

Short report

CSF choline levels in groups of patients with cranial trauma or extrapyramidal disorders

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SUMMARY Choline levels in lumbar cerebrospinal fluid (CSF) were measured in patients with craniocerebral trauma (N = 67), Parkinson's disease (N = 20), miscellaneous extrapyramidal disorders (N = 28) and Huntington's chorea (N = 5). No differences in CSF choline levels were observed between these diagnostic groups and a group of neurological controls (N = 22). However, CSF choline levels were found to increase with age.

From studies on choline metabolism in rabbits it appears that 42% of CSF choline originates from plasma choline and the remaining part from plasma or brain phospholipids, while no contribution from acetylcholine metabolism in the brain could be detected.^{1,2}

Reported findings of normal CSF choline levels in Parkinson's disease,^{3,4} Huntington's chorea^{4,5} and Alzheimer's disease^{6,7} suggest that also in humans impaired central cholinergic activity is not reflected in the CSF choline levels. Part of the present study is an attempt to confirm these findings in Parkinson's disease and Huntington's chorea.

Accepting the view that CSF choline levels are largely determined by blood choline levels and by choline derived from the breakdown of phospholipids in the brain, we might expect to find abnormal CSF choline levels in those diseases in which disturbances of the blood-brain barrier or of brain phospholipid metabolism may occur. We therefore measured also CSF choline levels in patients with cranial trauma in whom the blood-brain barrier may be disturbed,⁸ and in patients with extrapyramidal disorders in whom degenerative processes might be assumed.

Methods

The lumbar cerebrospinal fluid used in the choline assay was a small aliquot of the first 10 ml of CSF obtained as a routine procedure for neurological diagnostic purposes, only 20 μ l of CSF being required for the choline assay. In 14 controls and six Parkinsonian patients it was possible to obtain also an aliquot of the second 10 ml fraction of CSF. The samples were immediately frozen after collection and kept at -20°C until analysed. No special dietary precautions were taken, the patients receiving normal hospital diets containing an estimated amount of 250-600 mg choline/24 h.

The patients were divided in three main groups.

(1) *Controls*. This group consisted of 22 individuals, who were admitted for myelography on suspicion of a herniated disk.

(2) *Cranial trauma*. This group consisted of 67 patients who were admitted following cranial trauma, most of whom suffered from severe concussion; three patients had a subdural or epidural haematoma and two patients had post-traumatic complaints. Spinal taps were performed respectively between 1 and 14 days (n = 43), between 15 and 28 days (n = 12), and between 29 and 90 days (n = 10) following the accident. In the two patients with post-traumatic complaints CSF was obtained respectively 2 and 7 years after the accident.

(3) *Extrapyramidal disorders*. This group comprised patients suffering from so-called extrapyramidal disorders. At the time of collection of CSF the patients were admitted for clinical evaluation and commonly did not receive any treatment, with a few exceptions. In the Gilles de la Tourette patients and in four of the five patients with Huntington's chorea the haloperidol medication was continued. It was common practice to discontinue anti-Parkinsonism medication before admission, but in four cases orphenadrine therapy was continued. It has been shown before that

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orphenadrine³ and anti-Parkinsonism drugs in general⁴ did not affect CSF choline levels. This group is divided into three subgroups:

(A) Miscellaneous extrapyramidal disorders. This subgroup of 28 individuals comprised a variety of (heredo) degenerative diseases: cerebellar ataxias (8), chorea athetoses (3), essential or familial tremor (4), myoclonias (2), hypokinetic rigid syndromes (4), Mills syndrome (2), Gilles de la Tourette disease (2) and heredo-degenerative disorders of undetermined origin (3).

(B) This subgroup contained 20 patients with Parkinson's disease.

(C) This subgroup consisted of five patients suffering from Huntington's chorea.

Choline assay. 20 μ l of CSF was used for the determination of choline with a radioenzymatic assay as previously described.^{2,9}

Statistical analysis. Analysis of covariance of the data was performed with the Anova Program of the Statistical Package for the Social Sciences, version 8.0 from the Vogelback Computing Center of the Northwestern University.

Results

Nearly identical choline levels were found in two consecutive 10 ml fractions of lumbar CSF of both a group of 14 controls (mean \pm SD resp. 2.21 ± 0.54 and 2.17 ± 0.58 nmoles/ml) and a group of six Parkinson patients (resp. 2.24 ± 0.28 and 2.20 ± 0.29 nmoles/ml).

