Growth hormone response to arginine test differentiates between two subgroups of Huntington's disease patients

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ABSTRACT

Objective Huntington's disease (HD) is an autosomal dominant disorder characterised by motor, cognitive and psychiatric disturbances. Several studies have demonstrated that hypothalamic dysfunction is part of the phenotypic spectrum. The aim of the study was to evaluate the growth hormone (GH) response to arginine infusion in a cohort of HD patients, to search for an in vivo biomarker of hypothalamic dysfunction.

Methods The authors investigated 17 HD patients and 17 age-, sex- and BMI-matched healthy controls. Clinical assessment of patients was performed using the Unified Huntington's Disease Rating Scale motor section and total function capacity. Metabolic and endocrine investigations included total, LDL and HDL cholesterol, basal insulin, GH, insulin-like growth factor 1 (IGF-1), SD Score IGF-1 (SDS IGF-1) and the GH response to arginine stimulation.

Results HD patients showed lower plasma IGF-1 and SDS IGF-1 levels and a higher baseline GH in comparison with control subjects. The arginine test induced a normal GH peak in nine patients (53%; Arg+), whereas the response was absent in the remaining eight (47%; Arg−). Arg+ and Arg− also showed two distinct endocrine/metabolic profiles with differences in insulin and lipid metabolism.

Conclusion It remains to be clarified if these two subgroups of patients, according to the GH response to arginine, correspond to different disease stages or to different patterns of neurodegeneration.

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder caused by an expanded CAG repeat within the *HD* gene.[1] It is characterised by the triad of motor disturbances, personality changes and cognitive decline. Hypothalamic dysfunction may also contribute to the clinical spectrum of HD, as several studies, in animals and humans, have underlined. Hypothalamic atrophy has been shown to occur in the early stages of the disease by voxel-based MRI studies.[2] Loss of cells, especially in the somatostatin-containing neurons of the nucleus tuberalis lateralis (NTL) of the hypothalamus, has also been demonstrated.[3 4] Hypothalamic dysfunction in HD may account for several well-known manifestations of the disease such as weight loss,[5] sleep disorders,[6 7] hyperactivity of the hypothalamic–pituitary–adrenal axis[8] and decreased levels of luteinising hormone and testosterone in male patients.[9]

Circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels have recently been found to be higher in HD patients.[10] GH secretion from the pituitary gland is stimulated by the GH-releasing hormone (GHRH) and inhibited by somatostatin (SS): both these hypothalamic neurohormones have a pulsatile secretion modulated mainly by noradrenergic and cholinergic networks.[11 12] Both clonidine, an α2-adrenoceptor agonist, and arginine, an amino acid activating the cholinergic system, induce GH release (the former by stimulation of GHRH, the latter by inhibition of SS release), and they have been widely used to evaluate pituitary GH secretion and reserve.[13] The aim of our study was to evaluate the GH response to arginine in a cohort of molecularly confirmed HD patients, in order to look for an in vivo demonstration of hypothalamic dysfunction in HD. We also investigated the relationship between the GH response and clinical, metabolic and endocrine variables, to understand if GH response abnormalities may represent a biomarker of disease progression.

MATERIALS AND METHODS

Study participants (n=17, ten males, seven females) were recruited among consecutive patients afferent to the HD Clinics at the Department of Neurological Sciences, from February 2008 to February 2009. Disease-specific inclusion criteria were: age 18–70 years, manifest signs and symptoms of the disease, and positive molecular test for the presence of a CAG triplet repeat number >35 in the *HD* gene. Exclusion criteria were: history of endocrine disorders, chronic systemic diseases, substance abuse or inability to cooperate with the study. Eleven patients were drug-naïve. To avoid possible interactions, administration of antipsychotic agents or any other dopamine receptor blockers was interrupted at least 2 weeks before the test in further four patients. One patient was allowed to take 25 mg/day of tetrabenazine and another 5 mg/day of olanzapine. The age of onset was considered the time when motor symptoms were first noticed. The phenotype at onset was also defined as psychiatric, if psychiatric disturbances were present prior to motor onset, as motor, if only motor symptoms were present at onset, and as mixed, if motor and psychiatric symptoms appeared

