Arch. Psychiat. Nervenkr. 223, 265—270 (1977)

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

The Cerebrospinal Fluid Choline Levels in Patients with Huntington's Chorea

Negative Effect of Haloperidol Treatment

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Summary. Lumbar cerebrospinal fluid (CSF) choline (CH) levels were measured in patients with Huntington's chorea ($n = 14$). This group was found not to differ significantly from normal controls ($n = 13$). The values for lumbar CSF Ch levels in the normal subjects were comparable with previously reported values. Of the choreic patients, seven were put on haloperidol treatment (4—6 mg daily). The CSF choline level remained unchanged with this treatment after 20 days. CSF cholinesterase activity was measured in the control and choreic group. The results were not significantly different.

Key words: Huntington's chorea – C.S.F. – Choline – Haloperidol therapy.

Zusammenfassung. Im lumbalen Liquor cerebrospinalis wurde der Cholingehalt bei 14 Fällen von Huntington bestimmt. Im Vergleich zu 13 Gesunden wurden keine signifikanten Unterschiede gefunden. 7 Chorea-Patienten wurden mit Haloperidol 4—6 mg täglich behandelt. Der Cholingehalt des Liquors blieb auch nach Halloperidol über 20 Tage unverändert. Auch die Cholinesteraseaktivität im Liquor war bei Chorea-Kranken und Kontrollen unverändert.

Schlüsselwörter: Chorea Huntington – Liquor – Cholingehalt – Haloperidol-Therapie.

Introduction

The primary underlying biochemical defect in Huntington's chorea is still unclear although the neuropathology of this disease has been extensively studied and is characterized by a loss of small cells in the basal ganglia (Bruyn, 1968, 1973).

Clinical data suggest that one mechanism regulating motor activity might include a balance between dopaminergic and cholinergic activity in the extrapyramidal system (Hornykiewicz, 1966; Cotzias et al., 1967). A link between these

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two neuronal systems at the level of the striatum in the rat has, in fact, been amply demonstrated (Ladinsky et al., 1975; Guyenet et al., 1975).

In Huntington's chorea, some indirect clinical evidence suggests abnormal function of neostriatal cholinergic neurons since anticholinergic agents aggravate choreic symptoms while physostigmine has been reported to reduce hyperkinesia (Duvoisin, 1967; Klawans and Rubowits, 1972). Furthermore, both choline o-acetyltransferase activity (Aquilonius et al., 1972; Bird and Iversen, 1974; McGeer et al., 1973; Stahl and Swanson, 1974; Enna et al., 1976) and muscarinic receptor binding (Enna et al., 1976; Hiley and Bird, 1974) are lowered in the caudate nucleus of choreic patients.

Therefore one hypothesis on the cause of Huntington's chorea is that the hypofunction of the cholinergic system might result in an overbalance of dopaminergic influence on the remaining cholinergic neurons, particularly since the dopaminergic system appears to be unaffected in this extrapyramidal disease (Hornykiewicz, 1966; Bird and Iversen, 1974; Ehringer and Hornykiewicz, 1960). In the light of this possibility, we were prompted to determine whether the level of choline, which is both the precursor and end product of acetylcholine, is abnormal in the cerebrospinal fluid of choreic patients and whether haloperidol, a dopamine receptor blocker that effectively relieves choreic symptoms, could alter the CSF choline level.

Materials and Methods

The investigation was performed in a group of 14 patients, men and women, aged between 26 and 60 years with a mean age of 44 ± 3.0 years. All patients exhibited the typical symptoms of Huntington's chorea: choreiform movements of varying severity, dementia, and an autosomal dominant inheritance. A clear rigidity appearing late in the evolution of the disease was evident in two subjects (DMP; CF). Furthermore, in one patient (DMP), it was impossible to demonstrate a genetic component.

The choreic patients were divided into two groups, 'fast' and 'slow,' based on significant differences in motor performance tests, I.Q. and duration of disease (Caraceni et al., manuscript in press). A control group consisted of 13 persons with no sign or history of neurological diseases. The patients were submitted to the Istituto Neurologico 'C. Besta,' Milan, for the diagnosis of suspected herniatic disc. The age distribution of the controls corresponded satisfactorily with that of the choreic patients.

Lumbar cerebrospinal fluid was withdrawn at 9:00 a.m. from patients in the clinostatic position. The patients were fasted for at least 8 h prior to the procedure. The CSF was collected in plastic tubes, frozen immediately in liquid nitrogen, and stored at —20° until analysis.

The CSF samples were collected a first time 15 days after discontinuation of any previous therapy and a second time after 20 days of treatment with haloperidol, 4—6 mg daily.

CSF choline was measured on 20 μl samples performed in duplicate by the radiochemical micromethod of Saelens et al. (1970) with some modifications (Ladinsky et al., 1976). Cholinesterase activity was determined by the radiochemical method of McCaman et al. (1968).

Results

The choreic group includes the 'slow' and 'fast' patients since no differences between these two groups were found in the choline level or cholinesterase activity.

