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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy

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Background: Although Wernicke encephalopathy (WE) is a preventable and treatable disease it still often remains undiagnosed during life.

Objectives: To create practical guidelines for diagnosis, management and prevention of the disease.

Methods: We searched MEDLINE, EMBASE, LILACS, Cochrane Library.

Conclusions and recommendations:

1 The clinical diagnosis of WE should take into account the different presentations of clinical signs between alcoholics and non alcoholics (Recommendation Level C); although prevalence is higher in alcoholics, WE should be suspected in all clinical conditions which could lead to thiamine deficiency (good practice point – GPP).

2 The clinical diagnosis of WE in alcoholics requires two of the following four signs; (i) dietary deficiencies (ii) eye signs, (iii) cerebellar dysfunction, and (iv) either an altered mental state or mild memory impairment (Level B).

3 Total thiamine in blood sample should be measured immediately before its administration (GPP).

4 MRI should be used to support the diagnosis of acute WE both in alcoholics and non alcoholics (Level B).

5 Thiamine is indicated for the treatment of suspected or manifest WE. It should be given, before any carbohydrate, 200 mg thrice daily, preferably intravenously (Level C).

6 The overall safety of thiamine is very good (Level B).

7 After bariatric surgery we recommend follow-up of thiamine status for at least 6 months (Level B) and parenteral thiamine supplementation (GPP).

8 Parenteral thiamine should be given to all at-risk subjects admitted to the Emergency Room (GPP).

9 Patients dying from symptoms suggesting WE should have an autopsy (GPP).

Introduction

Wernicke encephalopathy (WE) is a devastating acute or subacute neurological disorder due to thiamine (Vitamin B1) deficiency. Although vitamins were discovered at the beginning of the 20th century and we learned to treat thiamine deficiency some decades later, WE remains the most important encephalopathy due to a single vitamin deficiency. The disease we now recognise as wet beriberi caused by thiamine deficiency from eating polished rice was probably recognized 1000 years ago in China [1] but WE and the associated Korsakoff amnestic syndrome were not described until the late 19th century [2–4]. The classical clinical triad of signs of WE comprises ocular signs, cerebellar dysfunction and confusion.

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Table 1 Frequency of Wernicke encephalopathy in series of consecutive autopsies

Author [reference]	Years of survey	Area	Source	Alcoholics and non alcoholics			Alcoholics			Non alcoholics		
				N	WE	%	*N*	WE	%	*N*	WE	%
Cravioto [38]	1957–60	USA, New York	H	1600	28	1.7						
Jellinger [39]	NS	Austria	H	1009	11	1.1						
Victor [40]	1963–66	USA	H	1539	29	1.9						
Torvik [41]	1975–79	Norway	H	8735	75	0.9	713	70	9.8			
Harper [42,43]	1973–81	Australia, Perth	H + CO	4677	131	2.8						
Hauw [44]	1952–83	France	H	8200	111	1.4						
Harper [45]	NS	Australia, Sydney	H + CO	285	6	2.1						
Lindboe [46]	1983–87	Norway	H	6964	52	0.7	604	40	6.6	6360	12	0.2
Pollak [47]	NS	Germany	H				154	13	8.4			
Skullerud [48]	1984–87	Norway	CO				127	18	14.2			
Naidoo [49]	1988–89	South Africa	H				29	17	58.6			
Riethdorf [50]	1983–86	Germany	H	2372	14	0.6	223	14	6.3			
Vege [51]	1988	Norway	H	279	4	1.4						
Lana-Peixoto [52]	1978–90	Brazil	H	1655	36	2.2						
Boldorini [53]	NS	Italy	H							380	65	17.1
Harper [54]	1989–94	France	H + CO	256	1	0.4						
Sheedy [55], Harper [56]	1996–97	Australia, Sydney	CO	2212	25	1.1						
Bleggi-Torres [57]	1987–98	Brazil	H							180	10	5.6
Bertrand, [58]	2001–06	France	CJD national register							657	19	2.9
Total				39 783	523	1.3	1850	172	9.3	6920	87	1.3

NS, not specified; H, hospital series; CO, Coroner series; WE, Wernicke encephalopathy.