Table 1 Clinical features and baseline characteristics of Huntington's disease patients and control subjects

	Patients	Control subjects
No	17	17
Male/female	10/7	10/7
Age (years)†	48.8±11.6 (27 to 67)	49.2±12.3 (27 to 68)
CAG (triplets)†	44.8±4.9 (41 to 61)	NA
Disease duration (months)†	64.2±41.3 (24 to 142)	NA
Disease stage	6-I, 5-II, 5-III, 1-IV	NA
Unified Huntington's Disease Rating Scale motor score†	26.2±15.0 (9 to 57)	NA
Total functional capacity score†	8.3±3.7 (1 to 13)	NA
BMI†	23.8±4.4 (16.0 to 33.9)	23.8±3.3 (19.2 to 32.1)
Glucose (mg/dl)†	82.7±12.9 (59 to 105)	82.9±8.8 (68 to 102)
Insulin (μIU/ml)†	5.4±3.4 (2 to 11)	6.6±2.0 (3 to 10)
Homeostasis model assessment-insulin resistance†	1.0±0.9 (0 to 2.5)	1.4±0.5 (0.6 to 2.2)
Total cholesterol (mg/dl)†	203±39 (125 to 272)	183±26 (150 to 228)
Low-density lipoprotein cholesterol (mg/dl)†	129±47 (63 to 214)	103±24 (75 to 149)
High-density lipoprotein cholesterol (mg/dl)†	56±23 (32 to 88)	60±5 (51 to 70)
Growth hormone baseline (ng/ml)†	0.76±0.94 (0.07 to 3.40)*	0.06±0.05 (0.01 to 0.20)
Insulin growth factor 1 (μg/l)†	159±55 (70 to 263)*	216±39 (139 to 288)
SD score of insulin growth factor 1†	−0.36±1.0 (−2.6 to 1.77)*	0.70±0.58 (−0.3 to 1.6)

*$p<0.01$.
†Data are means±SD (range).
NA, not applicable.

together. Motor symptoms and total function capacity (TFC) were evaluated by one experienced neurologist using the Unified Huntington's Disease Rating Scale (UHDRS).[14] The motor component of the UHDRS scale consists of 31 questions rated on a 0–4-point scale, with 4 indicating the most severe impairment. The TFC is a standardised scale (range 0 to 13) most sensitive to early changes in disability, with higher scores indicating better function.[15] Disease stage was determined according to TFC: stage I represents scores from 11 to 13; stage II, from 7 to 10; stage III, from 3 to 6; stage IV, from 1 to 2; and stage V, a score of 0.[16] Control subjects (n=17, ten males and seven females) were recruited among healthy volunteers matched to the patients according to age (±2 years), sex and BMI (±2). The only exception was for a male patient, aged 67 years and with a BMI of 16.0, who was matched with a man with a BMI of 20.3, as it was not possible to find a healthy control of that age with a similar BMI. Control subjects were free from any neurological and endocrine disease, and none of them was taking medications. The study protocol was approved by the local Ethics Committee, and informed consent was obtained from all the study participants. For HD patients lacking capacity of making decisions, the informed consent was obtained from the relatives.

In the early morning, after a 12 h fasting, patients and control subjects underwent routine investigations and an endocrine study, inclusive of basal insulin, total cholesterol, LDL and HDL determination, and the arginine test. After subjects had rested in a supine position for at least 30 min, baseline samples (T0) were collected from a cannulated antecubital vein. Then, 30 g of arginine (arginine hydrochloride, 30% solution, Salf, Italy) was infused intravenously over 30 min, and blood was sampled every 30 min for 1 h (T30, T60 and T90) thereafter. Blood pressure and heart rate were monitored through the test. Blood samples were centrifuged immediately after sampling, and the supernatants stored at −80°C until analysis. Assays were performed according to the manufacturer's instructions. Serum GH was measured with commercially available immunoradiometric kit (Chematil, Angri, Italy). The sensitivity of the assay was 0.015 ng/ml. A peak serum GH lower than 1.4 ng/ml at T60 or T90 time points was considered abnormal, as for guidelines for adult GH deficiency (GHD) diagnosis.[17] Basal IGF-1 was also measured, using a chemoluminescent IGF-1 assay (Immunolite 2000, Medical System, Genoa, Italy) with the limit of detection of 20 μg/l. Homeostatis model assessment of insulin resistance (HOMA-IR) was computed as follows: fasting insulin (μIU/ml)×fasting glucose (mmol/ml)/22.5. Inter- and intragroup analyses were performed using the Yates χ^2 test and t test (paired or unpaired), when appropriate. Relationships between variables are expressed by the Pearson correlation coefficient. Differences were considered statistically significant when $p<0.01$. All analyses were conducted using the STATA 10 for Windows Package.

