Original Research Article

Thiamine deficiency related peripheral neuropathy in peripartum women of Kashmir, India: a hospital based study

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ABSTRACT

Background: Beri Beri is still seen in Asian countries due to the large-scale consumption of thiamine depleted polished rice. Thiamine deficiency related disorders are increasingly being reported from Kashmir from last two decades. Specifically, a sensorimotor axonal neuropathy occasionally develops from thiamine deficiency and may occur even without associated Wernicke’s encephalopathy.

Methods: This study is a retrospective observational study. All peripartum females referred to our departments from January 2016 to December 2017 with complaints of generalized weakness and or sensory symptoms in form of paresthesias/numbness in limbs were enrolled. Clinical features, electrophysiological features, course in hospital and response to treatment in suspected thiamine deficiency related neuropathy patients were recorded.

Results: Forty-three cases were included in the study. Twenty-nine patients were suspected to have nutritional neuropathy because of thiamine deficiency at the time of admission. Out of these 27 showed improvement on treatment with thiamine.

Conclusions: Thiamine responsive neuropathy is common in peripartum women of this part of world. Diagnosis is usually made clinically, in at risk individuals presenting with characteristic clinical features.

Keywords: Beri Beri, Neuropathy, Peripartum, Pregnancy, Thiamine deficiency

INTRODUCTION

Peripartum females may develop neuropathies because of various reasons and at different stages of the pregnancy. These neuropathies range from mononeuropathies like carpal tunnel syndrome which usually occurs during 2nd and 3rd trimester, to lumbosacral plexopathy caused by compression of fetal head in third trimester or during labour, nutritional neuropathies because of marginal nutritional status or hyperemesis gravidorum and obturator neuropathy during protracted labour.¹ Thiamine deficiency is associated with a specific sensorimotor neuropathy and may occur even without associated Wernicke’s encephalopathy. This is usually an axonal polyneuropathy and may be demonstrated by electrophysiological studies.²

Beri Beri occurs most frequently in Asian countries due to the large-scale consumption of thiamine depleted polished rice. The prevalence of thiamine deficiency in this population has been previously found to be as high as 58% to 66%.³ ⁴ Thiamine deficiency related disorders are increasingly being reported from Kashmir from last two decades. Varied manifestations of thiamine deficiency have been reported from Kashmir ranging from exclusion cardiac dysfunction (wet beriberi) to neurological...
disorders (peripheral neuropathy and Wernicke’s encephalopathy). Initially it was described by adult cardiologists as a treatable cause of high output cardiac failure.5,6 Similarly it has been described in children presenting as encephalopathy which was thiamine responsive.7 As for neurologists; thiamine deficiency has been reportedly increasingly in both of its forms viz neuropathy and Wernicke’s encephalopathy.5,9 The presence of wet Beri-beri in adults suggests thiamine deficiency in general population. While as Wernicke’s encephalopathy in exclusively breast bed infants suggests a maternal thiamine deficiency.7 The central nervous system is considered more likely to be affected when the thiamine deficiency is severe and abrupt, whereas the peripheral nerves are usually disturbed by a long-term thiamine deficiency.10

In a hospital based study done in Kashmir, Mohsin N et al, found that out of 106 patients of acute flaccid paralysis, eight patients had neuropathy because of thiamine deficiency, out of which 6 were females.9 Thus there is a suggestion that thiamine deficiency related neuropathy (TDRNP) may be common in females especially in peripartum period in Kashmiri community; but there is lack of literature on this.

METHODS

This study was a retrospective observational and was done at two hospitals. One a community hospital and another referral multispecialty hospital. Both the hospitals had departments of obstetrics and neurology. These hospitals are located in Srinagar and cater to both urban and rural patients. Peripartum period was defined as entire pregnancy plus first 6 weeks after child birth (puerperium). Peripartum females referred to us from January 2016 to December 2017 with complaints of generalized weakness and or sensory symptoms in form of paresthesias/ numbness in limbs were enrolled. All cases of post traumatic weakness, spasticity, chronic neuropathy with onset before pregnancy and sudden onset of weakness as in stroke were excluded from this study. The clinical features including chief complaints, general physical examination, neurological examination, delay in presenting to hospital, line of treatment initiated in the hospital and course during hospital was recorded. The initial and discharge diagnosis of the patients was looked into.

