Activities and Kinetic Properties of Lumbar Cerebrospinal Fluid Cholinesterases in Relation to Clinical Diagnosis, Severity, and Progression of Alzheimer's Disease

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ABSTRACT: Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities of lumbar cerebrospinal fluid (CSF) have been measured in seventeen patients with a clinical diagnosis of probable Alzheimer's disease (Prob AD), possible Alzheimer's disease (Poss AD), or dementia of non-Alzheimer aetiology (Non-AD). The three diagnostic groups did not differ with regard to the K_m or saturation kinetic properties of AChE and BChE. The CSF AChE activity was significantly higher in Prob AD than in Non-AD patients. The groups did not differ significantly in BChE activity. The ratio of AChE to BChE activity was significantly higher in both the Prob AD and Poss AD groups than in the Non-AD group, and the ranges of values in the Prob AD and Non-AD groups did not overlap. Among patients in the Prob AD group, severity of dementia was correlated with both AChE activity and the AChE/BChE ratio, and progression of dementia over time was also correlated with AChE/BChE.

The AChE/BChE ratio correlated more strongly than AChE with severity and progression of dementia in Prob AD patients, and also better distinguished them from Non-AD patients, suggesting that AChE/BChE may be the more useful marker for diagnosis of AD. It is not clear from the results whether AChE/BChE is useful for diagnosis of the complex dementia cases in the Poss AD group.

RÉSUMÉ: Activité et propriétés cinétiques des cholinestérases du liquide céphalo-rachidien lombaire en relation avec le diagnostic clinique, la sévérité et la progression de la maladie d'Alzheimer L'activité de l'acétylcholinestérase (AChE) et de la butyrylcholinestérase (BChE) du liquide céphalo-rachidien (LCR) lombaire ont été mesurées chez dix-sept patients avec un diagnostic de maladie d'Alzheimer probable (Prob MA), maladie d'Alzheimer possible (Poss MA), ou démence d'étiologie autre (Non-MA). Les trois groupes de patients ne différaient pas quant au K_m ou auz propriétés cinétiques de saturation de l'AChE et de la BChE. L'activité de l'AChE dans le LCR était significativement plus élevée chez les Prob MA que chez les Non-MA. Les deux groupes ne différaient pas significativement quant à l'activité de la BChE. Le rapport entre l'activité AChE et l'activité BChE était significativement plus élevé dans les groupes Prob MA et Poss MA que dans le groupe Non-MA, et l'écart des valeurs dans les groupes Prob MA et Non-MA ne se chevauchaient pas. Parmi les patients du groupe Prob MA, la sévérité de la démence était en corrélation avec l'activité de l'AChE et le rapport AChE/BChE, et la progression de la démence dans le temps était également en corrélation avec l'activité de l'AChE et le rapport AChE/BChE, et la progression de la démence dans le temps était également en corrélation avec l'AChE/BChE.

La corrélation entre le rapport AChE/BChE et la sévérité et la progression de la démence chez les patients Prob MA était plus forte que celle de l'AChE et les distinguait mieux des patients Non-MA, suggérant que l'AChE/BChE peut être le marqueur le plus utile pour le diagnostic de la MA. Ces résultats ne nous permettent pas de déterminer si l'AChE/BChE est utile dans le diagnostic des cas complexes de déménce du groupe Poss MA.

A deficiency of acetylcholinesterase (AChE) has been observed in brain tissue from patients with Alzheimer's disease (AD), and association of this deficit with a deficiency of choline acetyltransferase[1] suggests that it results from a loss of cholinergic neurons in the brain.[2,3] An increase in nonspecific cholinesterase activity attributable to butyrylcholinesterase (BChE) has also been found in AD brain, and the decreased AChE and increased BChE in AD are correlated both with the number of senile plaques in the brain and the clinical severity of dementia.[1,4] Because both AChE and BChE activities are mea-

surable in the cerebrospinal fluid (CSF), numerous studies have attempted to establish whether or not the brain abnormalities of these enzymes in AD are detectable in the CSF. Studies comparing AD patients to nondemented control cases have produced conflicting results: AChE in lumbar CSF and AD cases has been reported to be decreased in some studies[5-10] but unchanged in others[11-18] whereas BChE activity has been variously reported to be decreased[10,15,18] or unchanged.[9,14,16,17] Because the brain abnormalities of AChE and BChE in AD are in opposite directions from the norm, the AChE/BChE ratio in CSF has been studied, again with conflicting results.[6,9,10,14,15,17,18]

