Short report

Thiamine deficiency and cerebrospinal fluid 5-hydroxyindoleacetic acid: a preliminary study

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SUMMARY In three out of five patients with low cerebrospinal fluid thiamine concentrations, the 5-hydroxyindoleacetic acid (5HIAA) values also were low. All patients received thiamine replacement therapy; they underwent a second lumbar puncture after 13, 6, 7, 5 and 45 days of treatment. In all patients blood and cerebrospinal fluid thiamine values rose after treatment. In those patients with initially low CSF 5HIAA, thiamine treatment increased 5HIAA markedly.

Thiamine deficiency is associated with an impairment of 5-hydroxytryptamine (5HT) neurons in experimental animals.¹ In rats, a long-lasting folate deficiency can induce a secondary thiamine deficiency² and some of the behavioural changes in these animals can be reversed by administration of high doses of thiamine.³ Recently we have reported⁴ that folate deficient patients, who exhibit a folate-responsive neuropsychiatric syndrome have low levels of the 5HIAA in their cerebrospinal fluid (CSF). Low values of CSF 5-hydroxyindoleacetic acid (5HIAA) were also reported in patients with inborn errors of folate metabolism.⁵ We now wish to report on CSF 5HIAA levels in a small group of thiamine deficient patients before and after thiamine supplementation. To our knowledge, this is the first study on the correlations between thiamine and 5HIAA in the human CSF.

Methods and Patients

Five patients were studied. Blood and CSF were taken before and after thiamine replacement therapy, for the measurement of blood and CSF thiamine, serum and CSF folate, and CSF tryptophan and 5HIAA levels. Blood and CSF samples were collected at 9.00–9.30 a.m. The last dose of thiamine was taken 14 hours before the second

lumbar puncture. The whole blood and CSF thiamine levels were assayed in duplicate, using *Lactobacillus fermenti*.⁶ When low values of thiamine were found, an additional incubation was carried out with added thiamine to check that no inhibitors of bacterial growth were present.⁷

The folate determinations (serum and CSF) were carried out using both *Lactobacillus casei*⁸ and radioisotope methods.⁹ Values for the two methods were in agreement and only the values for the radioisotope method are shown in the table. Tryptophan and 5HIAA were measured by high performance liquid chromatography with fluorometric detection.¹⁰ Informed consent was obtained in all patients for the second lumbar puncture.

Patients 1–4 (table) had alcohol-induced neurological disorders. Patients 1, 3 and 4 had cerebellar ataxia and patient 2 suffered from alcoholic polyneuropathy. Patient 5 who abstained totally from alcohol had cerebellar ataxia resulting from 25 years of treatment for epilepsy with 300 mg/day of phenytoin. On admission to the hospital she had also anticonvulsant-induced dyskinesias.¹¹ The first four patients received 300 mg/day of thiamine orally for 13, 6, 7 and 5 days respectively between the collection of the two CSF samples. The dietary habits were not modified during the thiamine replacement therapy. The fifth patient received 100 mg of thiamine orally per day for 45 days. None of the patients were receiving thiamine before hospitalisation but patient 1 received 100 µg of vitamin B₁₂ daily for two months before the first lumbar puncture; the same patient received 10 mg of folic acid intramuscularly between the two CSF samples.

Results

The table shows that all five patients had low CSF thiamine values initially but that these values rose

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Table Laboratory findings

Patient	Age	Sex	Pre or post Thiamine treatment	Folate (ng/ml)		Thiamine (ng/ml)		CSF indoles (ng/ml)	
				Serum	CSF	blood	CSF	tryptophan	5HIAA
1	52	M	Pre	2.5	7.4	32	10	478	22.0
			Post	7.2	8.3	90	142	470	24.0
2	37	M	Pre	5.4	7.5	32	25	640	11.0
			Post	4.2	7.8	98	68	750	11.4
3	39	M	Pre	1.3	9.4	51	22	507	1.9
			Post	2.5	6.6	83	59	566	6.9
4	60	M	Pre	2.6	11.0	42	29	390	1.2
			Post	2.4	10.6	58	48	163	7.2
5	69	F	Pre	8.5	12.5	34	18	289	1.9
			Post	6.6	16.7	140	115	236	24.7
Control values* (mean $\pm$ SD)				6.11 ± 1.53	19.7 ± 3.9	66.7 ± 12.8	44.0 ± 6.9	380 ± 108	27.1 ± 10.9

*Control values are the mean of 41 for the folate, 22 for the thiamine and 15 for the CSF indoles. Values for the controls were obtained from patients undergoing lumbar puncture for routine diagnostic purposes. They were on a normal diet and none of them were suffering from any clinical condition or were on any drugs known to affect folate, thiamine or indole metabolism.

after thiamine treatment. Patient 3 had a pretreatment blood thiamine in the normal range. However, blood levels are more dependent on variations in the diet and a true vitamin deficiency is sometimes seen only in the CSF.¹² Patients 1–4 had some evidence of borderline folate deficiency but patient 5 was normal in this respect.

CSF tryptophan values were normal in all patients (table). The mean pretreatment CSF 5HIAA for the folate deficient patients (7.6 ng/ml) was less than control values ($p < 0.005$, two-tailed Student's *t* test). Pretreatment CSF 5HIAA values were low (below mean $-2 \times$ SD of controls) in three out of five patients (nos 3–5). In these three patients thiamine treatment increased CSF 5HIAA markedly and the largest rise was seen in the patient no 5 who had been treated for the longest time with thiamine.

Discussion

The changes in CSF 5HIAA values appeared to result from thiamine treatment and not from some other nutritional factors because the dietary habits were not modified during the thiamine replacement therapy, and because the serum and CSF folate values (except case no 1), as well as the CSF tryptophan levels, did not differ significantly in the whole group before *versus* after thiamine therapy. Our data suggest that thiamine deficiency can decrease 5HT metabolism in human by an unknown mechanism that can be reversed by thiamine supplementation. However, two of the five patients had normal 5HIAA values which were only increased minimally by thiamine supplementation. This suggests that thiamine deficiency alone does not necessarily impair brain 5HT metabolism in so far as this is indicated by CSF 5HIAA values.

The last point to be stressed is that patient no 5

who had been treated with phenytoin had low CSF 5HIAA values and low blood and CSF thiamine levels. In previous studies^{13,14} we found abnormally low thiamine values in both whole blood and CSF in phenytoin-treated epileptics. One of us (MIB unpublished observations) studied recently two other cases of chronic PHT-induced cerebellar ataxia: with low blood and CSF thiamine values. Therefore this study raises some important questions for future research namely: (1) to what extent is the phenytoin-induced chronic cerebellar ataxia¹⁵ correlated with a lowering of thiamine levels?; (2) what is the mechanism by which phenytoin usually lowers the levels of CSF 5HIAA¹⁶; is this mechanism correlated with folate deficiency, with thiamine deficiency or with both? Further studies are needed in both humans (epileptic and non-epileptic patients) and animals to verify to what extent the disturbed serotonin metabolism is correlated not only with folate values as has been already emphasized^{16,17} but also with thiamine metabolism.

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