Dietary history was recorded and analyzed. In addition to routine baseline investigations, lactate dehydrogenase, creatine kinase, arterial blood gas analysis, electrolytes, thyroid profile, electrophysiological studies (nerve conduction studies etc.), cerebrospinal fluid (CSF) examination, imaging of the spine and brain (magnetic resonance imaging) in relevant cases had been done in the patients. The diagnosis of thiamine deficiency related neuropathy was made in patients having subacute onset neuropathy, who had a clinical setting of recurrent vomiting or poor oral intake; along with intake of thiamine deficient diet. Other causes of weakness were ruled out by clinical features or investigations. And response to thiamine was deemed to have established the diagnosis of thiamine deficiency related neuropathy (TDRNP). Figure 1 gives the description how the diagnosis of TDRNP was reached at.

![Figure 1: Pathway shows how the diagnosis of Thiamine deficiency related neuropathy was made.](image)

RESULTS

During the study period 43 peripartum females with complaints of generalized weakness and or sensory symptoms in the form of paresthesia’s or numbness in limbs reported to our department. One patient was found to be having weakness because of hypokalemia and improved with correction of same. Thirteen cases were diagnosed as Gullain Barre syndrome at the time of admission at the outset as per the Ashbury criteria.11 Twenty-nine patients were suspected as having nutritional neuropathy because of thiamine deficiency at the time of admission. Out of these 29 patients, 27 showed improvement in symptoms within 24-72 hours in the form of improvement in weakness, resolution of edema, improvement of associated signs of wernicke’s encephalopathy (altered mental status, opthalmoparesis, nystagmus). Two patients did not improve and showed features of clinical worsening and were diagnosed and managed as acute motor sensory axonal neuropathy AMSAN variant of GBS and were treated with intravenous immunoglobulin IVIG (Figure 2).
Seventeen patients presented to the hospital within 1 week of onset of symptoms out of which 4 were managed as TDRNP. Twenty-five patients presented to us after a delay of one week out of which 23 were managed as TDRNP. Seventeen patients were pregnant, out of which 4 were in second trimester and 13 in third trimester and 10 were in puerperium. Of the 10 patients who presented in puerperium all of the patients had onset of symptoms within first 7 days of delivery.

Out of 29 patients initially suspected of thiamine deficiency related neuropathy, 21 gave history of hyperemesis gravidorum. Eight gave history of nausea and history of poor intake in previous 4 weeks before the neuropathy. There was no history of any preceding illness or febrile illness. All other patients reported use of only routine ante partum tetanus toxoid vaccinations.

None of the patients consumed alcohol in the past 25 patients gave history of taking supplemental calcium and vitamin D combinations or iron tablets. All the patients had combination of weakness and sensory symptoms in TDRNP group. Sensory symptoms were seen in all the patients in form of painful paresthesias, numbness, cramping in TDRNP. Nine patients had paraparesis in TDRNP group while as 19 had quadriparesis (Table 1). Five patients had neck flexor weakness. Four patients had opthalmoparesis and gaze evoke nystagmus; while as 3 patients had all features of wernicke’s encephalopathy in form of altered mental status, opthalmoplegia, gaze evoked nystagmus apart from features of neuropathy.

Table 1: Frequency of various clinical features and investigations.

<table>
<thead>
<tr>
<th>Feature</th>
<th>N=27</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.1 (SD=3.6)</td>
<td></td>
</tr>
<tr>
<td>Trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st trimester</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>4</td>
<td>14.8</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>13</td>
<td>48</td>
</tr>
<tr>
<td>Puerperium</td>
<td>10</td>
<td>20.8</td>
</tr>
<tr>
<td>Vomiting/ nausea history</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>Facial or bulbar weakness</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>Descending weakness</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>27</td>
<td>100</td>
</tr>
<tr>
<td>Pure motor</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>Nuchal weakness</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>Quadriparesis</td>
<td>19</td>
<td>70.3</td>
</tr>
<tr>
<td>Paraparetic</td>
<td>8</td>
<td>29.6</td>
</tr>
<tr>
<td>Shin edema</td>
<td>24</td>
<td>88.8</td>
</tr>
<tr>
<td>Features of wernicke’s encephalopathy</td>
<td>3</td>
<td>11.1</td>
</tr>
<tr>
<td>Ophalmoparesis</td>
<td>4</td>
<td>14.8</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axonal neuropathy</td>
<td>27</td>
<td>100</td>
</tr>
<tr>
<td>Demyelinating neuropathy</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>Need for Ventilation</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>Delayed presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 days</td>
<td>4</td>
<td>14.8</td>
</tr>
<tr>
<td>7-28 days</td>
<td>13</td>
<td>48</td>
</tr>
<tr>
<td>&gt;4 weeks</td>
<td>10</td>
<td>20.8</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>100</td>
</tr>
<tr>
<td>High output cardiac failure</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>5</td>
<td>18.5</td>
</tr>
</tbody>
</table>
All of the patients underwent Nerve conduction studies showed that all patients had an axonal sensorimotor polyneuropathy. While 20 had patients had pure axonal neuropathy 7 patients had mixed (predominantly axonal) polyneuropathy. No patients had predominantly demyelinating neuropathy and conduction blocks were not seen in TDRNP. Other investigations that were done revealed anemia in 23 patients (20 had microcytic hypochromic type; while as 3 had dual deficiency type). Four patients had raised liver enzymes, and ALP; 6 had low albumin and 5 had raised lactate level. 19 patients were given intravenous thiamine; 200 to 500 mg thrice a day for 3 days to 5 days, followed by oral thiamine. Eight patients were giving thiamine orally in doses of 300 mg thrice a day initially followed by tapering oral dose.

