong et al27            | Non-alcoholic Wernicke’s encephalopathy | 06                       | 02                                  | Nausea and vomiting               |
| White et al20            | Wernicke’s encephalopathy        | 03                       | 03                                  | Nausea and vomiting               |
| Sun et al28              | Non-alcoholic Wernicke’s encephalopathy | 04                       | 03                                  | Nausea and vomiting               |
| Kirbas et al29           | Non-alcoholic Wernicke’s encephalopathy | 25                       | 07                                  | Nausea and vomiting               |
| Zuecoli et al30          | Wernicke’s encephalopathy        | 56                       | 11                                  | Nausea and vomiting               |
| Francini-Pesenti et al31 | Non-alcoholic Wernicke’s encephalopathy | 07                       | 03                                  | Nausea and vomiting               |
| Dabar et al32            | Shoshin Beriberi                 | 04                       | 02                                  | Abdominal pain, vomiting          |
| Qureshi et al33          | Lactic acidosis                  | 23                       | 12                                  | reflux                            |
| Qureshi et al37          | Infantile Wernickes encephalopathy | 03                       | 03                                  | vomiting                          |
| Duca et al34             | GI Beriberi                     | 01                       | 01                                  | vomiting                          |

Present study and the subsequent review of literature underscores gastrointestinal syndrome as a prominent manifestation of thiamine deficiency that may preceed or co-occur with Wernicke’s encephalopathy and other related disorders. Gastrointestinal beriberi thus should be suspected in any patient who has a setting for thiamine deficiency and develops gastrointestinal symptoms.
especially in population consuming thiamine deficient diet.

Lactic acidosis may not be found in all patients with gastrointestinal manifestations of thiamine and should not be necessary for diagnosis of gastrointestinal beriberi. Early recognition and treatment of this syndrome may prevent the development of more severe manifestations of thiamine deficiency like Wernicke’s encephalopathy.

The study highlights the importance of recognizing gastrointestinal beriberi as a distinct syndrome that may precede the development of serious manifestations of thiamine deficiency like Wernicke’s encephalopathy.

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