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Cerebrospinal fluid levels of thiamine in patients with Alzheimer's disease

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Summary. Thiamine is an essential cofactor for several important enzymes involved in brain oxidative metabolism, such as the alpha-ketoglutarate dehydrogenase complex (KGDHC), pyruvate-dehydrogenase complex (PDHC), and transketolase. Some investigators reported decreased thiamine-diphosphate levels and decreased activities of KGDHC, pyruvate-dehydrogenase complex and transketolase in the brain tissue of Alzheimer's disease (AD) patients. We measured cerebrospinal (CSF) levels of thiamine-diphosphate, thiamine-monophosphate, free thiamine, and total thiamine, using ion-pair reversed phase high performance liquid chromatography, in 33 patients with sporadic AD and 32 matched controls.

The mean CSF levels of thiamine-derivatives did not differ significantly from those of controls, while the mean plasma levels of thiamine-diphosphate, free and total thiamine were significantly lower in the AD-patient group. CSF and plasma thiamine levels were not correlated with age, age at onset, duration of the disease, and scores of the MiniMental State Examination, with the exception of plasma thiamine-diphosphate with MiniMental State Examination ($r = 0.41$, $p < 0.05$) in the AD-patients group. CSF and plasma values did not predict dementia progression, assessed with the Minimental State Examination scores. These results suggest that CSF thiamine levels are not related with the risk for and the progression of AD.

Keywords: Alzheimer's disease, thiamine, cerebrospinal fluid levels, serum levels.

Introduction

The etiology and pathogenesis of Alzheimer's disease (AD) is unknown. Mutations in the genes of beta-amyloid precursor protein, presenilin 1 and presenilin 2, can cause familial Alzheimer's disease (AD), and inheritance of the ApoE4 allele confers increased risk for AD (Goate, 1997). It is likely that there could be additional risk factors, including environmental factors and aging (Katzman and Kawas, 1994).

The biological forms of thiamine are phosphorylated derivatives. Thiamine-diphosphate or pyrophosphate is an essential cofactor for several important enzymes involved in brain oxidative metabolism, such as the alpha-ketoglutarate dehydrogenase (KGDHC) and pyruvate dehydrogenase complexes (PDHC), and transketolase (Blass, 1994). Thiamine deficiency or inhibition in experimental models can induce a reduction in the KGDHC activity (Munujos et al., 1996). In addition, thiamine may play a role in the modulation of cholinergic status of the brain (Bettendorf, 1994). The transport of thiamine across the blood-brain barrier seems to be a carrier-mediated process which can be saturated by raised levels of thiamine (Greenwood et al., 1982). The most abundant dietary sources of thiamine are unrefined cereal grains, liver, heart, kidney and lean cuts of pork (McCormick, 1988).

Some authors reported decreased activities of KGDHC (Butterworth and Besnard, 1990; Gibson et al., 1988; Mastrogiacomo et al., 1993), PDHC (Butterworth and Besnard, 1990; Gibson et al., 1988), transketolase (Butterworth and Besnard, 1990; Gibson et al., 1988), and thiamine diphosphatase (Rao et al., 1993) in the brains of patients with AD. Mastrogiacomo et al. (1996) found normal levels of free thiamine and thiamine monophosphate, and decreased levels of thiamine-diphosphate, with normality of thiamine-diphosphate-metabolizing enzymes, in the brain of 18 AD patients compared with 20 controls.

Serum, plasma or erythrocyte thiamine levels, or erythrocyte transketolase activity have been found normal (Mimori et al., 1996; Renvall et al., 1989; Scileppi et al., 1984; Winograd et al., 1991) or decreased (Agbayewa et al., 1992; Gold et al., 1995, 1998). To our knowledge, there is no previous information concerning cerebrospinal fluid thiamine levels in patients with AD. The aim of this study was to assess the lumbar cerebrospinal fluid levels of thiamine and their phosphate esters in patients with sporadic AD compared with a control population, trying to elucidate whether low cerebrospinal fluid thiamine levels could be related with the risk for AD. In addition, we also measured plasma thiamine levels.

