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Neuropsychomotor manifestations of juvenile Huntington's disease: signs and symptoms and imaging findings

Manifestações neuropsicomotoras da doença de Huntington juvenil: sinais e sintomas e achados de imagem

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RESUMO: A doença de Huntington Juvenil (JHD) consiste na neurodegeração de células nervosas causada pela formação da proteína alterada denominada huntingtina, acumulada no citoplasma e núcleo de neurônios, capaz de gerar morte progressiva destas células de forma mais evidente no corpo estriado, que engloba os núcleos caudado e putâmen. A variante juvenil da doença de Huntington manifesta-se em pacientes com idades entre 0 a 20 anos, com variedade de distúrbios motores, cognitivos e comportamentais. Com o objetivo de estudar os mais prevalentes sinais, sintomas e achados de imagem, bem como as manifestações iniciais e a evolução sintomatológica ao decorrer da doença, foi realizada uma revisão integrativa de literaturas, incluindo o total de 25 artigos selecionados após a adequação de critérios de exclusão e inclusão. Após a análise dos dados, concluiu-se que os sintomas mais destacados foram rigidez muscular, disartria, convulsões, bradicinesia e disfunções cognitivas e comportamentais. Em se tratando de achados de imagem, prevaleceram atrofia de núcleos da base e cerebelo em pacientes com a doença mais avançada e diagnosticados em tempo maior.

Descritores: Doença de Huntington; Transtornos cognitivos; Adolescente, Criança.

ABSTRACT: Juvenile Huntington's disease consists of neurodegeneration of nerve cells, caused by the formation of a defective protein called huntingtin, which accumulates in the cytoplasm and nucleus of neurons and is capable of generating progressive death of these cells. This is more evident in the striatum, which includes the caudate nucleus and putamen. The juvenile Huntington's disease manifests in patients aged 0 to 20 years, with a variety of motor, cognitive and behavioral disorders. In order to study the most prevalent signs, symptoms and imaging findings, as well as the initial manifestations and the symptomatic evolution during the course of the disease, an integrative literature review was carried out, including a total of 25 articles selected after application of inclusion and exclusion criteria. After analyzing the data, it was concluded that the most prominent symptoms were muscle rigidity, dysarthria, seizures, bradykinesia and cognitive and behavioral dysfunctions. In terms of imaging findings, atrophy of the caudate nucleus and cerebellum prevailed and was associated with advanced stages of disease or longer time since diagnosis.

Keywords: Huntington disease; Cognition disorders; Adolescent; Child.

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INTRODUCTION

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by CAG trinucleotide repeat expansions, resulting in a defective misfolded protein called huntingtin, which accumulates in the cytoplasm and nucleus of neurons. The accumulation of this protein leads to neuronal dysfunction and death, mainly in the caudate nucleus, putamen, globus pallidus and cortex[1].

Huntington's Disease (HD) occurs when an individual has 40 or more CAG repeats[1,2,3]. Juvenile Huntington's Disease (JHD) occurs when the onset of the disease occurs before the age of 20 years[4]. These cases represent about 10% of the total number of HD cases[2,5,6,7]. The onset of the disease before 10 years of age is even rarer, representing about 1% of all HD cases[2,4,5,6].

The first one to describe JHD was Lyon, in 1863, 9 years before the Huntington report[7], which does not detract from Huntington's merit in describing the pathology. The disease manifests as a triad of psychiatric, motor and cognitive symptoms[5]. Psychiatric manifestations precede motor symptoms[8], differing from adult HD and making the diagnosis more difficult.

Paternal transmission of JHD is more reccurent[5,9,10,11,12], which can be explained by the higher instability of the CAG repeat in spermatogenesis when compared to oogenesis [5,12]. The age of onset of JHD is inversely correlated with the number of CAG repeats[4,7]; however, there is still no consensus, since factors other than number of repeats can affect the age of onset[2]. Therefore, the objective of the present study is to discuss JHD, and its recurrent symptoms and clinical manifestations through an integrative literature review.

METHOD

The research was guided by the combination of the descriptors "Huntington' disease", "Huntington", "infantile", "juvenile", and "Juvenile Huntington disease". The search for the articles was conducted individually by the authors in the databases SciELO, BVS-LILACS, PubMed and MedLine. Studies published between January 1, 1999 and December 31, 2018 were selected. Case reports, longitudinal studies and literature reviews were considered. All studies from the period established were independently selected by the authors. The studies available were evaluated for inclusion and exclusion criteria. The exclusion criteria were abstracts and texts that did not correspond to the topic of study, duplicate articles and studies that were not published between 1999 and 2018. Inclusion criteria were articles addressing different symptoms, differential diagnosis and imaging findings.

