



HAL
open science

Clinical diagnosis, outcomes and treatment of thiamine deficiency in a tertiary hospital

François Mifsud, Diane Messenger, Anne-Sophie Jannot, Benoît Védie, Nadia Aissaoui Balanant, Tigran Poghosyan, Edouard Flamarion, Claire Carette, Léa Lucas-Martini, Sébastien Czernichow, et al.

► To cite this version:

François Mifsud, Diane Messenger, Anne-Sophie Jannot, Benoît Védie, Nadia Aissaoui Balanant, et al.. Clinical diagnosis, outcomes and treatment of thiamine deficiency in a tertiary hospital. *Clinical Nutrition*, 2022, 41 (1), pp.33-39. 10.1016/j.clnu.2021.10.021 . hal-03560923

HAL Id: hal-03560923

<https://hal.science/hal-03560923>

Submitted on 5 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Clinical diagnosis, outcomes and treatment of thiamine deficiency in a tertiary hospital.

François Mifsud^{a,b}, Diane Messenger^c, Anne-Sophie Jannot^{b,d}, Benoît Védie^{b,e}, Nadia Aissaoui Balanant^{b,f}, Tigran Poghosyan^{b,g}, Edouard Flamarion^{b,h}, Claire Carette^{a,b}, Léa Lucas-Martini^c, Sébastien Czernichow^{a,b}, Claire Rives-Lange^{a,b}

- a. Hôpital Européen Georges Pompidou, Service de Nutrition, Centre Spécialisé Obésité (CSO) Ile-de-France-Sud, APHP-centre, Université de Paris, France.
- b. Université de Paris, F-75015, Paris, France
- c. Hôpital Cognaq-Jay, Service de Nutrition, Paris, France
- d. Hôpital Européen Georges Pompidou, Service d'Informatique, Biostatistiques et Santé Publique, APHP-centre, Université de Paris, France.
- e. Hôpital Européen Georges Pompidou, Service de Biochimie, APHP-centre, Université de Paris, France.
- f. Hôpital Européen Georges Pompidou, Service de médecine intensive Réanimation, APHP-centre, Université de Paris, France.
- g. Hôpital Européen Georges Pompidou, Service de chirurgie digestive, APHP-centre, Université de Paris, France.
- h. Hôpital Européen Georges Pompidou, Service de médecine interne, APHP-centre, Université de Paris, France.

Corresponding author: Claire Rives-Lange, electronic address: claire.rives-lange@aphp.fr

1 **Abstract**

2 **Background:** Acute thiamine deficiency can occur in patients with or without history of
3 alcohol abuse and can lead to life-threatening complications. Clinical diagnosis is challenging,
4 often resulting in delayed recognition and treatment. Patients may present with heterogenous
5 symptoms, more diverse than the historical neurological description. Cerebral MRI can
6 contribute to the diagnosis in patients with neurological signs but it is not always feasible in
7 emergency settings. Prompt parenteral supplementation is required to obtain the improvement
8 of symptoms and avoid chronic complications.

9 **Aims:** To describe the clinical presentation of reported cases of thiamine deficiency, assess
10 prescription and results of cerebral imaging, review treatments that had been prescribed in
11 accordance or not with available guidelines, and study the short-term outcome of these
12 patients.

13 **Methods:** This is a monocentric retrospective analysis of all reported cases of thiamine
14 deficiency in a French tertiary hospital between January 1st 2008 and December 31th 2018.

15 **Results:** Fifty-six cases were identified during the study period. Forty-five (80%) patients had
16 a history of alcohol abuse. Most patients were diagnosed based on neurological symptoms but
17 non-specific and digestive symptoms were frequent. Thirty-four percent of patients fulfilled
18 clinical criteria for malnutrition. A brain MRI was performed in 54% of patients and was
19 abnormal in 63% of these cases. Eighty-five percent of patients were treated by parenteral
20 thiamine administration and the supplementation was continued orally in 55% of them. The
21 majority of patients initially received 1000 mg daily of IV thiamine but the dose and duration
22 of thiamine supplementation were variable. At the time of discharge, partial or complete
23 improvement of symptoms was noted in 59% of patients.

24 **Conclusion:** This study highlights the clinical and radiological heterogeneity of thiamine
25 deficiency. These observations should encourage starting thiamine supplementation early in

26 patients with risk factors or suggestive symptoms even in non-alcoholic patients, and
27 underline the importance of early nutritional support.

28

29 **Keywords:** Thiamine deficiency, Wernicke's Encephalopathy, Malnutrition, Alcohol-Related
30 Disorders.

31 **Introduction**

32 Thiamine is an important cofactor for several enzymes that are essential for energy
33 metabolism including the Krebs cycle. It also has a critical protective role in neuronal
34 structure and function, both in the central nervous system and in peripheral nerves.(1) In case
35 of insufficient intake, decrease of intestinal absorption or increased renal excretion, clinical
36 manifestations of thiamine deficiency can develop in only a few weeks especially in situations
37 of high carbohydrate intake, chronic alcohol consumption, or when the metabolic demand is
38 high.(2) Thiamine deficiency can rapidly lead to irreversible neurological damage, heart
39 disease and life-threatening complications.(3,4) Prompt diagnosis and supplementation are
40 thus required to limit short- and long-term consequences. However, diagnosis of thiamine
41 deficiency is challenging and several autopsy studies suggest that it often remains
42 undiagnosed during life. (5–7) The most frequent form of acute or subacute thiamine
43 deficiency is Wernicke’s encephalopathy (WE), historically defined by a triad of gait ataxia,
44 nystagmus or ophthalmoplegia and global confusion. However in a 1986 study, only 16% of
45 patients with confirmed WE presented with the classical clinical triad and 19% had none of
46 them.(6) To improve the identification of patients with WE, Caine and al. modified the
47 classical triad to propose an operational criteria with better sensitivity and specificity (8) : this
48 criteria require only two of the four following signs : 1- dietary deficiency or malnutrition ; 2-
49 oculomotor abnormalities ; 3- cerebellar dysfunction ; 4- either an altered mental state or mild
50 memory impairment. As measurement of blood thiamine does not necessarily reflect the
51 vitamin store and is not performed urgently, it is recommended to rely on clinical criteria to
52 start treatment and then assess clinical evolution.(9)

