Short Report

Chinese patients with Huntington’s disease initially presenting with spinocerebellar ataxia


Recent studies have described Huntington’s disease (HD) patients with atypical onset of ataxia. Symptoms in these patients can overlap with those of spinocerebellar ataxia (SCA). We retrospectively examined clinical data for 82 HD probands and found 7 had initially been clinically diagnosed as SCA cases. Clinical features in these patients were further investigated and the number of CAG repeats in the huntingtin (HTT) gene was determined by direct sequencing. Genetic screenings for SCAs in the 7 patients were all negative. By contrast, HTT was heterozygous in each patient. The distribution of CAG number in the 7 patients was statistically the same as that in the other 75 patients. Each of 7 HD patients had presented with atypical onset of ataxia. The mean time from onset to HTT genetic testing was 5.6 ± 5.52 years. Three of the patients developed chorea, but the others did not. Our observations confirm the clinical heterogeneity of HD in Han Chinese. Based on these findings, testing for HTT expansions should be considered for clinically diagnosed SCA patients who test negatively in genetic screening of SCA genes.

Conflict of interest

The authors report no conflicts of interest.

Huntington’s disease (HD) is a neurodegenerative disease characterized by chorea, behavioral or psychiatric disorders and progressive dementia (1). Symptoms usually begin insidiously in mid-adult life and progress gradually. HD is autosomal-dominant inherited and caused by variably expanded CAG trinucleotide repeats in exon 1 of the huntingtin (HTT) gene, which is located on chromosome 4p16.3 (2). The normal allele contains 6-35 CAG triplets, while expanded alleles have larger numbers of repeats. The length of the CAG repeats influences penetrance and age of onset of symptoms. CAG expansions comprising 36–39 repeats have reduced penetrance, while expansions with 40 or more repeats are fully penetrant. The number of CAG repeats is inversely correlated with the age of onset of symptoms (3).

Atypical onset symptoms, such as ataxia rather than chorea, have been reported in Italian HD patients (4). Symptoms of atypical HD patients may overlap with those of spinocerebellar ataxia (SCA), since several SCAs, including SCA1, SCA2 and SCA17, are autosomal-dominant disorders and present with uncoordinated movements and cognitive impairment. In addition, HD patients with atypical onset of ataxia are
easily misdiagnosed with SCA3, prior to the appearance of cognitive impairments.

Here, we report seven unrelated HD patients who initially presented with atypical onset of ataxia and were misdiagnosed as SCA cases prior to molecular testing. We described their clinical and genetic features and emphasized the importance of \(HTT\) genetic screening in ataxia patients who test negatively for SCAs.

**Materials and methods**

**Subjects**

Eighty-two Han Chinese HD probands with clinical diagnoses were retrospectively studied. All were consecutively enrolled between February 2008 and August 2011 in the Genetic Clinic of Huashan Hospital, a general-service hospital in Shanghai. We reviewed their clinical data and found that seven had presented with atypical onset of ataxia and had been initially misdiagnosed as SCA but with negative results in SCA1, 2, 3 and 17 genetic screening. The medical records of these seven patients were further investigated and the number of CAG repeat in \(HTT\) was identified by direct sequencing. Written informed consent was obtained from each of the 82 patients and the study was approved by the ethics committee of Huashan Hospital.

**Genetic analyses**

Genomic DNA was extracted from peripheral EDTA blood using a DNA extraction kit (Shanghai Lifefeng Biotechnology Co., Ltd., Shanghai, China). Genetic testing for SCA1, 2, 3 and 17 was performed as previously described (5–8). \(HTT\) genetic testing was applied according to our previous reports (9, 10). In brief, a pair of primers (Hunt-E1F: 5’-CAGAGCCCCATT CATTGCC-3’, Hunt-E1R: 5’-TGAGGAAGCTGAGGAGGC-3’) was designed to amplify a DNA fragment in exon 1 of \(HTT\) containing the CAG triplet repeat under standard conditions. Polymerase chain reaction products were resolved by electrophoresis in an 8% polyacrylamide gel at 27 V/cm at 55°C for 3 h and the abnormal \(HTT\) allele were further sequenced to verify the CAG repeat numbers.

