Caudate nucleus atrophy in Huntington’s disease and its relationship with clinical and genetic parameters

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Summary

We analysed clinical data in 80 genetically confirmed Huntington’s disease (HD) patients and measured the severity of the head of the caudate nucleus (HCN) atrophy using computed tomography-guided planimetry. The results were compared with measurements obtained in 43 age-matched healthy subjects. Mean planimetric measurements of the HCN differed significantly between the HD patients and healthy controls (p<0.001). We observed a significant inverse correlation between duration of HD and HCN planimetric values (p<0.001). Physiological atrophy of the HCN with age was also present in healthy controls, but did not overlap with values obtained in HD patients (p<0.01). Furthermore, we found in our patients a statistically significant inverse correlation between the number of CAG triplet repeats and the age at onset of HD (p<0.001). Neither the number of CAG triplet repeats, nor the age at onset of HD was found to be related to the character of the initial clinical symptoms (motor vs mental). Similarly, no relationship emerged between maternal or paternal inheritance and the number of CAG triplet repeats. Moreover, the type of inheritance did not influence the age at onset of HD in our patients. Planimetric measurement of the HCN appears to be a simple and useful paraclinical tool for the diagnosis of HD.

KEY WORDS: CAG triplet, caudate nucleus, computed tomography, Huntington’s disease, neuroimaging.

Introduction

Huntington’s disease (HD) is an autosomal dominant inherited progressive neurodegenerative disease. HD patients suffer from personality and behavioural changes, motor impairment and dementia. The genetic defect, an expansion of CAG triplet repeats (40 repeats and more) has been mapped to 4p 16.3 (1). Aberrant CAG repetition is translated into an enlarged polyglutamine stretch of the protein called huntingtin. The pathogenic role of mutant huntingtin has not yet been sufficiently explored, but abnormal folding and aggregation are likely to be central to it (2).

The predominant neuronal loss occurs in the striatum, especially in the caudate nucleus, and is followed by widespread subcortical and cortical neuropathological changes in the advanced stages of the disease (3). The aims of our study were to obtain and compare computed tomography-guided planimetric measurements of the head of the caudate nucleus (HCN) in HD patients and healthy controls, and then to analyse the relationship between clinical aspects, genetic findings and HCN measurements in our HD cohort.

Materials and methods

During the period 1992-2002 we examined 80 patients with genetically confirmed HD (36 men and 44 women). Table I details the clinical data of the sample. Inheritance was found to be paternal in 42 patients (52.5%), maternal in 20 patients (25%) and remained unknown in 18 patients (22.5%). The initial symptoms of HD were motor in 54 patients (67.5%), mental in 22 patients (27.5%) and unknown in 4 patients (5%).

CT scans were performed on Pace Plus scanner (General Electrics Medical Systems, USA). In addition to standard brain computed tomography (CT) scan, the basal assessment of the HCN was carried out manually using the cursor, Trace and ROI functions on the slice in

Table I - Clinical data in eighty Huntington’s disease patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (yrs)</th>
<th>SD (yrs)</th>
<th>Maximum (yrs)</th>
<th>Minimum (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.2</td>
<td>12.7</td>
<td>76</td>
<td>20</td>
</tr>
<tr>
<td>Age at onset of HD</td>
<td>42.8</td>
<td>12.8</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Duration of HD</td>
<td>6.3</td>
<td>4.3</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>CAG triplet repeats</td>
<td>46.5</td>
<td>6.25</td>
<td>81</td>
<td>38</td>
</tr>
</tbody>
</table>

Abbreviations: SD=standard deviation; HD=Huntington’s disease.

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which, on visual inspection, the HCN area was found to be the largest. The measurement was repeated three times on both the right and the left side to reduce deviations produced by single measurement inaccuracy. The mean value was calculated from data obtained on both sides.

Controls [43 healthy subjects, 14 men and 29 women, mean age 52.6 years (±14.6 years), range 19-80 years] were chosen from a group of patients with headache or transient ischaemic attack in whom no structural changes were detectable on CT scan. Patients with a past history of any neuropsychiatric disorder were excluded.

For statistical analysis the SPSS 11.5 software was used. Normality of data distribution was tested using the Kolmogorov-Smirnov test. Parameters with normal distribution were tested using the univariate ANOVA and Pearson correlation analysis. Other parameters were analysed using the Mann-Whitney test.

**Results**

We found a significant difference in the planimetric measurements of HCN between the two groups (p<0.001); the mean value in the HD patients was 0.44 cm² (±0.13 cm², range 0.70-0.13 cm²) versus 1.17 cm² (±0.12 cm², range 1.45-0.83 cm²) in the control group (Fig. 1).