RESULTS

Demographic, clinical and laboratory data of the patients and the controls are summarised in table 1. Disease severity was mild to moderate in most. Compared with control subjects, the HD

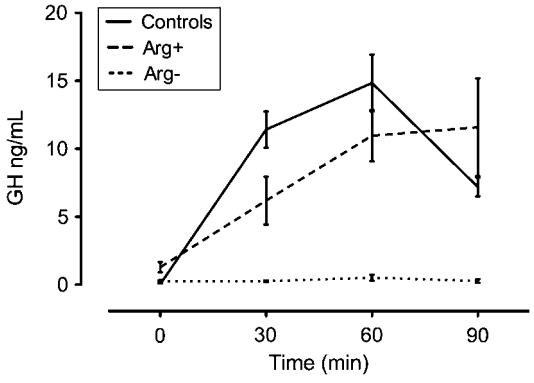

Figure 1 Serum concentration of growth hormone (GH; mean±SEM) at baseline and 30, 60 and 90 min after arginine infusion. According to the results of the stimulation test, Huntington's disease patients can be divided in two groups: Arg+ (n=9), with a normal GH response, and Arg− (n=8), with a blunted response compared with controls (n=17).

Table 2 Clinical features of Huntington's disease patients according to growth hormone response to arginine

	Patients with normal arginine test (Arg+)	Patients with altered arginine test (Arg−)
No (%)	9/17 (53%)	8/17 (47%)
Male/female	5/4	5/3
Age (years)‡	49.7±14.4 (27 to 67)	48.4±8.7 (35 to 61)
CAG (triplets)‡	45.7±7.4 (41 to 61)	44.5±2.4 (42 to 49)
Onset phenotype	4-Mo, 1-Ps, 4-Mx	4-Mo, 3-Ps, 1-Mx
Disease duration (months)‡	72.0±47.6 (24 to 142)	55.5±33.9 (25 to 120)
Disease stage	1-I, 3-II, 4-III, 1-IV	5-I, 2-II, 1-III
Unified Huntington's Disease Rating Scale motor score‡	31.2±17.8 (9 to 57)	20.7±9.3 (11 to 38)
Total functional capacity score‡	6.6±3.7 (1 to 13)	10.2±2.9 (4 to 13)
BMI‡	21.5±3.8 (16.0 to 25.9)	26.1±4.0 (20.3 to 33.9)
Glucose (mg/dl)‡	77.3±14.5 (59 to 105)	88.8±7.4 (79 to 99)
Insulin (μIU/ml)‡	3.4±2.0 (2 to 8)*	7.6±3.4 (2 to 11)
Homeostasis model assessment-insulin resistance‡	0.4±0.5 (0 to 1.5)*	1.6±0.8 (0 to 2.5)
Total cholesterol (mg/dl)‡	185±38 (125 to 229)	229±23 (202 to 272)
Low-density lipoprotein cholesterol (mg/dl)‡	107±34 (63 to 156)	162±34 (109 to 214)*
High-density lipoprotein cholesterol (mg/dl)‡	62±12 (51 to 88)	41±14 (32 to 68)*
Growth hormone baseline (ng/ml)‡	1.21±1.13 (0.15 to 3.40)	0.26±0.21 (0.07 to 0.77)
Growth hormone peak (ng/ml)‡	16.4±8.8 (5.7 to 37.6)	0.6±0.4 (0.2 to 1.4)†
Insulin growth factor 1 (μg/l)‡	135±44 (70.2 to 200)	191±54 (124 to 263)
SD Score insulin growth factor 1	−0.5±0.5 (−1.44 to 0.58)	−0.1±1.2 (−2.5 to 1.8)

