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Peripheral Neuropathy Outbreaks in Bhutan, 2020–2021

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Abstract

Thiamine (vitamin B1) deficiency can cause beriberi leading to cardiac involvement or, more commonly, peripheral neuropathy. Common causes of thiamine deficiency are alcohol use, maternal thiamine deficiency, poor dietary diversity, unhygienic food preparation, and unsafe cooking practices. This report presents an analysis of suspected peripheral neuropathy outbreaks recorded at the Royal Centre for Disease Control between 2020 and 2021. The suspected outbreaks were reported from schools and monastic institutes with the main complaints of numbness and swelling of lower limbs. Three of the four events were confirmed due to thiamine deficiency by laboratory analysis. Of 34 samples tested, 27 (79%) had thiamine deficiency, defined as a thiamine diphosphate (ThDP) level <75.0 nmol/L. The mean ThDP level was 56.5 nmol/L. There were no statistically significant differences in the average ThDP level among the patients of different age groups. Given the fact that micronutrient deficiency was established as the cause of the current peripheral neuropathy outbreaks, we recommend that the supply of fortified rice across both government and private institutes in the country be initiated. Holistic approaches should be implemented to reduce the burden of micronutrient deficiencies in the country.

Keywords: beriberi, Bhutan, peripheral neuropathy, thiamine, vitamin

Introduction

Thiamine (vitamin B1) plays an important role in energy metabolism and is naturally soluble in water.[1] Beriberi is a condition related to severe thiamine deficiency due to inadequate content in daily diet. Thiamine deficiency can develop within 2–3 months of inadequate thiamine consumption leading to cardiac involvement or, more commonly, peripheral neuropathy (PN) and, if not treated in time, can be fatal.[2] In patients with Wernicke encephalopathy, thiamine deficiency causes irreversible neurologic damage in about 85% of cases.[3] Alcohol use is the most common risk factor for thiamine deficiency among adults. Maternal thiamine deficiency, insufficient thiamine in breast milk, poor dietary diversity, food preparation and cooking practices are other causes in infants and young adults.[4]

Common sources of thiamine are meat products, particularly pork, and whole grains, yeast, and legumes.[5] The recommended nutrient intake (RNI) of thiamine is 1.2 milligrams per day (mg/day) for men and 1.1 mg/day for women, and for pregnant and lactating women, the RNI levels are 1.4 and 1.5 mg/day, respectively.[6] The biologically active form of thiamine, known as thiamine diphosphate (ThDP), is required as a cofactor for the functions of enzymatic pathways.[7] The two biomarkers for assessing thiamine status in the body are erythrocyte transketolase assay and measuring thiamine metabolites.[6] Diagnostic cut-off values for measuring whole blood total ThDP range from 75–180 nanomoles per litre (nmol/L).[8]

Thiamine deficiency was recently recognized as a public health concern in Southeast Asian countries.[9] Thiamine deficiency cases have previously been reported in Bhutan affecting young school-going students with loss of productive time and a few reported deaths.[10,11] Pradhan et al., (2021) found that infantile beriberi was the main cause of infant mortality (>70%) in Bhutan.[12] In 2017 several sporadic thiamine deficiency outbreaks were recorded in Bhutan among school children, thus fortified rice supplementation was initiated. Several PN outbreaks were reported from the institutes where fortified rice is not provided. We aim to present results of our investigation of suspected outbreaks of PN in the country between 2020 and 2021 for better public health interventions and to prevent future disease outbreaks.

Methods

Data on suspected outbreaks of PN were extracted from the National Early Warning and Response Alert Surveillance System, maintained by the Royal Centre for Disease Control (RCDC). The laboratory analysis report was retrieved from the Food and Nutrition Laboratory. As shown in Table 1, four events of suspected PN outbreaks from four separate districts were reported during the study period.

A PN outbreak is suspected by a physician when patients visit a health center with chief complaints of numbness, weakness and tingling sensations of the lower limbs. Medical teams from the field (hospitals and primary health centers) upon suspicion of PN reported the outbreaks through the National Early Warning and Response Alert Surveillance System. The surveillance unit from RCDC confirmed the outbreak and initiated the outbreak investigation.[13,14]

Whole blood samples were collected in ethylenediaminetetraacetic acid (EDTA) vacutainers from outbreak investigation sites and were immediately wrapped with aluminum foil to prevent deterioration due to exposure to light. The samples were shipped to RCDC immediately maintaining a cold chain at 2–8 °C. All samples were immediately stored at −40 °C until tested.