Patients and methods

We assessed the cerebrospinal fluid and plasma levels of thiamine-diphosphate, thiamine-monophosphate, free thiamine and total thiamine, in 33 patients with AD and 32 controls. Unselected AD patients were recruited from outpatients making the first visit to the departments of neurology of two hospitals. Evaluation of each patient included: anamnesis and neurological examination, Mini-Mental State Examination (Folstein et al., 1975), Hachinski Ischemic Score (Hachinski et al., 1975), Hamilton's Rating Scale for depression (Hamilton, 1960), and laboratory tests (blood cell count, urinalysis, blood routine bio-

chemistry including calcium, CSF analysis, serologic tests for syphilis in serum and CSF, serum levels of thyroid hormones, vitamin B_{12} and folic acid, electroencephalogram, and cranial CT or MRI). The following inclusion criteria were applied to AD patients:

A) Criteria for diagnosis of AD according to DSM-IV (American Psychiatric Association, 1994).

B) Criteria for "probable AD" according to the NINCDS-ADRDA Work Group criteria (McKhann et al., 1984). No patient had "definite AD" because the inclusion in this group requires brain biopsy, but the accuracy of the diagnosis of AD based upon clinical and laboratory evaluation is estimated around 80% (Sulkava et al., 1983).

C) Scores of the MiniMental State Examination lower than 23 points, Hachinski ischemic score lower than 4 points, and Hamilton's scale for depression lower than 17 points.

The control group comprised 32 "healthy" non-demented patients, who underwent lumbar puncture because of suspected (but not confirmed) subarachnoid hemorrhage or pseudotumor cerebri, oculomotor palsies or other indications in the usual neurological survey. Routine CSF analysis was normal in each patient or control. The study was approved by the Ethics Committee of the Hospital "Doce de Octubre" and by the Investigation Committee of the Hospital "Príncipe de Asturias". Informed consent was obtained in each case. The clinical features of both groups are summarized in Table 1.

The following exclusion criteria were applied to both patients and controls: A) Therapy with pharmacological vitamin supplements in the last 6 months, B) Ethanol intake higher than 80 g/day in the last 6 months, C) Previous history of chronic hepatopathy, gastrectomy, pancreatic disease, diseases causing malabsorption, and chronic renal failure, D) Atypical dietary habits (diets constituted exclusively by one type of foodstuff, such as vegetables, fruits, meat, or others, special diets because of religious reasons, etc), E) Undernutrition, F) Previous history of severe systemic disease.

Lumbar CSF and venous blood samples were taken from each fasted patient or control between 8.00 and 10.00 a.m. Lumbar punctures were performed with the patients in a lateral recumbent knee flexed to chest position. The blood samples were obtained with Vacutainer and stainless steel needles, collected on ice and centrifuged after adding EDTA. Traumatic spinal punctures were excluded from the study. The first 2 ml of CSF were used for routine analyses, and a pool of the following 3–7 ml was used for special analyses, including those of thiamine. The CSF and plasma specimens were frozen at $-30°C$, in polyethylene tubes, and protected from light exposure with aluminum foil until analysis. The determinations were performed blindly.

The analysis of thiamine in plasma and in CSF was performed by ion-pair reversed phase high performance liquid chromatography using a XTerraRP18 (μm, 4.6×150 mm) Waters column and an Alliance 2690-Millenium chromatrography system with a 474 fluorescence detector. The methods have been reported in full detail elsewhere (Jiménez-Jiménez et al., 1999; Molina et al., 1994). The interday and intraday coefficients of variation for thiamine-diphosphate were, respectively, 8.7% and 6.1%, for thiamine-monophosphate 8.5% and 5.9%, and for free thiamine 7.1% and 4.3%. The results have been expressed as nmol/l.

The results were expressed as mean $\pm$ SD. The statistical analysis used the Biostatistical Packet of "R-Sigma Data Base" (Horus Hardware) (Moreu et al., 1990), and included the two-tailed student's t test, the Mann-Whitney test, ANOVA, and calculation of Pearson's correlation coefficient when appropriate.