RESULTS

A total of 9 studies were eliminated in the database research. Twenty-five articles met the criteria for the final literature review and were part of the present research.

Among the 25 studies included, there were 17 case reports, 4 longitudinal studies, 1 retrospective data analysis, 1 literature review, 1 morphometric analysis and 1 cohort study.

Table 1 presents the articles according to the journal, year of publication, title, and research design.

DISCUSSION

JHD is a condition that is difficult to diagnose, since it is associated with motor, cognitive and psychiatric disorders[7,13]. In addition, its phenotype is very different from adult-onset HD[6]. Table 2 displays all the main symptoms found in the articles selected for this review. It should be noted that only 18 of the 25 articles are included in table 2, since only these 18 presented the initial symptoms, age of onset, number of patients and general signs and symptoms according to the evolution of the condition.

The data in the table shows that, among the motor disorders, the most common in JHD are gait disturbances, namely ataxic gait, rigidity, spasticity, pyramidal signs, and ataxia. Some patients had an impairment of fine motor skills, which require high dexterity, such as writing, and grosser movements in general. Dysarthria, dystonia and dysphagia, as well as seizures, were also common characteristics. Growth delay and low weight gain were observed among younger patients.

In addition, many patients who are included in the table presented cognitive impairment, progressive cognitive decline, learning difficulties and speech delay. The most common psychiatric disorders were behavioral changes, including irritability and depression. Some authors affirm that patients with JHD have higher rates of suicidal ideation[8,14]. Higher rates of suicide also occur when one of the parents has HD[3].

The remaining articles reinforce the findings listed in table 2. A study with 29 patients with paternally inherited JHD found that they tended to have greater anticipation and a larger number of CAG repeats and, consequently, more severe disorders[13]. This was reinforced by another study that compared adult-onset HD and JHD and concluded that younger people have higher instability of the CAG repeat and more rapid disease progression[1]. Authors also point out that the symptoms at onset may include alterations in executive function and school performance, depression, anxiety and gait disorders[2,4,5,7,8,15,16]. The seizures presented by the patients may be of different types[17]. Another symptom, which resembles adult-onset HD, consists of abnormalities of saccade eye movements, which may be directly related to the severity of JHD[14].

Table 1. Studies selected

Journal	Year	Title	Type of study
Arq Neuropsiquiatr	1999	Juvenile Huntington's disease confirmed by genetic examination in twins.	Case report
Clin Genet	2003	PCR for the detection of large trinucleotide expansions in juvenile Huntington's disease.	Case report
J Child Neurol	2003	Unusual early-onset Huntington's disease.	Case report
Pediatr Radiol	2004	MR imaging and spectroscopy in juvenile Huntington disease.	Case report
J Child Neurol	2006	Huntington disease in a 9-year-old boy: clinical course and neuropathologic examination.	Case report
Neurology	2006	Speech and language delay are early manifestations of juvenile-onset Huntington disease.	Case report
J Child Neurol	2006	Huntington disease: report of 12 patients and review of literature.	Case report and Literature review
Arq Neuropsiquiatr	2006	Clinical presentation of juvenile Huntington disease.	Case report
Arch Neurol	2007	Psychiatric and cognitive difficulties and indicators of juvenile Huntington disease onset in 29 patients.	Longitudinal study
J Mov Disord	2010	A case of juvenile Huntington disease in a 6-year-old boy.	Case report
Am J Med Genet	2011	Juvenile Huntington disease in an 18-month-old boy revealed by global developmental delay and reduced cerebellar volume.	Case report
Gen Hosp Psychiatr	2012	Huntington's disease presenting as difficult to treat seizure and the first episode of psychosis.	Case report
Neurology	2012	Measures of growth in children at risk for Huntington disease.	Longitudinal study
Mov Disord	2012	Seizures in juvenile Huntington's disease: frequency characterization in a multicenter cohort.	Case report
Pediatr Neurol	2013	Typical clinical findings should prompt investigation for juvenile Huntington disease	Case report
Polish J Neurol Neurosurg	2014	Saccadic eye movements in juvenile variant of Huntington disease.	Cohort study
Arch Argentinos Pediatria	2014	Retraso en el diagnostico de un cuadro grave de enfermedad de Huntington juvenil: um reporte de caso.	Case report
Med Infantil	2015	Manifestaciones psiquiátricas en efermedad de Huntington de inicio infantil.	Case report
Pediatr Neurosci	2015	Chilhdood-onset Huntington's disease: a rare case report	Case report
Arq Neuropsiquiatr	2016	Juvenile Huntington disease in Argentina	Longitudinal study
J Huntington's Dis	2017	Neuropathological Comparison of Adult Onset and Juvenile Huntington's disease with cerebellar atrophy: a report of a father and son	Case report
Curr Psychiatry Rep	2017	Juvenile Huntington's disease: diagnostic and treatment considerations for the psychiatrist.	Literature review
BMC Neurol	2017	Tics as an initial manifestation of juvenile Huntington's disease: case report and literature review	Case report and Literature review
Lancet Neurol	2018	Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis.	Retrospective analysis
Pediatr Radiol	2018	Morphological features in juvenile Huntington disease associated with cerebellar atrophy.	Morphometric analysis