The variable results in these studies may be due to methodological differences among them. Many investigators did not inhibit BChE when assaying AChE activity, and thus measured total cholinesterase activity rather than specific AChE activity. Most studies have relied on clinical criteria for diagnosis of AD, and inclusion of patients with mixed dementia in the AD group of some studies may have affected the results, in view of the evidence that patients with Non-AD dementia have different patterns of CSF cholinesterase abnormalities than patients with AD.[16,18] In a recent study of lumbar CSF in AD cases diagnosed on the basis of cortical biopsy,[18] BChE activity was decreased and the AChE/BChE ratio was increased in AD compared to non-demented control cases. In the same study, the AChE/BChE ratio was increased in ventricular CSF from AD cases diagnosed by autopsy. These results provide strong evidence that the cholinesterase abnormalities in AD brain are reflected in CSF, and suggest that the AChE/BChE ratio in lumbar CSF may be useful in the diagnosis of AD.

The present investigation incorporated a number of methodological improvements over previous clinical studies. AChE was measured in the presence of an inhibitor of BChE. Moreover, the quantitative measures of AChE and BChE activity used in the present study were extrapolated estimates of V_{max} derived from assays at five subsaturation substrate concentrations. Under conditions of substrate saturation, AChE undergoes inhibition, whereas BChE activity is enhanced due to cooperative kinetics,[19] resulting in a lower estimation of the AChE activity and a higher estimation of the BChE activity in a specimen. The extrapolated V_{max} measures used in the present study thus enhance the precision in determining the AChE/BChE ratio, and also allow determination of the degree of substrate inhibition of AChE. Previous studies have indicated that AChE from cerebral cortex and ventricular CSF[18] of patients with AD does not exhibit the normal substrate inhibition.

Another methodological issue addressed in the present study was the diagnostic classification of patients. Patients were diagnosed according to the NINCDS-ADRDA criteria, which were developed by a Task Force convened under the auspices of the National Institutes of Health of the United States.[20] These criteria distinguish patients with "probable AD", in whom all other identifiable causes of dementia have been excluded, from patients with "possible AD", in whom another condition that may cause dementia is present but is not considered to be sufficient alone to account for the patient's dementia symptoms. By distinguishing patients in these diagnostic categories, the present investigation permitted analyses of the degree to which the relationship of CSF cholinesterases to the severity and rate of progression of dementia may be specific to AD, and of possible differences in the sensitivity of CSF cholinesterases for diagnosing

AD depending on whether the latter is the sole aetiology for dementia or is present in conjunction with other aetiologies. The comparison group for evaluating the usefulness of CSF cholinesterases in the diagnosis of AD was a group of patients with dementia that was entirely attributable to an aetiology other than AD. In an effort to enhance the accuracy of the clinical diagnoses, as well as to measure the progression of dementia, patients in the present investigation were re-examined longitudinally after their initial examination.

METHODS

Patients

All patients or a relative responsible for them gave informed consent prior to their participation in the investigation.

Probable AD (Prob AD) was diagnosed in six women and one man based on confirmation of dementia by neurological history and examination, and exclusion of aetiologies other than AD that could cause or contribute to the dementia. All patients had a CT brain scan, electroencephalogram, blood tests of thyroid, hepatic and renal function, vitamin B_{12} and folic acid levels, and a serologic test for treponemal disease. A Hachinski Ischemia Scale[21] score of five or more was exclusionary. The Dementia Rating Scale (DRS) of Mattis[22,23] was administered in all cases in order to confirm the diagnosis of dementia and to quantitate its severity. Table 1 describes the ages and DRS scores of patients in the Prob AD and other diagnostic groups.

Possible AD (Poss AD) was diagnosed in three women and four men on the basis of the same diagnostic evaluation used for Prob AD. Patients with Poss AD had a neurological history and examination compatible with AD, but either had atypical features in their clinical presentation, or had another disorder that could contribute to the aetiology of their dementia.[20] Two patients had Poss AD with atypical features: one had prominent aphasic symptoms and the other had prominent visuospatial impairment, these being the first symptoms of dementia described historically and also the most prominent symptoms at the time of their respective examinations. Three patients were diagnosed as Poss AD with cerebrovascular disease, either because the Hachinski Scale score was 5 or greater, or because a single cerebrovascular accident was documented on neurological examination or CT brain scan. One patient had a diagnosis of Poss AD with major depression. Another patient had a history of alcohol abuse with persistent dementia after six months of abstinence.

