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35 CAG repeats in the HTT gene and clinical features of Huntington's disease in two sisters

35 powtórzeń trinukleotydu CAG w genie HTT i objawy kliniczne choroby Huntingtona u dwóch sióstr

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S u m m a r y

Huntington's disease (HD) is a genetic disorder resulting from CAG trinucleotide repeats expansion in the HTT gene. HD main symptoms comprise: chorea, neurocognitive deficits and psychiatric disturbances. Up till now the lowest number of 36 CAG repeats has been reported to be associated with unequivocal HD phenotype. There are three categories of HTT alleles distinguished: normal range with fewer than 26 repeats, intermediate alleles (27-35 CAG called also "mutable alleles" prone to expansion during transmission to the following generation and pathogenic range from ≥ 36 repeats. Within alleles causing HD further classification is recognized: incomplete penetrance alleles (36-39 repeats) and full penetrance alleles with ≥ 40 CAG triplets.

Here we report two sisters aged 64 and 60 years probably affected with HD, but with only 35 repeats in HTT identified in both of them.

Key words: Huntington's disease, HTT gene, CAG trinucleotide repeats expansion

S t r e s z c z e n i e

Choroba Huntingtona (ch.H.) jest chorobą genetyczną powodowaną ekspansją powtórzeń trinukleotydu CAG w genie HTT. Charakterystycznymi dla niej cechami są: pląsawica, zaburzenia funkcji poznawczych i objawy psychiatryczne. Za najniższą liczbę powtórzeń CAG, która niezaprzeczalnie związana jest z fenotypem ch.H. uznaje się 36 trinukleotydów. Wyróżniono trzy kategorie alleli genu HTT: w zakresie prawidłowym zawierające ≤ 26 powtórzeń, allele pośrednie (27-35 CAG), które cechują się podatnością na ekspansję podczas przekazywania z pokolenia na pokolenie i zakres patogenny alleli zawierających ≥ 36 powtórzeń. Wśród nieprawidłowych alleli wywołujących ch.H. dokonano dalszej klasyfikacji: allele o niekompletnej penetracji mutacji w przedziale 36-39 powtórzeń CAG i allele o pełnej penetracji z ≥ 40 CAG. Poniżej zaprezentowany zostanie przypadek kliniczny obejmujący dwie siostry w wieku 64 i 60 lat, u których prawdopodobne jest występowanie ch.H., jednak u obu kobiet obserwuje się jedynie 35 powtórzeń trinukleotydu CAG w genie HTT.

Słowa kluczowe: choroba Huntingtona, gen HTT, ekspansja powtórzeń trinukleotydu CAG

Huntington's disease (HD) (OMIM +143100.) is an autosomal dominant neurodegenerative disorder. It is caused by CAG trinucleotide repeats expansion in the HTT gene, which is located on 4p16.3 (1). In HD patients, the CAG tract can be expanded to over 200 repeats. Detection of a minimum of 36 repeats is associated with (confirms a clinical diagnosis of HD) a diagnosis of HD (2). Individuals with an allele in the intermediate range: 27-35 CAG repeats, will not be affected with HD, but due to instability in the CAG tract, may be at risk of transmitting an allele in the HD-causing range to the subsequent generations (3).

The clinical presentation of HD is believed to be associated with number of CAG repeats greater than 35, i.e. 36 and more. The number of 36-39 repeats has been classified as the range of incomplete penetrance of the mutated gene, which means that a carrier of such allele may not develop symptoms of HD during the lifetime. Full-penetrance HD alleles with 40 or more CAG repeats are certainly associated with the clinical phenotype of the disease.

The most prominent symptoms of HD are: chorea, neurocognitive deficits and psychiatric disturbances (2, 4).

CASES PRESENTATIONS

Case 1

A 64-year-old retired female assembler has been suffering from choreatic movements of the limbs and abnormalities of cognition since she was 44. At the age of 54, falls started occurring (3-4 times a year). At the age of 62, the diagnosis of epilepsy was established, because the patient had lost her consciousness with convulsions two times and since then has been treated with valproate sodium (2 x 300 mg daily).