53 There is currently no formal evidence on the optimal administration of thiamine in patients
54 with thiamine deficiency. Because of the frequent decreased intestinal absorption and limited
55 biodisponibility of orally administered thiamine, it is widely recommended to use the IV

56 route, at least during the initial phase.(9) However, there is no evidence available regarding
57 the optimal dosage and duration of treatment.(10) A Cochrane review concluded that a dose
58 of 200 mg per day was more effective than lower doses on the neurologic and cognitive
59 symptoms. (11,12) Many authors recommend higher doses of 50 to 1000 mg per injection per
60 day, and based on the 96 min half-life of free thiamine in the blood multiple daily injections
61 are now recommended, but their superiority has not been demonstrated to date.(13–17) The
62 benefit of a switch to an oral thiamine supplementation and the total duration of treatment has
63 never been proven but it is considered good practice to continue the latter for at least several
64 weeks, as the tolerance is generally excellent.(18,19) Given the difficulty of the diagnosis and
65 the uncertainties in treatment modalities, the aim of this study was to review all cases of
66 thiamine deficiency reported in a tertiary hospital in France over a 10 years period. The
67 objectives were to describe the clinical presentation of cases as well as imaging results,
68 review treatments that had been prescribed in accordance or not with available guidelines, and
69 study the short-term outcome of these patients.

70

71 **Patients and methods**

72 This is a retrospective analysis of all cases of thiamine deficiency reported in health medical
73 records of the Georges Pompidou European Hospital in Paris (France) between January 1st
74 2008 and December 31th 2018. Cases were identified by searching electronic medical charts
75 over this period for the corresponding ICD-10 diagnosis encoded by physicians. All medical
76 charts were then manually reviewed by an investigator to confirm diagnosis and collect data
77 from medical history, physical examination, lab and imaging results, treatment and clinical
78 evolution during the hospital stay. Nutritional status was determined by body mass index
79 (kg/m^2) and weight loss percent criteria. The diagnosis of malnutrition was established
80 retrospectively based on the Global Leadership Initiative on Malnutrition (GLIM) that

81 requires at least one etiologic criterion among reduced food intake or assimilation,
82 inflammation or disease burden, and at least one phenotypic criterion among non-volitional
83 weight loss, low BMI and reduced muscle mass.(20) Phenotypic criteria were assessed using
84 BMI and percent weight loss. Moderate malnutrition was defined by weight loss of 5 to 10
85 percents within the past 6 months or 10 to 20 percents over more than 6 months and/or BMI
86 $<20 \text{ kg/m}^2$ (if age <70 years) or BMI $<22 \text{ kg/m}^2$ (if age >70). Severe malnutrition was defined
87 by weight loss greater than 10 percents within the past 6 months or greater than 20 percents
88 over more than 6 months and/or BMI $<18.5 \text{ kg/m}^2$ (if age <70 years) or BMI $<20 \text{ kg/m}^2$ (if
89 age >70). (20) The study protocol was approved by the local ethic committee (CERAPHP.5)

90

91 **Statistical analysis**

92 The collected characteristics are reported using median, 25th (Q1) and 75th (Q3) percentiles for
93 quantitative variables. For categorical variables counts and percentages are reported.
94 Differences between groups were tested with a Fischer's exact test for categorial variables and
95 with the Mann-Whitney test for quantitative variables. The association between studied
96 variables and improvement of symptoms was tested by univariate logistic regression; odds
97 ratios and their confidence intervals were calculated to quantify their prognostic impact.
98 Quantitative variables were dichotomized to plot the corresponding odds ratios along with
99 binary variables' odds ratios. The cut-off was the median value for age, number of infusions
100 and duration of supplementation. For BMI, oral and IV doses the cut-offs were respectively
101 $\geq 20 \text{ kg/m}^2$ and $\geq 1000 \text{ mg}$. The absence of significant association with symptoms
102 improvement was also verified when these variables were analyzed as continuous. All
103 statistical tests were performed in R statistical software at a 95% confidence level.(21)

104 **Results**

105 The electronic search identified 86 patients with a diagnosis of thiamine deficiency encoded
106 during the study period. In 30 patients, individual review of the medical charts found no
107 justification for this encoding and did not confirm suspicion of thiamine deficiency. Fifty-six
108 cases of thiamine deficiency were identified, from 8 different departments including the
109 intensive care unit. The total number of reported cases varied from 2 to 8 per year and was
110 stable over the study period (**supplementary figure 1**). All patients had at least two of the
111 four practical criteria as defined by Caine and al for the diagnosis of WE.(8) The repartition of
112 patients in the different hospital departments is shown in **supplementary table 1**.

