SHORT REPORT

Genetically confirmed clinical Huntington's disease with no observable cell loss

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J Neurol Neurosurg Psychiatry 2003;**74**:968–970

Huntington's disease (HD) results from neurodegeneration of the neostriatum. The mutation on chromosome 4 is an expansion in a triplet repeat (CAG)_n located within the *IT15* gene. Only six patients have been reported with clinical features of HD in association with limited neuropathology. Of these, only one has had the diagnosis confirmed by genetic (DNA) testing. We describe a patient with the clinical phenotype and genetically confirmed HD but unexpected limited neuropathology. The patient was seen because of aggressive behaviour and memory problems of two years duration. The differential diagnosis included HD although there was no family history. DNA testing was positive for the HD mutation. Clinical follow up three months later confirmed classic features of HD. Progression of the disease was rapid with death three years later. Neuropathology revealed a largely intact neostriatum with bilateral ischaemic damage and cell loss in the external globus pallidus. Such pathology alone could explain the clinical features of HD. This is only the second report of genetically confirmed clinically manifest HD with little evidence of HD neuropathology. There are several unusual features which could not have been predicted by the clinical picture, in particular the progressive course of bilateral ischaemic changes restricted to the external globus pallidus. The potential to miss other HD cases at post-mortem examination, and the implications of this for family members, are discussed.

HD is an autosomal dominant neurodegenerative disease characterised clinically by variable chorea and dystonia, behavioural and affective changes, and a progressive subcortical dementia.¹ Typically, the brain shows progressive atrophy first due to ongoing loss of medium spiny neurons in the tail of the caudate nucleus, and then involving the body and head, the putamen, and finally the globus pallidus.² In a series of 163 patients, Vonsattel and colleagues reported five cases without discernible neuropathological findings.³ Since this report, very few HD cases without significant neuronal loss have been described.⁴

Direct DNA testing for preclinical or predictive testing for HD became available in 1993 when the underlying abnormality was identified as an expanding CAG repeat in the coding region of the gene *IT15*.⁵ There are normally ≤ 26 CAG repeats with ≥ 40 repeats in definite HD. People with repeats of 36–39 may have variable penetrance, and repeats in the 27–35 range are associated with a normal phenotype but a possible increased risk of HD in offspring if further expansion occurs (anticipation).^{6,7}

There has been only one detailed description of a patient with clinically diagnosed HD confirmed by DNA testing in which there were no specific neuropathological features of

HD.⁴ We describe a further case with definitive clinical and molecular diagnosis of HD but atypical neuropathological findings.

MATERIALS AND METHODS

Testing for HD was performed on DNA extracted from whole blood. Regions of *IT15* were amplified by PCR using primers HD344 and HDC2⁸ for the CAG repeat, and primers HU3 and HU4⁹ for both the CAG repeat and the adjacent but non-pathogenic CCG repeat. Consent for autopsy was obtained from the next of kin and the studies approved by the relevant Human Research Ethics Committees. The brain was removed (postmortem delay nine hours), and fixed in 15% buffered formalin for two weeks. Tissue samples were paraffin embedded, cut, and stained histologically to identify cell pathologies.³ Ubiquitin and N-terminal Huntington (Chemicon, Temecula, California, USA) immunostaining was performed to identify any intranuclear inclusions, and immunohistochemistry for glial fibrillary acidic acid was used to determine the degree of gliosis.

CASE REPORT

Clinical

A 58 year old Caucasian woman presented in 1999 because of family concerns regarding increasing irritability, aggressive behaviour, and changes in short term memory of two years' duration. The patient herself was only concerned with her deafness. Meniere's disease had been diagnosed and treated in 1976. On specific questioning, she admitted to noticing deterioration in her handwriting due to jerking. She did not smoke, but drank up to four standard drinks a day. Both her parents died at an early age. Her mother died of carcinoma of the cervix, and her father's death was alcohol related. Of her two siblings, one brother died of alcohol abuse aged 32. The other was well, but his age was unknown. The causes of death for the grandparents were not known.

On physical examination the patient was noted to have markedly reduced hearing. Her gait was wide based and ataxic with a positive Romberg's test. She had marked motor restlessness of her legs and frequent jerking of her right shoulder. Her eye movements were full, and reflexes were brisk. Her reduced score on mini mental state testing was possibly influenced by her deafness. FBC, ESR, EUC, LFT, TSH, B12, Folate, Lipids, ANA, and VDRL were performed, and were unremarkable except for a mildly elevated cholesterol of 5.6 mmol/l. An MRI scan showed generalised dilatation of the ventricular system and cerebral sulci indicative of some atrophic change. There were no ischaemic changes. EEG showed a low amplitude tracing and was essentially normal. The differential diagnosis included HD.

Abbreviations: HD, Huntington's disease

Figure 1 Examples of the main neuropathological findings. (A) 3 mm coronal section through the head of the caudate nucleus (C) shows enlargement of the lateral ventricles (V), but no obvious degeneration in the basal ganglia. Some enlarged blood vessels are evident in the inferior aspects of the putamen (arrows). The white matter of the corpus callosum is of a normal thickness and no other abnormalities are evident. (B) There was no loss of neurons and no increase in neuroglia in the head of the caudate nucleus. Haematoxylin and eosin stain. (C) Neuronal loss and rarefaction was obvious in the tail of the caudate nucleus, particularly along the ventricular surface. Haematoxylin and eosin stain. Scale equivalent to that in D. (D) Immunohistochemistry for glial fibrillary acidic protein revealed a significant upregulation of astrocytes in the region of neurodegeneration along the ventricular surface. Cresyl violet counterstain. (E) There was a substantial loss of neurons and an increase in neuroglia in the external segment of the globus pallidus. Few neurons remain in this haematoxylin and eosin stained section. (F) There were many tortuous blood vessels in the external segment of the globus pallidus with dark calcification on haematoxylin and eosin sections. Haemosiderin-laden macrophages (arrow) were commonly associated with these vessels. Only rare neurons (arrowhead) were observed near these abnormalities. C, caudate nucleus; V, lateral ventricle.

