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Serum and CSF Cholinesterase Activity in Various Kinds of Dementia

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Summary. The activity of acetyl- and butyrylcholinesterase was determined in serum and CSF of controls and patients suffering from different types of dementia. A statistically significant decrease in the activities of both esterases was observed in CSF of demented patients, however, primary degenerative and vascular dementia did not differ in their CSF cholinesterase levels. Compared to age-matched controls the serum butyrylcholinesterase activity was also significantly lowered in the overall dementia group. No typical serum and CSF cholinesterase isoenzyme pattern was found for dementia or any of its subgroups. It is concluded that the cholinesterase levels reflect metabolic alterations associated with dementia as a collective group but cannot be used for differential diagnosis of subgroups.

Key words: CSF – Cholinesterases – Dementia

Introduction

An abnormality in cholinergic transmission within the brain is found in various kinds of dementia (Perry et al. 1977, 1978; Perry 1980). This subject was recently reviewed by Whitehouse et al. (1985). The findings and results can be summarized as follows: the activity of cholineacetyltransferase and acetylcholinesterase (AChE) was significantly lower in the brain tissue of demented patients than in that of non-demented neuropsychiatric patients and age-matched controls while the muscarinic binding capacity was unaltered. The most prominent differences were found in cases of Alzheimer's dementia in autopsy material deriving from the cerebral cortex, temporal lobe and hippocampus.

Recently these statements have gained new significance and stimulated relevant investigations in order to find out whether the alterations observed in brain tissue are reflected in plasma (Atack et al. 1983; Marquis et al. 1985; Smith et al. 1982), erythrocytes (Chipperfield et al. 1981; Marquis et al. 1985) and, especially, in CSF (Arendt et al. 1984; Huff et al. 1986; Marquis et al. 1985; Soininen et al. 1981) and whether they offer new potential possibilities for a refined and more reliable diagnosis of dementia. However, the results of these investigations generally dealing with differences in the activity of AChE and butyrylcholinesterase (BChE) are contradictory in many respects. The aim of the present paper was to obtain information on the suitability of the described alterations as diagnostic tools.

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Subjects and Methods

In-patients suffering from dementia of different origin were included in this study. Non-demented in-patients (5–72 years old) suffering from various neuropsychiatric diseases were regarded as controls, however, this group did not contain cases of myasthenia gravis, malignancy or hepatic diseases. Hepatic function was monitored by determination of the activity of glutamic oxaloacetic transaminase, glutamic pyruvate transaminase, creatine phosphokinase and γ-glutamyl transferase in serum. CSF samples for diagnostic purposes were obtained from fasting patients in a standardized position by lumbar and cisternal puncture, (generally up to 5 ml in volume) and stored at −20°C. Neither repeated deep-freezing and thawing (Deutsch et al. 1983) nor low-temperature storage up to 50 days (Johnson and Domino 1971) substantially influenced the activity of the cholinesterases (ChE) investigated in the present study. As a rule, serum and CSF from the same patient were examined simultaneously.

In general DSM III was used as clinical diagnostic criterion. From the demented group patients suffering from vascular multi-infarct dementia (MID) and primary degenerative dementia of the Alzheimer type (DAT) were gathered in subgroups consisting of 11 and 6 cases, respectively. The differentiation of dementia was made according to our own clinical battery (Szilágyi et al. 1986) based on several psychological scales and clinical chemical data. In 8 of 9 cases the diagnoses based on this complex differentiation procedure and on results of the pathological and histopathological examination of brain tissue of deceased patients were in accord.

The protein concentration in CSF was measured by Lowry's method (Lowry et al. 1951). Activity determination of the so-called specific (AChE) (Knedel and Böttger 1967) and non-specific (BChE) cholinesterase (Ellmann et al. 1961) were performed on 5 µl serum and 50 µl CSF samples, respectively, by the enzymatic programme FP-9 (Labsystem, Finland) using test substances from Boehringer, Ingelheim, FRG. Acetyl- and butyrylthiocholine iodide were used as substrates, however, specific inhibitors were not applied. Enzyme activities are given in units/l ($\mu mol \cdot min^{-1} \cdot l^{-1}$) at 25°C. Serum ChE isoenzymes were studied by gradient polyacrylamide gel electrophoresis according to the method of Nagy et al. (1974). This method was adapted to CSF ChE isoenzymes using acetyl-instead of butyrylthiocholine iodide as substrate and applying the CSF after concentration (about 10-fold) by Amicon ultrafiltration.

Results and Discussion

The mean values of the activity of AChE and BChE in serum and CSF of demented patients and controls and the corresponding standard deviations (given in parentheses) are summarized in Table 1.

In agreement with results of Huff et al. (1986) and Marquis et al. (1985) AChE exhibited significantly higher activities than BChE in CSF of both the demented and the control group. On the contrary, in serum the BChE activity significantly exceeded that of AChE. No correlation existed between AChE activity and total protein concentration of CSF (correlation coefficient = 0.17) as reported by Johnson and Domino (1971). Consequently, CSF ChE activities are not dominantly influenced by the serum levels and may reflect acute metabolic events happening in the CNS, at least as long as the blood-CSF barrier function is not disturbed.

Compared to controls the overall demented group and both subgroups of dementia showed significantly lower CSF activities of AChE and BChE. The decrease in AChE activity seemed to be more pronounced in DAT while BChE was more affected in MID. However, in all cases there was a more or less strong overlap between the groups revealed by the relatively high standard deviation. Therefore, the diagnostic reliability of a method based on these differences is limited.