113

114 The characteristics and reasons for hospitalization of all cases are shown in **table 1**. Patients
115 were predominantly males over 50 years old. The main reason for admission was neurological
116 symptoms, followed by general status alteration, a very unspecific symptom. One third of
117 patients had a known chronic liver disease or cirrhosis and two thirds had abnormal liver test
118 results at admission. Eighty-eight percent of patients had at least one comorbidity (liver, lung,
119 heart, kidney, pancreatic, neurological or psychiatric disease). Eighty percent of patients had a
120 history of alcohol abuse. History of bariatric surgery was found in 4 of the 11 non-alcoholic
121 patients. Twenty five percents of patients met the GLIM criteria for malnutrition, all of them
122 in the group of patients with history of alcohol abuse. Sixteen percents had severe
123 malnutrition. Hypoalbuminemia was found in 73% of cases. Hyponatremia and hypokalemia
124 were frequent at admission (25% and 40% respectively), the latter occurred more specifically
125 in patients with alcohol abuse. The detailed symptoms of patients at admission are described
126 in **table 2**. All patients had at least one neurologic or psychiatric symptom. The elements of
127 the historical WE triad were the most frequent neurological symptoms but no patient was
128 reported to have the three elements simultaneously. Nystagmus was reported in 36% of

129 patients. No ocular motor palsy was reported at admission but four patients complained of
130 diplopia. Ocular motor paresis was likely present in these patients but could have been missed
131 because the examination was not performed by an ophthalmologist or neuro-ophthalmologist.
132 Eighty-four percents of patients were initially diagnosed with WE and 16% with Korsakoff
133 syndrome. Digestive symptoms however were present in 25% of cases.

134

135 A brain MRI was performed in 54% of cases (**table 3**). The MRI was abnormal in 63% of
136 these patients. The interpretation mentioned lesions typical of WE in 8 of the 30 MRIs, and
137 typical of Korsakoff syndrome in 2 of them. One third of MRIs showed a combination of non-
138 specific anomalies and one third were considered normal. A brain CT was performed in 50%
139 of cases and was normal in 75% of those patients.

140

141 Eighty-four percent of patients were treated by parenteral thiamine administration (**table 4**).
142 Thiamine supplementation was continued orally after the period of IV administration in sixty-
143 six percent of them. The majority of patients received infusions of 1000 mg. The prescribed
144 IV dose was higher among patients with history of alcohol abuse. The total number of
145 infusions ranged from 1 to 40. The oral supplementation was prescribed for a median time of
146 19 days. The oral thiamine dose was heterogenous, predominantly of 1000 mg in patients with
147 history of alcohol abuse and 500 mg in patients without. The duration of the hospital stay was
148 shorter in non-alcoholic patients. At the time of discharge, partial or complete improvement of
149 symptoms was noted in 59% of patients. The prognostic value of relevant clinical,
150 radiological and therapeutic variables was tested by logistic regression on symptoms
151 improvement. Odds ratios for symptoms improvement after thiamine supplementation and
152 their confidence intervals are shown in **figure 1**. Apart from serum albumin below 30 g/L,
153 none of these variables were significantly associated with a better outcome. Abnormal brain

154 MRIs seemed associated with a lesser chance of symptoms improvement but the effect was at
155 the limit of statistical significance.

156

157 **Discussion:**

158 We present a retrospective analysis of all reported cases of thiamine deficiency in a French
159 tertiary hospital. All reported patients had neurological or psychiatric symptoms. As only
160 diagnosed and electronically encoded cases were retrieved, this study does not allow to
161 estimate the prevalence of thiamine deficiency in this population. Given that the prevalence of
162 WE was estimated around 1% on autopsy studies (5,22), the annual number of diagnosed
163 cases was low in comparison with the 253659 hospital stays over the study period in this
164 center. This suggests that thiamine deficiency remains underdiagnosed even in this tertiary
165 care setting mainly because of insidious symptoms and poor awareness among physicians.(23)
166 Almost two thirds of thiamine deficiency cases were diagnosed in the internal medicine
167 department; patients with unexplained neurological symptoms or alcohol misuse are mostly
168 referred to this unit.

169 Alcohol intake significantly reduces thiamine absorption in the gut and is often associated
170 with malnutrition.(24) Thiamine deficiency is commonly suspected among alcohol-dependent
171 subjects, but can also occur in non-alcoholic patients : hundreds of cases have been reported
172 in patients with no history of alcohol use, mainly in clinical settings involving malnutrition,
173 digestive and non-digestive cancer, bariatric surgery, gastro-intestinal diseases, hyperemesis
174 of pregnancy, prolonged parenteral nutrition without thiamine supplementation, AIDS, bone
175 marrow transplantation, chronic kidney disease and genetic disorder of thiamine
176 metabolism.(25–38) The vast predominance of alcohol dependent patients in our series could
177 suggest that thiamine deficiency is particularly underdiagnosed outside of this population. In
178 spite of the important increase in the number of bariatric surgeries during the study period we

179 did not find a significant increase of thiamine deficiency cases. Nonetheless 4 of the 11 cases
180 unrelated to alcohol abuse had history of bariatric surgery, confirming the vulnerability of
181 these patients.(39)

182 The neuropsychological manifestations of thiamine deficiency are known to be more diverse
183 than the classic triad.(22,40) Although some neuro-ophtalmologic signs may have been
184 missed by the non-specialized physicians performing the initial examination, nystagmus was
185 found in 36% of cases. This confirms that nystagmus is one of the most frequent and early
186 sign of thiamine deficiency.(41–46) It is the most common ocular finding. The most frequent
187 type is an early horizontal nystagmus, followed by the installation of a gaze-holding failure.
188 Position upbeat nystagmus has also been described and can convert to a permanent downbeat
189 nystagmus.(47,48) Vestibular reflexes should thus be tested at the bedside in every patient
190 with a clinical history compatible with early WE. Nystagmus is easy to detect and does not
191 depend on the patient’s ability to stand. Patients with diplopia should undergo a detailed
192 evaluation including a cross-cover test or a red glass test to uncover a possible abducens
193 paresis.(49,50) Thiamine deficiency can also cause peripheral neuropathy resulting in
194 polyneuritis, as well as non-specific memory disorders. Non-neurological consequences such
195 as heart failure (with high-output heart failure in the classic form of the “wet Beri-Beri”),
196 gastrointestinal manifestations, lactic acidosis or isolated coma have also been frequently
197 reported.(3,51) In this study the initial clinical description of cases is indeed heterogeneous
198 and demonstrates that the diagnosis should be considered in patients admitted for non-specific
199 reasons such as general status alteration or fall, when associated with history of alcohol abuse
200 or malnutrition. However, it is remarkable that only 25% of cases fulfilled the GLIM criteria
201 for malnutrition, suggesting that manifestations of thiamin deficiency can appear before
202 significant weight loss occurs. Nevertheless, the high frequency of hypoalbuminemia attests
203 of the severity of pre-existing diseases and their potential impact on the nutritional status.