The reported prevalence of WE in autopsy studies ranges from 0.4% to 2.8%, accounting on average for 1.3% of all autopsies (Table 1), and seems to be much higher in alcoholics than in non alcoholics. WE is traditionally regarded as a condition related to alcohol abuse. Interestingly, one of Carl Wernicke's index cases was a young woman with repeated vomiting following the ingestion of sulphuric acid and we now increasingly recognize that WE can arise in many situations other than alcohol abuse.

The disease is rare, catastrophic in onset, clinically complex and often delayed in diagnosis. We lack controlled studies on its management although the literature abounds with small series and individual case reports. Because of ethical problems in conducting controlled trials in a disease with a high mortality and an established therapy, new controlled data are also unlikely to be published in the future. Evidence is scarce for many aspects concerning the diagnosis and treatment of WE but we consider guidelines to be important because it is potentially preventable and treatable and frequently remains undiagnosed particularly in non alcoholic situations.

Search strategy

We searched MEDLINE with the following string: (i) *Wernicke Encephalopathy/OR (ii) ('Thiamine Deficiency/complications'[Mesh] OR 'Thiamine Deficiency/diagnosis'[Mesh] OR 'Thiamine Deficiency/drug therapy'[Mesh] OR 'Thiamine Deficiency/epidemiology'[Mesh] OR 'Thiamine Deficiency/etiology'[Mesh] OR 'Thiamine Deficiency/prevention and control'[Mesh]) OR (iii) Korsakoff Syndrome/NOT Wernicke Encephalopathy/). We also searched EMBASE, LILACS (Wernicke Encephalopathy OR Thiamine), and the Cochrane Library. All searches were done from data-base inception up to May 31, 2009. All papers published in European languages were considered. Titles and abstracts were double checked by two blinded panel members and relevant papers were fully read. Secondary searching was performed using the bibliography of relevant articles. Congress abstracts were not searched.

Methods for reaching consensus

Articles were graded for evidence according to the revised EFNS scientific task force guidance for guidelines [5] by two members of the panel; in case of disagreement, grading was discussed in a panel meeting. Each successive guideline draft was circulated among panellists and modified after their comments. All members of the task force agreed to all recommendations unanimously; where there was lack of evidence, but consensus was clear, we have stated our opinion as a good practice point (GPP).

Findings

How often is WE diagnosed in life?

Autopsy studies indicate that WE is frequently undiagnosed during life. Table 2 lists the autopsy studies reporting the percentage of alcoholic and non alcoholic patients with WE diagnosed ante mortem. All were Class IV studies. WE was suspected during life in only about one-third of alcoholic and 6% of non alcoholic patients. These series are likely to be biased towards more severe cases and the number of patients remaining undiagnosed before death is probably higher. These observations would suggest that thiamine deficiency and its consequences are likely to remain undiagnosed during life in significant numbers of cases. We are probably underestimating the real incidence of the disease and it seems reasonable to recommend that an autopsy has to be performed when patients die in situations with a suspicion of thiamine deficiency.

Recommendation
Patients dying from symptoms suggesting WE should have an autopsy (GPP).

When should we suspect WE in non alcoholic subjects?

