Studies of hypothalamic function in Huntington's chorea

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SUMMARY In eight patients with classical Huntington's chorea hypothalamic function was assessed by the insulin tolerance test, the thyrotrophin releasing hormone test, the gonadotrophin releasing hormone test and water deprivation and the results compared with those of 10 control subjects. All patients ceased to have choreiform movements for approximately 60 minutes during the insulin tolerance test. Four of the patients failed to show clinical features of stress in response to hypoglycaemia. The fasting blood glucose level and blood glucose response to insulin were similar for the two groups. However, the response of plasma cortisol ($p < 0.05$) and of growth hormone ($p < 0.05$) to hypoglycaemia was earlier in patients than controls, though peak responses were the same for each group. The thyrotrophin releasing hormone test revealed no difference in basal levels of thyroid stimulating hormone in either group, or in peak response to thyrotrophin releasing hormone or in the increment at 20 minutes. One of the patients had a delayed response typical of a hypothalamic disorder, whereas none of the controls had such a response. Mean free thyroxine index levels for each group were similar. There was no difference in basal prolactin level, or in the increment or in the peak level in response to thyrotrophin releasing hormone between each group as a whole or when the males and females were analysed separately. Because of small subgroups, the data from the gonadotrophin releasing hormone test were difficult to analyse, but no clear differences or obvious abnormalities emerged. Water deprivation revealed no evidence of inability to concentrate urine in either group and hence no indication of impaired antidiuretic hormone function. The study supports previous findings of altered hypothalamic function in patients with Huntington's chorea but further suggests that serotonergic rather than dopaminergic mechanisms may be altered.

Pathological involvement of the hypothalamus in patients with Huntington's chorea has been well documented.¹⁻⁴ This takes the form of cell degeneration and gliosis of the supraoptic, paraventricular and tuberal nuclei. Hypothalamic involvement may manifest itself clinically during the course of the disease by cachexia, excessive sweating, hyperphagia and various autonomic disturbances.³ It is not clear whether hypothalamic changes occur early or late in the disorder.

In recent years, several studies have shown biochemical evidence of hypothalamic dysfunction

in Huntington's chorea. Podolsky and Leopold⁵ proposed altered release of the growth hormone (GH) in patients with Huntington's chorea when they found that an oral load of glucose failed to suppress GH release in 14 patients. Repeating the glucose load following administration of levodopa resulted in suppression of GH release. An early rise in GH in response to insulin-induced hypoglycaemia was shown by Phillipson and Bird⁶ and Keogh *et al.*⁷ They suggested altered control of GH release in Huntington's chorea was possibly due to a change in dopaminergic influences, for Boyd *et al.*⁸ had postulated that GH release was mediated by elevated levels of dopamine in the tubero-infundibular region of the hypothalamus causing release of growth hormone releasing factor. Impaired prolactin responses to chlorpromazine and thyrotrophin releasing hormone (TRH) have recently been shown,⁹ supporting the suggestion

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of enhanced dopaminergic activity in the hypothalamus of patients with Huntington's chorea. We have sought to elucidate the problem further by examining a wide range of hypothalamic functions, including control of GH, corticotrophin, gonadotrophin, thyroid stimulating hormone (TSH), prolactin and antidiuretic hormone (ADH) secretion in patients with Huntington's chorea.

Patients and methods

Patients

Eight patients with classical, that is non-rigid, Huntington's chorea and 10 control subjects were studied. The patients (four males, four females) had an average age of 52.5 years (range 35–64 years) and the average duration of disease was seven years (range 1–11 years). The 10 controls (three female, seven male) whose average age was 53.5 years (range 46–64 years) comprised six non-blood relatives of Huntington's chorea sufferers and four patients with either cervical spondylosis or lumbar disc degeneration. Fully informed consent was obtained from the patients or their relatives where necessary, and from the control subjects.