Table 1: Age and Dementia Rating Scale Scores.[1]

Group	Age (Years)	Baseline DRS	Change in DRS (points per month)
Prob AD (n=6)	72.3 (6.6) (64 to 84)	105 (20) (78 to 133)	1.6 (1.2) (0.2 to 3.3)
Poss AD (n-7)[2]	69.0 (8.5) (55 to 82)	89 (58) (3 to 140)	1.9 (4.0) (-1.0 to 8.8)
Non-AD (n=4)	61.2 (22) (39 to 88)	123 (15) (107 to 142)	0.3 (0.9) (-0.8 to 1.4)

[1]Table entries indicate the group mean followed by (standard deviation)/(range).
[2]n=5 for change in DRS: a second DRS score was not obtained in 2 cases.

Non-AD Dementia was diagnosed in one woman and three men. Two patients had multiple infarct dementia (MID) diagnosed on the basis of multiple cerebral infarctions documented by clinical examination and CT brain scan. Another had a mild dementia, dysarthria and ataxia associated with a chromosome 4;6 translocation.[24] The fourth patient had a slowly progressive dementia syndrome without other neurological signs, but had multiple relatives with either amyotrophic lateral sclerosis or Parkinson's disease; a temporal lobe biopsy showed only minimal astrocytic gliosis.

Procedure

Lumbar Puncture Patients were not given psychoactive drugs for two weeks prior to the lumbar puncture, which in all cases was performed between 9 and 10 AM after a night of recumbency monitored by nursing staff. All CSF samples used for the study were free of blood, and one patient with Prob AD (not described in Table 1) was excluded because of traumatic blood contamination of the CSF. The 3rd through 18th milliliter (ml) of CSF were collected in 4 sequential 4 ml samples, from which equal volume aliquots were combined to create the final samples used for the cholinesterase measurements described below.

Neuropsychological Testing Baseline neuropsychological testing was performed within 3 days of the lumbar puncture, and was repeated after an interval of 8 to 23 months. Two patients, both diagnosed as Poss AD with atypical features, did not have follow-up neuropsychological testing. The patient with prominent aphasia had progressed to the point of being untestable; his baseline DRS was 3, and repeat testing would thus have been of limited value for measuring progression. The other patient declined to have repeat testing.

CSF cholinesterase measurements Biochemical analyses were performed without knowledge of the diagnosis. CSF AChE was measured using a single-vial radiometric method with ^{3}H-acetyl-labeled acetylcholine as the substrate.[25] Assays were performed at 30°C, pH 8.0, in the presence of 150mM sodium and $10^{-5.33}$M ethopropazine. In preliminary studies, this concentration of ethopropazine was found to inhibit 90 to 95% of BChE activity and only 5 to 10% of AChE activity.[26] The K_m of each CSF sample was estimated as the slope of the Eadie-Hofstee plot for five substrate levels (0.3 to 500 uM), each run in triplicate, and V_{max} was determined by extrapolation from the same slope. AChE activity in nanomoles of substrate hydrolyzed per minute per ml of CSF was calculated from V_{max}. Using this method, the coefficients of variation for repeated assays of the same specimen on difference days were .022 for Km and .029 for AChE activity. CSF BChE was measured by a similar assay using ^{3}H-butyryl-labeled butyrylcholine as the substrate, in five concentrations ranging from 0.01 to 80 uM. The coefficients of variation for this assay were .069 for Km and .020 for BChE activity. Enzyme specific activities were calculated on basis of CSF protein determinations using the Bio-Rad method. Saturation kinetics were measured using higher substrate levels in the AChE and BChE assays. For AChE, substrate inhibition was measured by determining the ratio of enzyme activities at substrate concentrations of 10 mM and 1 mM of ACh. For BChE, the ratio of activities at 2 mM and 0.08 mM of BCh was used to measure the increase in enzyme activity due to cooperative kinetics at the higher substrate concentration.

Statistical Analysis Results were analyzed by Student's *t* test and by the Spearman rank correlation (r_s) test.

RESULTS

Table 1 presents the baseline DRS scores and change in scores between the baseline and follow-up testing for patients in the Prob AD, Poss AD and Non-AD groups. Means for the Prob AD and Poss AD groups did not differ from one another or from the Non-AD group mean for either measure.

Table 2 presents the CSF activities of AChE and BChE and their ratio. Enzyme activities were evaluated both in units of nanomoles (nmol) of substrate hydrolyzed per minute (min) per milliliter (ml) of CSF and in specific activity units (nmol/min/milligram of protein). The pattern of results was the same using either unit of measure, and the data are therefore presented only for the volumetric (nmol/min/ml) units. Means for the Prob AD and Poss AD groups did not differ for any measure. The mean AChE activity was significantly greater in the Prob AD than in the Non-AD group, although the range of values in the two groups overlapped. The mean AChE/BChE ratio was significantly greater in both the Prob AD and Poss AD groups than in the Non-AD group, and the ranges of values for the Prob AD and Non-AD groups were distinct.

