UPDATE ON WERNICKE'S: CONSIDERATIONS ON EPIDEMIOLOGY (II)

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ABSTRACT

Wernicke Encephalopathy (WE) is frequently missed out in clinical practice. The consequences of under diagnosing WE are deleterious. WE is caused by thiamine (vitamin B1) deficiency and may occur in alcoholic and non-alcoholic patients. A better knowledge on epidemiology may shed light on the real nature of this condition. In this short review we outline epidemiological factors associated with WE.

Key words: Wernicke's encephalopathy, thiamine deficiency, epidemiology

Wernicke Encephalopathy (WE) is a complex neurologic disorder caused by thiamine (vitamin B1) deficiency. Thiamine deficiency is necessary but not sufficient for the development of WE (and is directly correlated with other distinct clinical entities including neuropathic and cardiovascular beriberi. The susceptibility of developing WE in the presence of thiamine deficiency is conditioned by less known genetic and environmental factors (Donnino, Vega et al. 2007; Sechi and Serra 2007). Although WE is a potentially fatal disease, complete reversibility may be achieved providing adequate treatment is promptly supplied. Unfortunately, WE is often misdiagnosed. The classical triad – i.e. mental status changes, ocular signs and gait ataxia – occurs in only up to one third of the cases, but it may be completely absent (Victor 1989); moreover, other populations at risk besides chronic alcohol abusers have been described (Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007; Hazell and Butterworth 2009). However, the misconception that WE is a rare stereotypic disease of the alcoholics still persists (Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007; Hazell and Butterworth 2009).

Most of the epidemiological data regarding WE are based on necroptic studies. To the best of our knowledge, Romanian national statistics are not available. According to international clinical studies, WE has a prevalence ranging from 0.04% to 0.13% and thus might be considered a rare disease. However, extrapolating the results of necroptic studies, up to 35% of alcoholics and 1.5% of the general population may develop WE during their lifetime (Thomson and Marshall 2006; Hazell and Butterworth 2009). Necroptic studies identify WE lesions in 0.4-2.8% of the general population, 12% of the alcoholics and 59% of those with alcohol related deaths (Victor, Adams et al. 1971; Harper 1979; Torvik 1991; Harper 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007). Besides alcoholics, significantly higher prevalence was identified in AIDS patients and in those that underwent bone marrow transplant, i.e. 10% respectively 6% (Butterworth, Gaudreau et al. 1991; Butterworth, Gaudreau et al. 1991; Donnino, Vega et al. 2007). Prior to necropsy, WE is diagnosed in only 30% of the

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alcohol-related cases and in almost 5% of the non-alcohol-related cases (Victor, Adams et al. 1971; Sechi and Serra 2007; Serra, Sechi et al. 2007). In pediatric population only 58% of the cases are correctly diagnosed prior to necropsy (Victor, Adams et al. 1971; Vasconcelos, Silva et al. 1999; Serra, Sechi et al. 2007) (Sechi and Serra 2007). Therefore, WE is under-diagnosed during life time (Butterworth, Gaudreau et al. 1991). Moreover, since necroptic studies may be biased towards identifying only the more severe cases, the prevalence of WE might be even higher than that estimated (Galvin, Brathen et al. 2010). However, some suggested that the hystopatological changes may precede the clinical onset of WE, and therefore that necropsies may also identify mild subclinical cases (Harper 1979; Caine, Halliday et al. 1997). For further clarification, the 2010 EFNS guideline recommends performing necropsies in all patients dying from diseases compatible WE (Galvin, Brathen et al. 2010).

WE affect individuals throughout the world. The geographic prevalence and incidence varies. The prevalence of thiamine deficiency influences the prevalence of WE. However, lesser known environmental and genetic factors that predispose to the development of WE in the presence of thiamine deficiency should not be ignored. Also, it should be taken into account that magnesium depletion may cause WE even in the presence of adequate thiamine levels. Magnesium is necessary for the conversion of thiamine in its biologically active form and also for the functioning of thiamine-dependent enzymes (McLean and Manchip 1999; Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007). In the recent years the impact of local socio-economic situation, regional particularities of diet and alcohol use, and national guidelines for prevention of iatrogenic cases on the prevalence of thiamine deficiency and WE has been better defined.

