Juvenile Huntington’s disease in northern Brazil: a case series report

Doença de Huntington juvenil no norte do Brasil: relato de uma série de casos

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Abstract

Introduction: Huntington’s disease (HD) is a neurodegenerative disorder caused by CAG expansion repeats in the HTT gene. Usually, the symptoms start to manifest in adulthood. In about 5% of cases, however, the signs begin before the age of 20 years. These cases are known as juvenile HD (JHD). Objective: here we report a case series of JHD from Amazonas, a state where data are scarce due to the restricted access to specialized medical assistance for diagnosis and care. Case series: the patients were attended by neurologists specialized in movement disorders at Manaus. Two cases manifested the disease in childhood (6 and 7 years old) and two cases, in adolescence (12 and 16 years old). All cases showed dystonia and parkinsonism as predominant motor disorders. Moreover, signs of cognitive decline, depression, and psychosis were observed in all patients. Conversely, cerebellar signs, gait disturbances, seizures, and some psychiatric symptoms were variable among the cases. Expansion size varied from 66 to 84 to CAG repeats and the difference in age at onset between parent and child varied from 23 to 43 years. Conclusion: to our knowledge, these are the first clinical reports of JHD in northern Brazil. These cases illustrate the variability in clinical phenotypes and genetic features of JHD cases. Furthermore, they can contribute to the awareness of HD here, both by professionals and the public in general.

Keywords: Juvenile Onset Huntington’s Disease. Hereditary Neurodegenerative Diseases. Trinucleotide Repeat Expansion. Phenotypic Variation. Anticipation. Genetic.

Resumo

Introdução: a doença de Huntington (DH) é um distúrbio neurodegenerativo causado pela expansão de repetições CAG no gene HTT. Geralmente, os sintomas começam a se manifestar na vida adulta tardia. Em cerca de 5% dos casos, no entanto, os sinais começam antes da idade de 20 anos. Esses casos são conhecidos como DH juvenil (DHJ). Objetivo: neste estudo, nós reportamos uma série de casos de DHJ do Amazonas, um estado onde os dados ainda são escassos devido ao acesso restrito à assistência médica especializada para o diagnóstico e cuidado. Série de casos: os pacientes foram atendidos por neurologistas especializados em transtornos do movimento em Manaus. Dois casos manifestaram a doença na infância (6 e 7 anos) e dois casos, na adolescência (12 e 16 anos). Todos os casos apresentaram distonia e parkinsonismo como sintomas motores predominantes. Sinais de declínio cognitivo, depressão e psicose também foram observados em todos os pacientes. Por outro lado, sinais cerebelares, distúrbios da marcha, convulsões e alguns sintomas psiquiátricos foram variáveis entre os casos. O tamanho da expansão CAG variou de 66 a 84 repetições e a diferença na idade de início dos sintomas entre pais e filhos variou de 23 a 43 anos. Conclusão: ao nosso conhecimento, estes são os primeiros relatos clínicos da DHJ no norte do país. Esses casos ilustram a variabilidade nos fenôtipos clínicos e nas características genéticas dos casos de DHJ. Além disso, eles podem contribuir para a conscientização da DH na região, tanto pelos profissionais quanto pelo público geral.

Palavras-chave: Doença de Huntington de Início Juvenil. Doenças Neurodegenerativas Hereditárias. Expansão de repetição de trinucleotídeos. Variação fenotípica. Antecipação genética.

INTRODUCTION

Huntington’s disease (HD) is a progressive neurodegenerative disorder, with an autosomal dominant inheritance. Clinically, HD is characterized by a triad of motor, cognitive and psychiatric symptoms¹. Chorea is the hallmark motor sign of HD, which is characterized by involuntary, abrupt, and nonrhythmic movements because of random muscle contractions². Age at onset is typically between 30 and 50 years. In about 5% of HD cases (with a range of 1-15%), however, disease onset is before 20 years old. These cases are known as Juvenile HD (JHD)¹-³. HD is caused by an expansion in the number of CAG repeats (≥ 36 repeats) within the first exon of the Huntington (HTT) gene⁴. The number of CAG repeats in the HTT gene has a strong negative correlation to the age when symptoms start to manifest. Also, these trinucleotide repeats are unstable when transmitted from parent to child, which leads
mostly to expansion. Thus, there is a tendency to increase in CAG length in successive generations affected by HD, which, in turn, leads to age at onset progressively earlier within families. This phenomenon is known as anticipation. JHD is the case of extreme anticipation.²,⁴