The AChE/BChE values of 3 Poss AD patients overlapped the Prob AD group range: two of these were the Poss AD patients with atypical features, and the third was a case of Poss AD with associated CVD. The remaining Poss AD patients had AChE/BChE values that overlapped the Non-AD range. Two of these were cases of Poss AD with CVD; the others represented Poss AD with associated depression and alcoholism, respectively. The case with alcoholism had an AChE/BChE value of 3.3 and a DRS change score of -1.0, indicating improvement during a year of abstinence from alcohol, and suggesting that alcoholism and not AD was the aetiology of dementia. The follow-up examinations in the remaining Poss AD cases did not establish the aetiology of dementia, and it is not clear in these cases whether the ratio of AChE to BChE differentiates those with AD from those who do not have AD.

Among patients in the Prob AD group, baseline DRS scores were strongly correlated with both CSF AChE (r_s=.77, $p<.05$) and the AChE/BChE ratio (r_s=.94, $p<.001$). Changes in DRS scores over time were also highly correlated with the AChE/BChE ratio (r_s=.77, $p<.05$). When patients with Prob AD and Poss AD were examined as a pooled group, the correla-

Table 2: CSF Cholinesterase Activities[1]

| Group | Activity (nmol/min/ml) | | AChE/BChE Ratio |
	AChE	BChE	
Prob AD (n=6)	29.6* (7.6) (23 to 44)	7.0 (1.6) (5.6 to 10)	4.3** (0.6) (3.8 to 5.3)
Poss AD (n-7)	23.8 (4.8) (17 to 33)	6.6 (1.0) (5.2 to 8.3)	3.6* (0.3) (3.3 to 4.0)
Non-AD (n=4)	17.1 (9.4) (5.5 to 28)	5.6 (2.8) (2.4 to 9.0)	3.0 (0.6) (2.3 to 3.7)

[1]The table entries indicate group mean (standard deviation)/(range). Means that differed from the Non-AD mean by *t* - test: *$p<.05$, **$p<.01$.

tion between baseline DRS and CSF AChE remained strong (r_s=.50, p<.05), although it was lower than that in the Prob AD group alone, and the significance of the other correlations fell below an alpha level of .05. When all cases were examined, pooling the Non-AD group with the others, none of the correlations were significant statistically.

Table 3 presents the K_m values and measures of saturation kinetics for AChE and BChE. There were no significant differences among the diagnostic groups for any of these measures. The trend toward less substrate inhibition in the Non-AD group is attributable to one subject in that group who did not manifest substrate inhibition.

DISCUSSION

In the Introduction we indicated that previous studies of CSF cholinesterases comparing AD cases with non-demented control cases have produced equivocal results. The present investigation examined a different but clinically important diagnostic question: are CSF cholinesterase measurements useful for differentiating AD cases from cases of Non-AD dementia? Our findings of increased AChE and AChE/BChE ratio in AD compared to Non-AD cases correspond to the results of Appleyard et al[18] for lumbar CSF from patients diagnosed by cortical biopsy as well as by clinical criteria. Other studies have reported overlap in the values of AD and Non-AD dementia cases for AChE[7,13,16,27] and for BChE,[16,27] but none of those studies examined the AChE/BChE ratio.

The original reason[6] for examining the AChE/BChE ratio was that the brain abnormalities of AChE and BChE were reported to differ in opposite directions from the norm,[4] and on the assumption that these abnormalities would be reflected in CSF it was expected that the CSF AChE/BChE ratio would enhance the discrimination between AD and non-AD cases beyond the discrimination achieved using either enzyme alone. There is no direct evidence that AChE and BChE are metabolically related, but the observation in the present investigation that the AChE/BChE ratio correlated more strongly than did AChE alone with severity and progression of dementia supports the hypothesis that abnormalities in both AChE and BChE are associated with the pathophysiologic process in AD.

These observations suggest that the AChE/BChE ratio in lumbar CSF may be more useful for diagnosis of AD than measurement of either AChE or BChE alone. Although the ratio measure distinguished Prob AD from Non-AD dementia cases, it is not clear from the results whether it is useful for diagnosis of the complex dementia cases in the Poss AD group. Resolution of that question awaits histopathological diagnosis by postmortem autopsy in those cases.

