Childhood-onset Huntignton´s disease. A rare presentation

Amín Gauto, Emanuel Bellantonio, Paula Pedernera-Bradichansky, Pablo Cafiero, Estela Rodríguez, Pilar Massaro

Introduction. Huntington's disease (HD) is a rare autosomal dominant disease caused by the expansion of CAG triplets in the gene that encodes huntingtin. There are earlier symptoms' onset in offspring due to the phenomenon of anticipation. The clinical features of childhood-onset HD, before age 10 years, differs from adult-onset form. It is characterized by motor impairment, behavioral difficulties and delay or regression in areas of development; while chorea is rarely seen. In this case we describe clinical aspects of a patient with childhood-onset Huntington's disease.

Case report. A 5-year-old girl with a family history of HD and typical development up to 3 years of age. She progressively acquired language impairment with skills that were below her age in expressive and receptive areas, without deficits in pragmatic and social skills. Regarding motor skills, she manifested instability at walking and standing, with rigidity, dystonia and choreic movements. Atrophy of the basal ganglia was evident on MRI, EEG was normal, and molecular confirmation of CAG triplet revealed repeat length of 51 copies.

Conclusion. Childhood-onset HD differs from adult-form´s clinical manifestations. It should be considered in patients with progressive motor and cognitive impairment. Due to family inheritance, it is important to carefully examine family history and take it into account even without relatives affected, considering the anticipation phenomenon.

Key words. Childhood-onset Huntington disease. Genetic anticipation. Gait disorder. Language regression. Neurodevelopment. Pediatric neurodegenerative disease.

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Introduction

Huntington's disease (HD) is a rare autosomal dominant disease caused by the abnormal expansion of cytosine-adenine-guanine (CAG) triplets in the gene that encodes huntingtin, located on chromosome 4 (4p16.3) [1]. Typical presentation includes changes in mood and personality, motor and cognitive alterations [2]. HD must be suspected when clinical manifestations and a positive family history are present, and its confirmation is reached by molecular study. The average age of onset is 45 years (range from 2 to 87 years). When the symptoms appear before the age of 21, it is called juvenile-onset Huntington's disease, which is seen in 5-10% of all HD cases [3]. The term pediatric HD is reserved for those patients with disease onset before the age of 18. Further distinction is made between two subgroups based on clinical presentation [4]: adolescent-onset Huntington's disease, when it occurs between the ages from 10 to 18; and childhood-onset Huntington's disease, when the onset is before the age of 10 and is very rare (20% of the juvenile form) [3]. Childhood-onset Huntington's disease's clinical features differ widely from those seen in adults [2,5]. Chorea is rarely seen [6] and behavioural disturbances [7], motor impairments such as rigidity, dystonia and bradykinesia, seizures and developmental delay or regression may be observed [3,4,8]. About 80% of juvenile-onset Huntington's disease patients inherit the repeat expansion via paternal transmission [9]. The onset of symptoms in the offspring is earlier, due to anticipation phenomenon [10]. We describe a patient with an early onset of the disease with motor and language impairments.

Case report

A 5-year-old girl, with no relevant perinatal history, consulting for unintelligible speech and gait instability, with a paternal history of HD diagnosis, as well as three uncles and her grandmother, all from the paternal side of the family, with some degree of motor disability or psychiatric disorder (Fig. 1). Her development was normal until the age of 3, when she began to experience regression of previously acquired language patterns. By 5 years, major impairment in gross motor function was apparent,

Figure 1. Genealogy, the index case has been marked with an arrow. HD: Huntington's disease.