Clinical manifestation of JHD is different than in adults. The common motor signs initially in juvenile forms are gait disturbances; oral-motor dysfunctions (such as speech/swallowing disturbances); and parkinsonian features of bradykinesia, which is the slowness of movements, and rigidity, which refers to an increased muscle tone in both flexion and extension movements.²,⁵ Cognitive impairments (such as declining in school performance and developmental delay) and behavioral changes are also common presenting symptoms in JHD. Also, in contrast to adult HD, the predominant motor symptoms in JHD are often parkinsonism and dystonia (i.e., an abnormal posture or twisting movements caused by sustained muscle contractions).²,³

In around 80% of JHD cases, the expanded allele is inherited from the father. There is no specific CAG repeat range that defines a juvenile-onset. Individuals with CAG repeats > 60 usually show a disease onset before 20 years. However, there are JHD cases associated with repeat lengths below. The instability in CAG length that leads to larger expansions is greater in spermatogenesis than in oogenesis, which explains the predominance of paternal inheritance in JHD.²,³ Moreover, JHD can be divided into two subgroups according to the age at onset: childhood-onset, with the presentation of first symptoms ≤ 10 years; and adolescent-onset, with initial manifestation between 11 and 20 years. Childhood HD is rarer, corresponding to about 20% of all JHD cases. Clinical and genetic features can be variable among these subgroups. The phenotypic variation and unspecific features cause difficulties in the diagnosis.²,³,⁵,⁶

Here we present a cases series of JHD in patients from northern Brazil. In this region, access to medical specialists (especially outside the capital cities) and genetic testing is very restricted. Thus, underdiagnosis and misdiagnosis of HD are serious public health problems. Here we described two cases with childhood-onset and two with adolescent-onset, comparing their clinical presentation, disease progression, and familial inheritance of expanded alleles.

CASE SERIES

The four patients were attended by neurologists of the Araújo Lima Outpatient Clinic (Manaus, Amazonas), which is the referral center for movement disorders attendance of the state, and the Hospital Foundation Adriano Jorge. All patients were born in Amazonas: patient 1 in the capital city, Mânus; patient 2, in the city of Itacoatiara; and patients 3 and 4, which are siblings, in the city of Barcelos. These cases are part of the study approved by the Research Ethics Committee (CEP) of the State University of Amazonas (UEA) under protocol number 95704617.0.0000.5016. The legal representatives of all patients and family members that participated in the genetic testing signed an Informed Consent Form. Genetic testing was performed in the Laboratory of Human Genetics, located in the Health Sciences Superior School (ESA/UEA). Genotyping of HTT alleles was performed by PCR with fluorescently labeled primers, followed by capillary electrophoresis in an automatic sequencer.

Case 1

A 13-year-old boy had normal development until age six when he started to fall recurrently. Afterward, he started to present slurred speech (dysarthria) and signs of dystonia. A decline in school performance was also noticed. At age 11, he was referred to the Araújo Lima Outpatient Clinic. His evaluation showed mild bradykinesia and slight rigidity in one arm. From then on, the patient’s neurological condition worsened quickly. Examination at age 13, seven years after the first symptoms, revealed generalized dystonia, worsening in bradykinesia, and rigidity in both arms (especially severe in the right one). His gait was unsteady, with frequent falls, and he was only able to walk with assistance. He was also presenting severe dysphagia, sialorrhea, and weight loss. His psychiatric symptoms were depression, irritability, and psychosis. Brain MRI showed a volume reduction of the caudate nucleus and putamen.