The blood samples were collected and prepared as per the existing standard operating procedure of the Food and Nutrition Laboratory, RCDC. Briefly, the samples were thawed quickly and homogenized. A 200 µl vial of whole blood was mixed with a 100 µl internal solution followed by the addition of a 300 µl precipitation reagent and centrifuged at 14,000 rotations per minute for 5 minutes. In a light-protected vial, 250 µl neutralization reagent, 100 µl derivatization reagent, and 250 µl supernatant were mixed and incubated at 60 °C for 25 minutes. The samples were cooled to room temperature and then centrifuged at 14,000 rotations per minute for 2 minutes. The supernatant was filtered using a 0.2-micron syringe filter into the light-protected sample vial and stored at 2–4 °C. The reagents kits and consumables for the determination of thiamine and the high-performance liquid chromatography (HPLC) column were purchased from Chromsystem, Germany. HPLC with a fluorescent detector from Agilent Technologies, Inc. was used for the analysis of samples as per the method mentioned by Korner et al., (2009).[15] The mobile phase was delivered at a flow rate of 1.0 ml/min, the speed at which the detector was set; excitation at 375 nanometers and emission at 430 nanometers. Instrument control and data acquisition were performed using Chromeleon software.

For the quality control of the test results, the control samples level 1 and level 2 were purchased from Chromsystem. The lyophilized sample was prepared using HPLC grade water. Control samples were run for three times prior to testing. Prepared quality control samples were stored at −20 °C.

Data were imported into SPSS software for analysis. Data were presented as frequency, percentage, and mean wherever applicable. The ThDP level of <75.0 nmol/L was considered as deficiency as defined by the New York Academy of Sciences.[6] Analysis of variance was used to compare the differences between age groups and a *p*-value of <0.05 was considered significant.

Ethical clearance was not sought from the ethical board as all the data presented were secondary laboratory data obtained from an outbreak investigation. Confidentiality was strictly maintained and no patient identifying details were divulged. Administration clearance for the retrospective analysis of data was also sought from the RCDC.

Results

A total of four suspected PN outbreaks from private schools and monastic institutes were reported during the study period. All outbreaks were reported from the Eastern region of the country (Figure 1). Overall, there were 107 cases involved. Samples from the three outbreaks were collected except the one from the Trongsa District (Table 1). The common clinical signs and symptoms reported among the suspected PN patients included pain and swelling of lower extremities, weakness of lower limbs, foot drop, paresthesia, and numbness.

Table 1. Number, signs and symptoms of cases in the suspected peripheral neuropathy outbreaks reported in four districts of Bhutan during 2020 to 2021 (n=107)

District	Date of event	Initial number of suspected cases	Signs and symptoms
Pema Gatshsel	5 Nov 2020	8	Suspected peripheral neuropathy
Trongsa	25 Jan 2021	51	Pain and swelling of lower extremities, weakness of lower limbs, foot drop
Tashigang	20 Jan 2021	39	Paresthesia, numbness, swelling of lower limbs
Tashiyangtse	2 Dec 2021	9	Suspected peripheral neuropathy