Arendt et al. (1984) reported decreased AChE and increased BChE levels and, consequently, a more pronounced decrease in the ratio of AChE to BChE in the CSF of DAT patients and they regarded this ratio as a more reliable potential indicator for diagnostic purposes. However, these findings could not be confirmed by Marquis et al. (1985) who found that in the CSF of DAT patients the BChE level was lower and the AChE/BChE mean value even higher than in CSF of controls. Our data (Table 1) support the results reported by Marquis et al. (1985).

The serum activity values (Table 1) revealed no significant differences between controls and the demented group. BChE values could be subdivided according to age. Children showed a somewhat higher mean serum BChE level than adult controls. In agreement with data in the literature, no correlation was found between serum BChE and age in the control group up to 60 years, however, the non-demented patients over 60 years old showed significantly higher levels of activity (Table 1). Compared to controls of the same age group the demented group involving only patients older than 60 years differed significantly in the serum BChE level but there was no difference between the two subgroups of dementia. It seems that in both types of dementia the trend of increasing serum BChE is overcompensated in advanced age. From the diagnostic point of view it seems necessary to choose age-matched non-demented patients as controls. It may be that such a procedure increases the reliability of diagnostic conclusions drawn from CSF ChE activity levels.

Atack et al. (1983) indicated the possibility that not the totality but only one of the molecular forms of AChE and BChE, respectively, may play a role in the genesis of DAT. In postmortem-obtained neocortical tissue of DAT patients they found a selective activity decrease of only one of three AChE isoenzymes distinguished by gradient centrifugation. We tried to obtain information on the ChE isoenzyme distribution in serum and CSF of controls and demented patients. With the electrophoretic method used generally 7 isoenzymes could be separated and detected in serum. The isoenzyme with the lowest mobility was always the most active. Individual differences were observed only in the activity distribution of isoenzymes 3–6 (Fig. 1), however, these were not specific for particular diseases and may be explained as genetic variants. In CSF the characteristic serum isoenzymes 3–6 were only detectable when the blood-CSF barrier is damaged, i.e. in cases of extremely high CSF protein content. In general only 3–4 bands appeared on the electropherograms of CSF samples, one of which (band 3) was CSF-specific (Fig. 2). No characteristic CSF isoenzyme pattern for dementia or its subgroups was observed, however, the overall intensity of the bands reflected the same tendency as the total AChE and BChE activity given in Table 1.

Though a statistically significant decrease in the ChE activities could be demonstrated in CSF of demented patients it was not possible to make use of this phenomenon for the subdifferentiation of dementia. It is supposed that the relatively large variance of individual ChE levels may be due first of all to the fact that acetylcholine synthesis is affected by metabolic disorders of different, e.g. hypoxic nature. This often disregarded aspect has been recently stressed in a review by Blass

Table 1. Activities of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in serum and CSF of controls and demented patients

Body fluid	Patient group	*n*	AchE units/l (SD)	*P*	*n*	BChE units/l (SD) (±)	*P*	*n*	AChE/BChE units/l (SD)	*P*
Serum	Control (total)	31	2600 (730)	*	86	4940 (1590)				
	Control < 14 years				37	5360 (970)				
	Control 20–60 years				34	4650 (1180)				
	Control > 60 years				15	5620 (1260)	*			
	Dementia > 60 years	18	2350 (635)	N.S.	33	4050 (1090)	≪0.001			
	Dementia – Alzheimer type > 60 years				9	4200 (970)	~0.005			
CSF	Controls	31	17.2 (5.4)	*	31	7.8 (6.0)	*	31	4.8 (5.2)	*
	Dementia	18	12.9 (4.3)	~0.003	18	2.8 (2.8)	~0.001	18	10.4 (7.8)	~0.002
	Multi-infarct dementia	11	13.4 (5.1)	≪0.001	11	2.7 (3.0)	~0.005	11	11.7 (8.1)	~0.001
	DAT	6	10.2 (4.9)	~0.002	6	3.1 (2.8)	~0.025	6	9.6 (7.3)	~0.03

The significance limits *P* of the Student distribution derived from the comparison with the group marked by the asterisk in the same row

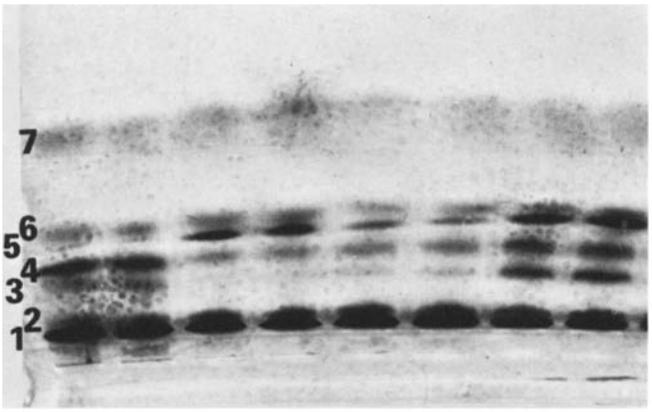

Fig. 1. Polyacrylamide gel electropherograms of serum cholinesterase isoenzymes of 4 control persons (2 runs from each)

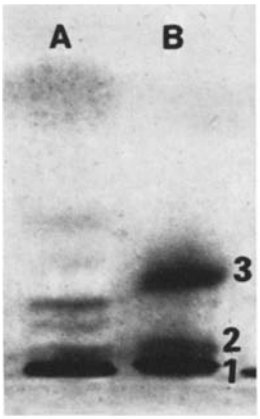

Fig. 2A, B. Polyacrylamide gel electropherograms of serum (**A**) and CSF (**B**) from the same control person

and Plum (1983). Lowered ChE activities in CSF of demented patients may therefore reflect reduced cholinergic metabolism in the CNS resulting in dementia.

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