The patient had a paternal family history of undiagnosed neurodegenerative disorders. His father was referred to our clinic for the first time together with him, presenting chorea, which lead to the diagnostic hypothesis of HD. His wife reported that he started to manifest symptoms at age 35. He passed away shortly after attending our clinic, due to complications of his severe dysphagia (age 42). Genetic testing for CAG expansion in the HTT gene demonstrated the presence of an expanded allele with 76 CAG repeats in the patient, and 44 repeats in his father (Figure 1a). Thus, there was an intergenerational increase of 32 repeats and anticipation of 29 years. An expanded allele was also found in the patient’s older brother. He was presymptomatic at 18 years old.

Case 2

A 20-year-old male developed initially a loss of hand dexterity, cervical pain, and difficulty walking at age 12. Irritability and aggressiveness were also noticed. He was referred to a neurologist of the Araújo Lima Outpatient Clinic at age 20, eight years after the first symptoms. He didn’t have access to specialized care during this period, especially because he lived in the countryside of Amazonas (city of Itacoatiara). His examination showed generalized dystonia as a predominant feature, severe parkinsonism (bradykinesia and rigidity), and abnormal saccades. By that time, he was aphasic and unable to walk (wheelchair user). Also, seizures were observed frequently. Depression and apathy were the main psychiatric symptoms. Regarding his cognitive function, he already had developed dementia. Brain MRI demonstrated atrophy of the caudate nucleus and putamen.

In this case, there was also a family history of neurodegenerative disorders on the father’s side previously undiagnosed. Family members reported that his father
started to present symptoms at age 35, with involuntary hand movements followed by behavioral changes (especially aggressiveness). At examination (age 49), he was bedridden and showing chorea, dystonia, and dysphagia. Genetic testing confirmed HD, with an expanded allele of 72 CAG repeats in the patient and 47 repeats in his father. Therefore, there was an intergenerational expansion of 25 repeats and anticipation of 23 years (Figure 1b).

**Cases 3 and 4**

Two siblings, one with 18-years-old (case 3) and the other with 28 (case 4), showed initial motor signs of bradykinesia followed by dystonia at ages seven and 16, respectively. They were referred to the Hospital Foundation Adriano Jorge for investigating their motor symptoms. At the examination, they presented severe parkinsonism, dystonia, and abnormal saccades. Patient 3 showed a rigid and ataxic gait, while patient 4 presented a parkinsonian gait, with festination. Hyperreflexia was observed only in patient 4. Both did not develop chorea. Psychiatric symptoms were more pronounced in patient 3. She showed irritability, aggressiveness, depression, and psychosis. Patient 4 demonstrated mild signs of apathy, depression, and psychosis. A cognitive decline was identified in both cases.

Their father (55 years old) was attended together with them. His symptoms began years after their daughters started to manifest the disease (age 50), and he presented less severe motor symptoms. His evaluation showed moderate parkinsonism, abnormal saccades, mild dystonia, gait ataxia, and hyperreflexia. The father also did not show chorea. The absence of chorea in all three family members and the unknown family history of previous generations delayed the HD hypothesis at first. After the brain imaging results come out, showing atrophy of the caudate nucleus and putamen for both cases patients 3 and 4, and considering the disease anticipation, genetic testing for HD was performed. It was confirmed the presence of an expanded allele of 84 CAG repeats for patient 3, 66 repeats for patient 4, and 45 repeats for the father. Thus, an expansion of 39 and 21 CAG repeats and anticipation of 43 and 34 years was estimated for patients 3 and 4, respectively (Figure 1c).

**Figure 1** – Pedigree analysis in two families with juvenile Huntington's disease cases. Individuals that were genetically tested for CAG expansion in the HTT gene have their genotype shown below their identification. Genotypes are given by the number of CAG repeats in HTT alleles.
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(a) Family 1, with a case of childhood-onset HD. Patient III.2 (13 years old, age at onset: 6 years) and his father II.2 (deceased, age at onset: 35 years) have an expanded allele with 76 and 44 CAG repeats, respectively. Thus, was an increase of 32 repeats in the father-son transmission (anticipation: 29 years). His brother (III.1, presymptomatic at 18 years old), two aunts (II.6, age at onset: 40 years; II.8, age at onset: 31 years), and one cousin (III.5, presymptomatic at 18 years old) were also genetically confirmed.