Procedure

The subjects were admitted for 48 hours, all drugs having been stopped for at least 72 hours. After an overnight fast, an intravenous cannula (19G butterfly) was placed in an antecubital vein at 8.30 am and the tests commenced at 9.00 am. The cannula was anticoagulated with diluted heparin. Basal samples were taken for serum follicle stimulating hormone (FSH), luteinising hormone (LH), growth hormone (GH), prolactin, total thyroxine, triiodothyronine uptake and thyroid stimulating hormone (TSH) into four plain 10 ml tubes, for plasma cortisol into a 10 ml heparinised tube and for blood glucose into a 1 ml fluoride tube. At 9.00 am, 200 µgms of TRH (Roche) and 100 µgms of gonadotrophin releasing hormone (Gn-RH) (HRF Ayerst) were injected from separate syringes via the cannula and further samples were taken for LH, FSH, prolactin and TSH after 20 minutes. At 60 minutes samples were taken for cortisol, GH, glucose, LH, FSH, prolactin and TSH, immediately following which bovine soluble insulin (0.1 units/kg) was injected and samples for cortisol, GH and glucose were taken at 10, 20, 25, 30, 35, 40, 45, 60 and 90 minutes. 100 mg of hydrocortisone and 50 ml of a 50% glucose solution were at hand throughout the insulin tolerance test. On the second morning, the subjects were allowed a light breakfast, but no tea, coffee or nicotine. At 8.00 am the subjects began an eight-hour water deprivation test. Blood samples were taken into a 10 ml heparinised tube at 9.00 am and 4.00 pm. Urine samples were also collected, when possible, between 8.30–9.30 am and 3.30–4.30 pm. The patients were weighed hourly

throughout the test, no subject losing 3% or more of body weight.

Estimations

Blood glucose was measured by an automated glucose oxidase method. Free thyroxine index was derived from the results of measurement of serum total thyroxine (Thyopac-4, Radiochemical Centre, Amersham) and uptake of ¹²⁵I labelled triiodothyronine (Thyopac-3, Radiochemical Centre, Amersham). Commercial radioimmunoassay kits were used to determine serum GH (HGH kit, Lepetit), plasma cortisol (Cortisol kit, Lepetit), serum LH (LH kit, Lepetit), serum FSH (FSH kit, Lepetit), serum TSH (TSH RIA kit, Radiochemical Centre, Amersham) and serum prolactin (Immuno Nuclear Corporation). Plasma and urine osmolality were measured by the freezing point method using the Osmette 5 osmometer. All data were analysed using the Mann-Whitney U test for small groups except the FTI results, for which Student's *t* test was employed.

Results

Clinical

In all patients, choreiform movements disappeared 23–35 minutes following administration of insulin and remained absent for at least an hour and for over four hours in one case. Four patients failed to show features of hypoglycaemia despite a fall in blood glucose to less than 2.0 mmol/l. Three control subjects failed to develop hypoglycaemia at all, that is blood glucose did not fall below 2.0 mmol/l despite standardisation of insulin dosage. These three patients did not develop clinical features of hypoglycaemia and, appropriately, did not show GH and cortisol responses.

Biochemical

There was no difference in fasting blood glucose and blood glucose response to insulin in patients and controls, including those control subjects who did not develop hypoglycaemia. Figures 1 and 2 show the mean GH and cortisol levels respectively, excluding the data from the three control subjects who did not develop sufficient hypoglycaemia to stress the hypothalamus. The rise in both GH and cortisol and response to hypoglycaemia was earlier in patients than in controls and the difference was significant ($p < 0.05$) at 30 minutes.

Mean free thyroxine index for patients was 123 and for controls was 89 which was not a statistically significant difference. Mean basal TSH level for patients was 5.7 mU/l and for controls was 5.6 mU/l. The mean peak levels for patients and controls were 12.3 mU/l and 13.3 mU/l respec-

Fig 1 Mean growth hormone responses to hypoglycaemia in patients and controls. The asterisk indicates a significant difference ($p < 0.05$, Mann-Whitney U test).

tively and the mean increments above basal level were 6.6 mU/l and 7.8 mU/l respectively. At no stage of the test did the patient group differ significantly from the control group. However, one patient showed a delayed response in which the level of TSH 60 minutes after TRH had been given was greater than that at 20 minutes. Such a response has been found in hypothalamic dysfunction.¹⁰

There was no difference in basal prolactin levels between patients (mean: 212 mU/l) and controls (mean: 234 mU/l), nor was there any difference in peak levels (patients: 1036 mU/l; controls 858 mU/l) nor in incremental levels (patients: 824 mU/l; controls 594 mU/l). Moreover, when males and females were analysed separately, no differences emerged: for female patients and controls respectively mean basal levels were 250 and 366 mU/l; mean peak levels were 1220 and 1240 mU/l and mean increments were 960 and 940 mU/l. For male patients and controls respectively the mean basal levels were 180 and 190 mU/l; mean peak levels were 840 and 720 mU/l and mean increments were 660 and 520 mU/l.

Fig 2 Mean cortisol responses to hypoglycaemia in patients and controls. The asterisk indicates a significant difference ($p < 0.05$, Mann-Whitney U test).

