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Thiamine Deficiency and Wernicke's Encephalopathy in AIDS

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Several neuropathological reports in the last 5 years have described brain lesions characteristic of Wernicke's Encephalopathy in patients with AIDS. Using the erythrocyte transketolase activation assay, we now report biochemical evidence of thiamine deficiency in 9/39 (23%) of patients with AIDS or AIDS-related complex. In no cases was there history of alcohol abuse nor were there clinical signs of Wernicke's Encephalopathy. Thiamine deficiency in these patients most likely results from the cachexia and catabolic state characteristic of AIDS. In view of (i) the confirmed neuropathological evidence of Wernicke's Encephalopathy in AIDS patients, (ii) the significant thiamine deficiency in these patients and (iii) the difficulties of clinical diagnosis of Wernicke's Encephalopathy, it is recommended that dietary thiamine supplementation be initiated in all newly diagnosed cases of AIDS or AIDS-related complex.

KEY WORDS: AIDS; AIDS-related complex; thiamine deficiency; Wernicke's Encephalopathy; α-ketoglutarate dehydrogenase; transketolase.

INTRODUCTION

In the last 5 years, six independent reports have described neuropathological evidence for Wernicke's Encephalopathy in patients with AIDS. Necropsy findings included peticheal

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hemorrhagic lesions of mammillary bodies as well as focal neuronal loss in thalamus and pons (Foresti *et al.*, 1986; Rosemberg *et al.*, 1986; Foresti and Confalonieri, 1987; Davtyan and Vinters, 1987; Lindboe and Loberg, 1989; Soffer *et al.*, 1989; Schwenk *et al.*, 1990), lesions that are characteristic of Wernicke's Encephalopathy (Victor *et al.*, 1989). In none of the above-described cases was there a history of alcohol abuse and in only 2/7 cases had a clinical diagnosis of Wernicke's Encephalopathy been entertained prior to death.

Wernicke's Encephalopathy results from thiamine deficiency (Victor *et al.*, 1989; Butterworth, 1989). The present report describes results of a study of thiamine status in 39 patients with AIDS or AIDS-related complex. A preliminary communication of these findings has appeared recently (Butterworth *et al.*, 1991).

METHODS

39 patients (36 male, 3 female, ages 22-67) with AIDS or AIDS-related complex were studied at various stages of the disease. In none of the cases was there history of alcohol abuse nor were there any neurological symptoms of Wernicke's Encephalopathy. No patients were taking thiamine supplements. Thiamine status was measured by means of the transketolase activation assay whereby activities of the thiamine-dependent enzyme transketolase are measured in erythrocyte hemolysates both without and with excess thiamine pyrophosphate (TPP) added *in vitro* as previously described (Butterworth, 1987). The % activation (or "TPP Effect") is a reliable indicator of thiamine status. In our laboratory, as elsewhere, "TPP Effect" values in excess of 15% indicate moderate (or borderline) to severe thiamine deficiency.

Effects of AZT *in vitro* on activities of α-ketoglutarate dehydrogenase were evaluated in homogenates of cerebral cortex of male Sprague-Dawley rats (175-200 g). Enzyme activities were measured as previously described (Butterworth *et al.*, 1986).

RESULTS AND DISCUSSION

6/39 patients with AIDS or AIDS-related complex were found to be thiamine deficient as reflected by transketolase activation assay ("TPP Effect" values in excess of 15%). A follow-up study performed 6-9 months later on 15 of the original 39 patients revealed a further 3 cases of thiamine deficiency for a total of 9/39 (23%). The distribution of "TPP Effect" values in these patients are shown in Figure 1.

Thiamine deficiency and Wernicke's Encephalopathy in patients with AIDS most probably result from the severe cachexia and catabolic state characteristic of the disease. Wernicke's Encephalopathy is encountered in other disorders of grossly impaired nutritional status such as gastrointestinal carcinoma, chronic bowel disease and hyperemesis gravidarum (Hutchin, 1987; Butterworth, 1989; Lindboe and Loberg, 1989). Further studies are required to determine whether the thiamine deficiency state in patients with AIDS or AIDS-complex results from insufficient dietary intake as a result of loss of appetite or from malabsorption of the vitamin as a consequence of gastrointestinal complications of the disease.