Figure 1 shows a histogram of the lumbar CSF levels in the 13 control and 14 choreic patients. No significant difference was found in the biochemical

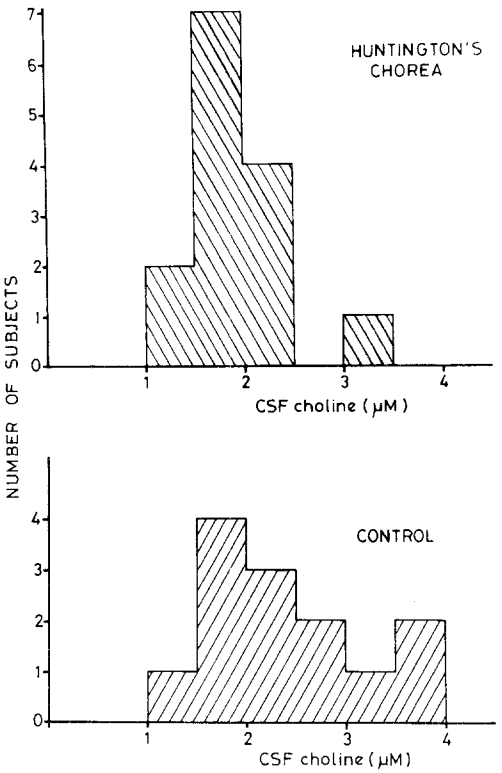

Fig. 1. Histogram of the distribution of the choline level in the cerebrospinal fluid of 13 control and 14 choreic patients

Table 1. Lumbar CSF choline levels in choreic patients before and during haloperidol treatment

Patient	Lumbar CSF (μM)	
	before haloperidol	during haloperidol
C. F.	1.34	1.44
D. M. P.	1.73	1.63
V. A.	3.07	2.21
G. G.	2.50	1.54
Z. G.	1.92	2.69
F. A.	2.01	2.11
P. G.	1.73	1.63
Mean ± SE	2.04 ± 0.21	1.89 ± 0.17

Haloperidol was administered at a dose of 4.6 mg daily. Lumbar CSF was taken on day 20. N.S., by Student's *t*-test for paired data

cholinergic parameters considered ($P = 0.06$ Student's t-test). The mean value for CSF choline in the control group was 2.41 ± 0.21 μM while in the choreic group it was 1.93 ± 0.12 μM. The range of values was 1.34 to 3.84 μM and 1.34 to 2.50 μM in the two groups, respectively.

Of the 14 choreic patients, seven were then put on haloperidol treatment (4—6 mg daily). The CSF choline level remained unchanged with this treatment after 20 days (Table 1; Student's t-test for paired data).

CSF cholinesterase activity was 2.31 ± 0.19 and 1.97 ± 0.38 μmol ACh hydrolyzed/h per mg protein in the control and choreic group, respectively. The difference was not significant (Student's t-test).

Discussion

We have found that the CSF choline level in choreic patients was similar to the control group, although there was a tendency for it to be lowered. Our results therefore are in accordance with those of Welch et al. (1976).

The lack of enhancement of the CSF choline values after haloperidol treatment is contrary to the marked influence exerted by this drug on cholinergic activity in experimental animals. Haloperidol, in fact, was shown to decrease the level of acetylcholine and increase the turnover rate and release of this transmitter in rats and cats through its inhibitory activity on dopaminergic receptors (Ladinsky et al., 1975; Guyenet et al., 1975; Trabucchi et al., 1974; Stadler et al., 1973). Our results could be interpreted in two ways: either the 20-day time period after haloperidol was too long and the pretreatment steady state level was reestablished, or the compromised cholinergic system (see Introduction) in Huntington's chorea could not respond sufficiently to the blockade of dopamine receptors which are anatomically intact and functionally hyperactive (Agid, 1975).

Furthermore, it is still controversial whether the CSF choline level reflects completely cholinergic activity in the central nervous system (Schuberth and Jenden, 1975; Aquilonius et al., 1970; Welch et al., 1976; Aquilonius et al., 1972). Bowers (1967) and Welch et al. (1976) have suggested that a downhill ventricular-lumbar concentration gradient for choline exists and that an important source of choline in CSF is the brain surrounding the ventricles. However, there is no data to show whether, and to what extent, the CSF choline stems from brain acetylcholine, plasma choline or brain phospholipids in humans. Moreover, if CSF choline were only the end product of acetylcholine, then we would expect that a concentration gradient also exists for this amine. The equal distribution of acetylcholine in ventricular and lumbar CSF (Bowers, 1967; Welch et al., 1976) is contrary to this idea, although the presence of cholinesterase throughout the CSF, reducing the acetylcholine to an equally low level (Duvoisin and Dettbarn, 1967), makes it difficult to establish such a gradient.

In conclusion, the significance of the choline level in CSF must be interpreted with caution. Whatever the biochemical source of choline may be, the existence of a choline gradient would be of importance in furnishing information on certain metabolic processes involving this quaternary amine in neurological diseases.

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Received December 20, 1976