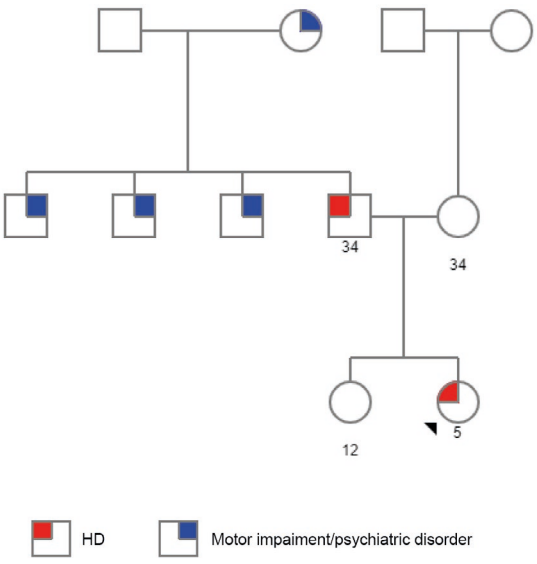
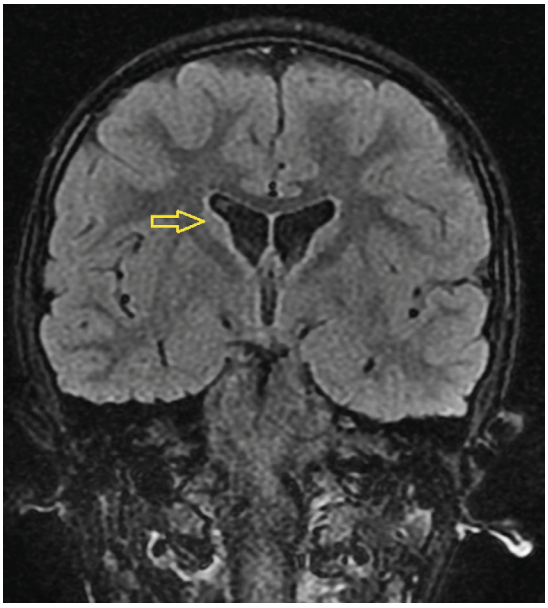


Figure 2. Striatal atrophy on brain magnetic resonance imaging.



with frequent falls and dystonic gait, which was the source of concern. Her condition progressed and by the time of examination she was dependent on every activity of daily living. Her language skills were below her age in expressive aspects (unintelligible speech due to severe motor impairment). Receptive language was also affected, improving with visual aids. She smiled responsively and made eye contact with the examiner, evidencing reciprocity in her communication skills and showed interest in peers. She had non-verbal resources such as pointing, and gestures sometimes accompanied by single words. Physical examination revealed disturbances in walking secondary to dystonia with frequent falls. Sporadic choreic movements of the upper limbs were observed, with a low frequency of appearance. Drooling and lack of mouth closure were seen, with slowed and uncoordinated oral movements. Behavioural difficulties were not reported unless minor episodes of irritability in frustrating situations.

Among the complementary studies requested, magnetic resonance imaging of the brain showed atrophy of both caudate nuclei as well as symmetrically shaped lenticular (Fig. 2) and the electroencephalogram study was normal. Subsequent molecular analysis (CAG triplet expansion) showed CAG repeat length of 51 ± 1 in the 4p16.3 *locus*, which confirms the diagnosis, showing a phenomenon of anticipation due to the early onset of the disease.

The family was provided with advice on the use of augmentative and alternative communication systems to improve communication and manage behaviour. Speech therapy and physiotherapy treatment was indicated in her area of residence, and to continue in a regular school with inclusion support modality.

Discussion

HD is a progressive and severe neurodegenerative disease characterized by motor, behavioral and cognitive impairments affecting both genders. The prevalence has been estimated to be 5-10 per 100,000, while the juvenile variant (under 21 years old) is seen in 5-10% of all HD cases [4]. Of the juvenile presentation, only 20% start before the age of 10 years, conventionally defined as childhood-onset Huntington's disease [3]. The clinical presentation in childhood differs from adult and adolescence-onset. While changes in mood, depression, suicidal ideation and motor disorders are common in adolescents, boys and girls usually show gait disorders, falls, speech difficulties, seizures and developmental delays or regression patterns [3]. Diag-

nostic criteria have been proposed for childhood presentation (Table) being family history of HD the most relevant data and predictor of molecular confirmation [6]. Motor features such as rigidity, tremor, dysarthria and signs of cerebellar dysfunction are more frequent than chorea. However, due to atypical clinical presentation, childhood-onset Huntington's disease´s patients are often misdiagnosed especially when family confirmation is not clear, or the condition has been anticipated and appears before the adult generation [5]. Women tend to have a worse prognosis, and those who debut with rigidity develop a faster course of the disease than those with other hyperkinetic movement disorders. This is the case of the patient described, who presents severe symptoms of rigidity and spasticity, with an early onset of the manifestations. Both delay and regression in language and speech can be signs of initial presentation, even preceding non oral motor dysfunction by up to 2 years [8]. The mentioned patient shows a similar pattern, beginning with language regression followed by gait alterations. In some reports, the impairment is found in both expressive and receptive language is related to motor and cognitive impairment [7,8], as the case exhibits. Behavioural disturbances are frequently reported. Oppositional-defiant behaviour and hyperactivity are often seen in childhood-onset Huntington's disease [7]. In a series presented with local data, the juvenile form represented 16,9% of HD cases, with a mean age of symptom onset of 15 years; while clinical manifestations were bradykinesia, learning difficulties, seizures, and behavioural problems [10].