*p<0.01.
†p<0.001 (asterisks mark values which differ also from normal controls).
‡Data are means±SD (range).
Mo, motor; Mx, mixed (motor and psychiatric); Ps, psychiatric.

patients showed higher baseline GH and lower IGF-1 and SDS IGF-1 serum levels. During arginine infusion, no changes in blood pressure or heart rate were observed in any group. The arginine test induced a GH peak higher than 1.4 ng/ml in all control subjects (mean peak value±SD: 16.6 ng/ml±8.3; 35% of the subjects at T30, 65% at T60) and in nine patients (53%) (16.4 ng/ml±8.8; 67% at T60, 33% at T90). In the remaining eight patients (47%) the GH response to arginine stimulation test was blunted (0.6 ng/ml±0.4) (figure 1 and supplementary online table 4).

Among the two subgroups of patients (with normal GH response to arginine, Arg+, and with absent GH response, Arg−) there were no differences in age, sex distribution, CAG triplet repeats, phenotype at onset, disease duration and stage, and UHDRS motor score; a slightly lower TFC score (p=0.04) and BMI (p=0.02) value were observed in Arg+ patients (table 2). Previous exposition to neuroleptics did not affect GH response to arginine, since six drug-naïve patients were Arg+, and five were Arg−. The patient who was still taking olanzapine had a normal GH peak, whereas the patient who was still taking tetrabenazine showed a blunted response. Arg− patients showed a higher LDL cholesterol and lower HDL cholesterol compared with Arg+ patients (table 2). Arg+ patients showed lower insulin and HOMA-IR compared with Arg− (table 2). Table 3 shows the relationship between clinical and laboratory variables in the 17 HD patients. As expected, BMI was shown to correlate positively with total cholesterol and insulin, and negatively with baseline GH. A positive correlation between baseline and peak value GH was found. Also expected was the negative correlation between TFC score and UHDRS motor score.

DISCUSSION

Several signs of a hypothalamic–endocrine dysfunction have been reported in HD.[5–7 10 18] Hypothalamic involvement in HD has been confirmed by neuropathological studies, showing a dramatic neuronal loss primarily of somatostatin-containing neurons in the NTL.[3 4] Recently, higher levels of circulating GH in HD patients have been found in a large case–control study,

Table 3 Relationships between clinical and laboratory variables

	Unified Huntington's Disease Rating Scale motor score	Total functional capacity score	BMI	Growth hormone (T0)	Growth hormone (peak)	Insulin growth factor 1	Total cholesterol	Insulin
Unified Huntington's Disease Rating Scale motor score								
Total functional capacity score	−0.71*							
BMI	−0.22	0.52						
Growth hormone (T0)	0.42	−0.38	−0.71*					
Growth hormone (peak)	0.21	−0.34	−0.54	0.56*				
Insulin growth factor 1	−0.22	−0.08	0.17	−0.42	−0.40			
Total cholesterol	−0.27	0.51	0.69*	−0.52	−0.66	0.23		
Insulin	0.03	0.19	0.65*	−0.41	−0.51	0.12	0.48	

Data are correlation coefficients (r).
*p<0.01.

showing a correlation with disease severity and weight loss.[10] GH is a protein hormone synthesised and secreted by the somatotroph cells of the anterior pituitary gland, under two hypothalamic hormone controllers: GHRH and SS. It is a major participant in several complex physiological processes, including growth and metabolism, exerting its role either directly on target cells or mediated by its peripheral effector, IGF-1.[11 12]

The present study aimed to investigate the metabolic/endocrine profile and the GH response after the arginine stimulation test in a cohort of HD patients and controls. The arginine test was chosen, because it induces GH release by inhibition of somatostatin release, thus potentially representing a marker of hypothalamic dysfunction in vivo. Moreover, it is a safe test and has been widely used to evaluate pituitary GH secretion and reserve.[13 17]