Seven patients had been started on oral low dose thiamine (100 mg - 200 mg per day) before presenting to our hospital. All of these 7 patients had stabilization of symptoms at that time and no ongoing progression. All patients also received Iron and Calcium supplementation. In addition to the above, 15 patients were given medication for neuropathic pain in the form of pregablain 75 mg once a day. Patients showed improvement within 3 days of starting treatment.

All pregnant females were delivered without any complication. Only one patient who had TDRNP in 3\textsuperscript{rd} trimester and also had low lying placenta developed postpartum hemorrhage and had to undergo hysterectomy. Twenty one patients could be seen on follow up. Sensory symptoms were persisting after 6 weeks. All of the patients had significant improvement in weakness and were ambulatory with no evidence of worsening or recurrence of symptoms.

**DISCUSSION**

In present study authors have found that 27 out of the 43 peripartum female patients (pregnant or in their puerperium) who presented to us with complaints of weakness and sensory symptoms like numbness or paresthesia’s, had thiamine responsive polynmyopathy.

Present study is the first such study from northern India. In a study done in eastern India, out of 112 patients with confirmed peripheral neuropathy (54 males and 58 females) twenty four patients were peripartum women.\textsuperscript{12} These 24 peripartum women were having features of thiamine deficiency related neuropathy and were treated with thiamine. Of these 18 had a documented improvement in neurological deficits after receiving thiamine.\textsuperscript{12}

In this study the weakness was subacute in presentation with 23 out of 27 patients having symptoms for more than 7 days at presentation. There was no cranial nerve involvement, though nuchal weakness was seen in 5 (out of 27) patients.

All the patients had sensorimotor type of neuropathy clinically. Associated clinical features of wet Beri Beri like shin edema, high output cardiac failure helped to make a diagnosis of TDRNP. Many of these patients had a history of hyperemesis gravidarum and or poor intake in at least previous 4 weeks, further corroborating our diagnosis. Clinical signs like altered mental status and ophthalmoparesis were seen in 3 subjects with associated Wernicke’s encephalopathy. Descending weakness was not seen in any patient. Electrophysiological studies revealed findings of axonal motor sensory polyneuropathy in all patients of TDRNP. Other features helping in making diagnosis of thiamine deficiency were resting tachycardia, lactic acidosis.\textsuperscript{13}

In present study out of 43 patients, 15 were diagnosed as GBS and one was diagnosed as hypokalemia. Authors found that response to thiamine was most important in confirming with the diagnosis of TDRNP. A positive response meant either objective stabilization/improvement of motor power, subjective improvement in weakness described by patient and amelioration of edema. Furthermore, there was improvement in signs and symptoms of Wernicke's encephalopathy if they were associated. Sensory symptoms persisted after treatment with thiamine and required medications for neuropathic pain. Authors found that 27 out of 29 patients initially suspected of the TDRNP showed response to treatment within 72 hours. Two patients showed no improvement in weakness and were treated as GBS with IVIG. The dose of thiamine varied in our patients. The improvement of axonal dysfunction, possibly caused by decreased Na⁺/K⁺-ATPase activity due to thiamine deficiency, may be responsible, if not exclusively, for rapid recovery from the neuropathic symptoms and NCS.\textsuperscript{13} There is insufficient level I data to recommend standard doses for the treatment of vitamin B1 deficiency.\textsuperscript{14} Dosing regimens are therefore based on consensus expert opinion. As oral thiamine is poorly absorbed, it should be given intravenously in the hospital setting or intramuscularly in the community.\textsuperscript{15}