Results

The results are summarized in Table 1. The mean CSF levels (Fig. 1) and the CSF/plasma ratios of thiamine-diphosphate, thiamine-monophosphate, free thiamine and total thiamine, and the mean plasma levels of thiamine-monophosphate of AD patients did not differ significantly from those of

Table 1. Clinical data and results of AD patient and control groups. Data of quantitative variables are expressed as mean (SD)

	AD-patients (n = 33)	Controls (n = 32)	p values
Clinical data			
Age (years)	72.6 (8.8)	70.2 (7.6)	n.s.
Female	18	18	
Male	15	14	
Height (cm)	159 (9.2)	160 (8.3)	n.s.
Weight (Kg)	61.3 (10.4)	72.1 (8.5)	<0.001
Body mass index (Kg/m^2)	24.4 (4.7)	28.2 (3.4)	<0.001
Age at onset of AD (years)	70.3 (7.8)		
Duration of AD (years)	2.3 (1.8)		
Minimental State Examination	13.5 (5.9)		
Nutritional markers			
Retinol (μmol/L)	1.56 (0.39)	1.80 (0.53)	<0.05
Total protein (g/dL)	6.9 (0.5)	7.0 (0.6)	n.s.
Albumin (g/dL)	4.1 (0.4)	4.2 (0.5)	n.s.
CSF thiamine levels (nmol/L)			
Thiamine-diphosphate	2.55 (1.70)	3.21 (2.28)	n.s.
Thiamine-monophosphate	3.57 (3.84)	4.30 (2.40)	n.s.
Free thiamine	1.17 (3.03)	2.17 (1.42)	n.s.
Total thiamine	7.29 (6.98)	9.46 (4.52)	n.s.
Plasma thiamine levels (nmol/L)			
Thiamine-diphosphate	2.22 (1.74)	3.23 (1.87)	<0.05
Thiamine-monophosphate	1.32 (2.02)	2.20 (3.20)	n.s.
Free thiamine	1.16 (1.21)	2.61 (2.93)	<0.05
Total thiamine	4.75 (7.72)	7.88 (5.79)	<0.05
CSF/plasma thiamine ratios			
Thiamine-diphosphate	3.02 (5.89)	1.56 (2.22)	n.s.
Thiamine-monophosphate	5.83 (4.80)	5.32 (6.64)	n.s.
Free thiamine	1.45 (2.74)	1.81 (3.45)	n.s.
Total thiamine	2.41 (2.10)	1.87 (1.75)	n.s.

AD Alzheimer's disease, *n.s.* non-significant

controls. Plasma thiamine-diphosphate, free thiamine and total thiamine levels were significantly lower in AD patients. When compared with controls, AD patients had lower weight ($p < 0.001$) and body mass index ($p < 0.001$). There was also a significant decrease in the serum retinol concentrations ($p < 0.05$) in AD patients, although the serum levels of total protein and albumin were similar in AD patients and controls.

There was no significant correlation in AD patients between the CSF or plasma levels of thiamine and the following values: age, age at onset of AD, duration of AD, and scores of the MiniMental State Examination, with the exception of plasma thiamine-diphosphate with MiniMental State Examination ($r = 0.41$, $p < 0.05$). CSF and plasma thiamine levels were not correlated with the exception of free thiamine, both in AD-patients ($r = 0.84$, $p < 0.01$) and in controls ($r = 0.40$, $p < 0.05$).