We found more than 600 cases of WE reported in clinical settings other than alcohol use (Table 3). Among the most frequent settings were malignant disease, gastrointestinal disease and surgery, and vomiting due to hyperemesis gravidarum. Other causes included fasting, starvation, malnutrition and the use of unbalanced diets. Systematic reviews have been published for bariatric surgery [6,7] and hyperemesis gravidarum [8]. After bariatric surgery, i.e. the surgical procedures for obesity (gastric banding, gastric by-pass, bilio-pancreatic diversion, etc.), the risk for WE is long-lasting. According to one report, 94% of WE cases were seen within 6 months after surgery [6]. Whenever a pregnant subject with persistent vomiting develops neurological signs or symptoms, WE should be considered [8]. Prevalence studies of WE among non alcoholics have not been done and we can only speculate about the real prevalence of the disease in at-risk situations. Some conditions, such as bariatric surgery, may increase in the future, whereas others may disappear.

Recommendation
The level of suspicion for WE should be high in all clinical conditions that could lead to thiamine deficiency in the absence of alcoholism (GPP). After

Table 2 Number of cases of Wernicke encephalopathy diagnosed ante mortem in autopsy series

				Alcoholics			Non alcoholics		
Authors [reference]	Years of the survey	Area	Evidence class	Source	No. of autopsies	No. of diagnosed ante mortem	%	No. of autopsies	No. of diagnosed ante mortem	%
Victor [40]	1950–61	USA	IV	H	53	45	84.9			
Torvik [41]	1975–79	Norway	IV	H	19	1	5.3			
Harper [42,43]	1973–81	Australia, Perth[a]	IV	H + CO	131	26	19.8			
Harper [45]	NS	Australia, Sydney	IV	H + CO	6	2	33.3			
Lindboe [46]	1983–87	Norway	IV	H	11	4	36.4	7	0	0
Naidoo [49]	1988–89	South Africa	IV	H	17	0	0			
Riethdorf [50]	1983–86	Germany	IV	H	14	3	21.4			
Vege [51]	1988	Norway	IV	H	3	1	33.3	1	0	0
Sheedy [55] Harper [56]	1996–97	Australia, Sydney	IV	CO	18	4	22.2			
Ogershok [59]	1984–99	USA	IV	H	1	1	100.0	3	1	33
Kuo [60]	NS	USA	IV	H				5	1	20
Bertrand [58]	2001–06	France	IV	CJD national register				19	0	
Total					273	87	31.9	35	2	5.7

NS, not specified; H, hospital series; CO, Coroner series. [a] > 90% alcoholics.

bariatric surgery we recommend follow-up of the thiamine status for at least 6 months (Recommendation Level B).

Table 3 List of cases of Wernicke encephalopathy reported in non alcoholic subjects[a]

Clinical condition	No.	%
Cancer	113	18.1
Gastrointestinal surgery	105	16.8
Hyperemesis gravidarum	76	12.2
Starvation/Fasting	64	10.2
Gastrointestinal tract diseases	48	7.7
AIDS	31	5.0
Malnutrition	26	4.2
Dialysis and renal diseases	24	3.8
Parenteral nutrition	24	3.8
Vomiting	15	2.4
Psychiatric diseases	15	2.4
Stem cell/marrow transplantation	14	2.2
Infections	9	1.4
Intoxication	9	1.4
Thyroid diseases	8	1.3
Unbalanced diet	6	1.0
Iatrogenic	5	0.8
Hypoxic encephalopathy	2	0.3
Others	12	1.9
Unknown etiology	19	3.0
Total	625	100.0

[a]Search performed in Medline, Embase, LILACS from data-base inception through May 31, 2009.

Which clinical features accurately identify WE?

Table 4 lists the studies comparing autopsy series (including ≥3 cases) with clinical features of patients with acute WE. Most patients were alcoholics. Consecutive autopsies were collected without knowledge of clinical data. However, it is unknown whether the clinical data evaluation was blinded to autopsy results; thus all these studies are considered Class IV. The classical diagnostic triad (eye signs, cerebellar signs and confusion) was reported only in 8% of patients with clinical details. Although it should be considered as a minimum estimate due to a possible reporting bias, this figure prompts the need to reconsider diagnostic criteria for in-life diagnosis of WE. Caine *et al*. [9] (Class II) studied clinical features of 28 autopsy-proven alcoholic patients with WE that were well-evaluated during life. They divided signs and symptoms into eight clinical domains (see Table 4 for definitions): dietary deficiencies, eye signs, cerebellar signs, seizures, frontal lobe dysfunction, amnesia, mild memory impairment, and altered mental state. Reproducibility and validity of the criteria were then tested on 106 autopsied alcoholic patients. Clinical records of the patients were blindly reviewed by three researchers: sensitivity of each domain (recalculated from the paper) ranged from 20% (seizures) to 75%