As patients not fully cooperative and those under heavy drug treatment were excluded from the study, recruitment was biased for the inclusion mostly of patients in early disease stages. HD patients showed higher basal GH values, as already shown in previous reports,[10 19] and lower IGF-1 and SDS IGF-1 levels in comparison with age-, sex- and BMI-matched healthy controls. The last finding does not confirm the results of a recent paper,[10] which described a slight IGF-1 increase in HD patients. It is noteworthy that IGF-1 levels of the French HD cohort[10] are comparable with ours (153±48 vs 159±55 μg/l), but the values of their control subjects, recruited among patients' spouses and relatives, are lower than ours, which are healthy volunteers (141±42 vs 216±39 μg/l). As previously reported,[10] BMI was significantly related with baseline GH levels and was independent from motor and functional score.

The most relevant result of our study was that almost half of our patients showed no GH response to arginine infusion. The remaining patients had a normal peak, although somewhat delayed (at T90 in a third of them) in comparison with controls. Differences in insulin and cholesterol metabolism were also observed in the two groups.

These findings are unexpected and puzzling. We could speculate that the hypothalamic dysfunction primarily in somatostatin-containing neurons may determine the lack of response of GH to arginine stimulus in the Arg− patients. The imbalance in GH/IGF-1 axis regulation may also be responsible for the impaired lipid profile in this subgroup of patients.

However, in Arg+ patients, a situation of negative energy balance appears to be likely for the following reasons: (1) high GH levels with reduced IGF-1, insulin and HOMA-IR levels are a frequent finding in critical illness and catabolic state, and it has been proposed that GH hypersecretion may be driven by decreased circulating IGF-1 through a feedback mechanism in states of chronic starvation;[20 21] (2) IGF-1 levels are a good index of nutritional status per se;[22] (3) BMI values are slightly lower than in Arg− patients. The clinical picture of this subgroup of patients also appears to be slighlty more severe, according to the TFC score, suggesting that GH response is not a useful progression biomarker.

The evidence of these two sharply outlined endocrine/metabolic profiles in HD is difficult to understand. These results may reflect two different stages of the disease. Otherwise, we found no differences in age, sex distribution, CAG triplet size, phenotype at onset and disease stage between the two groups. Another possible explanation is that the GH response to arginine infusion may disclose two different patterns of hypothalamic involvement in HD. It has been recently assessed in an in vivo PET study that hypothalamic changes in HD occur in almost 50% of HD patients and premanifest carriers, without correlation with disease duration and striatal dysfunction.[23] In this view, the degree of hypothalamic dysfunction may be different among patients, as well as the motor, cognitive or psychiatric phenotype may be largely heterogeneous in HD.

In conclusion, these data clearly demonstrate a dysfunction in the somatotropic axis in HD. According to the GH responses to arginine stimulation, we observed two distinct metabolic/endocrine profiles in our cohort of patients. The main limitation of our study is the relatively small number of patients, partially due to the rigorous inclusion criteria. To confirm the data, replication of the study with larger numbers of patients together with further neuropathological studies and extensively neuroendocrine assessment should be performed. Prospective studies are also necessary to determine whether these changes occur at an early stage and whether they are linked to disease progression.

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Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Ethics Committee of the University of Federico II, Naples, Italy.

Contributors ES and CR contributed equally.

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Neurological picture

Pott's puffy tumour: harbinger of intracranial sepsis

A 60-year-old woman presented with a 4-week history of unilateral forehead swelling following a coryzal episode. She described frontomaxillary pain and nasal discharge. Examination confirmed a fluctuant non-tender swelling (figure 1A) and ipsilateral mucopurulent rhinorrhoea. Neuro-ophthalmic examinations were unremarkable. A contrast-enhanced CT scan revealed a right-sided pansinusitis (figure 1B), an external subperiosteal collection with an underlying small extradural collection (figure 1C) and an interposed rarefied frontal bone (figure 1D). She underwent endoscopic sinus drainage with external frontal sinus trephine. The intracranial collection was managed conservatively with intravenous antibiotics and serial CT scans.