Diagnostic (DNA) testing for the HD mutation was undertaken, with patient consent. Her CAG repeats were 41/23, consistent with a diagnosis of HD. At this stage, she was referred to a second neurologist (EM), and on review four months later was found to have incomplete pursuit eye movements in the vertical plane, minor difficulty with rapid alternating movements and motor sequencing (Luria test) in addition to her previous signs. She was also complaining of swallowing difficulties, and had become more aggressive and irritable. Her features were now more typical of HD, and molecular studies were repeated. These confirmed previous results.

As expected, the patient's condition gradually deteriorated over the next three years, with increasing dementia, chorea, and apraxia. There was also an increasing dependence on alcohol. On her final admission in 2001, she was drowsy and disorientated. She had limited eye movements, an increase in axial and limb tone, chorea, a resting tremor, and brisk reflexes. Nursing home placement was arranged, and she died four months later. Her deterioration and death were felt to be due to progression of HD, no other cause being identified. Duration was short for HD but the onset could not be accurately determined.

Neuropathology

The brain was of normal appearance and size and, following fixation, weighed 1066 g. Examination of the 3 mm coronal slices revealed that the lateral ventricles were slightly enlarged (fig 1A), suggestive of mild atrophy of the caudate. However, the head of the caudate was convex (fig 1A). No other macroscopic abnormalities were noted.

On microscopic examination, there was no observable cell loss, intraneuronal inclusions or morphological changes in the head or body of the caudate nucleus (fig 1B) or the putamen. There was some upregulation of astrocytes along the ventricular surface, but otherwise these regions were completely unaffected. Cell loss and gliosis was evident in the tail of the caudate nucleus (fig 1C, D), but again no intranuclear inclusions were evident in this region. These changes were consistent with an extremely early stage of Huntington's disease.³

There was a substantial loss of neurons in both the left and right globus pallidus (fig 1E) with enlargement and calcification of some of the blood vessels in this region (fig 1F) associated with haemosiderin-laden macrophages (arrow, fig 1F).

This pathology concentrated in the external segment and was suggestive of past ischaemia.

There was no cell loss, gliosis, spongiosis, plaques, tangles, or inclusions present in any neocortical area. The remaining sections sampled were unremarkable. The overall neuropathological profile was consistent with bilateral ischaemic infarction of the globus pallidus and early HD pathology.

DISCUSSION

This is the second case of genetically confirmed HD with little histopathological evidence of HD. In Vonsattel's neuropathological grading of HD, involvement of only the tail and body of the caudate constitutes early level 1 disease. When the globus pallidus is involved, there is preferential damage of the external segment, as evidenced in this case. However, this is not seen until grades 3 or 4, by which time one expects to find moderate to severe cell loss and astrogliosis in the entire caudate and putamen. In our case, there was sparing of the head and body of the caudate as well as the putamen relative to the globus pallidus in a patient who died with HD. The clinical phenotype was consistent with late stage HD. The genotype confirmed the diagnosis, but the histopathology is not consistent with severe disease. Mizuno *et al* (2000) described a case with minimal neuropathological features in a patient who died as a result of DNA confirmed HD, but there has been no description of relative sparing of the neostriatum with proven clinical and genetic diagnosis.⁴ The absence of intranuclear inclusions suggests a failure to sequester Huntington fragments in this patient, a finding which may explain the relatively rapid clinical progression, as the ability to form inclusions is thought to be neuroprotective.¹⁰ However, some of the clinical features could have resulted from the ischaemic changes and cell loss in the globus pallidus, but the damage was bilateral, which is unusual for ischaemia. The gradual clinical deterioration is also unusual but not unheard of for subcortical vascular events. Therefore, it is possible that other cases have or will come to postmortem examination, but may not be recognised as HD.

DNA triplet repeats in the 27–35 range do not cause disease but such individuals represent reservoirs within the population for new mutations.¹¹ This is because of the phenomenon of anticipation, where the unstable CAG repeat can expand in the next generation. The case presented had no positive family history of HD, which may be explained by a “pre-mutation”, particularly in her father. Alternatively, her father or mother could have died before manifestations of HD developed, or another illness including alcoholism could have masked the underlying HD. DNA testing verified the clinical disease and illustrates the value of DNA testing in patients with a phenotype consistent with HD but without positive

family histories. DNA testing on blood collected postmortem may also prove fruitful for diagnosing HD in cases with unusual bilateral basal ganglia pathology. Apart from confirming the underlying cause of death, the correct diagnosis of HD has implications for family members who are at risk, and so require follow up with appropriate counselling including the option for predictive DNA testing.

ACKNOWLEDGEMENTS

We would like to thank Heather McCann for help with the laboratory work and Heidi Cartwright for the preparation of the photomicrographs. We thank Dr G Herkes for his assistance.

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