Table 4 Clinical features of patients with an autopsy proved diagnosis of Wernicke encephalopathy

Authors [reference]	Evidence class	Total no. of patients	Dietary deficiencies	Nausea and vomiting	Any eye sign	Cerebellar signs	Seizures	Amnesia, mild memory impairment	Altered mental state	Triad
Cravioto [38]	IV	28	14		9	5			26	4
Grunnet [61]	IV	24	1		9	3	4	4	17	0
Torvik [41]	IV	19			4	0			18	0
Harper [62]	IV	97			28	36		29	41	16
Lindboe [46]	IV	18			3	0			11	0
Naidoo [49]	IV	17	1	8	0	2			9	0
Vege [51]	IV	4	2	1	0	0	1	2	3	0
Ogershok [59]	IV	4	3		4	1			4	1
Bleggi-Torres [63]	IV	8			3	0			6	0
Harper [56]	IV	18			0	3	3	6		0
Bertrand [58]	IV	19			2	15		19	1	0
Total *N* (%)		256	21 (8.2)	9 (3.5)	62 (24.2)	65 (25.4)	8 (3.1)	60 (23.4)	136 (53.1)	21 (8.2)

Empty cell = not mentioned; 0 = specified as absent.

Definition of domains [9] Domain 6 and 7 are combined in the table. Domain 5 was sporadically mentioned in the papers and it is not included here.

(i) dietary deficiencies (a body mass index lower than 2 SD below normal as evidence of undernutrition, a history of grossly impaired dietary intake, or an abnormal thiamine status); the column including nausea and vomiting is added here, but they were not considered by Caine *et al*. (ii) eye signs (oculomotor abnormalities such as ophthalmoplegia, nystagmus, or gaze palsy); (iii) cerebellar signs (ataxia, unsteadiness, abnormalities of past pointing, dysdiadokokinesia, impaired heel-shin testing); (iv) seizures (either as part of a withdrawal syndrome or in isolation, or a longstanding history of anticonvulsant medication); (v) frontal lobe dysfunction (abnormalities in planning, insight, or abstraction with formal neuropsychological testing or when neurological examination elicited these characteristics); (vi) amnesia (a stable and persisting inability to form new memories); (vii) mild memory impairment (failure to remember two or more words in the four item memory test, or impairment on more elaborate neuropsychological tests of memory function); (viii) altered mental state (disorientation in two of three fields, confused, an abnormal digit span, or comatose).

(cerebellar signs). Sensitivity of the classic triad was 23%, but rose to 85% if the patients had at least two of the four following features: dietary deficiencies, eye signs, cerebellar signs, and either mild memory impairment or an altered mental state.

Thiamine deficiency may also result in other manifestations such as dry beriberi (neuropathy), wet beriberi (neuropathy with high-output congestive heart failure), gastrointestinal beriberi (abdominal pain, vomiting and lactic acidosis) and coma followed by Marchiafava-Bignami syndrome [10,11]. Heart failure with lactic acidosis is an important syndrome to be noted, because several papers have reported favourable outcome after thiamine treatment [12,13].

Recommendation

The clinical diagnosis of WE in alcoholics requires two of the following four signs; (i) dietary deficiencies, (ii) eye signs, (iii) cerebellar dysfunction, and (iv) either an altered mental state or mild memory impairment (Level B). It is reasonable to apply the same criteria to non alcoholic patients (GPP).