**Statistics**

Statistical analyses were carried out using SPSS version 12.0 (SPSS Inc., Chicago, IL). The comparison of CAG number distribution between the seven patients with atypical onset of ataxia and the other 75 HD patients was performed by a Kolmogorov–Smirnov test.

**Results**

**Genetic analyses of \(HTT\) and SCAs in seven patients**

Based on polyacrylamide gel electrophoresis analysis, each of the seven HD patients was shown to harbor a CAG expansion in one \(HTT\) allele (Fig. S1; Supporting Information). The number of CAG repeats was determined by DNA sequencing (Table 1; chromatograms shown Fig. S2). The mean number of CAG triplets in the expanded allele was 48 ± 2.0, ranging from 43 to 55. The distribution of CAG number in the seven patients with atypical onset of ataxia were statistical the same as that in other 75 HD patients of ours (\(Z = 0.763, p = 0.605\)). The number of CAG repeats within SCA genes (SCA1, 2, 3, 17) was within the normal range.

**Clinical characteristics of seven patients**

Ataxia, swallowing problems and dysarthria occurred in each of the seven HD patients. Several patients had abnormal signs in reflex, muscle tone and coordinate movements (Table 2). All showed paternal inheritance, except patient 4 for whom parental DNA was not available. The mean age at onset was 38 ± 9.9, ranging from 25 to 55. The mean time between the onset and the molecular diagnosis of HD was 5.6 ± 5.52 years (ranging from 1.2 to 14 years).

We further investigated the development of symptoms and found that patient 3 exhibited head and hands tremors, change of personality and memory loss. Patients 3, 4 and 7 presented chorea, 4, 9 and 0.5 years after onset, respectively. No typical chorea symptoms occurred in the remaining four patients, even though their HD diagnosis was confirmed by genetic screening.

All the seven patients underwent cerebral magnetic resonance imaging (MRI) or computed tomography

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at onset (years)/sex</th>
<th>Inheritance</th>
<th>CAG repeats</th>
<th>Years from onset to the diagnosis of HD</th>
<th>Developed chorea?/years before onset of chorea</th>
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<tbody>
<tr>
<td>1</td>
<td>45/F</td>
<td>Paternal</td>
<td>18/44</td>
<td>13.0</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>31/F</td>
<td>Paternal</td>
<td>17/53</td>
<td>2.3</td>
<td>No</td>
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<tr>
<td>3</td>
<td>33/F</td>
<td>Paternal</td>
<td>17/52</td>
<td>4.8</td>
<td>Yes/4</td>
</tr>
<tr>
<td>4</td>
<td>51/M</td>
<td>NA</td>
<td>17/43</td>
<td>14.0</td>
<td>Yes/9</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>Paternal</td>
<td>19/43</td>
<td>1.5</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>25/M</td>
<td>Paternal</td>
<td>17/55</td>
<td>2.5</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>39/F</td>
<td>Paternal</td>
<td>17/46</td>
<td>1.2</td>
<td>Yes/0.5</td>
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</tbody>
</table>

NA, not available.
Dong et al.

Table 2. Symptoms and signs of seven HD patients with the onset symptom of ataxia

<table>
<thead>
<tr>
<th>No.</th>
<th>Dysphagia</th>
<th>Dysarthria</th>
<th>Nystagmus</th>
<th>Reflex</th>
<th>Muscle tone</th>
<th>Finger-nose test</th>
<th>Heel-knee-tibia test</th>
<th>Babinski signs</th>
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<tr>
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<td>++</td>
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<td>−</td>
<td>↑</td>
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<td>−</td>
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<tr>
<td>2</td>
<td>++</td>
<td>++</td>
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<td>↑</td>
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<td>−</td>
</tr>
<tr>
<td>3</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>Normal</td>
<td>Normal</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>Normal</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
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<td>+</td>
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<td>+</td>
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<td>↑</td>
<td>Normal</td>
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<td>+</td>
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</table>

(CT). Four patients (nos. 1, 4, 5, 7) showed brain atrophy, while the brains of the others were normal.