204 Indeed, a serum albumin below 30g/L at admission was associated with significantly lower
205 chances of clinical improvement. Digestive symptoms were frequent and could be related to
206 the numerous comorbidities or to a specific gastro-intestinal manifestation of thiamine
207 deficiency that has been suggested by previous works.(51) Vomiting or malabsorption also
208 contribute directly to the occurrence of thiamine deficiency. Only one patient with heart
209 failure was reported; patients with an unexplained cardiomyopathy and a poor nutritional
210 status should however be evaluated for thiamine deficiency.(52) Five patients presented with
211 concomitant magnesium deficiency, which might have been implicated in the occurrence of
212 WE. Magnesium has been reported to be an essential cofactor of thiamine into its active
213 diphosphate and triphosphate forms.(53) Even if thiamine blood concentration is neither
214 necessary nor sufficient for the diagnosis, the lack of a systematic thiamine measurement
215 before supplementation is a limitation of our study. This underlines that clinicians do not use
216 blood thiamine measurement for the practical diagnosis in our center, probably due the long
217 delivery time of results.

218 WE can also be confirmed by brain magnetic resonance imaging (MRI) : specific alterations
219 of the thalami, mammillary bodies, tectal plate, and periaqueductal area have been described
220 on T2 and fluid-attenuated inversion recovery (FLAIR) sequences, and are often associated
221 with non-specific or “atypical” signal alterations of the brain, forebrain, cerebellum and
222 corpus callosum.(54–56) Mamillary body atrophy is a relatively specific abnormality
223 described on MRI: it has been identified in approximately 80 percent of chronic Wernicke's
224 encephalopathy and was not founded in controls or in patients with Alzheimer disease.(57)
225 Mamillary body atrophy can be detected within one week of the onset of acute WE.(58) A
226 study comparing 15 patients with acute WE with 15 asymptomatic alcohol abusers and 15
227 controls reported sensitivity of brain MRI of 53% and specificity of 93% for the diagnosis of
228 WE but the results were not compared to autopsy.(59) Abnormal T2 signal could disappear

229 within 2 days after treatment with thiamine.(58) On the contrary brain computed tomography
230 (CT) has a low sensitivity to detect WE. In this series, brain MRI was performed in only 54%
231 of cases in spite of its previously reported utility. Sixty-three percents of these MRIs were
232 abnormal but only 8 showed specific anomalies allowing to formally confirm of the diagnosis.
233 The lack of diagnostic value of MRI in this series emphasizes the difficulty of this diagnosis.
234 Although brain CT was often performed, mainly to rule out an alternative diagnosis at
235 admission, it was normal in 75% of patients. This confirms the low sensitivity of CT scan in
236 this indication. Although at the limit of statistical significance the presence of lesions on the
237 brain MRI was associated with a lower chance of clinical improvement after treatment.
238 If not rapidly treated, WE can progress to permanent damages of mamillary bodies and
239 diencephalon causing amnesia, confabulations and dementia known as Korsakoff
240 syndrome.(60) The important heterogeneity in the treatment strategies chosen inside a single
241 center underlines the need for more consensual and widely communicated guidelines across
242 medical specialties. The current lack of clinical trials to validate the administration route and
243 dosage of thiamine supplementation is the main obstacle to such a consensus. Parenteral
244 administration leads to high cerebral concentrations due a to a passive blood-brain barrier
245 passage and is the initial recommended route. The actual recommendations to favor high dose
246 infusions in alcohol-dependent patients were followed in a majority of cases but the dose was
247 more variable outside this group. The duration of the IV and oral supplementation was highly
248 heterogenous and reflects the lack of current evidence on this matter. These observations also
249 confirm the need for intra-hospital referrals or teams specialized in nutritional medicine, able
250 to provide homogenous management advice across the different specialty wards.(23) The low
251 cost and safety of thiamine argue for widespread supplementation, along with other vitamins
252 or magnesium replacement in alcohol abusers and others patients prone to thiamine
253 deficiency.

254 The retrospective collection of clinical data was the main study's limit and prevented access
255 to a systematic and detailed evaluation of neurological symptoms and particularly eye
256 movements. We also lacked statistical power to identify predictors of symptoms reversibility
257 after thiamine supplementation. As expected, patients initially diagnosed with Korsakoff
258 rarely saw an improvement of their neurological symptoms. The administration route,
259 duration and dose were not associated with the probability of symptoms improvement in this
260 series, but the statistical power was limited by the small number of patients.

261

262 **Conclusion**

263 This retrospective review of thiamine deficiency cases highlights the clinical and radiological
264 heterogeneity of this under-diagnosed but life-threatening condition. The difficulty of
265 diagnosis should lead to starting thiamine supplementation in patients with risk factors or
266 suggestive symptoms, especially in patients with an history of alcohol abuse, as an early
267 supplementation may allow a regression of symptoms. Evidence-based guidelines widely
268 spread across medical specialties are strongly needed to validate and unify the management of
269 this medical emergency.