Are clinical features of alcoholic WE different from non-alcoholic WE?

Table 5 lists case series (including ≥3 cases) published after Caine's criteria and compares clinical features of alcoholic and non alcoholic patients with WE. All but two were Class IV studies. In most studies, the MRI investigations were not performed blind to clinical evaluation and vice versa. Although these studies cannot give reliable information on the frequency of clinical features, they allow a comparison of the clinical features in alcoholics and non alcoholics. There is evidence that clinical features were unevenly distributed; dietary deficiency and vomiting were more frequent among non alcoholics ($P < 0.0001$), whereas eye and cerebellar signs were more frequent among alcoholics ($P < 0.0001$). The classical triad was significantly more frequent in alcoholics than in the non alcoholics ($P < 0.005$). Reasons for the difference are unclear, but may be due to the fact that WE in non alcoholics usually presents as a dramatic acute syndrome, whereas WE in alcoholics may more

Table 5 Clinical features of alcoholic and non alcoholic patients with Wernicke encephalopathy

Authors [reference]	Evidence class	Total no. of patients	Dietary deficiencies	Nausea and vomiting	Any eye sign	Cerebellar signs	Seizures	Amnesia, mild memory impairment	Altered mental state	Triad
Alcoholics										
Gallucci [64]	IV	5		5	5	4			3	3
Antunez [19]	II	15			14	12			10	9
Park [65]	III	12			11	10		1	5	4
Varnet [66]	IV	25			20	22			19	11
Ogershok [59]	IV	6	1		6	3			6	3
Weidauer [67]	IV	11			11	10		5	10	9
Chung [68]	IV	1	1		0	1			1	0
Halavaara [69]	IV	2	1	1	2	2		2	2	2
White [70]	IV	1	1	1	1	1		1	1	1
Zuccoli [71]	IV	24			22	17			20	13
Total *N* (%)		102	4 (3.9)	7 (6.9)	92 (90.2)	82 (80.4)	0 (–)	9 (8.8)	77 (75.5)	55 (53.9)
Non alcoholics										
Shikata [72]	IV	3	3		3	1		3		1
Merkin-Zaborsky [73]	IV	3	1	2	3	3				0
Park [65]	III	3	2	2	2	2		1	3	2
Ogershok [59]	IV	6	6	3	5	2			6	2
Weidauer [67]	IV	1		1	1	1		1	1	1
Chung [68]	IV	3	1	0	1	3			3	1
Halavaara [69]	IV	3	3	2	3	3		1	2	2
Zhong [74]	IV	6	6		2	2		2	6	
White [70]	IV	2	2	2	2	2		1	1	1
Sun [75]	IV	4	1	3	3	0		1	4	0
Unlu [76]	IV	6	6		6	6			6	6
Fei [77]	IV	12	12		9	3		3		2
Kirbas [78]	IV	25	25	7	14	10			9	4
Francini-Pesenti [80]	IV	7	7	3	6	7			7	6
Zuccoli [71]	IV	32	21	11	22	13			30	11
Total		116	96 (82.8)	36 (31.0)	82 (70.7)	58 (50.0)	0 (–)	13 (11.2)	78 (67.2)	39 (33.6)

Empty cell = not mentioned; 0 = specified as absent. See Table 4 for the definition of domains.

frequently present as a subclinical syndrome. Furthermore, alcoholics may develop thiamine deficiency several times during their life span, whereas non alcoholics are not likely to do so. Magnesium deficiency could also contribute to the poor recovery from WE in alcoholics [14].

Recommendation
The clinical diagnosis of WE should take into account the different presentations of clinical signs between alcoholics and non alcoholics and the higher prevalence of the disease in alcoholics (Level C).

Is there any laboratory test that accurately identifies patients with thiamine deficiency?