The decrease in lumbar CSF BChE activity and increase in AChE/BChE ratio in AD cases compared to non-demented control cases that were observed in two previous investigations[15,18] were not found in two other large case series that have recently been published.[9,17] Those negative results sound a note of caution regarding the prospect of using the CSF AChE/BChE ratio for the diagnosis of AD. However, the clinical diagnosis of AD remains vulnerable to error, and it is possible that misclassification of some cases in those studies altered the discrimination between the AD and control groups using the AChE/BChE ratio. Another factor that may have altered the discrimination is the fact that in one of those studies[9] the activities of BChE and to a lesser degree AChE were measured using high substrate concentrations. (The other report did not specify the substrate concentrations that were used.) As the present investigation has demonstrated, at high substrate concentrations the measured activity of AChE decreases whereas that of BChE increases. Both of these effects diminish the AChE/BChE ratio, and may have the consequence of reducing or reversing the direction of differences in that ratio among cases or between diagnostic groups.

No differences in the saturation kinetic properties of K_m values for AChE or BChE in lumbar CSF were found in the present study. Appleyard et al[18] found that AChE in ventricular CSF from patients with AD did not exhibit substrate inhibition, which is consistent with previous observations by Perry and Perry[28] on brain AChE in AD. As in the present investigation, AChE in lumbar CSF from AD cases examined by Appleyard et al did exhibit substrate inhibition. These observations suggest that some of the AChE in lumbar CSF originates from sources other that the brain. Lal et al[13] found no gradient in AChE activity levels from sequential samples of lumbar CSF, suggesting that CSF AChE originates from the spinal cord as well as the brain. We also found no gradient in the activities of AChE or BChE in sequential 4 ml samples of CSF examined in 7 of our cases (data not shown). The apparently diffuse origin of cholinesterases in lumbar CSF may diminish their sensitivity as indicators of the brain cholinesterase abnormalities in AD. However, even if some lumbar CSF cholinesterases originate from sources other than the brain, changes in brain activities may result in altered activities in lumbar CSF.

Strong correlations between lumbar CSF cholinesterase activities and dementia severity in Prob AD cases have been found in previous studies[15,18] based on different case series and using different neuropsychological and neurochemical methods. Others, however, have failed to find such strong correlations.[7,13,16,17] These discrepancies may be attributable to differences in the sensitivities of the severity measures that were used, or to differences in the subject populations studied. In the present investigation, severity was measured using the Mattis Dementia Rating Scale, which has a range of 144 points along which scores may be distributed, thereby enhancing sensitivity to dif-

Table 3: Kinetic Properties of CSF Cholinesterases[1]

| Group | K_m (μmol/L) | | Saturation Kinetics | |
	AChE	BChE	AChE[2]	BChE[3]
Prob AD (n=6)	130 (5.3) (124 to 140)	18.9 (1.3) (17.4 to 20.7)	0.67 (0.05) (0.59 to 0.73)	1.48 (0.04) (1.4 to 1.5)
Poss AD (n-7)	132 (6.8) (122 to 140)	19.7 (1.2) (18.2 to 21.3)	0.71 (0.06) (0.61 to 0.76)	1.43 (0.11) (1.3 to 1.6)
Non-AD (n=4)	129 (4.9) (123 to 135)	18.1 (1.6) (17.0 to 20.4)	0.84 (0.20) (0.65 to 1.12)	1.50 (0.14) (1.4 to 1.7)

[1]The table entries indicate group mean (standard deviation)/(range). The group means did not differ at p<.05 by t - test for any of the variables.
[2]Values represent the ratio of AChE activities at substrate concentrations of 10 mM and 1 mM of ACh.
[3]Values represent the ratio of BChE activities at substrate concentrations of 2 mM and .08 mM of BCh.

ferences in severity between cases beyond what is detectable by the brief scales used in other studies. The strong correlations between severity and CSF cholinesterase measures in the Prob AD group were not observed when Prob AD and Poss AD cases were pooled together. The lower correlations found in other studies may have resulted from inclusion of some cases whose dementia results from a combination of AD and other aetiologies for dementia. If the relationship between CSF cholinesterases and dementia is unique to AD, inclusion of cases with mixed aetiologies of dementia would have the effect of reducing the ability to detect the correlation.

Although CSF cholinesterases have been measured longitudinally,[9,17] no previous study has examined the longitudinal progression of dementia in relation to CSF cholinesterase activities. The observation in the present study that the CSF AChE/BChE ratio correlates with rate of dementia progression in cases with Prob AD raises the possibility that this measure may be useful in clinical prognosis. The fact that the correlation is significant only for the Prob AD group again suggests the specificity of the relationship to AD in contrast to other aetiologies of dementia.

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