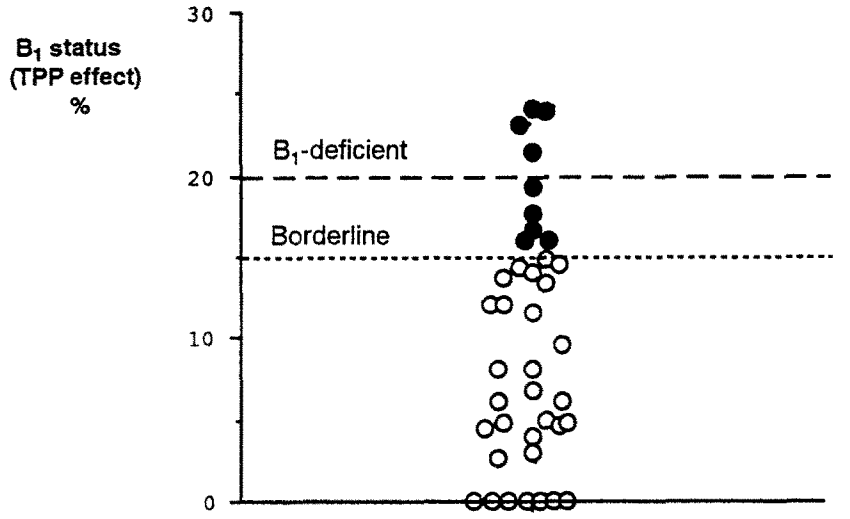

Fig. 1. Thiamine status in patients with AIDS or AIDS-related complex.

Table 1. Effects of AZT on αKGDH Activities in Homogenates of Rat Cerebral Cortex [a]

Treatment	αKGDH Activity (nmole/min/mg protein)
None	14.78 ± 0.92
AZT, 1 μM	14.26 ± 1.07
AZT, 100 μM	14.52 ± 0.78

[a] Values shown are means ± SE of triplicate determinations.

It was suggested in an earlier study that AZT could have contributed to Wernicke's Encephalopathy (Davtyan and Vinters, 1987). However, in a subsequent report of 2 cases of Wernicke's Encephalopathy in AIDS patients, neither had been treated with the drug (Schwenk *et al.*, 1990). Eight out of the nine thiamine-deficient patients in the present study had been treated with AZT. Drug-induced Wernicke's Encephalopathy is not without

precedent. In 1983, Kwee and Nakada described a 40 year old diabetic patient who developed Wernicke's Encephalopathy after treatment with the oral hyperglycaemic agent tolazamide. In a subsequent study of the patient, thiamine deficiency was confirmed by transketolase activation assay (Mukherjee *et al.*, 1986). Symptoms of Wernicke's Encephalopathy including nystagmus, ataxia and memory loss were described in 10 cancer patients treated with doxifluridine (Heier and Foss, 1986); neurotoxicity was dose-related and it was suggested that the drug interferes with thiamine-dependent enzyme function in brain. Currently available evidence suggests that Wernicke's Encephalopathy results from decreased activities of the thiamine dependent enzyme α-ketoglutarate dehydrogenase (α-KGDH) in brain (Butterworth, 1989). Like doxifluridine, AZT crosses the blood-brain barrier. However, preliminary studies showed no effect of AZT *in vitro* on brain activities of α-KGDH (Table 1). Studies are presently underway to determine whether or not AZT or one of its metabolites results in alterations of other thiamine-dependent enzymes *in vitro* and *in vivo*.

The frequency of thiamine deficiency in AIDS observed in the present study is comparable to that reported in a recent study of alcoholic patients admitted to a Detoxification Unit (D'Amour *et al.*, 1991). In these latter patients, reduced peroneal nerve conduction velocities were correlated with thiamine deficiency. Peripheral neuropathy is common in AIDS patients (Parry, 1988) raising the possibility that thiamine deficiency may play a role in the etiology of this neurological complication. Further studies are required in order to assess this possibility.

The clinical diagnosis of Wernicke's Encephalopathy is frequently missed. Of the 7 cases of autopsy-proven Wernicke's Encephalopathy in AIDS patients reported in the literature, only 2 were diagnosed clinically prior to death (Table 2). Similarly, in a review of autopsies in Norway, 52 cases of Wernicke's Encephalopathy were discovered including 12 in non-alcoholics. Only 4/52, all in alcoholics, had been diagnosed clinically (Lindboe and Loberg, 1989). Studies by Harper (1979) revealed 51 cases of Wernicke's Encephalopathy in Perth, Australia, most of whom were alcoholics. Again, only 7/51 had been diagnosed in life. One possible explanation for the difficulties in diagnosing Wernicke's Encephalopathy may relate to the variability of symptoms reported in these patients. Rather than the classical triad of ophthalmoplegia, ataxia and confusion generally described in patients with Wernicke's Encephalopathy, some reports describe only disorientation and depressed levels of consciousness (Torvik *et al.*, 1982; Lindboe and Loberg, 1989).

In the light of the difficulties in clinical diagnosis of Wernicke's Encephalopathy, and the finding of thiamine deficiency in patients with AIDS or AIDS-related complex, we suggest that dietary thiamine supplementation should be initiated in all newly diagnosed cases of these disorders.