The erythrocyte transketolase activity assay including thiamine pyrophosphate effect has been replaced by direct measurement of thiamine and its phosphate esters in human blood by high-performance liquid chromatography (HPLC) [15,16]. This thiamine assay is now commercially available in many countries. Adult normal range (60–220 nM) and the lowest detectable level (3–35 nM) are given. The sample (2 ml EDTA blood) should be taken before administration of thiamine and should be protected from light. However, normal thiamine levels do not necessarily exclude WE in exceptional cases, i.e. in the presence of thiamine transporter gene mutations [17].

The concentration of thiamine and thiamine monophosphate and diphosphate in plasma and whole blood samples were assessed in six healthy subjects for 12 h and in urine for 24 h following either intravenous or oral bolus dose of 50 mg thiamine HCl. Unphosphorylated thiamine increased rapidly in plasma after intravenous administration and then decreased to its initial value within 12 h. The half-life was 96 min. Thiamine mono and diphosphate increased moderately (56%), and decreased slowly; the half-life of diphosphate was 664 min. Within 24 h, 53% of the administered dose was recovered in the urine, indicating a restricted distribution [18].

Recommendation
Whenever WE is suspected a blood sample for measurement of total thiamine should be drawn immediately before administration of thiamine and sent for HPLC analysis (GPP).

Does radiology accurately identify patients with WE?

CT scanning is not a reliable test for WE [19] (Class II). Table 6 lists MRI series including ≥3 cases of WE. Seven compare alcoholics to non alcoholics and one additional paper alcoholics with acute WE to controls and asymptomatic alcoholics without WE. In this Class II retrospective study alcoholics with and without WE were compared and MRIs were randomly and blindly assessed by two neuroradiologists [19]. The sensitivity and specificity of MRI were 53% and 93%. Positive predictive value was 89%.

Pooled data in Table 6 showed that among alcoholics with a clinically verified acute WE, conventional MRI revealed lesions in nearly two-thirds of the subjects. Little additional information was obtained by using fluid-attenuated inversion recovery (FLAIR) images and diffusion-weighted imaging (DWI). In non alcoholics, the available data showed a higher yield of lesions varying from 97% (DWI), 99% (conventional) and 100% (FLAIR). Location of lesions was more frequently atypical among non alcoholic than alcoholic patients whereas contrast enhancement of the thalamus and mamillary bodies was observed to associate more frequently with alcohol abuse [20]. Typically, the lesions were symmetrical and seen in the thalami, mamillary bodies, tectal plate and periaqueductal area. Atypical lesions were located in the cerebellum, vermis, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium and cerebral cortex. Reversible cytotoxic edema was considered the most distinctive lesion of WE [20]. The heterogeneity of MRI lesions may result from disease severity, acuteness of the disease and timing of imaging. We cannot say which of the MRI techniques used is most useful.

Recommendation
MRI is a powerful tool which should be used to support the diagnosis of acute WE both in alcoholics and non alcoholics (level B). It could also be used to follow the recovery of patients.

What is the efficacy of thiamine treatment in WE?

The efficacy of thiamine for WE has been assessed in only one double-blind randomized clinical trial [21]. Due to several methodological shortcomings it is in our opinion a class III study. Thiamine hydrochloride was given to 107 patients in doses of 5, 20, 50, 100 and 200 mg im daily for 2 days, with assessment of effect on the third day by a single neuropsychological test, suggested to be sensitive to cognitive impairment. The authors concluded that the 200 mg dose was superior to the mean result of all the other dosages. This study was evaluated in a Cochrane review concluding that in comparison to the 5 mg dose 200 mg was significantly more effective [22]. In another randomized double-blind study 10 mg thiamine or placebo were given to elderly people with subclinical thiamine deficiency [23]. These

people did not have WE. Quality of life was enhanced by providing thiamine supplements.