The patient past medical history also includes: hypertension and chronic obstructive pulmonary disease both diagnosed over 30 years ago, tick's biting that has lasted for 2 years. There was no history of neuroleptic treatment.

Genetic testing for HD was performed in 2005. DNA sample was obtained from peripheral blood by standard phenol-chlorophorm method. Molecular analysis revealed 35 CAG repeats in the HTT gene. Moreover, spinocerebellar ataxias type 1 (SCA1), type 2 (SCA2), type 3 (SCA3) and type 17 (SCA17) were excluded.

In 2007, the neurological examination revealed decline in cognitive function and choreo-atetotic movements of the right upper limb, especially fingers. In 2007, the first psychological examination showed moderate dementia. The patient obtained a score of 16/30 on the Mini Mental Status Examination. In 2008, the next psychological examination revealed progression and severe dementia.

Laboratory tests, such as cerebrospinal fluid routine analysis produced normal values. FTA-ABS test and oligoclonal IgG protein in blood serum and cerebrospinal fluid were negative. The levels of Borrelia Burgdorferi IgG and IgM antibodies in cerebrospinal fluid and IgG antibody in blood serum were negative, whereas IgM antibody in blood serum was positive (16.9 BBU/ml). In 2007 the patient received doxycyclinum for 21 days. The levels of total cholesterol and LDL cholesterol were high (220 mg/dl, 163 mg/dl, respectively), whereas the level of HDL cholesterol was low (38 mg/dl). The erythrocyte sedimentation rate was elevated (74 mm). The level of anti-cardiolipin antibodies IgG was low (5.60 GPL). Additional biochemical analyses, including levels of triglycerides, homocysteine, vitamin B12, folic acid, thyroid hormones (TSH, fT3, fT4), creatine kinase, copper in serum and blood smear for acanthocytes, results were normal. In 2007, EEG showed focal changes in the right temporal leads, whereas in 2008 no abnormalities were detected.

In 2007, the brain MRI revealed multiple focal hyperintens, ischemic lesions, cortical-subcortical atrophy and enlargement of the ventricles. Active hydrocephalus was excluded by neurosurgeon. In 2008 molecular analysis of DNA samples obtained from hair bulbs and skin fibroblasts was carried out. The test confirmed 35 repeats of CAG trinucleotide, in the IT15 gene. In 2008 the CT scan showed cortical-subcortical atrophy and enlargement of the ventricles, increased Evans Ratio – 0.47. The dimensions of the left and the right lentiform nucleuses were 23 x 14 mm and 29 x 13 mm, respectively. In 2009, the test for dentatorubral-pallidoluysian atrophy (DRPLA) was negative.

Case 2

A 60-year-old retired female engraver, has been suffering from choreatic movements since she was 55. The patient past medical history embrace: hypertension, colonic diverticula, esophagus erosions, osteoporosis, nephrolithiasis which caused left radical nefrectomy at the age of 38. There was no history of neuroleptic treatment.

Genetic testing for HD was performed in 2005 simultaneously with her older sister; the analysis was carried out using the same method mentioned above, SCA1, SCA2, SCA3 and SCA17 were also excluded. The patient was confirmed to be a carrier of 35 CAG repeats in IT15 gene.

In 2007, the neurological examination revealed choreo-atetotic movements of the head and the right upper limb, especially fingers. In 2007 the psychological examination revealed very little decrease in cognitive function. Laboratory tests, such as the levels of total cholesterol and LDL cholesterol were high (244 mg/dl, 179 mg/dl, respectively). The erythrocyte sedimentation rate was elevated (26 mm). Additional biochemical analyses such as triglycerides levels, HDL cholesterol, thyroid hormones, creatine kinase and blood smear for acanthocytes produced results within normal range. In 2007, the brain MRI revealed multiple focal hyperintens, ischemic lesions and cortical-subcortical atrophy. In 2008, molecular analysis of DNA samples obtained from hair bulbs and skin fibroblasts was carried out too. The test confirmed 35 repeats of CAG trinucleotide in the IT15 gene. In 2009, the test for DRPLA was negative.

