Autopsy-Proven Huntington Disease with 29 Trinucleotide Repeats

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ABSTRACT

Huntington disease (HD) is a neurodegenerative disorder associated with expansion of CAG trinucleotide repeats in the *huntingtin* gene. A minimum of 37 CAG repeats is usually reported in patients with clinical features of HD; 30-36 repeats represent an intermediate range. Here we report a 65 year-old male with autopsy-proven HD and 29 CAG repeats.

INTRODUCTION

Huntington disease (HD), a devastating neurodegenerative disorder with profound progressive psychiatric and neurological deficits, is inherited in an autosomal dominant fashion with high penetrance. The presence of 37 or more CAG trinucleotide repeats in the *huntingtin* gene essentially ensures the development of HD, while less than 30 repeats has been associated with a normal phenotype. The 30-36 CAG range repeats is considered "intermediate" and may or may not be associated with clinical features of HD. Therefore, genetic counseling for asymptomatic individuals with CAG repeats in the intermediate range can be challenging.

METHODS/RESULTS

•We report the case of a 62 year-old, right-handed, retired realtor who presented for an evaluation of progressively worsening involuntary appendicular and facial movements over a two-year period.
•His gait had also deteriorated leading to multiple falls.
•His wife described him as a "nervous" person, which culminated in the treatment for depression 7 years prior to presentation.
•There were no complaints of cognitive dysfunction.
•The family history revealed that his mother died at the age of 82 with a brain tumor and his father died at age 79 from "Alzheimer's disease".
•Upon further questioning, the patient's father had displayed involuntary movements in addition to cognitive dysfunction in the last year of his life.
•On examination, the patient obtained a score of 27/30 on the mini-mental status examination, missing one point for orientation and two points for delayed recall.
•The motor examination revealed hypotonia, mild generalized chorea, and random contractions of the frontalis muscle.
•Sustained tongue protrusion was impaired and his gait displayed a shuffling quality with superimposed choreiform movements of the upper extremities.

METHODS/RESULTS

•The brain MRI revealed both generalized and focal atrophy of the caudate bilaterally.
•The genetic test for HD revealed 29 CAG repeats on one allele of the *huntingtin* gene and 20 on the other.
•Additional studies were normal including creatine kinase, anti-cardiolipin antibody, erythrocyte sedimentation rate, thyroid function, serum protein electrophoresis, blood smear for acanthocytes, and DNA analysis for dentatorubral-pallido-luysian atrophy.
•Over the next 3 years, the patient's neurological function deteriorated modestly, but he died suddenly after falling down a flight of stairs in 1995.
•Autopsy revealed evidence of an acute subarachnoid hemorrhage in the right Sylvian fissure with no obvious source.
•More importantly, histological findings were notable for thinning of the cortical ribbon along with moderate gliosis and neuronal loss in the caudate and putamen (Figure 1).
•Recently, the patient's asymptomatic, 38 year-old son presented to our clinic after undergoing HD genetic testing with 32/19 CAG repeats. His neurological examination and brain MRI were normal. He sought genetic counseling and prognostication.

DISCUSSION

In the initial report of the expanded and unstable trinucleotide repeat characteristic of HD, the authors stated that the number of CAG repeats associated with disease development was greater than 42. Since then, the number of repeats associated with the HD phenotype has decreased. In fact, patients have been reported to manifest symptoms implicating HD with less than 30 copies, but clinical characterization and pathologic confirmation are often lacking, raising concerns about misdiagnosis, clerical errors, sample switching, and the possibility of phenocopies (Table 1).
The diagnosis of HD in our patient is supported by family history, the presence of chorea on neurological examination, evidence of caudate atrophy on MRI, and autopsy findings consistent with HD. **The absence of an expanded trinucleotide repeat in the *huntingtin* gene should prompt consideration of a phenocopy, but the increased number of CAG repeats in his son, indicates anticipation, a characteristic feature of the unstable *huntingtin* gene in HD.** Most publications addressing HD neuropathology since 1985 have utilized the micro- and macroscopic classification of Vonsattel *et al.* Using this methodology, our patient meets criteria for Grade 3 HD: moderate atrophy of the caudate>putamen along with moderate gliosis and neuronal loss (Figure 1). Likewise, thinning of the cortex is another characteristic feature of HD based on both pathologic and radiologic studies.