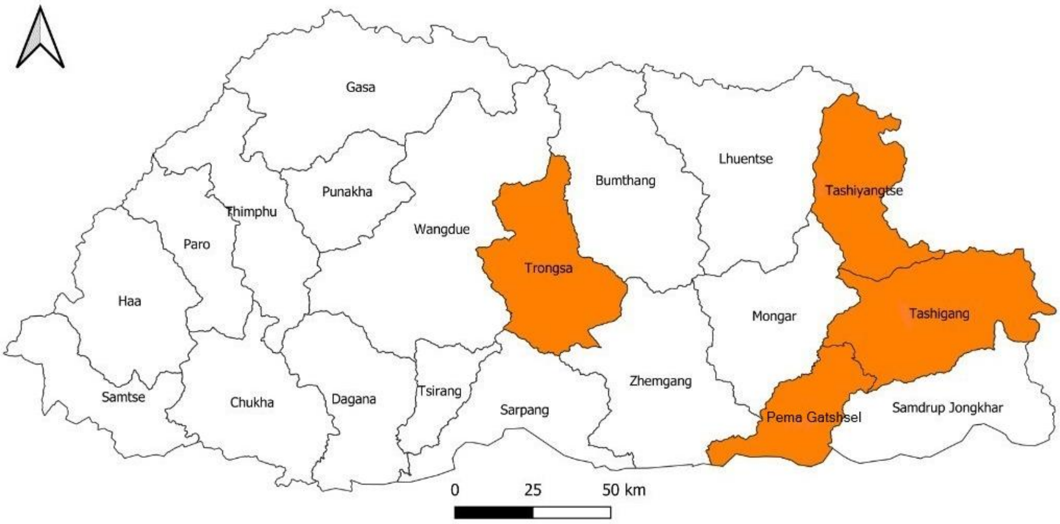

Figure 1. Four districts (highlighted) in Bhutan where suspected periphery neuropathy outbreaks were reported during 2020 to 2021

Among 56 cases in three suspected outbreaks, 34 blood samples were collected for laboratory tests. From the laboratory analysis of blood samples, thiamine deficiency was suspected to be the main cause of the outbreak. Of the 34 samples tested, 27 (79%) had ThDP levels <75.0 nmol/L and 7 (21%) had levels ≥75.0 nmol/L (Table 2). The mean ThDP level was 56.5 nmol/L and the mean age of those who had thiamine deficiency was 21 years (range 13–39).

Table 2. Characteristics and the whole blood ThDP levels of cases in suspected periphery neuropathy outbreak in three districts of Bhutan during 2020 to 2021 (n=34)

Outbreak district (year)	Mean age (years)	Gender n (%)		ThDP level n (%)	
		Male	Female	<75.0 nmol/L (Deficient)	>75.0 nmol/L (Adequate)
Pema Gatshsel (2020)	20	9 (45.0%)	11 (55.0%)	16 (80.0%)	4 (20.0%)
Tashigang (2021)	22	6 (100%)		4 (66.7%)	2 (33.3%)
Tashiyangtse (2021)	23	8 (100%)		7 (87.5%)	1 (12.5%)

Seventeen (50%) samples belonged to patients aged 10–20 years. Thiamine deficiency was found in 94.1%, 93.9% and 50% of those aged 10–20 years, 21–30 years and ≥30 years, respectively. The mean ThDP level was not significantly different among those in different age groups with p-value equal 0.79 (Table 3).

Table 3. The whole blood ThDP level of cases in suspected periphery neuropathy outbreak in three districts of Bhutan during 2020 to 2021, categorized by age group (n=34)

Age group (years)	Frequency n (%)	ThDP level (nmol/L) Mean (SD)	Thiamine deficiency, n (%)	*P*-value
10–20	17 (50.0%)	50.2 (24.6)	16 (94.1%)	0.79
21–30	15 (44.1%)	47.9 (23.6)	14 (93.3%)	
≥30	2 (5.9%)	174.7 (140.3)	1 (50.0%)	

Note: SD: Standard deviation

Discussion

Bhutan is experiencing a micronutrient deficiency problem. The National Nutrition Survey reported an anemia prevalence of 43.8% in children aged 6–23 months, 36.1% among females aged 10–49 years, 34.9% among women of reproductive age (15–49 years), 31.3% among adolescent girls, and 27.3% among pregnant women. Additionally, in 8% of the households surveyed, the residents had poor to borderline food consumption.[16] Realizing thiamine deficiency as a major problem among school-going children, the Nutrition Program, Department of Public Health recommended implementing a food fortification program in government feeding schools. The Ministry of Education shortly introduced fortified rice in 2017 in collaboration with the Ministry of Agriculture and Forests, the World Food Program, and the Ministry of Health. Fortified rice contains Vitamin A, B1 (Thiamine), B3 (Niacin), B6 (Pyridoxine), B9 (folic acid), B12 (cobalamin), iron and zinc.[17,18]