(b) Family 2, with a case of adolescent-onset HD. Patient II.3 (20 years old, age at onset: 12 years) and his father I.1 (49 years old, age at onset: 35 years) have an expanded allele with 72 and 47 CAG repeats, respectively. Thus, there was an intergenerational expansion of 25 repeats (anticipation: 23 years).

(c) Family 3, with two JHD cases, a childhood-onset (II.8), and an adolescent one (II.4). Patient II.8 (18 years old, age at onset: 7 years), II.4 (28 years old, age at onset: 16 years) and their father I.1 (55 years old, age at onset: 50 years) have an expanded allele with 84, 66 and 45 CAG repeats, respectively. Thus, there was an intergenerational increase of 39 repeats in the childhood-onset case (anticipation: 43 years) and 21 repeats in the adolescent one (anticipation: 34 years).

DISCUSSION

The juvenile form of HD may be presented at first within a wide range of clinical features. In the first two cases, cerebellar signs were reported as initial symptoms. Patient 1 showed falls at disease presentation. Gait disturbances are one of the most common first symptoms when HD initiates in childhood. Also, this case manifested dysarthria as an early sign. Patient 2, in turn, showed loss of hand dexterity as one of his first symptoms, which is common in adolescent-onset cases. Overall, cerebellar signs usually occur early in JHD, while they are seen only in later stages of disease progression in adult HD. In patients 3 and 4, conversely, the first symptoms noticed were dystonia and bradykinesia.

At disease progression, parkinsonism (bradykinesia and rigidity) and dystonia were the predominant clinical features in all patients here, which is usual for JHD, in contrast to adult HD, as previously mentioned. None of our patients manifested signs of chorea. Chorea, when present in JHD, is usually not an early sign but occurs during the disease course. There is evidence that the HD pathological process is more extensive in the brain of juveniles than in adult-onset cases. The atrophy of the globus pallidus is more severe in JHD, which might help to explain the predominance of the parkinsonism phenotype in such cases. Conversely, seizures, which are symptoms that occur frequently in JHD cases, were observed in only one patient in our study (patient 2). There is evidence that the risk of seizures is inversely proportional to the age at onset, i.e., they are more common when the disease onset is in childhood. Interestingly, no seizures were observed in the two childhood cases reported here.

Furthermore, gait disturbances are a common, but variable, clinical feature in JHD. In our cases, they were manifested in three distinct ways. Patient 1 showed unsteady gait and recurrent falls. In HD, falls are associated with both motor and cognitive symptoms. In the first case, they could be the result of a combination of bradykinesia, decreasing gait speed and step height; dystonic posture, interrupting the movement flow; and cognitive decline, making it difficult to walk while performing other cognitive tasks simultaneously. Moreover, patient 3 showed a wide-based ataxic gait. Ataxia used to be considered an unusual symptom of HD. However, recent evidence demonstrated that gait ataxia and other ataxic signs are common in HD, possibly as the result of cerebellar degeneration during the disease course. Interestingly, while a reduced velocity gait is typical of HD, patient 4 presented a narrow-based festinant gait. Festination is the tendency to walk with increasingly rapid, but shorter steps while leaning the center of gravity forward. This kind of gait disturbance is typical of advanced stages of Parkinson’s disease and parkinsonian syndromes.

Non-motor symptoms were prevalent in all patients. The first case showed a cognitive impairment trait (learning difficulties at school) at disease presentation, while psychiatric problems (irritability/aggressive behavior) were predominant since early in the second one. All cases showed a considerable cognitive decline. Depression
It has been proposed that many clinical differences of JHD to adult HD are related to fact that the disease onset happens before the brain development process is finished. Thus, JHD manifestation is not only related to HD pathology but also to abnormal neurodevelopment. In this way, many clinical characteristics of JHD overlap with neurodevelopmental disorders manifested in childhood and adolescence, such as cerebellar signs, seizures, and specific cognitive and behavioral problems.