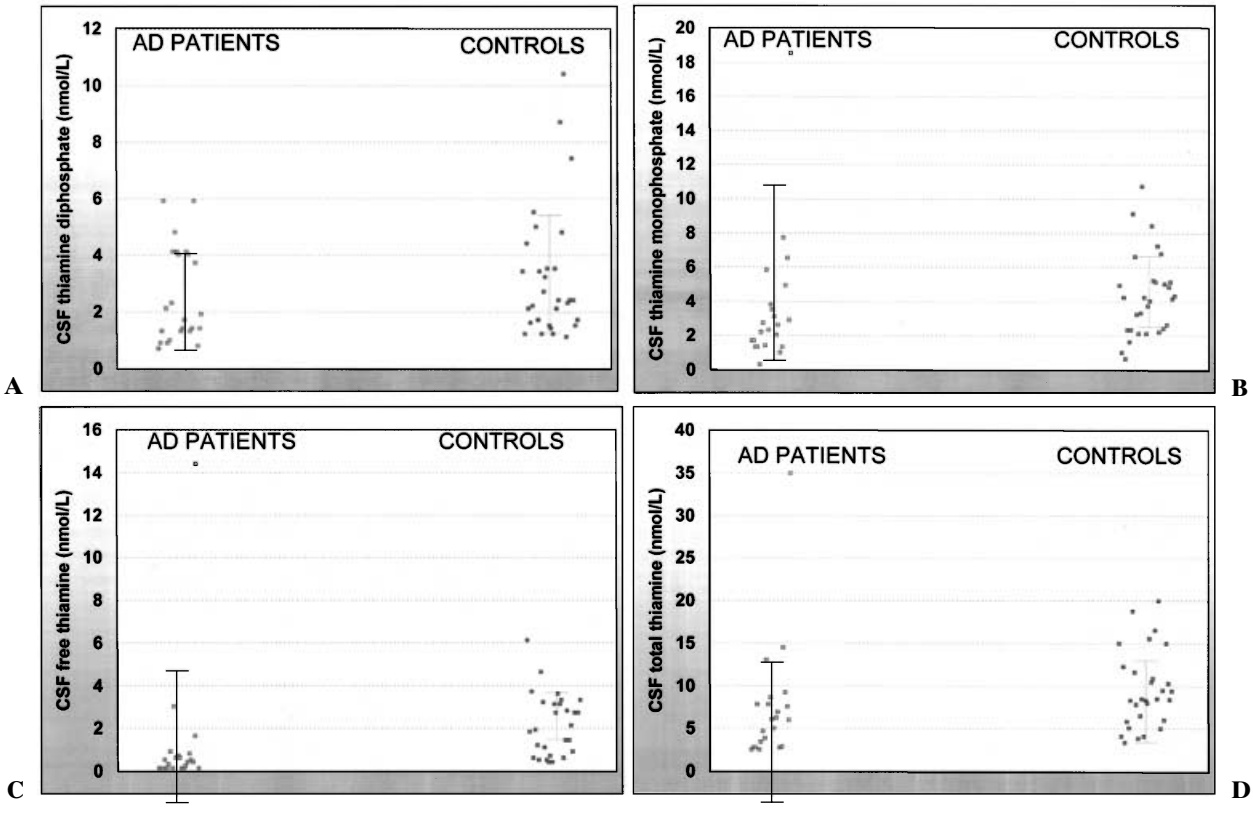

Fig. 1. Cerebrospinal fluid levels of thiamine-diphosphate (**A**), thiamine-monophosphate (**B**), free thiamine (**C**), and total thiamine (**D**) in AD patients and controls. Horizontal bars represent mean ± SD values

The mean decreases in the score of the MiniMental State Examination score per year could be assessed in 20 patients, and were not correlated with the CSF or plasma thiamine levels. Moreover, if we divided these patients into 2 groups taking as threshold the mean value of CSF or plasma thiamine values, the mean decreases in the score of the MiniMental State Examination in patients with "low thiamine levels" did not differ significantly from those of patients with "high thiamine levels" (Student's t test, Table 2). These data should suggest that thiamine values should not predict dementia progression.

Discussion

Thiamine has an important role in the brain oxidative metabolism. Mitochondrial fractions of rat brain are rich in thiamine derivatives (Bettendorf et al., 1994). This vitamin acts as a cofactor of several enzymes, namely the KGDHC, which is probably the most important and the rate-regulating enzyme in the Krebs cycle (Lai et al., 1977). KGDHC inhibition can induce mitochondrial respiratory chain dysfunction.

It has been reported decreased activity of KGDHC and other thiamine-dependent enzymes in the brain of AD patients (Butterworth and Besnard,

Table 2. Decreases in the score of the MiniMental State Examination per year – expressed as mean (SD)- of AD patients with "low thiamine levels" versus "high thiamine levels", taking as threshold the mean each thiamine values. Student's t test

	"Low thiamine levels"	"High thiamine levels"	p values
CSF thiamine levels			
Thiamine-diphosphate	1.22 (0.46) n = 13	1.21 (0.51) n = 7	n.s.
Thiamine-monophosphate	1.12 (0.46) n = 14	1.44 (0.41) n = 6	n.s.
Free thiamine	1.20 (0.50) n = 17	1.31 (0.05) n = 3	n.s.
Total thiamine	1.19 (0.46) n = 12	1.26 (0.49) n = 8	n.s.
Plasma thiamine levels			
Thiamine-diphosphate	1.19 (0.49) n = 14	1.33 (0.42) n = 6	n.s.
Thiamine-monophosphate	1.23 (0.46) n = 13	1.22 (0.38) n = 7	n.s.
Free thiamine	1.22 (0.45) n = 16	1.25 (0.49) n = 4	n.s.
Total thiamine	1.17 (0.51) n = 13	1.33 (0.33) n = 7	n.s.

