Biochemical aspects of Huntington's chorea

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SUMMARY Fifteen patients affected by Huntington's chorea were divided into two groups, 'slow' and 'fast', according to IQ scores on the Wechsler-Bellevue scale, and scores on some motor performance tests. A possible correlation was looked for between some biochemical data (cerebrospinal fluid (CSF), homovanillic acid (HVA), and 5-hydroxyindolacetic acid (5HIAA) levels, plasma dopamine-beta-hydroxylase (DBH), dopamine (DA) uptake by platelets, and clinical data (duration of illness, severity of symptoms, age of patients, IQ scores, 'slow' and 'fast' groups). The CSF, HVA, and 5HIAA levels were found to be significantly lowered in comparison with normal controls. DBH activity and DA uptake by platelets did not differ significantly from normal subjects. Treatment with haloperidol in all patients and with dipropylacetic acid in three patients did not appear to modify the CSF, HVA, and 5HIAA concentrations, the plasma DBH activity, or the DA uptake. There were no significant differences in the CSF, HVA, and 5HIAA contents between the two groups of patients, and there was no correlation between biochemical data and clinical features.

The neuropathology of Huntington's chorea has been extensively studied (Bruyn, 1968, 1973) and is marked by a loss of small cells of the basal ganglia, especially of the caudate nucleus and putamen. The most recent work has been devoted to determining the brain concentrations of neurotransmitters and of the enzymes involved in their formation and catabolism with the aim of elucidating any biochemical changes that may underlie the disease. The levels of dopamine (DA), its principal metabolite homovanillic acid (HVA), and of tyrosine hydroxylase (TOH) are normal (Yates *et al.*, 1973; Bird and Iversen, 1974; Stahl and Swanson, 1974). GABA and glutamic acid decarboxylase (GAD) are significantly decreased (McGeer *et al.*, 1973; Perry *et al.*, 1973; Bird and Iversen, 1974; McGeer and McGeer, 1976). Cholineacetyltransferase (CAT) is markedly reduced and acetylcholinesterase is normal (McGeer *et al.*, 1973; Bird and Iversen, 1974; Aquilonius *et al.*, 1975). There are no data indicating an alteration in serotonin content or metabolism.

Latterly attention has been directed particularly to the content of acid metabolites of the brain

monoamines in cerebrospinal fluid (CSF) in the hope of establishing an index of metabolic events in the brain from easily accessible material, since the CSF metabolites mostly derive from the catabolism of the brain amines. Thus the levels of HVA and 5-hydroxyindolacetic acid (5HIAA) (Curzon *et al.*, 1972; Chase *et al.*, 1972; Chase, 1973; Mattsson and Persson, 1973; Yates *et al.*, 1973; Buscaino *et al.*, 1975), of choline (Aquilonius and Sjöström, 1971; Aquilonius *et al.*, 1972), and of GABA (Glaeser *et al.*, 1975) have been determined in a fairly large number of patients with Huntington's chorea. Although agreement is not absolute, in general these studies indicate low CSF levels of HVA, choline, and GABA, and normal levels of 5HIAA which would suggest reduced metabolic activity of the DA, GABA, and cholinergic pathway.

In examining the possibility that Huntington's chorea may express a generalised alteration of the sympathetic nervous system, the blood level of dopamine-beta-hydroxylase (DBH) activity (whose plasma concentration may be considered an index of sympathetic activity) has also been studied in patients with Huntington's chorea (Wetterberg *et al.*, 1972; Lieberman *et al.*, 1973; Mattsson, 1973; Mattsson *et al.*, 1974). In fact, it has been suggested that an adrenergic hyperactivity may exist in Huntington's chorea as opposed to the

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adrenergic hypoactivity of Parkinson's disease (Lieberman *et al.*, 1973).

We have studied the uptake of DA by the platelets, taking platelets to be an accessible model of neuronal uptake. Aminoff *et al.* (1974) reported an increase of DA uptake in Huntington's chorea.

Patients and methods

We investigated 15 patients, nine men and six women, aged between 26 and 60 years, with a mean age of 44.3 ± 10.5 years. All patients exhibited the typical symptomatology of Huntington's chorea (choreiform movements of varying severity and dementia) and an autosomal dominant inheritance. Rigidity appearing late in the evolution of the disease was evident in two subjects (DMP and CF). Furthermore, in one patient (DMP) it was impossible to demonstrate any genetic component. All patients' IQs were rated on the Wechsler-Bellevue scale, and a neuropsychological study of frontal coordination and functions (Girotti *et al.*, in press) was also undertaken.

