Huntington disease in subjects from an Israeli Karaite community carrying alleles of intermediate and expanded CAG repeats in the HTT gene: Huntington disease or phenomenology?

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1. Introduction

Huntington disease (HD) is dominantly transmitted and caused by a CAG repeat expansion beyond 36 triplets [1]. The first manifestation of HD is often chorea, although in about 8% of the cases the disease may begin with atypical motor symptoms, other than choreic movements [2,3]. The small Jewish sect of Karaites (about 10,000 people in Israel today) represents a movement which broke away from mainstream Judaism in the 8th century in Persia and spread throughout the Middle East to Egypt, and to Southern Russia, Lithuania and Latvia. Because fundamental differences in religious practice prevent Karaites from inter-marrying with rabbinical (non-Karaite) Jews, the high consanguinity rate in the community favours genetic disease clustering.

In one of the Karaite communities, members of several families had HD that manifested with unusual clinical features in some cases associated with signs and symptoms of HD [4,5,6]. Qualitative brain imaging showed atrophy of brain predominantly involving cortex and cerebellum. Genetic testing revealed a variable mutation penetrance among family members, some affected members showing an upper allele size ranging from 34 to 49, whereas others remained unaffected despite the presence of the full mutation beyond 40 CAG repeats. Co-morbidity with recessive hereditary inclusion body myopathy was found in two subjects from one family. Although the main diagnosis of HD remains to be confirmed by further neuropathological studies, these cases may suggest that HD could manifest with as few as 34 CAG repeats, in some geographic areas, the disease phenotype most probably being influenced by additional, as yet unidentified, genes.

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2. Patients and methods

2.1. Family history and genetic testing

All subjects were recruited within the Israeli Karaite community, and came from different family branches in two of which the family history disclosed a clear relationship among subjects (Fig. 1). After

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During the past 15 years, four patients from an inbred family living in a village populated solely by Karaites were evaluated for adult-onset involuntary movements. All four patients underwent neurological, mini-mental state examination (MMSE) and brain imaging studies. Three of these patients who were sufficiently cooperative also underwent further neuropsychological assessment using the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) test [10]. Whenever possible, the Total Functional Capacity (TFC) scale was used to determine the HD stage (III-1 and III-4, Fig. 1) [11]. Computerized tomographic (CT) and magnetic resonance imaging (MRI) scans were acquired at the Neuroradiology Unit of Soroka University Medical Center.

3. Results

3.1. Family history and genetic testing

An expanded CAG repeat length of >36 was confirmed in subjects III-1, III-4, III-A and IV-E (Table 1 and Fig. 1). Subjects III-2 and III-3 are symptomatic siblings carrying an intermediate CAG repeat of 34 (see Supplementary Fig.). DNA analysis of the subject III-A, sibling of III-1, 2 and 3, showed co-existence of the full mutation (45 CAG repeats) with an intermediate repeat number (34 CAG repeats) in HTT gene, also associated with a homozygous mutation in the UDP-N-acetylglucosamine epimerase/N-acetylmannosamine kinase gene. This homozygous mutation was also found in subject III-3. Subjects III-B, III-C, III-4, IV-D and IV-E showed a variable association of intermediate-length alleles and a full mutation also including homozygous expansion mutations (subject IV-E) and pre-mutations (IV-D) (Fig. 1). All expanded and intermediate alleles shared an identical haplotype due to the high inbreeding in the members of this community, thus presumably suggesting an identical origin (Fig. 1). Mutations in SCA, DRPLA and HD-like 1 and 2 genes were excluded as well as neuroacanthocytosis and Wilson’s disease in all patients.

3.2. Patients’ clinical features

All four patients (three males and one female) (Fig. 1 and Table 1) showed signs and symptoms possibly related to HD, including slow saccades, variable cerebellar incoordination and dysdiadochokinesia, ubiquitous choreic movements, apraxia, dysphagia and dysarthria (Table 1). All of them showed remarkable features of dystonia. None of the patients but one (patient III-3), had marked cognitive impairment on bedside testing and MMSE, even after a HD history of 13 years (ranging from 1 to 13, Table 1). Further analysis, using the LOTCA test battery revealed normal orientation, perception and praxis combined with moderate defects in visuomotor organization and in ability of categorization and abstract thinking (Table 2). Patients manifested remarkable behavioural changes, in some cases leading to a schizophrenia-like syndrome (patients III-3 and III-4, Table 1). Imaging studies showed features of cortical and slight cerebellar atrophy in three patients. None of the imaging studies disclosed predominant

Table 1

Demographic, clinical, imaging and genetic features of Karaite patients with progressive chorea