Nevertheless, the role of genetic predisposition in WE's epidemiology has been better described. (Harper, Giles et al. 1986; Cipriani, Balzi et al. 1998; Sechi and Serra 2007; Serra, Sechi et al. 2007). Though race predisposition is not explicit, a population-specific predisposition seems to exist. It seems that Europeans with thiamine deficiency are prone to neurological beriberi and/or WE, while Asians with thiamine deficiency are prone to cardiovascular beriberi (Blass and Gibson 1977; Sechi and Serra 2007). Gender may influence the risk of developing WE. WE is more common in males. Some reported male to female ratio of 1.7 to 1, while others found it to be 3 to 1 (Victor, Adams et al. 1971; Harper 1979; Victor 1989; Serra, Sechi et al. 2007). Interestingly, neither one of these ratios seems to correlate with male to female alcohol consumption rate, probably because the prevalence of alcohol consumption is lower in women, but at the same time women are more susceptible to developing WE (Victor, Adams et al. 1971; Harper 1979). WE may affect individuals of all ages, and has a higher prevalence during the fifth decade of life (Harper 1979). In the presence of a predisposing condition both pediatric and elderly populations appear to be more vulnerable, therefore extreme age may represent a predisposing factor (Vasconcelos, Silva et al. 1999; Decker and Isaacman 2000; Donnino, Vega et al. 2007).

Thiamine deficiency occurs not only in underdeveloped countries as it might be expected. A study conducted in UK revealed that approximately 20% of the patients admitted to the emergency departments had thiamine deficiency (Jamieson, Obeid et al. 1999; Fattal-Valevski 2011). Also, a study conducted in USA found that 8 to 31% of the elderly living at home and 23 to 40% of those in nursing homes have thiamine deficiency (Harper 2006). Another study, in Canada, found thiamine deficiency in almost 13% of the critically ill children (Seear, Lockitch et al. 1992; Fattal-Valevski 2011). Thiamine deficiency was found in 10 to 23% of the AIDS patients (Davtyan and Vinters 1987; Foresti and Confalonieri 1987; Hutchin 1987; Burdge, Sparling et al. 1995; Alcaide, Jayaweera et al. 2003) and in up to 46% of the newly onset Alzheimer disease (AD) patients. Until present, the relationship between thiamine deficiency and AD pathogenesis has not been completely elucidated (Agbayewa, Bruce et al. 1992).

Thiamine deficiency may develop in all those with suboptimal thiamine dietary intake, excessive thiamine loss and increased metabolic requirements. Therefore, besides chronic alcohol abuse, other factors like staple diet of polished rice, eating disorders, persistent emesis, parenteral nutrition, gastrointestinal surgery, prolonged fasting or starvation, liver failure, chronic dialysis, systemic malignancy, transplantation, pregnancy, lactation, prolonged fever, thyreotoxicosis and infectious diseases including AIDS and malaria predispose to thiamine deficiency (Soffer, Zirkin et al. 1989; Schwenk, Gosztonyi et al. 1990; Parkin, Blunden et al. 1991; Ihara, Ito et al. 1999; Bleggi-Torres, de Medeiros et al. 2000; Bonucchi, Hassan et al. 2008; McCandless 2010; Fattal-Valevski 2011).

Several thiamine deficiency predisposing factors may overlap in the same person. Development of WE might be precipitated by an acute event that increases the metabolic requirements of thiamine (Thomson and Marshall 2006). In infants, breast feeding by a thiamine deficient woman is the most frequent cause of thiamine deficiency. In older children, malignancy seems to be the predisposing condition most frequently associated to WE (Vasconcelos, Silva et al. 1999; Decker and Isaacman 2000).

The prevalence of WE in alcoholics is at least 10 times higher than in non-alcoholics (Reuler, Girard et al. 1985; Agabio 2005). In the developed countries, up to 90% of WE cases are alcohol-related (Thomson 2000; Thomson and Marshall 2006). At the same time 25 to 80% of chronic alcoholics have a certain degree of thiamine deficiency (Caine, Halliday et al. 1997; Cook, Hallwood et al. 1998; Thomson and Marshall 2006; Hazell and Butterworth 2009). A correlation between the per capita consumption of alcohol and the prevalence of WE seems not to exist (Torvik 1991), probably due to the lower prevalence of other predisposing factors than alcohol abuse in the developed countries. The risk of developing WE seems not to be increased in alcoholics with adequate dietary thiamine intake. However, it is higher than in other populations prone to thiamine deficiency, possibly because of the co-occurrence of several factors predisposing to WE (Sechi and Serra 2007). Chronic alcohol abusers most often have inadequate thiamine intake (Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007), and commonly associate hypomagnesaemia (Morgan 1982; Majumdar, Shaw et al. 1983). Also, they may have increased renal elimination and higher thiamine daily requirements, thiamine being necessary for ethanol's metabolism (Thomson 2000; Thomson and Marshall 2006). Malnourished alcoholics probably have impaired thiamine absorption (Thomson and Marshall 2006), which seems to be reversible providing alcohol consumption stops (Bujanda 2000). Not all alcoholics with similar nutritional status develop WE, therefore other environmental or genetic factors than alcohol abuse may play a role (Sechi and Serra 2007). The prevalence of liver disease causing impaired thiamine storing and metabolism is higher in alcoholics (Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007). Occurrence of hepatic encephalopathy, alcohol withdrawal and recurrent seizures may render the brain more vulnerable to thiamine deficiency (Caine, Halliday et al. 1997). As mentioned, genetic particularities, related or not with the predisposition to alcohol dependence, may also play an important role in the development of WE in thiamine deficient individuals (Blass and Gibson 1977; Mukherjee, Svoronos et al. 1987; Alexander-Kaufman and Harper 2009).