Hyperkinesia was assessed by means of videotape recordings before and after drug treatment. Four neurologists scored 'blind' for four body territories (face, neck, trunk, and limb) on a scale from 0 to 3) where 0 represented absence of hyperkinesia, and 1 to 3 graded its severity and persistence. The final rating was the sum of the scores given by the four examiners. The total tongue protrusion time expressed in seconds was the mean of 10 determinations.

Motor dexterity was assessed by means of three motor performance tests:

1. *Nut and bolt test* This measured the total time taken to screw three nuts onto their bolts.
2. *Drawing test* Each patient was asked to draw four simple patterns (Figure), which were scored from 0 to 4—0 for a correct drawing, 1 for a drawing with minor defects, 2 for a drawing with major defects, 3 when the drawing was very bad but the pattern recognisable, and 4 when the pattern was unrecognisable. Performance was rated independently by four examiners and the mean score was taken as the rating.
3. *Spiral test* The patient was asked to run a metal-tipped pencil through the parallel rails of an electric spiral as quickly as possible without touching the rails. With this device, connected to an oscilloscope, the number of touches, total running time, and time of contact of pencil with rails were measured

Figure Drawing test—patterns

quite accurately. Each patient's rating was based on the sum of the running time in seconds and the total contact time expressed as a one second penalty per 100 ms of contact.

All patients were treated with haloperidol 4–6 mg daily, and three patients also received dipropylacetic acid (DPA) 2,500 mg daily.

Cerebrospinal fluid samples were collected initially 15 days after discontinuation of any previous therapy and again after 20 days of drug treatment.

In both instances sampling was performed at 0900, on fasted patients, who had been recumbent for at least eight hours. CSF was collected in plastic test tubes, immediately frozen at -40°C in liquid nitrogen and then stored at -20°C until analysis. A blood sample was collected at the same time for plasma DBH activity and platelet uptake of DA.

HVA and 5HIAA concentrations in CSF were measured according to the procedure described by Korf *et al.* (1971). The evaluation of the CSF choline level will be reported in another paper (Ladinsky *et al.*, in press).

The plasma DBH activity was assayed according to Nagatsu and Udenfriend (1972), and evaluation of platelet uptake of DA was performed according to Barbeau *et al.* (1975).

Control values for DBH activity were obtained from 76 healthy volunteers, for platelet DA uptake from 12 normal subjects, and for CSF, HVA, and 5HIAA levels from 12 patients before myelographic examination for a suspected herniated disk.

Results

CLINICAL DATA

The motor performance tests (Table 1) showed considerable difference in the degree of impairment of motor dexterity in our choreic patients: six cases had scores that were close to or only slightly above normal, while another nine cases had very high scores indicating a very bad motor performance. The former were classed as 'fast' and the latter as 'slow'.

Table 1 Data on two groups of patients with Huntington's chorea according to length of disease, IQ, and performance tests

	Patients	Sex	Y	IQ	Performance tests		
					A	B	C
Slow group	CF	F	10	28	480	4.0	100
	OMA	F	10	51	275	2.7	38
	DMP	M	5	28	480	4.0	100
	LM	F	5	61	190	2.5	74
	PE	F	5	61	190	1.7	49
	PB	M	5	65	170	1.5	38
	VA	M	4	87	195	2.3	66
	RT	M	3	67	180	1.5	45
	GG	M	2	64	190	2.5	42
Fast group	ZG	M	6	90	90	1.0	24
	PV	M	3	98	45	2.0	33
	PG	M	3	89	80	1.3	35
	SA	M	3	99	66	1.0	17
	FI	F	1	72	79	1.0	37
	PG	F	1	83	145	1.0	37

Y=Length of disease (years). IQ=Intelligence quotient (Wechsler-Bellevue scale); A=Nut and bolt test (seconds); B=Drawing (rating value); C=Spiral (seconds).

Student's *t* test between slow and fast group: Y, $P=0.05$; IQ, $P<0.001$; A, $P<0.01$; B, $P<0.01$; C, $P<0.05$.

Correlation coefficient: *r* significant only inside slow group for A $\neq$ B, $P<0.001$; A $\neq$ C, $P<0.01$; B $\neq$ C, $P<0.01$.

Linear regression analysis significant only inside slow group for IQ $\neq$ A, $P<0.01$; IQ $\neq$ B, $P<0.05$.