270

271 **Funding statement:** this research did not receive any specific grant from funding agencies in
272 the public, commercial, or not-for-profit sectors.

273

274 **Conflicts of interest:** the authors declare that they have no competing interests.

275

276 **Author contribution:** François Mifsud: Investigation, Formal analysis, Writing - Original
277 Draft. Diane Messenger: Investigation, Data Curation. Anne-Sophie Jannot: Investigation.
278 Benoît Védie: Resources, Writing - Review & Editing. Nadia Aissaoui Balanant: Resources,

- 279 Writing - Review & Editing. Tigran Poghosyan: Resources, Writing - Review & Editing.
- 280 Edouard Flamarion : Resources, Writing - Review & Editing. Claire Carette: Resources,
- 281 Writing - Review & Editing. Léa Lucas-Martini: Supervision, Writing - Review & Editing.
- 282 Sébastien Czernichow: Supervision, Writing - Review & Editing. Claire Rives-Lange:
- 283 Supervision, Writing - Review & Editing.

References

1. Frank LL. Thiamin in Clinical Practice. *Journal of Parenteral and Enteral Nutrition*. 2015;39(5):503–20.
2. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *The Lancet Neurology*. 2007 May 1;6(5):442–55.
3. Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med*. 2007 Dec;50(6):715–21.
4. Akhouri S, Kuhn J, Newton EJ. Wernicke-Korsakoff Syndrome. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2021
5. Harper C, Fornes P, Duyckaerts C, Lecomte D, Hauw JJ. An international perspective on the prevalence of the Wernicke-Korsakoff syndrome. *Metab Brain Dis*. 1995 Mar;10(1):17–24.
6. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. *J Neurol Neurosurg Psychiatry*. 1986 Apr;49(4):341–5.
7. Kohnke S, Meek CL. Don't seek, don't find: The diagnostic challenge of Wernicke's encephalopathy. *Ann Clin Biochem*. 2021 Jan;58(1):38–46.
8. Caine D, Halliday GM, Kril JJ, Harper CG. Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg Psychiatry*. 1997 Jan;62(1):51–60.
9. Galvin R, Bråthen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *European Journal of Neurology*. 2010;17(12):1408–18.
10. Onishi H, Uchida N, Itami K, Sato M, Tamura S, Kurosaki A, et al. Subclinical thiamine deficiency: What is the most appropriate method of diagnosis and treatment? *Palliat Support Care*. 2020 Oct;18(5):614–6.
11. Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. *Alcohol Clin Exp Res*. 2001 Jan;25(1):112–6.
12. Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse. *Cochrane Database Syst Rev*. 2004;(1):CD004033.

13. Tallaksen CM, Sande A, Bøhmer T, Bell H, Karlsen J. Kinetics of thiamin and thiamin phosphate esters in human blood, plasma and urine after 50 mg intravenously or orally. *Eur J Clin Pharmacol*. 1993;44(1):73–8.
14. Cook CCH, Hallwood PM, Thomson AD. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol*. 1998 Jul 1;33(4):317–36.
15. Boulanger AS, Paquette I, Létourneau G, Richard-Devantoy S. Wernicke encephalopathy: Guiding thiamine prescription. *Encephale*. 2017;43(3):259–67.
16. Chataway J, Hardman E. Thiamine in Wernicke’s syndrome--how much and how long? *Postgraduate Medical Journal*. 1995 Apr 1;71(834):249–249.
17. Nakamura ZM, Tatreau JR, Rosenstein DL, Park EM. Clinical Characteristics and Outcomes Associated With High-Dose Intravenous Thiamine Administration in Patients With Encephalopathy. *Psychosomatics*. 2018;59(4):379–87.
18. Latt N, Dore G. Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders. *Internal Medicine Journal*. 2014;44(9):911–5.
19. Shoaib S, Hyder M, May M. An Atypical Long-Term Thiamine Treatment Regimen for Wernicke Encephalopathy. *Fed Pract*. 2020 Sep;37(9):405–9.
20. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr*. 2019 Feb;38(1):1–9.
21. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2017.
22. Torvik A. Wernicke’s encephalopathy--prevalence and clinical spectrum. *Alcohol Alcohol Suppl*. 1991;1:381–4.
23. Peck NM, Bania TC, Chu J. Low rates of thiamine prescribing in adult patients with alcohol-related diagnoses in the emergency department. *Am J Drug Alcohol Abuse*. 2021 Mar 29;1–7.
24. Thomson AD, Baker H, Leevy CM. Patterns of 35S-thiamine hydrochloride absorption in the malnourished alcoholic patient. *J Lab Clin Med*. 1970 Jul;76(1):34–45.
25. Oudman E, Wijnia JW, Oey MJ, van Dam M, Postma A. Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports. *J Neurol Sci*. 2021 Jul 15;426:117482.
26. Scalzo SJ, Bowden SC, Ambrose ML, Whelan G, Cook MJ. Wernicke-Korsakoff syndrome not related to alcohol use: a systematic review. *J Neurol Neurosurg Psychiatry*. 2015 Dec;86(12):1362–8.

