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SHORT REPORT

Late-onset Huntington's disease with intermediate CAG-repeats: true or false?

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INTRODUCTION

Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disorder characterized by movement disorders, psychiatric symptoms, and cognitive dysfunction. HD is associated with expansion of CAG trinucleotide repeats in the coding region of the huntingtin-gene (OMIM 143100) on chromosome 4. In the general population, the CAG repeat length varies from 6 to 35 trinucleotides in the HD gene. A proliferation of 40 or more is invariably associated with HD, but at a lower CAG repeat range (36 to 39), reduced penetrance is present.[1] Alleles with 27 to 35 CAG repeats are generally considered 'intermediate'. The CAG repeats in this range show instability and have the potential to expand into the disease range within one generation through the paternal line.[2] A small number of cases with the HD phenotype and an intermediate repeat number have been reported[3,4 5]. In the present report, we present two additional patients with late-onset HD and an intermediate CAG repeat number. In light of recent insights in somatic CAG trinucleotide expansion and instability[6] we hypothesize that intermediate repeat alleles may cause late-onset HD.

CASE REPORTS

Case 1

This 72 year old man noticed involuntary movements of abdomen, chest, and throat at age 68. This resulted in walking problems and difficulties with speech. Continuous restlessness was present and worsened in stress situations. Gradually, unwanted movements developed in the hands, abdomen, and face. His short-term memory and concentration were impaired and his wife noticed behavioural changes. A sister of the patient died while diagnosed with olivo-ponto-cerebellar atrophy. This diagnosis is post-mortem changed into HD as her symptoms were identified by several family members as identical to the symptoms of her three children all having genetically confirmed HD (43 CAG repeats). One brother suffers from late-onset Parkinson's disease with normal CAG-repeats in HD-gene (17/18). The history of the parents was not suspect for HD.

Neurological examination showed chorea of the abdominal wall, spreading to the trunk, which affected breathing and speech. There is an interrupted ocular pursuit and increased latency of saccade initiation in both directions. Choreatic restlessness is present in the upper extremities. The signs did not improve with tiapride, sulpiride, levodopa/carbidopa, and amitriptyline. A postural tremor was present in both hands. Motor impersistence was not observed. The Mini Mental Status Examination score was 26 out of 30. Neuropsychological examination revealed memory impairment and increased irritability. Polymyography showed irregular bursts of muscle activity in the rectus abdominis muscle, consistent with chorea. MRI scan of the brain showed mild generalized atrophy. A [11C]-raclopride PET scan showed no abnormalities. Genetic testing for HD revealed 31 CAG repeats on one allele and 18 repeats on the other. Test results were confirmed in an independent sample.

Case 2

This 68 year old woman complained of involuntary movements of her mouth starting after the death of her husband 3 years ago. The restless movements worsened with stress and emotion, and were progressive, resulting in speech problems and neck pain. Her husband noticed frequent blinking. No abnormal movements of the tongue or other parts of the body were noticed. Except for a loss of interest, no psychiatric symptoms were present. The family history revealed a sister with psychiatric disease of unknown origin and possible jerky movements in both arms. Her mother suffered from Parkinson's disease. The father did not show any neurological or psychiatric symptoms.
On examination, she had dysarthria and chorea, especially around the mouth, and an increased latency of saccade initiation with mild slowing of saccade velocity. Chorea is present in all extremities with mild dystonia of the upper extremities. Furthermore, cervical dystonia with slight rotation (10 degrees) and lateroflexion (20 degrees) was detected. She had 30 CAG repeats on one huntingtin allele and 17 repeats on the other. This finding was confirmed in an independent sample.
Genetic tests for Huntington disease like-2, dentatorubropallidoluysian atrophy (DRPLA) and spinocerebellar ataxia (SCA) 3, 14 and 17 were all normal.

Both patients are of Caucasian origin. There is no history of neuroleptic medication. Laboratory tests for thyroid function, vitamins B1, B6, B12 and folic acid, syphilis, *B. burgdorferi*, plasma copper, ferritin, ceruloplasmin, antiphospholipid antibody and ANA are normal and the ESR is low. No acanthocytes are seen in the blood smear and creatine kinase is normal, MRI scans in both cases are normal, revealing no signs of Neurodegeneration with Brain Iron accumulation (NBIA). During follow-up by a movement disorder specialist (R.M.A.B. and M.A.J.T.) both patients slowly deteriorated over a course of 4 and 3 years, with a present UHDRS motor rating of 19 and 22, respectively.