There is no consensus on the optimal dose of thiamine, its preparation form, duration of treatment, or the number of daily doses. Pharmacokinetic studies show a blood half-life of free thiamine of only 96 min [18] so it can be speculated that giving thiamine in two or three daily doses might achieve better penetrance to the brain and other tissues than a single daily dose [24].

According to many case reports, treatment with either 100 or 200 mg thiamine given intravenously has cured the disease in non alcoholics. On the other hand, this has not always been the case in alcoholics. Alcoholic patients with WE may need higher daily doses and 500 mg three times daily has been recommended [25,26]. The reason for the discrepancy is unclear. Alcoholics may have had previous subclinical episodes of the disease leading to permanent damage in the brain before admission to hospital with WE or the often coexistent severe alcohol withdrawal syndrome may have resulted in permanent damage of the brain tissue due to excess glutamate liberated in the brain [27].

Experimental [18] and clinical data [28–30] indicate that orally administered thiamine hydrochloride is ineffective in increasing blood thiamine or curing WE. The critical blood concentrations of thiamine for treating WE have not been determined. It could be speculated that patients in a catabolic state and alcoholics have reduced ability to store thiamine because the enzymes depending on thiamine are down regulated or protein binding is altered by the influence of alcohol. In such patients even high doses of thiamine might not cause a sufficient increase of thiamine stores unless a balanced diet has been instituted at the same time. Thus, normalization of diet might be an important factor in the acute treatment of suspected or manifest WE.

As the unwanted side-effects to B vitamins are most commonly seen after multiple administrations, and the necessary dose of thiamine amounts to a rather painful volume when given intramuscularly, we

Table 6 MRI features of alcoholic and non alcoholic patients with Wernicke encephalopathy

			Conventional MRI		MRI-Gadolinium enhancement		FLAIR MRI		DWR MRI	
	Evidence class	Type of MRI	Total no.	Positive no. (%)	Total no.	Positive no. (%)	Total no.	Positive no. (%)	Total no.	Positive no. (%)
Alcoholics										
Gallucci [64]	IV	0.5 T	5	5						
Antunez [19]	II	1.5 T	15	8	2	0				
Park [65]	III	2.0 T	8	8						
Varnet [66]	III	1.0/1.5 T	25	16	25	3				
Ogershok [59]	IV	?	2	0						
Chung [68]	IV	1.5 T							1	1
Weidauer [67]	IV	1.5 T	11	2	11	4	11	3		
Halavaara [69]	IV	1.5 T	2	2	2	0	2	2	2	2
White [70]	IV	?	1	1			1	1	1	1
Zuccoli [71]	IV	1.0/1.5 T	24	17	18	17	24	17		
Total			93	59 (63.4)	58	24 (41.4)	38	23 (60.5)	4	4 (100)
Non alcoholics										
Mascalchi [79]	IV	?	3	3	2	1				
Park [65]	III	2.0 T	3	3						
Ogershok [59]	IV	?	1	1						
Chung [68]	IV	1.5T	1	1	1	1	1	1	1	1
Weidauer [67]	IV	1.5 T	1	0	1	1	1	1		
Halavaara [69]	IV	1.5 T	3	3	3	0	3	3	3	3
White [70]	IV	?	2	2			2	2	2	2
Zhong [74]	IV	1.5 T	6	6			6	6		
Unlu [76]	IV	1.0 T	6	6	6	5	6	6	6	6
Fei [77]	IV	1.5 T	12	12	3	3	10	10	4	3
Francini-Pesenti [80]	IV	?	7	7			7	7	7	7
Zuccoli [71]	IV	1.0/1.5 T	32	32	23	9	32	32		
Total			77	76 (98.7)	43	22 (51.0)	72	72 (100)	29	28 (97.0)

FLAIR, fluid-attenuated inversion recovery.

suggest an intravenous infusion of thiamine diluted with 100 ml of normal saline or 5% glucose, given over 30 min.

It is also important to give thiamine before any carbohydrate, because it is well known that glucose infusion precipitates WE in thiamine deficiency [26].