27. Isenberg-Grzeda E, Rahane S, DeRosa AP, Ellis J, Nicolson SE. Wernicke-Korsakoff syndrome in patients with cancer: a systematic review. *The Lancet Oncology*. 2016;17(4):e142–8.
28. Iannelli A, Addeo P, Novellas S, Gugenheim J. Wernicke’s encephalopathy after laparoscopic Roux-en-Y gastric bypass: a misdiagnosed complication. *Obes Surg*. 2010 Nov;20(11):1594–6.
29. Tang L, Alsulaim HA, Canner JK, Prokopowicz GP, Steele KE. Prevalence and predictors of postoperative thiamine deficiency after vertical sleeve gastrectomy. *Surg Obes Relat Dis*. 2018;14(7):943–50.
30. Singh S, Kumar A. Wernicke encephalopathy after obesity surgery: a systematic review. *Neurology*. 2007 Mar 13;68(11):807–11.
31. Chiossi G, Neri I, Cavazzuti M, Basso G, Facchinetti F. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. *Obstet Gynecol Surv*. 2006 Apr;61(4):255–68.
32. Butterworth RF, Gaudreau C, Vincelette J, Bourgault A-M, Lamothe F, Nutini A-M. Thiamine deficiency and wernicke’s encephalopathy in AIDS. *Metab Brain Dis*. 1991 Dec 1;6(4):207–12.
33. Ihara M, Ito T, Yanagihara C, Nishimura Y. Wernicke’s encephalopathy associated with hemodialysis: report of two cases and review of the literature. *Clinical Neurology and Neurosurgery*. 1999 Jun 1;101(2):118–21.
34. Oudman E, Wijnia JW, Oey M, van Dam M, Painter RC, Postma A. Wernicke’s encephalopathy in hyperemesis gravidarum: A systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2019 May;236:84–93.
35. Divya MB, Kubera NS, Jha N, Jha AK, Thabah MM. Atypical neurological manifestations in Wernicke’s encephalopathy due to hyperemesis gravidarum. *Nutr Neurosci*. 2021 May 27;1–6.
36. Long L, Cai X-D, Bao J, Wu A-M, Tian Q, Lu Z-Q. Total parenteral nutrition caused Wernicke’s encephalopathy accompanied by wet beriberi. *Am J Case Rep*. 2014;15:52–5.
37. Kono S, Miyajima H, Yoshida K, Togawa A, Shirakawa K, Suzuki H. Mutations in a thiamine-transporter gene and Wernicke’s-like encephalopathy. *N Engl J Med*. 2009 Apr 23;360(17):1792–4.
38. Oudman E, Wijnia JW, Oey MJ, van Dam M, Postma A. Wernicke’s encephalopathy in Crohn’s disease and ulcerative colitis. *Nutrition*. 2021 Jun;86:111182.

39. Zheng L. Wernicke Encephalopathy and Sleeve Gastrectomy: A Case Report and Literature Review. *Am J Ther.* 2016 Dec;23(6):e1958–61.
40. Ahmed S, Akadiri TV, Ata S, Ayub S. An Unusual Presentation of Catatonia in Non-alcoholic Wernicke Encephalopathy. *Cureus.* 2021 Jan 6;13(1):e12537.
41. DeWardener HE, Lennox B. Cerebral beriberi (Wernicke's encephalopathy); review of 52 cases in a Singapore prisoner-of-war hospital. *Lancet.* 1947 Jan 4;1(6436):11–7.
42. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemp Neurol Ser.* 1971;7:1–206.
43. Kattah JC, Dhanani SS, Pula JH, Mantokoudis G, Tehrani ASS, Toker DEN. Vestibular signs of thiamine deficiency during the early phase of suspected Wernicke encephalopathy. *Neurol Clin Pract.* 2013 Dec;3(6):460–8.
44. Kattah JC. Early Signs of Thiamine Deficiency: A Case Report. *Ann Intern Med.* 2020 Jul 7;173(1):72–3.
45. Ikeda K, Yano H, Higa T, Kinjo M. Nystagmus in non-alcoholic Wernicke encephalopathy. *BMJ Case Reports CP.* 2021 Feb 1;14(2):e241130.
46. Wiggl B, Kapitz S, Ahlhelm F, Tarnutzer AA. Early recognition of thiamine deficiency: ocular motor deficits in a patient with nutritional deprivation due to persistent antibiotic-related nausea. *Infection.* 2020 Feb 1;48(1):137–40.
47. Kattah JC, Tehrani AS, du Lac S, Newman-Toker DE, Zee DS. Conversion of upbeat to downbeat nystagmus in Wernicke encephalopathy. *Neurology.* 2018 Oct 23;91(17):790–6.
48. Kattah JC, McClelland C, Zee DS. Vertical nystagmus in Wernicke's encephalopathy: pathogenesis and role of central processing of information from the otoliths. *J Neurol.* 2019 Sep 1;266(1):139–45.
49. Leigh RJ, Zee DS. *The Neurology of Eye Movements. The Neurology of Eye Movements.* Oxford University Press.
50. Isen DR, Kline LB. Neuro-ophthalmic Manifestations of Wernicke Encephalopathy. *Eye Brain.* 2020;12:49–60.
51. Donnino M. Gastrointestinal Beriberi: A Previously Unrecognized Syndrome. *Ann Intern Med.* 2004 Dec 7;141(11):898–9.
52. Jain A, Mehta R, Al-Ani M, Hill JA, Winchester DE. Determining the Role of Thiamine Deficiency in Systolic Heart Failure: A Meta-Analysis and Systematic Review. *J Card Fail.* 2015 Dec;21(12):1000–7.