Globally, food fortification is recognized as the most effective intervention to combat micronutrient deficiencies.[19,20] Since the implementation of food fortification, no PN outbreaks have been reported from government feeding schools in Bhutan. However, the current PN outbreaks were reported from institutes and centers where fortified rice was not included in the daily meals. When staple crops such as polished rice or cassava are the main food items eaten by the population, thiamine deficiency is inevitable.[21] Dzed et al., (2015) reported that thiamine deficiency could be a huge problem in Bhutan as the intake of thiamine from dietary sources was very low.[11] The current PN outbreaks can be compared to the earlier sporadic PN outbreaks in the schools occurring before the implementation of food fortification where studies have attributed this to thiamine deficiency. An analysis of meals provided in feeding schools in Bhutan (2020) found that the meals served across the country were homogeneous with limited diversity, had a deficit in protein and most micronutrients, and non-vegetarian meals were served only 10 times (6.2%) out of 163 observations.[22] After the thiamine supplements were provided, the thiamine deficiency outbreak was resolved. Therefore, we conclude that the present outbreaks across three different districts could associate with thiamine insufficiency in regular diets.

The current outbreak was dominated by males (68%) and this could be because two of the three events occurred in institutes with high proportion of male, unlike in a previous study which found that all PN cases were female.[10] We also found that there was no significant difference in average ThDP level among the different age groups. Despite all the current outbreaks being reported from the Eastern region of the country, the limited sample size prevents generalizing thiamine outbreaks to this particular geographical location. However, the need for a national micronutrient survey is deemed necessary to create a baseline and for developing strategic programmatic interventions.

Limitations of the study

The main limitation of this study is that the history of individual cases, their symptoms and their potential risk factors were not available. Additionally, the limited number of samples tested prevented us from determining associated factors of developing thiamine deficiency.

Public Health Recommendations

Modifiable interventions such as dietary diversification, food fortification, including food processing and behavior change related to food procurement, and consumption practices and public awareness can help prevent micronutrient deficiencies.

Conclusion

This investigation found that of 34 samples tested for thiamine, 79% had ThDP levels <75.0 nmol/. Given the fact that micronutrient deficiency was established as the cause of the current PN outbreaks, we recommend that the supply of fortified rice across all the institutes (both government and private) in the country be initiated. Holistic approaches should be implemented to reduce the burden of micronutrient deficiencies in the country.

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Suggested Citation

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References

1. Smith TJ, Johnson CR, Koshy R, Hess SY, Qureshi UA, Mynak ML, et al. Thiamine deficiency disorders: a clinical perspective. Ann N Y Acad Sci. 2021 Aug;1498(1):9–28. doi:10.1111/nyas.14536.

2. Kliegman RM, Behrman RE, Jenson HB, Stanton BMD. Nelson textbook of pediatrics. 18th ed. Philadelphia (PA): Elsevier Health Sciences; 2007. Chapter 46.1, Thiamine (vitamin B1); p. 246–7.

3. Pawar RD, Balaji L, Grossestreuer AV, Thompson G, Holmberg MJ, Issa MS, et al. Thiamine supplementation in patients with alcohol use disorder presenting with acute critical illness: a nationwide retrospective observational study. Ann Intern Med. 2022 Feb;175(2):191–7. doi:10.7326/M21-2103.

4. Smith TJ, Hess SY. Infantile thiamine deficiency in South and Southeast Asia: an age-old problem needing new solutions. Nutr Bull. 2021 Mar;46(1):12–25. doi:10.1111/nbu.12481.

5. Bemeur C, Butterworth RF. Thiamin. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors, Modern nutrition in health and disease, 11th ed. Baltimore (MD): Lippincott Williams & Wilkins; 2014. p.317–24.

6. Whitfield KC, Bourassa MW, Adamolekun B, Bergeron G, Bettendorff L, Brown KH, et al. Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. Ann N Y Acad Sci. 2018 Oct;1430(1):3–43. doi:10.1111/nyas.13919.

7. Sauberlich H. Biochemical alterations in thiamine deficiency—their interpretation. The Am J Clin Nutr. 1967 Jun;20(6):528–42. doi:10.1093/ajcn/20.6.528.

8. Lu J, Frank EL. Rapid HPLC measurement of thiamine and its phosphate esters in whole blood. Clin Chem. 2008 May;54(5):901–6. doi:10.1373/clinchem.2007.099077.