A significant inverse correlation (r=-0.509, p<0.001) was found between the area of the HCN and the duration of HD (Fig. 2). Natural atrophy in healthy subjects was also observed, with HCN area showing a significant inverse correlation with age (r=-0.3656, p<0.01) (Fig. 3). Nevertheless, there was no overlap between the values obtained in healthy subjects and in HD patients.

We found a significant inverse correlation (r=-0.658, p<0.001) between the number of CAG triplet repeats and the age at onset of HD (Fig. 4). The mean number of CAG triplet repeats was 46.5 (±6.25, range 38-81). No relation was found between: the number of CAG triplet repeats and the character of the initial symptoms of HD (motor vs mental) (z=0.8, p=0.422); the type of inheritance (maternal vs paternal) and the number of CAG triplet repeats (z=0.1, p=0.921); or the age at HD onset and the type of inheritance (maternal vs paternal) (F=0.77, p=0.38).

Age at onset was not dependent on the character of the initial symptoms (motor vs mental) (F=0.02, p=0.89).

**Discussion**

In our study the size of the HCN was found to differ considerably between controls and HD patients (Fig.s 5,6). From many neuropathological studies (4-6) it is known that the first neuropathological changes in HD occur in the striatal region, mainly the caudate nucleus and puta-
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analysing individual data, only direct planimetric measurements of the HCN showed no overlapping of values between HD patients and controls, and could thus serve as useful diagnostic markers of HD. Several MRI studies are in concordance with our results and MRI-based volumetric measurements nowadays constitute the most sensitive imaging markers for prospective longitudinal scientific studies in HD (13-15). However, CT scanning is a universally available resource and CT data can include patients investigated many years ago, even before MR imaging was available.

HD is not the only disorder in which there is HCN atrophy associated with a clinical picture of behavioural changes and cognitive and motor impairment. Dentato-rubro-pallido-luysian atrophy, neuroacanthocytosis, Huntington-like autosomal recessive disorder and spinocerebellar ataxia type 3 can all manifest the above-mentioned features (16-18). All are rare disorders, especially in Europe.

We found an inverse correlation between the area of the HCN and the duration of HD. From Vonsattel’s grading system, we know that striatal atrophy correlates with the degree of neuropathological involvement in HD. One MRI study showed that the caudate nucleus atrophy could be detected even prior to the onset of symptoms in presymptomatic gene carriers (13). Our CT-guided results also revealed severe atrophy of the HCN in the earliest stages of the disease in our HD patients. From this, it can be deduced that there are functional compensatory mechanisms involved in the pathogenesis of HD. Our study confirmed the widely known fact that the number of CAG triplet repeats correlates inversely with the age at onset of HD. Numerous studies have described this, with CAG length accounting for up to 73% of the variance in age at onset (19,20). The number of CAG triplet repeats is thus the main factor encoding age at onset, but several (less important) “modifiers” of age at onset certainly exist, most probably of genetic origin, although environmental influences cannot be excluded (21,22). The significant association between the variance in age at onset and CAG suggests that the contribution of “modifiers” is less obvious in individuals with higher repeats (e.g., more than 44) due to the overwhelming effect of polyglutamine length (23). Brinkman (23) also developed a novel parametric survival model based on CAG repeat length (36-56) to predict accurately the probability of the disease onset (considering motor neurological symptoms rather than psychiatric onset) at different ages in individual patients. In line with our results no study to date has found any influence of the number of CAG triplet repeats on the character of the initial symptoms or on the rate of clinical progression (20).

Contrary to our expectations, we failed to find any relation between type of inheritance (paternal vs maternal) and number of CAG triplet repeats or age at onset of HD. The most probable explanation for our results is a lack of statistical power of our group as a result of the number of juvenile cases it contained – our group included only two juvenile patients, both with paternal inheritance and having 81 and 75 triplets, respectively. The number of CAG triplet repeats in the rest of the patients ranged from 38 to 48. Individuals with juvenile onset of HD usually have over 55 repeats and they usually inherit the gene from their fathers – instability of the number of CAG triplet repeats is characteristic of paten-
nal inheritance (19). The triplet expansion is thought to occur via slippage during DNA replication (24), although other mechanisms are discussed (25). We believe that had our group included more juvenile patients, the direct relationship between the age at HD onset and the number of CAG triplets (and thus paternal inheritance) would have been apparent.

In conclusion, the planimetric CT-guided measurement of the HCN is a simple and potentially useful paraclinical tool in the diagnosis of HD, especially in situations where genetic testing is not practicable or easily available. Nowadays, we cannot recommend CT-guided planimetry as a tool for prospective scientific studies, as MRI-based volumetry of subcortical areas offers more accurate and specific results.

Acknowledgments

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References