53. McLean J, Manchip S. Wernicke's encephalopathy induced by magnesium depletion. *Lancet*. 1999 May 22;353(9166):1768.
54. Suzuki S, Ichijo M, Fujii H, Matsuoka Y, Ogawa Y. Acute Wernicke's encephalopathy: comparison of magnetic resonance images and autopsy findings. *Intern Med*. 1996 Oct;35(10):831–4.
55. Manzo G, De Gennaro A, Cozzolino A, Serino A, Fenza G, Manto A. MR Imaging Findings in Alcoholic and Nonalcoholic Acute Wernicke's Encephalopathy: A Review. *Biomed Res Int*. 2014
56. Ota Y, Capizzano AA, Moritani T, Naganawa S, Kurokawa R, Srinivasan A. Comprehensive review of Wernicke encephalopathy: pathophysiology, clinical symptoms and imaging findings. *Jpn J Radiol*. 2020 Sep;38(9):809–20.
57. Charness ME, DeLaPaz RL. Mamillary body atrophy in Wernicke's encephalopathy: antemortem identification using magnetic resonance imaging. *Ann Neurol*. 1987 Nov;22(5):595–600.
58. Park SH, Kim M, Na DL, Jeon BS. Magnetic resonance reflects the pathological evolution of Wernicke encephalopathy. *J Neuroimaging*. 2001 Oct;11(4):406–11.
59. Antunez E, Estruch R, Cardenal C, Nicolas JM, Fernandez-Sola J, Urbano-Marquez A. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. *AJR Am J Roentgenol*. 1998 Oct;171(4):1131–7.
60. Foster J. The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition. 2nd Edition. *J Neurol Neurosurg Psychiatry*. 1989 Oct;52(10):1217–8.

Table 1. Characteristics of cases at admission

	All patients	History of alcohol abuse	
		No	Yes
N	56	11	45
Female gender (%)	10 (17.9)	5 (45.5)	5 (11.1)
Age (y) (median [Q1-Q3])	56.0 [49.0-64.0]	50.0 [48.5-59.5]	57.0 [49.0-64.0]
Cause for admission			
Neurological symptom (%)	36 (64.3)	8 (72.7)	28 (62.2)
General status alteration (%)	11 (19.6)	2 (18.2)	9 (20.0)
Fall (%)	8 (14.3)	1 (9.1)	7 (15.6)
Vitamin or trace element deficiency (%)	4 (7.1)	3 (27.3)	1 (2.2)
Psychiatric symptom (%)	4 (7.1)	0 (0.0)	4 (8.9)
Infection (%)	4 (7.1)	0 (0.0)	4 (8.9)
Respiratory failure (%)	3 (5.4)	1 (9.1)	2 (4.4)
Hydroelectrolytic disturbance (%)	3 (5.4)	0 (0.0)	3 (6.7)
Malnutrition (%)	2 (3.6)	0 (0.0)	2 (4.4)
Digestive symptoms, emesis (%)	2 (3.6)	1 (9.1)	1 (2.2)
Heart failure (%)	1 (1.8)	0 (0.0)	1 (2.2)
Other cause (%)	19 (33.9)	3 (27.3)	16 (35.6)
Comorbidities at admission			
Chronic hepatopathy, cirrhosis (%)	19 (33.9)	2 (18.2)	17 (37.8)
Mood disorder (%)	18 (32.1)	3 (27.3)	15 (33.3)
Chronic respiratory disease (%)	7 (12.5)	2 (18.2)	5 (11.1)
Chronic heart disease (%)	5 (8.9)	1 (9.1)	4 (8.9)
Dementia (%)	4 (7.1)	0 (0.0)	4 (8.9)
Diabetes mellitus (%)	3 (5.4)	1 (9.1)	2 (4.4)
Epilepsy (%)	3 (5.4)	0 (0.0)	3 (6.7)
Chronic pancreatitis (%)	2 (3.6)	0 (0.0)	2 (4.4)
Chronic psychosis (%)	2 (3.6)	0 (0.0)	2 (4.4)
Active cancer (%)	2 (3.6)	1 (9.1)	1 (2.2)
Chronic kidney disease (%)	1 (1.8)	0 (0.0)	1 (2.2)
Other comorbidity (%)	23 (41.1)	6 (54.5)	17 (37.8)
Alcohol withdrawal before hospitalization (%)	6 (10.7)	0 (0.0)	6 (13.3)
History of bariatric surgery (%)	5 (8.9)	4 (36.4)	1 (2.2)
Moderate malnutrition (%)	5 (8.9)	0 (0.0)	5 (11.1)
Severe malnutrition (%)	9 (16.1)	0 (0.0)	9 (20.0)
BMI (median [Q1-Q3])	21.7 [18.9-25.2]	29.2 [27.0-29.6]	20.9 [18.2-24.3]
Weight (kg) (median [Q1-Q3])	68.9 [55.2-72.0]	76.5 [71.3-96.0]	65.3 [54.5-70.2]
Serum albumin (g/L) (%)			
<30	18 (32.1)	3 (27.3)	15 (33.3)
30-35	11 (19.6)	2 (18.2)	9 (20.0)
>35	11 (19.6)	2 (18.2)	9 (20.0)
Not performed	16 (28.6)	4 (36.4)	12 (26.7)
Hyponatremia (%)	14 (25.0)	2 (18.2)	12 (26.7)
Serum potassium (%)			
Normal	33 (58.9)	9 (81.8)	24 (53.3)
Low	22 (39.3)	1 (9.1)	21 (46.7)
High	1 (1.8)	1 (9.1)	0 (0.0)

Serum phosphate (%)			
Normal	18 (32.1)	5 (45.5)	13 (28.9)
Low	9 (16.1)	1 (9.1)	8 (17.8)
Not performed	29 (51.8)	5 (45.5)	24 (53.3)
Serum magnesium (%)			
Normal	21 (37.5)	7 (63.6)	14 (31.1)
Low	5 (8.9)	0 (0.0)	5 (11.1)
Not performed	30 (53.6)	4 (36.4)	26 (57.8)
Liver tests anomaly (%)	37 (66.1)	3 (27.3)	34 (75.6)
Cytolysis >2N (%)	15 (26.8)	0 (0.0)	15 (33.3)
Cholestasis (%)	34 (60.7)	2 (18.2)	32 (71.1)
Factor V < 70% (%)	4 (7.1)	0 (0.0)	4 (8.9)
Prothrombin time (PT) < 70% (%)	6 (10.7)	0 (0.0)	6 (13.3)