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Table 2. Thiamine Deficiency and Wernicke's Encephalopathy in Patients with AIDS: A Review of the Literature

Reference	Number of AIDS Patients	Age	Thiamine Deficiency	Wernicke's Encephalopathy		AZT
				Clinical	Neuropathological	
Rosemberg, *et al.*, 1986	1	27	--	no	yes	?
Davtyan & Vinters, 1987	1	47	--	no	yes	yes
Foresti & Confalonieri, 1987	1	26	--	no	yes	?
Lindboe & Loberg, 1989	1	40	--	no	yes	?
Soffer *et al.*, 1989	1	40	--	yes	yes	?
Schwenk *et al.*, 1990	2	36-39	--	yes (1/2)	yes (2/2)	no (2/2)
Present study	39	22-67	yes (9/39)	no	--	yes (8/9)

REFERENCES

Butterworth R.F., Giguère J.-F. and Besnard A.-M. (1986). Activities of thiamine-dependent enzymes in two experimental models of thiamine-deficiency encephalopathy. 2. α-ketoglutarate dehydrogenase. *Neurochem. Res.* **11**: 567-577.

Butterworth R.F. (1989). Effects of thiamine deficiency on brain metabolism: implications for the pathogenesis of the Wernicke-Korsakoff Syndrome. *Alcohol & Alcoholism* **24**: 271-279.

Butterworth R.F., Gaudreau C., Vincelette J., Bourgault A.-M., Lamothe F. and Nutini A.-M. (1991). Thiamine deficiency in AIDS. *Lancet* **338**: 1086.

D'Amour M.L., Bruneau J. and Butterworth R.F. (1991). Abnormalities of peripheral nerve conduction in relation to thiamine status in alcoholic patients. *Can. J. Neurol. Sci.* **18**: 126-128.

Davtyan D.G. and Vinters H.V. (1987). Wernicke's Encephalopathy in AIDS patient treated with Zidovudine. *Lancet* **1**:919-920.

Foresti V., Parisio E., Scolari N., Sparacio F. and Confalonieri F. (1986). Sindrome da immunodeficienza acquisita associata a tubercolosi disseminata ed a encefalopatia cronica di Wernicke. *Recenti Progressi in Medicina* **77**: 350-352.

Foresti V. and Confalonieri F. (1987). Wernicke's Encephalopathy in AIDS. *Lancet* (i), 1499.

Harper C. (1979). Wernicke's Encephalopathy: a more common disease than realized. *J. Neurol. Neurosurg. Psychiat.* **42**: 226-231.

Heier M.S. and Fossa S.D. (1986). Wernicke-Korsakoff-like syndrome in patients with colorectal carcinoma treated with high-dose doxifluridine (5'-dFUrd). *Acta Neurol. Scand.* **73**: 449-457.

Hutchin K.C. (1987). Thiamine deficiency, Wernicke's Encephalopathy and AIDS. *Lancet*, 1200.

Kwee I.L. and Nakada T. (1983). Wernicke's Encephalopathy induced by tolazamide. *New Eng. J. Med.* **309**: 599-600.

Lindboe C.F. and Loberg E.M. (1989). Wernicke's Encephalopathy in non-alcoholics. An autopsy study. *J. Neurol. Sci.* **90**: 125-129.

Mukherjee A.B., Ghazanfari A., Svoronos S., Staton R.C., Nakata T. and Kwee I.L. (1986). Transketolase abnormality in tolazamide-induced Wernicke's Encephalopathy. *Neurol.* **36**: 1508-1510.

Rosemberg S., Lopes M.B.S. and Tsanaclis A.M. (1986). Neuropathology of acquired immunodeficiency syndrome (AIDS). Analysis of 22 Brazilian cases. *J. Neurol. Sci.* **76**: 187-198.

Parry G.J. (1988). Peripheral neuropathies associated with human immunodeficiency virus infection. *Ann. Neurol.* **23**: S49-S53.

Schwenk J., Gosztonyl G., Theraulf P., Iglesias J. and Langer E. (1990). Wernicke's encephalopathy in two patients with acquired immunodeficiency syndrome. *J. Neurol.* **237**: 445-447.

Soffer D., Zirkin H., Alkan M. and Berginer V.M. (1989). Wernicke's encephalopathy in acquired immune deficiency syndrome (AIDS): a case report. *Clin. Neuropathol.* **8**: 192-194.

Torvik A., Linboe C.F. and Rodge S. (1982). Brain lesions in alcoholics. A neuropathological study with clinical correlations. *J. Neurol. Sci.* **56**: 233-248.

Victor M., Adams R.D., Collins G.H. (1989). *The Wernicke Korsakoff Syndrome*, F.A. Davis, Philadelphia.