n.s. non-significant

1990; Gibson et al., 1988; Mastrogiacomo et al., 1993). Interestingly, experimental thiamine deficiency induced by thiamine deficient diet or injections of thiamine inhibitors in rodents, is able to cause accumulation of amyloid precursor protein-like immunoreactivity in some brain areas (Calingasan et al., 1995, 1996, 1997). In addition, thiamine is important in the metabolism of acetylcholine and in its release from the presynaptic neurons (Meador et al., 1993). However, some preliminary trials with thiamine have been in general unsuccessful in the therapy of AD (Blass et al., 1988; Meador et al., 1993; Mimori et al., 1996; Nolan et al., 1991; Rodríguez-Martín et al., 2000).

The data of the present study show that, when compared with controls, AD patients had similar cerebrospinal fluid levels of thiamine derivatives. There was no correlation between CSF thiamine levels and the analyzed clinical features of AD. These data do not rule out the possibility that there may be regional deficiencies of thiamine or its esters in some areas of the brain of patients with AD, as previously reported by Mastrogiacomo et al. (1996). To our knowledge, the possible relationship between postmortem brain thiamine levels and in vivo cerebrospinal fluid thiamine levels is unknown.

In addition, we found decreased plasma levels of thiamine-diphosphate, free and total thiamine in AD patients. Other authors found normal (Scileppi et al., 1984; Renvall et al., 1989; Winograd et al., 1991) or decreased total thiamine levels (Agbayewa et al., 1992; Gold et al., 1995) but, to our knowledge, there are no previous data on serum or plasma levels of free thiamine and thiamine-esters in patients with AD. It is possible that low plasma levels of thiamine could be related with a deficiency of dietary intake of this vitamin in the context of the poorer nutritional state of our AD patients.

Although the main objective of this study was to measure the CSF and plasma thiamine levels, we also found that our AD patients had lower weight and body mass index when compared with controls. This finding is not surprising, since most epidemiological studies have shown that weight loss is com-

monly associated with AD (Barrett-Connor et al., 1996; Cronin-Stubbs et al., 1997; Du et al., 1993; Franklin and Karkeck, 1989; Guyonnet et al., 1998; Gillette-Guyonnet et al., 2000; Knittweiss, 1998; Reyes-Ortega et al., 1997; Singh et al., 1988; Tavares and Rabins, 1987; White et al., 1996, 1998; Wolf-Klein et al., 1992; Wolf-Klein and Silverstone, 1994). Moreover, it has been suggested that weight loss could precede the onset of cognitive symptoms (Barrett-Connor et al., 1996; Knittweiss, 1998), and a possible association of weight loss with the severity and the risk of death in AD patients (White et al., 1998). Interestingly, a longitudinal study showed that weight gain of 5% or more was also more common among AD patients (White et al., 1996). The reasons for weight loss in patients with AD are not fully understood, although it has been suggested a possible relationship with dysfunction in body weight regulation (White et al., 1996), mesial temporal cortex atrophy (Grundman et al., 1996), or carrying the APOE4 allele (Vanhanen et al., 2001). The suggestion of a possible hypermetabolic state in AD by some investigators (Wolf-Klein et al., 1992, 1995) has not been confirmed by others (Poehlman et al., 1997).

The CSF thiamine levels found in the present study and in another study by our group in parkinsonian patients (Jiménez-Jiménez et al., 1999) are relatively low when compared with those of other previous reports, that ranged between 60 and 102 nmol/L (Tallaksen et al., 1992). This is likely to be related with methodological differences. For example, Rindi et al. (1981) used an electrophoretic-fluorometric method, and they stated that thiamine-monophosphate was the only phosphoric ester of thiamine in the cerebrospinal fluid. Pedraza and Botez (1992) measured total CSF thiamine levels using a microbiological method with Lactobacillus fermenti. In the present study, we used ion-pair reversed phase high-performance liquid chromatography. This is likely a more sensitive and specific method, that allows the measurement of thiamine-diphosphate (Jiménez-Jiménez et al., 1999).

In conclusion, although AD is associated with decreased activity of KGDHC in particular areas of the brain, these findings are unrelated with alterations of CSF levels of thiamine. These results suggest that CSF thiamine levels are apparently unrelated with the risk for AD.

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