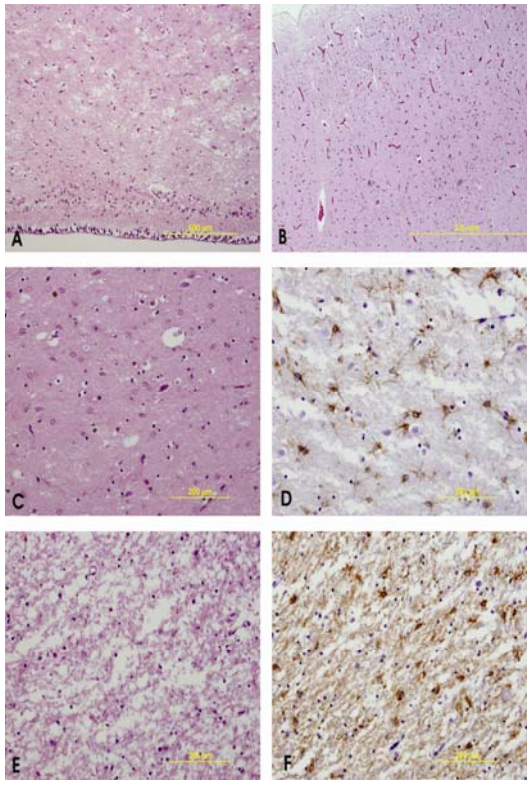

FIGURE 1. Pathology in Huntington disease with 29 trinucleotide repeats (A through F). (A) Caudate including ventricular surface with neuronal loss and reactive gliosis on a luxol fast-blue, hematoxylin and eosin (LH&E)-stained section (10X). (B) Occipital cortex revealing narrowing of the cortical ribbon on an LH&E-stained section (4X). (C) Caudate with neuronal loss and reactive gliosis on an LH&E-stained section (20X). (D) Caudate with extensive gliosis on a Glial Fibrillary Acidic Protein (GFAP)-stained section (20X). (E) Putamen with neuronal loss and reactive gliosis on an LH&E-stained section (20X). (F) Putamen with gliosis on a GFAP-stained section (20X).

TABLE 1. Reports of Presumed Huntington Disease with <30 CAG repeats

Author	Year	Number of patients with < 30 CAG repeats	Comments
MacMillan et al	1993	17/351	16-23 CAG repeats (concerns of misdiagnosis and sample switching)
Snell et al	1993	17/440	Same patient population as MacMillan et al
Rubinsztein et al	1993	2/45	21 CAG repeats
Kremer et al	1994	12/1007	16-21 CAG repeats
Andrew et al	1994	12/1007	Same patient population as Kremer et al
Persichetti et al	1994	3/268	**18-20 CAG repeats
Xuereb et al	1996	1/268	**22 CAG repeats

** Neuropathological findings consistent with Huntington disease

CONCLUSIONS

• To our knowledge, this is the least number of repeats reported in an autopsy-proven case of HD with clear evidence of anticipation.
•This clinical scenario highlights the ambiguity of genetic counseling, not only for the proband, but for family members when the number of CAG repeats lies in the normal or intermediate range.
•Clinicians should use caution "ruling-out" HD when less than 37 CAG repeats are identified in the *huntingtin* gene.
•It is certainly possible that the diagnosis of HD may be missed in a sub-population of patients with normal repeats, especially given the fact that these patients are less likely to have a positive family history and a higher chance of exhibiting a new mutation.

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