Thiamine daily requirements range from 1 to 1.5-2 mg, depending on each person's adequate caloric intake – i.e. 0.5 mg per 1000 kcal – (Thomson 2000; Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007; Fattal-Valevski 2011). The human body has thiamine deposits that last 18 to 42 days – i.e. 25-50 mg – (Thomson 2000; Thomson and Marshall 2006; Sechi and Serra 2007; Serra, Sechi et al. 2007; Fattal-Valevski 2011). Inadequate thiamine intake persisting for more than 14 to 21 days leads to thiamine deficiency (Watson, Walker et al. 1981; Sechi and Serra 2007; Serra, Sechi et al. 2007; Fattal-Valevski 2011). High carbohydrate intake increases the daily requirements of thiamine. As already mentioned, even with adequate thiamine intake, conditions leading to magnesium depletion may predispose to WE. White rice has very low thiamine content (Sechi and Serra 2007). Almost two thirds of the world's population have a diet based on polished rice. Interestingly, not WE, but beriberi is endemic in areas with staple diet of polished rice – i.e. South Asia (Sechi and Serra 2007). Thiamine's absorption may be impaired by the so-called 'anti-thiamine factors' (i.e. thiaminases, sulphites, polyphenols, caffeic acid, chlorogenic acid, tannic acid, tartaric acid, citric acid, ascorbic acid, quercetin and rutin). The high dietary intake of foods containing anti-thiamine factors (thiaminases from raw or fermented fish and shellfish or thiamine antagonists from coffee, tea, ferns, betel nuts, blueberries, red cabbage, herbal supplements, certain bacteria etc) may lead to thiamine deficiency (Sechi and Serra 2007).

Malnourished individuals may have impaired thiamine absorption due to impaired function of the energy requiring active thiamine transporters (Thomson and Marshall 2006). All eating disorders may lead to thiamine deficiency. Unbalanced diet may occur in other psychiatric patients like those with schizophrenia or dementia. Refeeding and hyperalimentation without adequate thiamine supplementation, especially if high in carbohydrates, may precipitate WE (Watson, Walker et al. 1981; Sechi and Serra 2007; Serra, Sechi et al. 2007). Prolonged fasting for religious, philosophical or political reasons also leads to thiamine deficiency (Basoglu, Yetimalar et al. 2006). Neglected children, elderly or disabled persons are prone to thiamine deficiency

(Sechi and Serra 2007). Recent significant weight loss has been proposed as red flag for thiamine deficiency and WE. However, not all WE patients are underweight (Wood, Currie et al. 1986; Thomson and Marshall 2006; Serra, Sechi et al. 2007; Singh and Kumar 2007).

The use of certain drugs such as antacids, phenytoin, cephalosporins, metronidazole, diuretics, tetracycline, nitroglycerin, tolazamide, 5-fluorouracil, cisplatin, and ifosfamide may, through different mechanism, impair thiamine levels and thiamine dependent processes, and thus predispose to WE. However, their relevance for clinical practice has not been clearly defined (Kondo, Fujiwara et al. 1996; Hamadani and Awan 2006; Sechi and Serra 2007; Imtiaz and Muzaffar 2010).

Physiologic and pathologic hypercatabolic states may predispose to thiamine deficiency (Otsuka, Tada et al. 1997; Bonucchi, Hassan et al. 2008). Persistent vomiting and diarrhea, irrespective of cause, may lead to thiamine deficiency if adequate parenteral supplementation is not provided (Serra, Sechi et al. 2007). Chronic renal failure may predispose to WE, because dialysis increases thiamine elimination (Ueda, Utsunomiya et al. 2007), but also because the frequently associated uraemic encephalopathy renders the brain more susceptible to thiamine deficiency induced injury (Brouns and De Deyn 2004). Chronic liver disease may predispose to thiamine deficiency and hepatic encephalopathy may represent an additional predisposition factor for WE (Caine, Halliday et al. 1997). Patients with acute pancreatitis, systemic malignancies and hyperemesis gravidarum are especially prone to developing WE (Ohkoshi, Ishii et al. 1994; Sechi and Serra 2007; Serra, Sechi et al. 2007). Gastrointestinal surgery that removes or by-passes parts of the gastrointestinal system involved in micronutrient absorption, including bariatric surgery, is an important predisposing factor for thiamine deficiency and also for deficits of other vitamins and minerals (Sechi and Serra 2007; Serra, Sechi et al. 2007).

