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 considered to be diagnostic of HD. However, 30-36 repeats have been associated with a normal phenotype. This report describes a 65 year-old male with 29 CAG repeats who presented for evaluation of gait deterioration. The diagnosis of HD was considered, and genetic testing revealed 29 repeats. The patient died suddenly from a cardiac event. Autopsy revealed characteristic features of HD, including caudate and putamen neuronal loss and reactive gliosis. This report highlights the importance of considering HD in patients with 29 repeats and the potential for this condition to be missed with routine clinical evaluation.

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 smears for acanthocytes, and DNA analysis for dentatorubral-pallidolysian 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 prognosis.

DISCUSSION

In the initial report of the expanded and unstable trinucleotide repeat characteristic 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 correlation are often lacking, raising concerns about misdiagnosis, clinical 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 Huntington gene panel provides additional consideratio 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.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients with &lt;30 CAG repeats</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacMillan et al</td>
<td>1993</td>
<td>17/351</td>
<td>16-23 CAG repeats (includes Huntington's disease)</td>
</tr>
<tr>
<td>Smillie et al</td>
<td>1993</td>
<td>17/440</td>
<td>Same patient population as MacMillan et al</td>
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<tr>
<td>Rubinstein et al</td>
<td>1993</td>
<td>2/45</td>
<td>21 CAG repeats</td>
</tr>
<tr>
<td>Kremer et al</td>
<td>1994</td>
<td>12/1007</td>
<td>16-21 CAG repeats</td>
</tr>
<tr>
<td>Andreev et al</td>
<td>1994</td>
<td>12/1007</td>
<td>Same patient population as Kremer et al</td>
</tr>
<tr>
<td>Persichetti et al</td>
<td>1994</td>
<td>3/268</td>
<td>**18-20 CAG repeats</td>
</tr>
<tr>
<td>Krebiel et al</td>
<td>1996</td>
<td>1/288</td>
<td>**22 CAG repeats</td>
</tr>
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**Neuropathological findings consistent with Huntington disease**

REFERENCES