9. Wieringa FT, Dijkhuizen MA, Berger J. Micronutrient deficiencies and their public health implications for South-East Asia. Curr Opin Clin Nutr Metab Care. 2019 Nov;22(6): 479–82. doi:10.1097/MCO.0000000000000603.

10. ten T, Dzed L, Thinley S, Tshomo D, Dechen K, mo Z, et al. Investigation of suspected peripheral neuropathy outbreak in Dechentsemo Central School, Thinleygang, Punakha. Public Health of Indonesia. 2016 Sep;2(3):118–24. doi:10.36685/phi.v2i3.76.

11. Dzed L, Dorji T, Pelzom D, Dhakal GP, Yangchen P, Wangmo K. Status of thiamin deficiency in boarding school children from seven districts in Bhutan with previous history of peripheral neuropathy outbreaks: a cohort study. Bhutan Health Journal. 2015;1(1):49–56. doi:10.47811/bhj.08.

12. Pradhan D, Bhandari P, Gyeltshen D. 587 Infantile beriberi as a cause of acute infantile encephalopathy in a referral hospital in Southern Bhutan. Arch Dis Child. 2021 Nov;106:A49. doi:10.1136/archdischild-2021-rcpch.84.

13. Chhetri V, Pokhrel HP, Dorji T. A review on foodborne disease outbreaks in Bhutan. WHO South East Asia J Public Health. 2021 Jul–Dec;10(2):101–4. doi:10.4103/WHO-SEAJPH.WHO-SEAJPH_117_21.

14. Chhetri V, Dorji T, Monger A. Foodborne disease outbreaks linked to consumption of bakery products in Bhutan. Science Technology and Engineering Journal (STEJ). 2022;8(1):30–8.

15. Korner RW, Vierzig A, Roth B, Muller C. Determination of thiamin diphosphate in whole blood samples by high-performance liquid chromatography—a method suitable for pediatric diagnostics. J Chromatogr B Analyt Technol Biomed Life Sci. 2009 Jul 1;877(20–21):1882–6. doi:10.1016/j.jchromb.2009.05.013.

16. 2015 national nutrition survey (NNS). Thimphu (BT): Nutrition Program, Department of Public Health, Ministry of Health; 2015. 139 p.

17. Andrade JE, Ali ANMA, Chowdhury R, Crost B, Hoffmann V, Mustafa S, et al. Rice fortification in Bangladesh: technical feasibility and regulatory requirement for introducing rice fortification in public modern storage/distribution of fortified rice through PFDS channels. Washington: International Food Policy Research Institute (IFPRI); 2021 Aug. 116 p. doi:10.2499/p15738coll2.134540. IFPRP Working Paper 10.

18. Tamang PS, Dhakal GP, Bajgai GP, Chhetri V, Dzed L, Pokhrel HP. Investigation of oral lesion outbreak among two boarding school students in Thimphu. Asian Journal of Dietetics. 2021;3(1):19–22.

19. Keats EC, Neufeld LM, Garrett GS, Mbuya MNN, Bhutta ZA. Improved micronutrient status and health outcomes in low- and middle-income countries following large-scale fortification: evidence from a systematic review and meta-analysis. Am J Clin Nutr. 2019 Jun 1;109(6):1696–708. doi:10.1093/ajcn/nqz023.

20. Mkambula P, Mbuya MNN, Rowe LA, Sablah M, Friesen VM, Chadha M, et al. The unfinished agenda for food fortification in low- and middle-income countries: quantifying progress, gaps and potential opportunities. Nutrients. 2020 Jan 29;12(2):354. doi: 10.3390/nu12020354.

21. Gomes F, Bergeron G, Bourassa MW, Fischer PR. Thiamine deficiency unrelated to alcohol consumption in high-income countries: a literature review. Ann N Y Acad Sci. 2021 Aug;1498(1):46–56. doi: 10.1111/nyas.14569.

22. Sherpa PL, Pokhrel HP, Dzed L, Deki K. Nutritive analysis of school meals: an investigation of a one-day meal provided in feeding schools of bhutan. Asian Journal of Dietetics. 2020;2(2):59–64.