The difference between the two groups was highly significant for all the performance tests, and within the slow group there was a close correlation between the various performance tests. In correlating IQ with motor performance, and length of history with IQ, we regarded the IQ as an expression of the grade of dementia and hence, indirectly, of the extent of brain damage. Table 1 shows a significant correlation for the slow group between IQ and the nut and bolt test, and between IQ and drawing test, and none between IQ and spiral test; for the fast group, on the other hand, no correlation between IQ and motor performance tests was possible.

This observation might well reflect the difference in brain damage between the two groups. In the

slow group, the brain damage is greater and the sample more homogeneous, and hence the correlation with motor performance appears to be closer. In the fast group, the brain damage is less severe and greater differentiation of intellectual performance is still possible.

The difference between the two groups was also highly significant for IQ scores.

Length of history was based on the memory of patients and relatives, and is not, therefore, a precise datum—relatives as well as patients are reluctant or slow to detect unwanted movements and so to date the onset of symptoms. It can be safely stated, however, that the length of history was on average greater in the slow group ($P=0.05$). The IQ and length of history did not correlate in either group and there was no significant difference with regard to age between the two groups.

The effect of treatment with haloperidol 4–6 mg daily was evaluated in the two groups by the tests described above. Statistical analysis shows that the drug was effective only on hyperkinesia in both groups (Tables 2, 3). However, it induced an adverse effect on one motor performance test (the spiral test) in the fast group. This might mean that in patients with less impaired motor capacity, haloperidol, while improving the unwanted movements, worsens normal movements as a side effect, perhaps because of the extrapyramidal action of the drug. In severely affected cases with more impaired motor capacity this adverse action has no opportunity of expression. No effects could be observed following DPA treatment at a dose level of 2500 mg/day for 20 days.

BIOCHEMICAL DATA

The differentiation between slow and fast patients was maintained for the tabulation of biochemical data to magnify possible relations between clinical pattern and biochemical data.

The plasma DBH activity was determined in 13 patients and proved to be slightly, but not significantly, higher than in the normal control group (Table 4). Comparison of the chorea patients' average value with that of a smaller group of age-matched normal control subjects elicited no statistical significance either.

Haloperidol treatment induced no substantial changes in DBH values either in fast ($31.4 \pm 5 \rightarrow 27.9 \pm 3.8$) or slow ($36.6 \pm 9.6 \rightarrow 30.3 \pm 10.9$) patients (Table 5).

The DA uptake by the platelets was slightly decreased in our patients, but the differences were not statistically significant: the DA uptake for the control subjects was $12.1 \pm \text{SD } 0.9\%$, for the

Table 2 Effect of haloperidol on performance tests of choreic patients

Slow patients	Before treatment					After treatment				
	A	B	C	D	E	A'	B'	C'	D'	E'
CF	480	4.0	100	40	1	480	4.0	100	40	1
OMA	275	2.7	38	22	6	170	1.3	43	18	6
DMP	480	4.0	100	32	6	480	4.0	110	29	1
LM	190	2.5	74	34	5	170	2.2	76	24	5
PE	190	1.7	49	30	5	150	1.0	48	24	4.7
PB	170	1.5	38	18	4	172	1.5	39	8	12
VA	195	2.3	66	43	6	180	2.3	69	29	3
RT	180	1.9	45	13	9	170	2.0	47	11	5
GG	190	2.5	42	13	2.5	180	2.0	32	11	4
Mean	261.11	2.57	61.33	27.22	4.94	239.11	2.26	61.55	21.55	4.63
±SE	± 42.56	± 0.30	± 8.38	± 3.73	± 0.76	± 45.61	± 0.36	± 8.61	± 3.50	± 1.09

A = Nut and bolt (seconds); B = Drawing (rating value); C = Spiral (seconds); D = Hyperkinesia (rating value); E = Tongue protrusion (seconds). Statistical analysis was performed using the paired Student's *t* test: $D \neq D'$, $p < 0.01$.

Table 3 Effects of haloperidol on performance test of choreic patients

Fast patients	Before treatment					After treatment				
	A	B	C	D	E	A'	B'	C'	D'	E'
ZG	90	1.0	24	9	30	70	1.0	34	5	30
PV	45	2.0	33	43	6	52	2.0	45	41	6.3
PG	80	1.3	35	24	6	83	1.0	58	22	6.3
SA	66	1.0	17	20	30	50	1.0	22	17	30
FI	79	1.0	27	22	30	74	0.9	30	13	28
PG	149	1.0	37	—	7	—	—	—	—	—
Mean	72.00	1.26	27.20	23.60	20.40	65.80	1.18	37.8	19.60	20.12
±SE	7.75	0.19	3.23	5.50	5.87	6.40	0.20	6.26	6.03	5.65

A = Nut and bolt (seconds); B = Drawing (rating value); C = Spiral (seconds); D = Hyperkinesia (rating value); E = Tongue protrusion (seconds). Statistical analysis was performed using the paired Student's *t* test: $C' \neq C$, $p < 0.05$; $D \neq D'$, $p < 0.05$.