Table 2. Clinical symptoms of cases noted at admission

N	All patients	History of alcohol abuse	
		No	Yes
	56	11	45
Neurologic or psychiatric (%)	56 (100)	11 (100)	45 (100)
Cerebellar syndrome (%)	33 (58.9)	4 (36.4)	29 (64.4)
Confusion and disorders of consciousness (%)	29 (51.8)	3 (27.3)	26 (57.8)
Walking disorders (%)	22 (39.3)	5 (45.5)	17 (37.8)
Nystagmus (%)	20 (35.7)	4 (36.4)	16 (35.6)
Temporal disorientation (%)	19 (33.9)	1 (9.1)	18 (40.0)
Spatial disorientation (%)	17 (30.4)	1 (9.1)	16 (35.6)
Memory problems (%)	14 (25.0)	2 (18.2)	12 (26.7)
Confabulations (%)	12 (21.4)	1 (9.1)	11 (24.4)
Balance disorders (%)	12 (21.4)	2 (18.2)	10 (22.2)
Cognitive disorders (%)	8 (14.3)	2 (18.2)	6 (13.3)
Polyneuropathy (%)	8 (14.3)	1 (9.1)	7 (15.6)
False recognitions (%)	7 (12.5)	1 (9.1)	6 (13.3)
Dizziness (%)	4 (7.1)	1 (9.1)	3 (6.7)
Diplopia (%)	4 (7.1)	3 (27.3)	1 (2.2)
Blurred vision (%)	2 (3.6)	2 (18.2)	0 (0.0)
Decreased visual acuity (%)	1 (1.8)	0 (0.0)	1 (2.2)
Ocular motor palsy (%)	0 (0.0)	0 (0.0)	0 (0.0)
Other neurological symptom (%)	4 (7.1)	1 (9.1)	3 (6.7)
Diagnosis of Korsakoff syndrom (%)	9 (16.1)	0 (0.0)	9 (20.0)
Digestive symptoms (%)	14 (25.0)	5 (45.5)	9 (20.0)
Emesis (%)	5 (8.9)	3 (27.3)	2 (4.4)
Diarrhea (%)	5 (8.9)	2 (18.2)	3 (6.7)
Pain/discomfort (%)	5 (8.9)	4 (36.4)	1 (2.2)
Other gastro-intestinal symptom (%)	5 (8.9)	1 (9.1)	4 (8.9)
Signs of heart failure (%)	1 (1.8)	0 (0.0)	1 (2.2)

Table 3. Neuroradiological investigations performed in cases

	All patients	History of alcohol abuse		p
		No	Yes	
n	56	11	45	
Brain MRI performed (%)	30 (53.6)	7 (63.6)	23 (51.1)	0.52
Brain CT performed (%)	28 (50.0)	5 (45.5)	23 (51.1)	1.00
Abnormal brain MRI (% of MRIs)	19 (63.3)	5 (71.4)	14 (60.8)	0.69
Typical of Wernicke's Encephalopathy (% of MRIs)	8 (26.6)	4 (57.1)	4 (17.4)	
Typical of Korsakoff syndrom (% of MRIs)	2 (6.7)	1 (14.2)	1 (4.3)	
Abnormal brain CT (%)	7 (25.0)	2 (40.0)	5 (21.7)	0.64

Table 4. Modalities of prescribed thiamine supplementation and outcome of cases

	All patients	History of alcohol abuse		p
		No	Yes	
N	56	11	45	
Form of thiamine administration (%)				0.04
Oral only	3 (5.4)	0 (0.0)	3 (6.7)	
IV only	16 (28.6)	2 (18.2)	14 (31.1)	
IV first then oral	31 (55.4)	5 (45.5)	26 (57.8)	
NA	6 (10.7)	4 (36.4)	2 (4.4)	
IV dose per infusion				0.02
< 500 mg	3 (5.4)	1 (9.1)	2 (4.4)	
500 mg	9 (16.0)	3 (27.2)	6 (13.3)	
1000 mg	31 (55.3)	2 (18.2)	29 (64.4)	
NA	13 (23.2)	5 (45.5)	8 (17.8)	
Number of infusions (median [Q1-Q3])	5.0 [3.0-12.0]	4.5 [1.5-15.8]	5.0 [3.0-11.5]	0.71
Oral dose per day (mg)				0.17
≤ 500 mg	7 (20.6)	3 (60.0)	4 (13.8)	
501-1000 mg	20 (58.8)	0 (0.0)	20 (69.0)	
> 1000 mg	6 (17.6)	1 (20.0)	5 (17.2)	
NA	1 (2.9)	1 (20.0)	0 (0.0)	
Duration of oral supplementation (d) (median [Q1-Q3])	19.0 [10.0, 31.0]	50.0 [9.3, 90.0]	19.0 [10.5, 25.5]	0.54
Duration of stay (d) (median [Q1-Q3])	15.5 [7.8-28.0]	8.0 [3.5-12.0]	19.0 [11.0-28.0]	0.05
Improvement of symptoms (%)	33 (58.9)	5 (45.5)	28 (62.2)	0.56
NA	7 (12.5)	2 (18.2)	5 (11.1)	

Figure 1. Odds ratios of symptoms improvement after thiamine supplementation and 95% confidence intervals