Genetic factors seem to predispose to the development of thiamine deficiency, but more importantly to the development of WE in the presence of thiamine deficiency. Occurrence of WE is more frequently encountered in both monozygotic twins than in heterozygotic twins, supporting the hypothesis of genetic predisposition (Martin, Singleton et al. 2003). Genetic defects might explain the inability of certain individuals to cope with borderline thiamine deficient states and also some of the rarely reported cases of resistance to adequate treatment. Some individuals may have suboptimal thiamine absorption in the absence of a local identifiable cause. The up-regulation of proteins responsible for the intestinal and renal uptake of thiamine – that in the presence of thiamine deficiency would increase its absorption and decrease its excretion – may be impaired in individuals who develop WE (Thomson and Marshall 2006). The presence of a transketolase with low thiamine affinity may be another predisposing factor for WE (Blass and Gibson 1977; Greenwood, Jeyasingham et al. 1984; Mukherjee, Svoronos et al. 1987) (McCool, Plonk et al. 1993; Sechi and Serra 2007; Serra, Sechi et al. 2007). Another genetic factor that may cause WE susceptibility is mutation of the X-linked transketolase-like 1 gene (Coy, Dubel et al. 1996; Serra, Sechi et al. 2007). Also, the cerebral thiamine transporting systems might be impaired in persons that develop WE. Mutation of the gene that encodes for human thiamine transporter 1 – SLCA19 – seems also to be involved in the genetic predisposition to WE (Guerrini, Thomson et al. 2005; Sechi and Serra 2007; Serra, Sechi et al. 2007). Genetic variants of the enzymes involved in ethanol metabolism may also predispose to WE (Sechi and Serra 2007). Further studies are needed for better characterization of genetic factors associated with WE.

A few thiamine deficiency epidemics have been recorded by modern history (Donnino, Vega et al. 2007). At the beginning of the 20th century the introduction of large scale use of cheap polished rice in urban Southeast Asia led to local outbreak. During the ‘80s and the ‘90s thiamine deficiency epidemics were recorded in Thailand, Guinea, Djibouti and Nepal (Fattal-Valevski 2011). In 2003 a thiamine deficiency epidemic affecting infants fed with a thiamine deficient soy milk formula emerged in Israel (Fattal-Valevski, Kesler et al. 2005; Fattal-Valevski 2011). Recently a trend towards an increased prevalence of WE has been observed in certain areas, i.e. UK, USA, and Japan. In USA this situation might be explained by the recent increase in bariatric surgery use and also by the shortage of intravenous vitamins (Ramayya and Jauhar 1997; Hahn, Berquist et al. 1998; Thomson 2000; Harper 2006). In Japan health care policy changes regarding vitamin supplementation for those with exclusive parenteral nutrition might be responsible (Harper 2006). In UK it was hypothesized that the increased practice of routine in-hospital supplementation with per os instead of parenteral thiamine in alcoholics with asymptomatic thiamine deficiency might have an influence (Thomson and Marshall 2006; Feeney and Connor 2008).

The prognosis of WE depends on the medical management. In the absence of adequate therapy WE results in death in up to 20% of the patients, and in permanent disability in 75-80% of the survivors (Thomson 2000; Thomson, Cook et al. 2002; Thomson and Marshall 2006; Donnino, Vega et al. 2007). The most frequent sequel of inappropriately treated WE is Korsakoff Psychosis (KP). Virtually all cases of WE are cured providing prompt and adequate treatment is administered. Only about 20% of the patients that develop KP fully recover (Victor 1989; Caine, Halliday et al. 1997).

Attempts to primary prophylaxis have been made, either by fortifying food or alcoholic beverages with thiamine or by administration of oral thiamine supplements to populations at risk. Their efficacy has not been clearly evaluated, but studies conducted in Australia showed that after the fortification of bread with thiamine an almost 40% decrease in the local incidence of acute WE and KP occurred (Rolland and Truswell 1998; Feeney and Connor 2008). Also, the importance of an adequate control of the content of meal replacements for infants or people with conditions impairing a balanced diet should not be neglected (Fattal-Valevski, Kesler et al. 2005). In UK no obvious explanation was found, and moreover, the bread from the affected areas was fortified with thiamine (Ramayya and Jauhar 1997; Thomson 2000).

Certainly, the spectrum of factors interfering with WE epidemiology is wide and remains matter of debate. Nevertheless, the steps to a unifying concept on WE genesis must certainly include the overlap between poor catabolic states and denutrition. Since not only alcohol consumption, but any setting in which the above are concomitant might predispose to WE, clinicians must be aware of the risk in order to prevent or early detect this condition. Considering the important burden that untreated WE puts on health care systems worldwide (Galvin, Brathen et al. 2010), further epidemiological studies are needed in order to better define the populations at risk, and to identify the efficient prophylactic approaches.

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