<table>
<thead>
<tr>
<th>Patient</th>
<th>III-1*</th>
<th>III-2</th>
<th>III-3**</th>
<th>III-4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>CAG repeats</td>
<td>44/18</td>
<td>34/16</td>
<td>34/16</td>
<td>43/33</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>46</td>
<td>48</td>
<td>Abut 52</td>
<td>52</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>52</td>
<td>49</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>Parent transmission</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>–</td>
</tr>
<tr>
<td>MMSE</td>
<td>28</td>
<td>29</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>Psychiatric manifestations</td>
<td>Rage attacks</td>
<td>Severe depression</td>
<td>Severe psychosis</td>
<td>Delusions, suicide attempt</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>*</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Caudate atrophy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Particular dystonic trunk and hand posturing with flexed metacarpophalangeal and extended interphalangeal joints. **Distal weakness of the legs with spared quadriceps due to the concomitant hereditary inclusion body myopathy. — did not undergo imaging/no scans available.

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caudate atrophy either in the three patients who underwent CT scanning (III-1, 2, 4) or in the patient who underwent MRI (III-1, Fig. 2a) and CT scan (III-2, Fig. 2d) (Table 1). Serially repeated MRI and CT scans of the brain at the ages of 53, 55 and 57 years showed little progression of cortical and cerebellar atrophy with no evidence of caudate atrophy in patient III-1 (Fig. 2, Table 1). Patients III-1 and III-4, affected for more than 5 years, also showed a particularly slow HD progression rate, one with a loss of 0.5 and the other of 0.4 TFC units per year [3]. All patients, except cases during their admission to psychiatric hospitals (patients III-3 and III-4), were taking low doses of haloperidol (1 mg a day) or tetrabenazine (25 mg a day).

3.3. Additional clinical data from patients carrying alleles of intermediate length

Patient III-2. A 49-year-old male was followed-up at the Movement Disorders Clinic of this hospital for five years because of progressive chorea. On his first visit he was found to be fully oriented in space and time, with intact recent and remote memory. Choreo-athetotic movements of the limbs were evident. He had slow saccades, dysarthria with a nasal component and overactive tendon jerks. LOTCA testing (at age 53, nine years after the onset of chorea) showed impaired visuo-motor coordination and abstract thinking (Table 2). Over five years follow-up, the abnormal movements had markedly worsened but his cognitive state had remained fairly stable and for four years he had maintained gainful employment as a clerk. He had been treated with low doses of haloperidol, and, later, with tetrabenazine 25 mg without marked effect on the chorea. At his last clinic visits severe depression, refractory to treatment, became evident. He also began to experience difficulty in swallowing and severe weight loss.

Patient III-3. This 45-year-old woman had been suffering from chronic progressive chorea for five years with marked mental deterioration. Over the years she was admitted repeatedly to a psychiatric ward because of psychotic symptoms leading to a presumed diagnosis of schizophrenia. In addition, she had progressive distal weakness of the legs with spared quadriceps due to concomitant hereditary inclusion body myopathy. Clinical examination disclosed loss of recent and immediate memory, slow saccades in all gaze directions, dysarthria, and choreo-athetotic movements in the upper limbs. She was not sufficiently cooperative to undergo further testing and was, therefore, not included in Table 2.

4. Discussion

Patients manifesting HD usually have at least 36–39 CAG repeats [12,13] and, to our knowledge, no reports have yet described typical HD with a classic family history in association with triplet lengths below 36 repeats. Previous reports describing persons with symptoms of HD but fewer than 36 CAG repeats attributed these unusual findings to HD phenocopies, misdiagnoses or biological sample confusion [14]. Our observation on subjects with repeat numbers in the intermediate range nevertheless receives strong support from a recent paper from Dr. Jankovic’s group describing neuroimaging evidence of pathological brain changes suggestive of HD associated with clinical symptoms typical of HD in a person with an unstable intermediate allele of only 29 CAG repeats [15]. Collectively these findings suggest that people with pre-mutations may show signs and symptoms of HD, especially if the repeat stretch is unstable. Indeed, in our series, individuals with 34 CAG repeats and others with various intermediate (33 CAG) and expanded lengths, share the same haplotype, thus highlighting the unstable polymorphic stretch in this community. The co-morbidity of HD with other disorders (i.e. inclusion body myopathy), the effect of gene modifiers [16] in small communities with strong inbreeding and clusters of HD, might therefore have acted in concert to slow down the edge of the pathological triplet range in this population. If so, our observation underlines the possibility that HD may manifest even when the repeat length is below the edge of 36 repeats.