Table 4 Plasma DBH activity* in healthy volunteers and in patients with Huntington's chorea

	Control I	Control II†	Choreic patients
Number of cases	76	14	13
Age			
Mean ± SE	29 ± 1.3	39 ± 2.7	42 ± 2.7
Range	16–55	28–55	26–60
DBH			
Mean ± SE	24.7 ± 2	29.8 ± 5	34.6 ± 6
Range	0–86.8	5–79.8	1–67.2

* DBH activity was assayed according to Nagatsu and Udenfriend (1972) and is expressed as $\mu\text{mol/litre/min}$.

† Controls II are normal subjects from group I selected to match the age of the patients.

Table 5 Plasma DBH activity before and after haloperidol in two groups of choreic patients: slow and fast

Group of patients	Number of cases	DBH mean ± SE	
		Before	After
Slow	8	36.6 ± 9.6	30.3 ± 10.9
Fast	5	31.4 ± 5	27.9 ± 3.8

DBH activity was assayed according to Nagatsu and Udenfriend (1972) and is expressed as $\mu\text{mol/litre/min}$.

slow patients (eight) $11.5 \pm 1.2\%$, and for the fast patients (four) $11.4 \pm 2.2\%$.

The mean CSF levels of acid metabolites of the brain monoamines, HVA, and 5HIAA, were significantly below the control mean values (Table 6). In most of the patients haloperidol treatment did not induce any evident increase of the CSF, HVA, and 5HIAA values. Only in case FI was a clear rise of HVA concentration but not of 5HIAA observed (Tables 7 and 8). The minor variation observed in the other cases did not show any significant difference on statistical analysis.

Furthermore it must be emphasised that in a few patients the CSF acid metabolite levels were even lower than before therapy. There was no statistically significant difference in the HVA and 5HIAA levels between the slow and fast groups, and no significant correlation could be demonstrated between the levels of these CSF metabolites and clinical parameters such as age, length of history, severity of the symptoms, and results of the performance tests. The DPA administered to three patients did not provoke any modification in the CSF content of HVA and 5HIAA.

Table 6 Baseline levels of HVA and 5HIAA (ng/ml) in patients with Huntington's chorea and controls

	HVA Mean $\pm$ SD	5HIAA Mean $\pm$ SD
Huntington's chorea (15 cases)	24.04 $\pm$ 18.17	16.46 $\pm$ 9.22
Controls (12 cases)	47 $\pm$ 9	30.00 $\pm$ 10

Student's *t* test: HVA, $P < 0.001$; 5HIAA, $P < 0.001$.

Table 7 Lumbar CSF levels (ng/ml) of HVA and 5HIAA in choreic patients (slow group) before and after haloperidol

Patients	Sex	Before		After	
		HVA	5HIAA	HVA	5HIAA
CF	F	14.20	4.00	17.80	24.00
DMP	M	22.30	32.90	19.00	20.00
LM	F	55.20	22.60	41.30	31.20
PE	F	19.80	20.90	24.10	20.20
PB	M	24.29	17.92	8.54	14.82
VA	M	72.40	33.00	99.20	22.00
GG	M	16.10	6.20	17.90	9.90
Mean		32.04	19.64	32.54	20.20
$\pm$ SE		$\pm$ 8.51	$\pm$ 4.34	$\pm$ 11.73	$\pm$ 2.55

Table 8 Lumbar CSF levels (ng/ml) of HVA and 5HIAA in choreic patients (fast group) before and after haloperidol

Patients	Sex	Before		After	
		HVA	5HIAA	HVA	5HIAA
ZG	M	7.40	9.20	5.00	6.60
PV	M	34.70	5.00	29.70	13.00
PG	M	17.20	8.70	38.70	8.00
FI	F	26.62	25.26	66.13	28.48
PG	F	5.00	15.28	13.55	13.44
Mean		18.18	12.68	30.61	13.90
$\pm$ SE		$\pm$ 5.63	$\pm$ 3.54	$\pm$ 10.66	$\pm$ 3.88

Discussion

By the motor performance tests we could differentiate two groups of patients, fast and slow. Although the division may appear rather arbitrary, the patients were undoubtedly in different stages of the disease. The correlation between the performance and intelligence tests within the slow group tends to support this concept, which is also suggested by the different response to haloperidol treatment and by the different IQ scores and length of the disease. This difference in the clinical features does not seem, however, to be present at the biochemical level.