Both patients were given genetic counselling and prognostication at the Department of Genetics, Institute of Psychiatry and Neurology.

In the whole family that we examined, none of the relatives has 35 CAG trinucleotide repeats and nobody has any neurological symptoms (fig. 1).

DISCUSSION

In the report we present two patients in whom 35 CAG repeats in the IT15 gene were found. The definitive diagnosis of HD can be established when there are at least 36 CAG repeats (4). However, patients with less than 36 CAG repeats and clinical symptoms of HD had already been reported (5-13).

The neuropathology of HD is not completely known. The cases with no neuropathological findings and CAG repeat expansion have already been described (12) and the discussion about the correlation between no characteristic brain pathology and the diagnosis of HD is still open. Somatic mosaicism of CAG repeats may explain a disease phenotype with only 35 or less repeats detectable in peripheral cells (14).

These two sisters are the first such cases in our experience and it is the first time we have established the diagnosis of HD in patients with 35 CAG repeats. In the cases we have reported, the choreo-atetotic movements, which are one of the most characteristic symptoms of

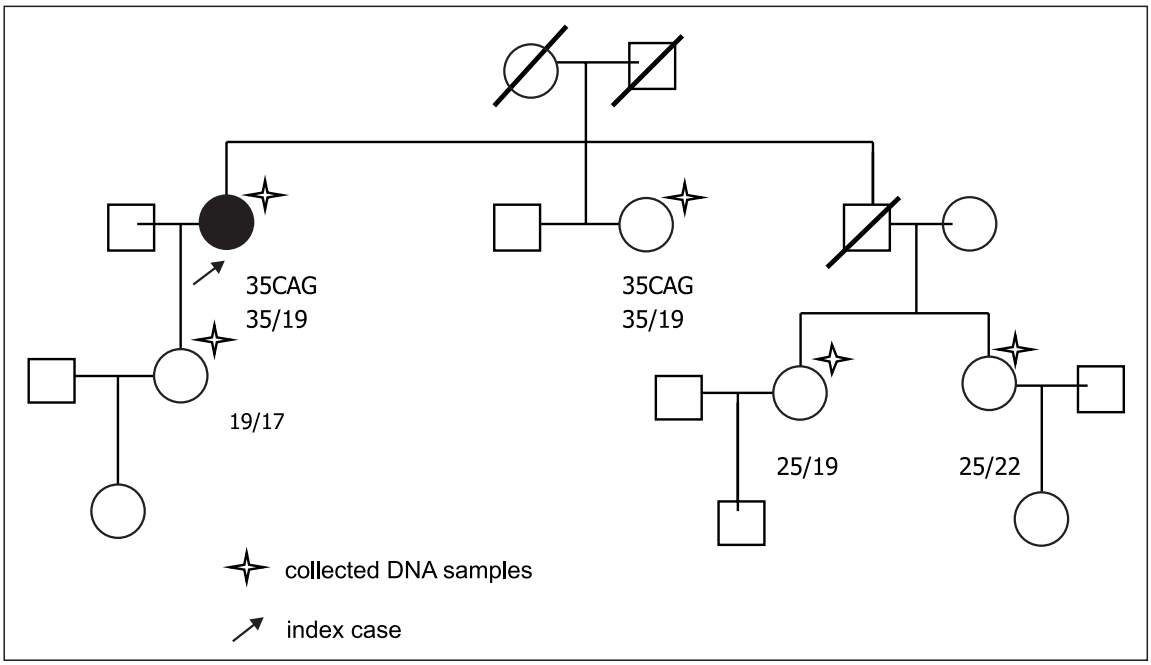

Fig. 1. Pedigree.

HD, were scanty, whereas the dementia was the most prominent feature. All differential diagnosis with signs and symptoms mimicking HD have been excluded (similarly in Andrich et al.), especially history of neuroleptic medications. We confirm that cases like those have to be considered clinically and in genetic counselling (13).

CONCLUSIONS

These patients are probably the rare examples of HD with 35 CAG repeats in the IT15 gene. In cases we have reported, there is no evidence for any other cause of the neurological symptoms than expansion of CAG trinucleotide repeats.

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