LH and FSH responses to Gn-RH were assessed, but results were difficult to interpret statistically because the small groups of patients and controls needed to be further sub-divided into males, premenopausal and postmenopausal females. However, no difference emerged when results from premenopausal subjects from each group were compared: for patients and controls respectively, mean basal LH levels were 22 and 35 $\mu\text{gm/l}$, mean peak LH levels were 103 and 105 $\mu\text{gm/l}$ and mean increments were 96 and 70 $\mu\text{gm/l}$. In the postmenopausal patients and controls respectively, basal LH levels were 270 and 198 $\mu\text{gm/l}$, mean peak levels were 442 and 266 $\mu\text{gm/l}$ and mean increments were 234 and 266 $\mu\text{gm/l}$ and these were not significant. Similar results accrued from the FSH data.

After eight hours of water deprivation, the mean plasma osmolality for patients was 293 mOsm/kg and for control subjects was 280 mOsm/kg. Mean urinary osmolality at the end of the test was 929 mOsm/kg for patients and

730 mOs/kg for controls; these differences were not significant. No subject in either group showed inability to concentrate urine appropriately.

Discussion

In our study and in that of Keogh *et al*⁷ the patients, although awake, lost their involuntary movements during the ITT. In our patients the disappearance of the movements coincided with the onset of hypoglycaemia, and possibly the explanation is that the basal ganglia in Huntington's chorea are especially susceptible to neuroglycopenia.

Abnormalities of GH and prolactin release in Huntington's chorea have been shown previously^{5-7,9} and have led to the suggestion of increased intracerebral dopaminergic activity in this condition. However, in the study of Hayden *et al*⁹ two patients with the rigid form of Huntington's chorea had paradoxical results. Moreover, Chalmers and his colleagues¹¹ produced data suggesting decreased dopaminergic activity. Our data for the slightly earlier GH response to hypoglycaemia are similar to the findings of Phillipson and Bird⁶ and Keogh *et al*,⁷ but do not necessarily implicate dopamine for there is evidence that serotonin rather than dopamine may be the principal brain monoamine causing stimulation of GH release.^{12,13} Moreover, while there is no evidence that dopamine plays any part in corticotrophin release,^{14,15} there is evidence that serotonin stimulates the release of corticotrophin.¹⁶ Since our data showed a similar response for cortisol as for GH, we conclude that serotonergic mechanisms rather than dopaminergic ones may be disordered in the hypothalamus in Huntington's chorea.

There is much evidence to suggest that dopamine is the major influence on prolactin secretion, the effect being one of tonic inhibition.^{17,18} The role of TRH is not understood. If enhanced dopaminergic activity is present in Huntington's chorea, impaired prolactin release might be anticipated. Hayden *et al*⁹ showed impaired prolactin release in response to chlorpromazine and TRH in patients with Huntington's chorea. In the present study, however, we were unable to demonstrate any impairment of prolactin release in patients, suggesting that dopamine is not involved. Chalmers *et al*¹¹ also failed to demonstrate impairment of prolactin release in patients with Huntington's chorea. Present evidence suggests that neither dopamine nor serotonin have major control over the secretion of TSH, LH, or

FSH.^{14,19,20} Our data showed no abnormalities of gonadotrophin release in patients with Huntington's chorea. One patient showed delayed release of TSH in response to TRH and a response of this type is thought to indicate hypothalamic dysfunction.¹⁰ Clearly, further study of TSH response to TRH in Huntington's chorea is necessary before firm conclusions can be drawn.

Neurotransmitter control of vasopressin release appears to be cholinergic and noradrenergic without any significant effect from dopamine or serotonin.²¹ Our data revealed nothing to suggest impairment of vasopressin release.

Thus, while our results are in agreement with those of others in suggesting alteration of neurotransmission in the hypothalamus in Huntington's chorea, the further data we provide suggest enhanced serotonin activity rather than increased dopamine activity. There has been previous indirect evidence suggesting a role for serotonin in Huntington's chorea but the data have given conflicting results suggesting in some studies that decreased serotonin levels may be present²²⁻²⁴ and in others that increased serotonin levels may occur in this condition.^{25,26} Yet further studies have found no evidence for altered serotonin activity.^{27,28}

Current evidence points to several neurotransmitter abnormalities in this condition including changes in the distribution of dopamine in the nigrostriatal and mesolimbic systems in post-mortem brain tissue,²⁹ reduction in γ -aminobutyric acid in the striatum, also in post-mortem tissue³⁰ and reduced concentration of choline acetyltransferase in the striatum and nucleus accumbens.^{29,30} It seems likely that the extent of the damage in Huntington's chorea leads to multiple neurotransmitter disorders which collectively result in the clinical features of the condition.

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