Discussion

Although chorea is observed in most HD patients (11), some studies have reported non-specific movement abnormalities, such as Parkinsonism, dystonia and tics during the course of the disease (12, 13). A few reports have focused on atypical movements at onset. Squitieri investigated 205 Italian HD patients and found 15 patients with atypical onset movement disorders. The authors classified these movements as Parkinsonism, ataxia or dystonia (4). In China, HD patients with atypical onset have rarely been described in case reports. Dong described one patient who exhibited speech impairments and instability of gait (14). Most clinical features in Chinese HD cases resemble those in other countries (15). Our sample size is small and the sample is unlikely to reflect the general HD population. Our observation indicated there was clinical heterogeneity of HD in China.

HD might be misdiagnosed as SCA1, SCA2, SCA3 and SCA17, because they are autosomal-dominant disorders, with SCA1, SCA2, SCA17 presenting uncoordinated movements and cognitive impairment, SCA3 presenting cerebellar ataxia. Most of our patients were initially diagnosed as SCA3, the main reason is that frequency of SCA3 in Chinese SCA kindreds was 51.1%–72.5% (16, 17).

In the current study, we summed up some symptoms and signs of our HD patients with atypical onset. But other features were helpful in distinguishing pure ataxia from HD, including saccade initiation delay, saccadic slowing, gaze incoordination, motor incoordination, bradykinesia and loss of postural reflexes (18, 19). However, the current study was retrospective, so important clinical information was missing besides those mentioned above. They might be able to give some hints for the underlying diagnosis.

Most of our seven cases were paternal inherited. During HTT mutation transmission from parent to offspring, instability of CAG repeat was prone to appear more frequent and stronger in a male than in a female with a tendency to an increased size (20). However, in the current study, the DNA samples of the parents were not able to be available, so whether the CAG numbers of the seven patients expanded during the transmission was unknown. The association between the paternal inherited pattern and the atypical onset of HD needs further investigation.

Juvenile HD, which is usually associated with expansions containing 60 or more CAG triplet repeats, often presents with dystonia or epilepsy (21). Patients who develop atypical movements during the course of the disease are also likely to harbor long expansions (12). However, in Squitieri’s study (4), no difference was found in the average CAG numbers between patients with atypical onset motor symptoms and patients with typical ones. As for our seven patients, the number of CAG expansion varied from 43 to 55, whose distribution was not different from that in the other 75 HD patients. In addition, the relationship between symptom progression and the CAG triplet number in our seven patients was inconsistent. Two patients (nos. 1, 4), harboring relatively low repeat numbers of 44 and 43, experienced 13 and 9 years of ataxia, respectively, suggesting that smaller CAG expansions produced a longer period of atypical symptoms. Patient 7 carrying 46 CAG repeats, however, presented chorea 0.5 years after onset and this duration was shorter than that of patient 3 who had 52 CAG triplet repeats. Our sample size was small with only seven patients (8.5%) with atypical onset of ataxia, so their distribution of CAG number was obscure, which might affect the results. Thus, the sample size should be enlarged in the further investigation and other factors which might influence the clinical symptoms should be explored (22).

In summary, the presentation of atypical symptoms or signs of ataxia in the absence of chorea combined with an autosomal-dominant family history can lead to the misdiagnosis of SCA in the early stages of HD. Thus when a clinically diagnosed SCA patient tests negatively in screenings for SCA genes, HIT genetic testing should be considered.

Supporting Information

The following Supporting information is available for this article:

Figure S1. Polyacrylamide gel electrophoresis analyses of HTT in the seven patients. M: D2000 ladder; M1: 10 bp ladder; M3: standard band for a 35-CAG repeat. N: control. Lanes 1–7: patients.

Figure S2. Chromatograms of the HTT CAG repeats in the seven patients. Lanes A–G: patients. Numbers of CAG repeats in normal and expanded HTT alleles were (A) 18/44, (B) 17/53, (C) 17/52, (D) 17/43, (E) 19/43, (F) 17/55 and (G) 17/46, respectively.
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References

Huntington’s disease versus spinocerebellar ataxia