Recommendation

There is sufficient evidence that thiamine is indicated for the treatment of suspected or manifest WE (level C). Since studies of sufficient quality to warrant a formal recommendation are lacking, there is no evidence to support conclusions as to dosage, route of administration, and treatment time. However, we recommend that thiamine should be given 200 mg three times daily and preferably via intravenous instead of intramuscular route (level C). Thiamine should be given before any carbohydrate, and a normal diet should be instituted immediately after thiamine (GPP). Treatment should be continued until there is no further improvement in signs and symptoms (GPP).

Is thiamine therapy safe?

The overall safety of intravenous thiamine is very good. In a prospective study of 989 patients receiving 100 mg thiamine hydrochloride as a single intravenous injection over 10 s or less, one patient reacted with generalized pruritus and 11 had transient local irritation [31] (Class II). In a retrospective survey Wrenn and Slovis [31] identified no cases of significant adverse reactions to thiamine in more than 300.000 treatments. Sporadic anaphylactic reactions have been reported, but it is not documented that thiamine was the cause in all cases. However, it has been suggested that thiamine should be given in circumstances where facilities for resuscitation are available [25]. This is preferable, but because a delay in treatment may cause irreversible brain damage and is life-threatening we recommend to start treatment immediately, even in the absence of facilities for resuscitation.

Recommendation

The overall safety of thiamine is very good, regardless of route of administration (level B). Thiamine should be given without delay in all circumstances irrespective of whether facilities for resuscitation are immediately available or not (GPP).

Is there a place for prophylactic thiamine therapy?

Studies from several countries show a thiamine deficiency in the elderly population [32]. Thiamine has been added to foods in many countries [33]. Some observational studies from Australia [33,34] suggest that this preventive effort has resulted in a decrease of the occurrence of the disease, although no controlled studies have been performed on this matter and are unlikely to be done in the future. Supplementation of thiamine to alcoholic beverages has been suggested too [32]. However, the mechanisms via which alcohol ingestion predisposes to thiamine deficiency suggest that adding thiamine into alcoholic beverages is a useless strategy. First, alcohol inhibits the absorption of thiamine from the intestine; second, during alcohol metabolism thiamine will neither be phosphorylated nor incorporated to enzymes in body tissues [35]. Thiamine ingested together with alcohol will be excreted in urine as free thiamine.

Thiamine deficiency is frequently not clinically apparent and WE can easily be worsened or precipitated if the treating physician gives glucose to a patient unaware that there is thiamine deficiency. In many countries emergency ward guidelines include recommendations to administer parenteral thiamine, e.g., to patients who are in status epilepticus [36] before any infusion of carbohydrates is started.

There are also other conditions (Table 3) in which administration of thiamine in food or oral preparation is inefficient (e.g. vomiting). Such conditions require parenteral administration of thiamine. In hunger strikers there is evidence from one cohort study (Class IV) [37] that up to 600 mg. thiamine orally together with one tablespoon of sugar daily did not prevent the development of WE. We did not find any other studies evaluating the prophylactic administration of thiamine in other risk conditions in alcoholics or in non alcoholics. Administration of multivitamin pills has been recommended following bariatric surgery. However, parenteral administration of vitamins may be a better strategy to prevent vitamin deficiency, because these patients frequently vomit [7].

Recommendation

Supplementation of thiamine to food may prevent the development of WE (GPP). There is no evidence that supplementation to beverages may be useful. We recommend prophylactic parenteral administration of 200 mg thiamine before carbohydrates are started in all subjects with a risk condition managed at the Emergency Room (GPP). After bariatric surgery we recommend parenteral thiamine supplementation (GPP). We think that hunger strikers should be carefully informed of the risk of WE and persuaded to accept a parenteral administration of thiamine followed by glucose (GPP). However, in both these situations we do not have any evidence of an effective dosage.

Disclosure of conflict of interest

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