The remarkable neurological symptoms observed in these Karaite patients consisted of relatively preserved cognitive functions and middle-age at onset of progressive chorea, cerebellar incoordination and dystonia, the latter predominating on choreic symptoms. Behavioural changes, mild intellectual decline (severe in one patient), and a movement disorder associated with a CAG expansion mutation in the HTT gene in some members of this community, would nevertheless strongly suggest a diagnosis of HD. Conversely, the predominant initial cerebellar incoordination and dystonia, possible atypical clinical features of HD [2,3,17] associated with unusual MRI appearances, may imply an as yet unknown syndrome, other than HD. This diagnostic possibility receives support also from the subjects’ inbreeding and associated co-morbidity in this community. Indeed, a distinctive feature in our series of Karaite patients with HD is the co-morbidity with hereditary inclusion body myopathy (HIBM), an

Table 2

<table>
<thead>
<tr>
<th>Patients</th>
<th>III-1</th>
<th>III-2</th>
<th>III-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration in years</td>
<td>9</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Orientation</td>
<td>8/8</td>
<td>8/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Perception</td>
<td>19/20</td>
<td>20/20</td>
<td>20/20</td>
</tr>
<tr>
<td>Praxis</td>
<td>4/4</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>Visuomotor organization</td>
<td>23/28</td>
<td>25/28</td>
<td>26/28</td>
</tr>
<tr>
<td>Thinking process</td>
<td>25/27</td>
<td>20/27</td>
<td>20/27</td>
</tr>
<tr>
<td>Total Score</td>
<td>79/87</td>
<td>77/87</td>
<td>78/87</td>
</tr>
</tbody>
</table>

Fig. 2. Magnetic resonance imaging (MRI) and computerized tomographic (CT) scans showing cerebellar and cortical atrophy without significant caudate nucleus atrophy or other macroscopic signal alterations. Follow-up studies of patient III-1 (MRI) at the ages of 53, 55 and 57 years (panels a, b and c respectively) and of patient III-2 (carrying an allele of intermediate length) at age 53 after four disease years (panels d, CT-scan). Arrows: Brain caudates appear of normal size. Asterisks: moderate cortical and cerebellar brain atrophy.

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autosomal recessive disorder. This condition is characterized by progressive distal and later proximal limb weakness with quadrieps sparing, slightly elevated serum creatine kinase values and characteristic vacuoles and inclusion bodies in the affected muscles. This condition was initially described in Jews of Iranian origin, but the recently found mutation in the UDP-N-acetylgalactosamine 2-epimerase/N-acetylmannosamine kinase gene on chromosome 9 is common in the middle eastern kindreds harbouring this syndrome [9]. The fact that the patient III-3 has HIBM and chorea with 34 CAG repeats, whereas her sister with HIBM and 44/34 CAG repeats has no features of HD, suggests that at least the HIBM mutated gene had no major role in modifying the phenotypic expression of the HD mutation in this family. The clustering of both conditions could reflect the common Persian origin of the two populations, but the co-occurrence in the same family is probably coincidental and related to the high rate of consanguinity among the Karaite population. Detection and characterization of distinct pedigrees with variant phenotypic expression, such as our atypical HD population, could enable future research into the type and function of the disease modifying factors.

Our study has some limitations. First, over these 15 years, the clinical features have generally been assessed qualitatively, only occasionally using standardized internationally-accepted scales such as the Unified Huntington's Disease Rating Scale (UHDRS) [18]. Second, imaging data were also analyzed qualitatively, before the advent of the volumetric quantitative automated technologies needed to assess the rate of progressive atrophy [19,20]. Third, subjects III-2 and III-3 might theoretically manifest a yet unknown movement disorder other than HD, although most confusing diseases have been accurately excluded by genetic analysis. Although we consider it highly unlikely we cannot exclude such an eventuality. Finally, because the repeat length of 34 CAG comes close to the pathological range of 36, we cannot exclude the possibility that a somatic triplet mosaicism of the CAG repeat polymorphism may have generated a full mutation that caused related pathological effects in patients’ nervous system [21]. Even if it did, our report provides further support for the hypothesis that mutation instability and repeat mosaicism in somatic tissues may theoretically contribute to disease development, probably unaffected by factors such as the uninterrupted mutated (CAA→CAG) parental DNA sequence, at least in the family we are describing (Supplementary Fig.).

These limitations notwithstanding, analysis of restricted communities such as the Karaites in Israel may offer an opportunity to study the role of the HD mutation within a well-selected genetic context thus providing further insight into how HD gene functions affect the phenotype. Genetic counselling of families whose members show intermediate length alleles should also proceed with caution if the polymorphic intermediate triplet stretch, although within the pre-mutated range, is unstable.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jns.2008.11.005.

References