The table shows that no large differences in CSF choline levels were found between the investigated groups. However, it can be seen that the sex and age distribution over the groups is quite dissimilar. Therefore, the differences between the patient groups and the control group were tested by analysis of covariance with sex and age as covariates and diagnosis as the main effect. Due to the small number the group of patients with Huntington's chorea was excluded from this analysis, but this group was found not to differ from the control group by Student's *t* test ($p > 0.05$). The analysis of covariance showed that no significant differences in CSF choline levels were detected between the control group and any of the patient groups we investigated. It was also found that CSF choline levels were

independent of the sex of the patients; however, these levels were highly significantly dependent on the age of the patients. ($F(1,135) = 17.783$, $p < 0.0001$ for the pooled results, with a Pearson correlation coefficient of 0.34, $p < 0.0001$).

After it was established that the slopes of the regression lines representing the relationship between CSF choline levels and age were not significantly different for the various patient groups, all data were pooled and the regression line calculated. From these calculations it follows that the regression coefficient is 0.016 ± 0.0038 nmoles/year (\pm SEM), while at age zero the extrapolated choline level is 1.59 ± 0.16 nmoles/ml (\pm SEM).

Discussion

From the groups of patients in whom we measured CSF choline levels in two consecutive 10 ml fractions, we obtained no indication of the existence of a choline gradient in the first 20 ml of lumbar CSF. However, a gradient might exist in the regions closer to the brain, as Welch *et al.*,⁴ measuring over a range of 35 ml of CSF, presented evidence in favour of such a gradient. Also, a small number of data have been published which shows that choline levels in ventricular CSF might be higher than those in lumbar CSF.^{3,4}

In support of this, we measured high choline levels in ventricular CSF obtained from one patient with essential tremor and one with Parkinson's disease (respectively 3.84 and 3.45 nmoles/ml).

It has been reported by Glen *et al.*⁷ that in a group of 35 neurological controls CSF choline increased significantly with age. In this paper we have shown that CSF choline levels are related to age in the control group as well as in the cranial trauma group, the group with miscellaneous extrapyramidal disorders and the Parkinson's disease group. As the increase per year was not significantly different for these groups, we were able to calculate that for the combined groups choline levels in lumbar CSF can be described by the formula: CSF choline (nmoles/ml) = $1.59 + 0.016 \times \text{age}$ (in years). This formula indicates that in comparing CSF choline levels of different groups it is necessary to correct for differences in age, which we did by introducing age as a covariate in the analysis of covariance.

Our finding that CSF choline levels of the control group was not different from those in the Parkinson group confirms earlier reports.^{3,4} Also, the unchanged CSF choline levels we found in Huntington's chorea are in agreement with the results of Welch *et al.*⁴ and Growdon *et al.*,⁵ but contrast with an early report of Aquilonius *et al.*³

In this connection it is interesting that unchanged

Table Summary of CSF choline levels in various patient groups

Patient group	N (δ/η)	Age (years)*	Choline (nmoles/ml)*
Controls	15/7	42 \pm 14	2.08 \pm 0.53
Cranial trauma	46/21	30 \pm 16	2.19 \pm 1.15
Miscellaneous extrapyramidal disorders	22/6	36 \pm 22	2.21 \pm 0.79
Parkinson's disease	13/7	63 \pm 8	2.34 \pm 0.50
Huntington's chorea	4/1	40 \pm 18	2.21 \pm 0.45

*Results expressed as mean \pm S.D.

CSF choline levels have also been reported for patients with Alzheimer's disease,^{6,7} a well documented cholinergic deficiency state.¹⁰⁻¹³ As central cholinergic activity is probably also impaired in Parkinson's disease⁴ and Huntington's chorea,¹⁴⁻¹⁶ it now seems well established that changes in the cholinergic activity of the CNS are not reflected in lumbar CSF choline levels, in accordance with the results of pharmacological experiments on rabbits.²

The lumbar CSF choline level of our group of patients with miscellaneous extrapyramidal disorders also was not different from that of the control group. It might have been possible that the presumed degenerative processes in this class of diseases would have led to an abnormal phospholipid metabolism, which probably is one of the sources of CSF choline.^{1,2} However, the finding that lumbar CSF choline levels were unchanged, gives no support to this hypothesis or shows that if these processes occur in the brain they do not result in changed choline levels in the lumbar region.

Blood-brain barrier disturbances may occur after cranial trauma⁸ and we could therefore expect that the transport of choline from blood to CSF would be changed. But again, our results showed that CSF choline levels in the cranial trauma group were not different from the control group. Also CSF choline levels in this group did not correlate with the time elapsed after the traumatic incident ($r = -0.1125$, $p = 0.205$).

In general, we may conclude that CSF choline levels are very stable and not indicative for any of the brain diseases investigated. The only systematic change being observed is the increase in CSF choline levels with age.

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