DISCUSSION

Here we describe two patients with an intermediate number of CAG repeats in the huntingtin gene and late-onset HD. Most of the currently known HD-phenocopies or HD-like disorders have been excluded.[7] In the first patient, family history proved to be positive for HD, in the second patient family history is suggestive for HD. The stringent cut-off point for disease causing repeat numbers (36 repeats or more) is under discussion as recently published reports [3 4 5] of mild, late onset HD with an intermediate CAG repeat length suggest that such cases, although rare, do occur. In the report of Kenney et al, the authors present a case with autopsy-proven HD and 29 repeats. This claim however, was discussed critically as known HD-phenocopies and HD-like syndromes were not excluded. Furthermore, no huntingtin inclusions were detected in the brain of this patient with autopsy.[8 9] In literature, a number of HD-phenotype cases with normal CAG alleles (<27 triplets) have been reported. In these reports the authors attribute the cases to HD-phenocopies and discuss the possibility of a mutation in yet unidentified genes. Furthermore, misdiagnosis and mistakes in sample processing were considered.[10-12] In contrast to normal alleles, the instability of intermediate repeat tracts is shown by anticipation. Therefore, we place the intermediate repeats with late onset HD at the

end of the phenotype spectrum of HD and suggest such cases have to be considered clinically and in genetic counselling.

The frequency of intermediate alleles (27-35 CAG repeats) in a selected population of patients and their partners was estimated as high as 3.9%[2], whereas the study of Kremer et al. shows a much lower prevalence of 30-35 repeats (0.75%).[13] Intermediate alleles have been categorized in 'general population intermediate alleles' and 'new mutation intermediate alleles' based on how the allele is ascertained within the context of a family. New mutation intermediate alleles are prone to repeat expansion in following generations. The likelihood of proliferation of general population intermediate allele carriers has shown to be very low.[14] The proven positive family history of the first patient indicates susceptibility to anticipation of the intermediate CAG allele. Whether genetic factors resulting in anticipation are similar to the factors leading to enhanced somatic CAG repeat expansion is not known.

The length of the CAG repeats accounts for about 70% of the variation in age of onset.[15] The late age at onset (65 and 68 years) observed in both patients is consistent with the inverse correlation between the age of onset and the number of CAG repeats. Laboratory and animal studies show that, besides the CAG trinucleotide expansion, other genetic factors modulate the pathogenicity of the HD gene. In humans, intermediate repeats on some specific 'HD-haplotypes' are prone for CAG expansion[16] and association studies revealed various disease modifiers.[17,18,19] In mouse models, different genetic backgrounds influence inter-generational and somatic instability, as well as nuclear accumulation of mutant huntingtin.[20] In polyglutamate disorders the expanded CAG sequence serves as a template for synthesis of an increasingly toxic HD protein in neurons. Based on the observation that somatic CAG trinucleotide expansion is dependent on a DNA glyocsylase (OGG1), a 'toxic oxidation cycle' model causing neurodegeneration was proposed.[21] Interestingly, recent studies show a striking somatic mosaicism of CAG repeats is present in brain, with prominent cell-specific expansion in the neuronal cells in the striatum. [6] Further studies of the factors which play a role in the somatic changes in repeat tracts and modulate toxicity in striatal neurons are required. However, the enhanced trinucleotide expansion in post-mitotic neurons emphasizes that other factors than CAG repeat number have to be considered and indicates that a CAG repeat number of 35 or less, extracted from peripheral blood samples, do not necessarily reflect the length and toxicity of the repeat tracts in neurons. Therefore, accurate neuropathological assessment of the symptomatic carriers of intermediate CAG-repeats will be of great value.

The present cases illustrate the difficulties in diagnostics and counselling in patients with intermediate CAG repeats in the HD-gene and chorea. In light of recent insights in the age-dependent somatic instability and mosaicism, we suggest that the development of HD – typically with a late age of onset – can occur with an intermediate CAG repeat number and should be considered in patients with mild and late-onset chorea. We treated both patients as such and offered them and their family members genetic counselling.

LEGEND TO THE VIDEO

Segment 1: This 72 year old man (Case 1) suffers from chorea of the abdominal wall spreading to the trunk. There is choreatic restlessness of the upper extremities. Segment 2: This 68 year old woman (Case 2) shows involuntary movements around the mouth and latency of saccade initiation. Chorea is present in all extremities with mild dystonia of the upper extremities and neck.

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