The DBH plasma activity in patients with Huntington's chorea was similar to values obtained in normal subjects; these data are in good agree-

ment with previous reports on DBH (Wetterberg *et al.*, 1972; Mattsson *et al.*, 1974; Lieberman *et al.*, 1973).

The platelet DA uptake observed in our patients is not significantly different from the control values, and this result is not in agreement with the preliminary report of Aminoff *et al.* (1974).

The determinations of HVA and 5HIAA in the CSF of our patients yielded information of greater interest. The CSF HVA levels, significantly lowered, agree with the data reported by the majority of workers. Curzon *et al.* (1972) found significantly reduced HVA values in 15 Huntington's chorea patients, and this reduction was subsequently confirmed by other authors (Chase *et al.*, 1972; Chase, 1973; Buscaino *et al.*, 1975). Normal HVA values were found only in few cases (Yates *et al.*, 1973; McLellan *et al.*, 1974), and high values are rather rare (Guilleminault *et al.*, 1973).

No correlation was generally possible between CSF metabolite levels and the principal clinical features (age, length of history, severity of symptoms, and IQ) either in our cases or in those reported in the literature. However, a positive correlation was found by Yates *et al.* (1973) between age and acid metabolites levels.

The 5HIAA values have been described as normal by several workers (Chase *et al.*, 1972; Curzon *et al.*, 1972; Chase, 1973; Mattsson and Persson, 1973; Yates *et al.*, 1973; McLellan *et al.*, 1974); at variance with their results, the CSF 5HIAA levels in our patients were considerably reduced. In our study the difference from the control group was highly significant ($P < 0.001$). Values lower than normal, although not significantly so, have also been reported by Buscaino *et al.* (1975). Of some interest could be the marked reduction of CSF HVA and 5HIAA levels in one (CF) of our two patients with rigidity.

The results we obtained with haloperidol treatment are also of undoubted interest: in fact no significant differences in HVA and 5HIAA levels were evident after DA-blocking therapy. There was only a modest increase in the mean HVA and 5HIAA values.

Similar findings have been reported by other workers. It has been found, for example, that suspension of phenothiazine and/or haloperidol treatment does not significantly affect the CSF HVA level in choreic patients (Mattsson and Persson, 1973).

Furthermore the DPA treatment in our three patients with Huntington's chorea did not modify the CSF monoamine metabolite levels, and this

finding is at variance with the results obtained by Shoulson *et al.* (1976).

These observations suggest that the various monoaminergic systems in the brain of Huntington's chorea patients are hardly responsive to drugs; this could be due to a diffuse degenerative impairment for which the various systems, and not only one, are very poorly functioning. Furthermore, the unresponsiveness of DA to the action of DA blockers might hypothetically be related to the existence of different DA receptors (as has recently been suggested by Cools and Van Rossum, 1976), which respond differently to the action of drugs in particular pathological situations, or to the different sensitivity and behaviour of the various DA systems (limbic—tuberoinfundibular—nigrostriatal) in the brain.

We would also draw attention to the lack of correlation between the extent of the decrease in CSF metabolite levels and the clinical features of the illness (history, slow and fast groups, grade of hyperkinesia, and so on). We feel that these data are against the hypothesis that in Huntington's chorea there is a specific alteration of the metabolism of a single neurotransmitter. In this connection we would recall that GABA and CAT were found to be greatly reduced in the basal ganglia of patients with this disease (McGeer *et al.*, 1973; Bird and Iversen, 1974; Aquilonius *et al.*, 1975).

Our data and those reported in the literature seem rather to support the hypothesis that the disease leads to extensive damage of different regions of the brain that are more particularly involved in the metabolism of the catecholamines and other neurotransmitters, such as the caudate nucleus, putamen, and substantia nigra.

As to the possible clinical-biochemical correlations in our patients, taking into account also our division into slow and fast performers, we conclude that the determination of the CSF levels of the acid catabolites of the monoamines is of little value for the purpose of assessing the severity of the disease, its duration, and its various clinical features.

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