Diagnostic confirmation (reached by molecular study to detect the expansion of CAG triplets) is being cost-effective, providing information for those who present symptoms of HD and ruling out the disease in those with another etiology [2]. There is a strong inverse correlation between the age of symptom onset and CAG repeats length, with large-sized CAG expansions in the group of patients with childhood-onset (over 100) [3]. Despite that, the patient in this case shows an earlier onset of the disease with a smaller CAG expansion [5]. The genetic anticipation phenomenon is usually associated with paternal inheritance, as in the reported case [3].

Regarding pathophysiology, the cleavage and accumulation of the amino-terminal fragments of the protein containing the expanded regions leads to cellular apoptosis in the central nervous system, especially in the striatum, the frontoparietal cerebral cortex and the cerebellum [4]. Some authors propose that these changes, if they occur at an early age, not only affect established circuits but also alter the normal development of some central nervous system connections (neurogenesis, neuronal migration, synaptogenesis and synaptic pruning), assigning a role for huntingtin in cognitive aspects and explaining the clinical manifestations of neurodevelopmental compromise [2,4].

Table. Suggested diagnostic criteria for Huntington's disease before the age of 10 years.

Family history of Huntington's disease and at least two of the following:
Declining school performance
Seizures
Oral motor dysfunction
Stiffness
Gait disturbances

The therapeutic approach should be interdisciplinary. Since at present there are no specific approved treatments, HD is managed symptomatically. Appropriate care must be considered on an individualized basis. The role and importance of different team members may vary as the disease progresses and new symptoms appear [6]. Cognitive impairment is the aspect that has the major impact on daily functioning [5], so continuous educational support is fundamental for the full participation of boys and girls with childhood-onset Huntington's disease, according to the support modalities within the community.

The genetic study must be indicated carefully and based on adequate criteria. It is not recommended in asymptomatic children under 18 years of age with a family history of HD for ethical and psychosocial reasons. However, the presence of frequent symptoms in the general population such as language delay or behavioural disturbances in a patient with a family history of HD implies a diagnostic challenge [6].

Conclusions

Childhood-onset Huntington's disease is a rare disease with clinical manifestations that differs from the adult form. It should be considered in patients with developmental delay or regression with motor compromise. We considered the study of the pa-

tient to be important in order to take into account language difficulties as early signs of HD, when accompanied by a positive family history in order to reach an adequate genetic counselling.

Family history is very indicative, but due to the phenomenon of anticipation, it is a pathology that must be considered even without having affected adult relatives.

The therapeutic approach by the time is supportive. Addressing asymptomatic family members remains a challenge. The role of the medical team should be to accompany family decisions at different times in life, respecting the decisions.

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Enfermedad de Huntington de inicio en la infancia. Una presentación poco frecuente

Introducción. La enfermedad de Huntington (EH) es una enfermedad de herencia autosómica dominante caracterizada por la expansión de tripletes de citosina-adenina-guanina (CAG) en el gen que codifica la huntingtina. Los síntomas en la descendencia suelen ser más tempranos por el fenómeno de anticipación. La clínica de inicio en la infancia, antes de los 10 años, difiere de la observada en la adultez. Se manifiesta por afectación motora, dificultades conductuales y retraso o regresión del desarrollo. La corea es infrecuente. El objetivo del caso es describir aspectos clínicos de una paciente con EH de inicio infantil.

Caso clínico. Niña de 5 años con antecedentes familiares de EH y desarrollo típico hasta los 3 años. Presentó progresivamente afectación del lenguaje con habilidades descendidas para su edad en aspectos expresivos y comprensivos, sin afectación en las habilidades pragmáticas y sociales. En cuanto a la motricidad, la marcha y la bipedestación eran inestables, y mostraba rigidez, distonía y movimientos coreicos. Presentó atrofia de los núcleos lenticulares y caudados en la resonancia magnética, y posteriormente se realizó el diagnóstico molecular con la expansión de tripletes CAG (51 copias).

Conclusión. La EH de inicio en la infancia presenta manifestaciones clínicas distintas a la forma del adulto. Debe considerarse en pacientes con afectación motora y cognitiva progresiva. Por la herencia familiar, es importante interrogar cuidadosamente sobre los antecedentes familiares y tenerla en cuenta aun sin familiares afectados por el fenómeno de anticipación.

Palabras clave. Enfermedad de Huntington de inicio en la infancia. Enfermedad neurodegenerativa pediátrica. Fenómeno de anticipación. Neurodesarrollo. Regresión del lenguaje. Trastorno de la marcha.