COMMENT

Pott's puffy tumour describes a subperiosteal abscess overlying frontal bone osteomyelitis. First documented as a sign of intracranial empyema following head injury (1768) and subsequently as a complication of frontal sinusitis (1775),[1] fewer than 20 adult cases have been reported in the post-antibiotic era.[2] It has

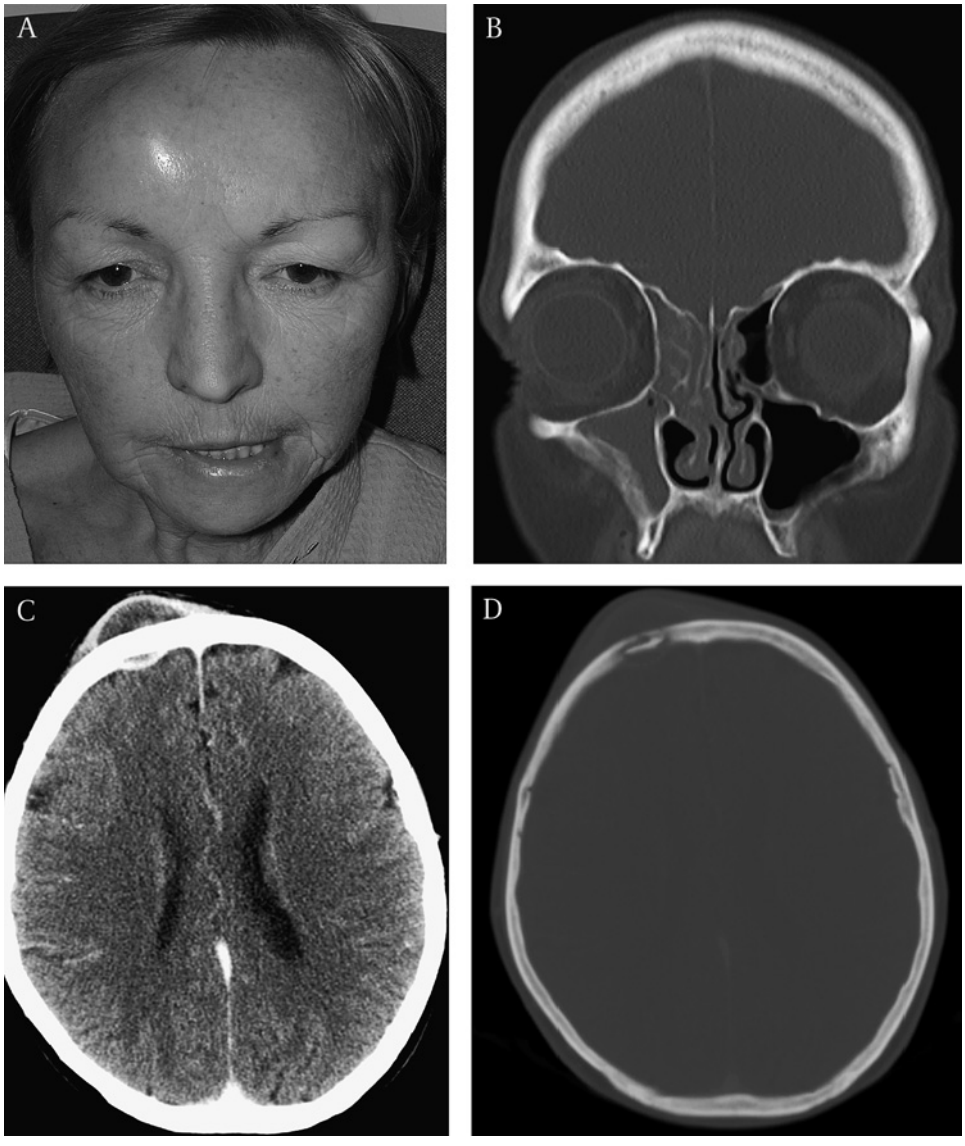

Figure 1 (A) Clinical photograph of unilateral forehead swelling. Coronal CT scans demonstrate (B) opacification of the right maxillary and ethmoid sinuses and nasofrontal duct. Axial CT images demonstrate (C) an extracranial subperiosteal collection and underlying extradural empyema with (D) rarefaction of the interposed frontal bone.