Thus, in a setting of an acute or subacute onset polyneuropathy in a patient with history of poor nutrition and or history of vomiting with or without associated features of wet Beriberi, a diagnosis of thiamine deficiency related neuropathy is very plausible. In fact, many cases of thiamine deficiency show a mixture of the two main features and are more properly termed thiamine deficiency with cardiopathy and peripheral neuropathy (WHO,1991). A clinical diagnosis becomes very important in this setting as it takes weeks to get laboratory report of thiamine blood status either by directly measuring thiamine diphosphate level, or RBC transketolase activity as it is not readily available and is to be shipped outside country. And if the neuropathy is of acute onset clinician has to be sure that he or she is not dealing with a patient of GBS as they mimic each other.\textsuperscript{16,18} Though there are criteria for clinical diagnosis
of Wernicke’s encephalopathy recommended by European federation of neurological societies (EFNS) guidelines 2010, only a few objective methods exist to determine thiamine deficiency clinically.14

There are at least two epidemiological surveys of thiamine deficiency neuropathy. In one MSF/ epicentre study (1992) a suspect case of thiamine deficiency in the field was a person having at least two of the following signs: bilateral edema of the lower limbs; dyspnea with exertion or at rest; paresthesia’s of the extremities (hands or feet) or a symmetrical drop in muscular strength or motor deficiencies; stepping or loss of balance.

Similar though slightly different criteria were laid in another study funded by SCF (UK) and conducted in Nepal.15 But there are no well described criteria (clinical and electrophysiological) which are specifically designed for diagnosing TDDR and differentiating it from GBS, and hence the response to treatment under these setting is important. Thiamine deficiency disorders TDD are most often associated with chronic alcoholism, malabsorption, poor dietary intake, increased metabolic requirement (e.g., during systemic illnesses), anorexia nervosa or dieting, hyperemesis of pregnancy, prolonged intravenous feeding without proper supplementation, prolonged fasting or starvation, or unbalanced nutrition, gastrointestinal surgery (including bariatric surgery), genetic disorder of thiamine metabolism.20,21 A number of studies have shown relationship between pregnancy and thiamine deficiency. In a study on Karen displaced population in Thailand 6 out of 18 pregnant females were deficient biochemically in thiamine at term. 6 Similarly thiamine deficiency has been shown in 22% in Mexican women, 25-30% in Dutch mothers.22,23 The causes of thiamine deficiency in pregnant females have been well documented. Thiamine is a water-soluble vitamin.24 The recommended daily requirement is 1.1 mg and the body stores are around 25–30 mg.24 During pregnancy, the requirement for thiamine increases parallel to the fetal development and the requirement increases to 1.5 mg/day.25 The body stores of thiamine usually last for around 18 days and inadequate oral intake and the recurrent vomiting increase the potential risk for thiamine deficiency.21

In patients with hyperemesis gravidorum, uncontrolled vomiting, prolonged intravenous feeding, and thiamine free glucose infusion may lead to the development to authors.26 The longest and shortest duration of vomiting until the development of authors have been reported as 17 weeks and 4 weeks, respectively.27 Local dietary habits/practices may contribute to the development of thiamine deficiency related disorders in our patients. The Kashmiri population consumes polished rice as their main stable diet which is thiamine deficient.5,8 The rice is washed 3-4 times thoroughly before cooking. Many a times rice is cooked in excess water and subsequently the extra water is drained, leading to substantial leaching of vitamins and minerals from it. Furthermore, most people have a preference for bread made from polished wheat flour, which again is thiamine deficient.8 People consume a good amount of green tea on daily basis which is reported to contain anti-thiamine factors and may further contribute to thiamine deficient state.28 Food faddism may also be contributory, especially in pregnant females.

A local study on the nutritional status of lactating females revealed inadequate dietary intake, especially micronutrient deficiency (hidden hunger) during lactation. Further, 49% studied women were found to be anemic.29 In another study done in pregnant females of Kashmir a high prevalence of anemia was attributed to the poor diet intake in pregnant females in this population.30

Studies from this region have reported high incidence of infantile Wernicke's encephalopathy and thiamine responsive lactic acidosis in exclusively breast-fed infants. This again highlights the state of thiamine deficiency of breast-feeding mothers, which is a reflection of the nutritional status of general population.

CONCLUSION

Thiamine responsive neuropathy is common in peripartum women of this world. Dietary and cooking practices possibly predispose patients to thiamine deficiency in Kashmiri pregnant females. Diagnosis is usually made clinically in individuals at risk presenting with a characteristic clinical feature. Further we suggest that in thiamine deficient areas, any pregnant patients or postpartum women with vomiting either because of hyper emesis gravidorum or otherwise be given thiamine. Further there is a need to look for thiamine status in our population at large and especially in high risk groups like pregnant and lactating women.

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REFERENCES