Furthermore, in our cases, CAG length in expanded alleles varied from 66 to 84 repeats and age at onset, from six to 16 years. CAG number is considered the most critical determinant of HD age at onset, especially in JHD cases. In a retrospective study with a large set of patients, Fusilli et al. proposed that JHD could be divided into two subgroups according to their CAG length, each one with a typical set of clinical features: highly expanded (≥ 80 repeats), which exhibit a childhood-onset; and low expansion (< 80 repeats), which is associated to an adolescent-onset. Here, one childhood-onset case was compatible with the highly expanded subgroup (patient 3), while the other one presented a repeat number lower than expected (patient 1). Conversely, both adolescent-onset cases fitted in all aspects of the low expansion group. Interestingly, in our study, the lowest age at onset (6 years, patient 1) did not correspond to the highest CAG length (84 repeats, patient 3).

The expanded allele was paternally inherited in all our JHD patients, as expected. The increase in CAG repeats from father to child varied from +21 to +39. In previous studies about intergenerational instability of HD expanded alleles, the estimated increase of CAG number in usual juvenile-onset cases varied from -4 to +47 repeats. The largest expansion registered so far from father to child was +211 CAG repeats, resulting in an expanded allele of 265 repeats, which is also the highest one reported for the HTT gene. Recent experimental evidence has demonstrated that the male expansion bias in CAG length instability is driven by chromatin remodeling in post meiotic events that are specific to spermatogenesis. It has been proposed that DNA double-stand breaks formation and repair mechanisms during the chromatin remodeling process in haploid spermatids are processes that contribute to the male-specific genetic instability.

In our study, anticipation varied from -23 to -43 years from father to child. Previous studies describing anticipation in JHD cases have reported a range of onset changes in parent to child transmissions of -7 to -35 years. Even in the case of very large CAG expansions (>100) from parent to child transmissions, changes in the onset years are around -30 years. Thus, the anticipation of 43 years observed here is very unusual. Interestingly, the intergenerational increase in CAG length was higher in patients 1 and 3 (+32 and +39, respectively), while anticipation was greater in patients 3 and 4 (43 and 34 years, respectively), which are from the same family. Although the anticipation phenomenon in HD is seen as the result of progressive CAG repeat expansion over successive generations, a large part of the change in age at onset from parent to child cannot be explained only by the intergenerational increase in CAG repeats. Given the trend towards the occurrence of multiple JHD cases within families, it has been suggested that there might be a familial component that increases the likelihood of juvenile cases in certain families, which could be the effect of either genetic factors or shared environments.

In Brazil, the prevalence of JHD is unknown. However, the occurrence of these cases has been investigated in previous screening studies in Southern and Southeastern regions. The proportion of juvenile-onset to total genetically confirmed HD cases ranged from 4% (3/75 cases) to 12.5% (4/32 cases). Childhood-onset cases were observed in two studies. The younger age at onset reported was 2 years old, and the largest CAG length was 88 repeats. To our knowledge, the JHD cases described here are the first ones reported in northern Brazil. Two of them were part of our previous report about HD occurrence in the referral center for movement disorders of Manaus/AM. These patients represent 10.8% (4/37 cases) of total confirmed HD cases so far (personal communication). In Amazonas, there are only a few medical doctors that are specialists in movement disorders. Also, most families cannot afford genetic testing. This situation is aggravated by the lack of public awareness of this disease, even among clinicians. According to family reports, members of two or three generations (and possibly more) suffered from HD but were not diagnosed. Also, three of our patients lived outside Manaus, which was especially critical since they did not receive specialized help for many years after the disease started to manifest.

CONCLUSION

In summary, we presented the clinical and genetic aspects of four JHD cases from northern Brazil, a large region in which the access to diagnosis of rare conditions is very restricted, and data are scarce. Interestingly, these cases illustrate the variability in clinical phenotypes of JHD and the inheritance of expanded CAG repeats within families. Reports of HD and JHD cases in this region can contribute to disease awareness, both by professionals and the public, which can, in turn, potentially improve access to correct diagnosis, proper care, and genetic counseling for the affected families in the future.
ACKNOWLEDGMENTS

This work was supported by the Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM); and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). D.V.B. received a PNPD/CAPES scholarship by the Programa de Pós-Graduação Mestrado em Biotecnologia e Recursos Naturais (PPGMBT/UEA).

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