Magnetic resonance findings corroborate the atrophy of the caudate nucleus and the putamen, as well as diffuse atrophy of the cerebellum, especially in the posterior lobe[18], reinforcing the lower anthropometric measures in relation to head circumference[19]. Children with HD also have lower weight and BMI[19]. A study with 3 patients between 2 and 6 years of age also revealed atrophy of the amygdala, hypothalamus and brainstem, which could explain the emotional and cognitive alterations, abnormal eye movements and sleep disturbances[18].

In a common form of manifestation, the disease begins with cognitive impairment[7], learning difficulties and decline in school performance, and it may be confused with other pathologies, such as ADHD[5,15]. Patients may also initially present behavior changes, such as aggressiveness, irritability or depression[15]. The disease progresses to worsening of cognitive and psychiatric symptoms and onset of motor symptoms[4,7]. The family may report, as early motor symptoms difficulty walking, frequent falls and dysarthria[6,12,20,21,22]. Postural instability, in association with falls, pyramidal signs and cognitive impairment may lead to the differential diagnosis of caudal regression syndrome[22]. Episodes of seizures without prior history may also occur[10,11,17].

Another characteristic found in children presenting CAG trinucleotide repeat expansions consists of significantly smaller measures of growth, namely lower weight, BMI and head circumference[2,8,19]. Smaller head circumference suggests a specific deficit in brain growth[19]. Weight loss[2,19] may be prior to motor symptoms, or it may become accentuated after motor disorders, due to the intense energy and protein expenditure.

More rarely, patients may initially manifest sexual disinhibition[23], emotional lability[3,8,18], progressive dystonia[8,24] or saccadic eye movements[14]. The initial manifestation of JHD hardly presents chorea, which is an initial symptom of adult-onset HD[13]. Juvenile patients may also have parkinsonism[4,5,13,20,22], making juvenile Parkinson's disease one of the possible differential diagnosis[15]. Disease progression is rapid, and younger age at onset is related to more rapid progression of the disease and larger number of CAG repeats[10]. Seizures tend to be myoclonic and resistant to anticonvulsants[16]. Throughout the disease course, choreic movements may occur[2,7,9,10].

Among the imaging findings, atrophies of the cerebellum[2,5,7,9,13], the caudate nucleus and the putamen (striatum)[1,5,7,10,16] were present in the vast majority of patients. Some patients had significant ventricular enlargement[5,10], found during disease progression and not seen in early diagnosis. As to MRI findings, measures of intracranial volume were smaller[19]. The electroencephalogram did not show major changes[17], but some patients may have epileptic focus within the occipital lobes[22].

Due to the multiple variations of JHD symptoms, the diagnosis is concluded with a family history of Huntington's disease and a genetic test to look for CAG repeat expansions. In this context, lack of family history may hinder the diagnosis[25], since in some cases parents have not yet been diagnosed or may not have manifested any of the symptoms, since in the adult variant the onset of the disease usually occurs in the third to fifth decades of life[12].

Currently, environmental factors are already considered as an influence on the symptomatology of JHD[20], as is the number of CAG repeats. A case report of twins showed different ages of onset (one at 17 and one at 20), as well as more intense symptoms and more rapid progression in one of the siblings (the one with earlier onset). Both had less than 8 years of formal education, but their Mini-Mental scores were 19 and 18[20].

CONCLUSION

Based on the literature review, it can be concluded that the diagnosis of JHD is of considerable difficulty, due to its phenotypic variation and varied symptoms. It is even more difficult when there is no family history.

Paternal transmission of the disease is more recurrent, and the age of onset is inversely correlated with the number of CAG repeats. However, studies disagree on the influence of environmental factors, considering that patients with the same number of CAG repeats can manifest the disease at different ages and intensity.

Symptomatology is associated with the triad of psychiatric, cognitive and motor symptoms. The most recurrent symptoms are cognitive and behavioral disorders, rigidity, bradykinesia, dysarthria and seizures. Low weight, motor tics and tremors can also be observed.

Imaging findings are mostly associated with advanced stages of disease or longer time since diagnosis. These findings are atrophies of the caudate nucleus, putamen and cerebellum. Ventricular enlargement is also found in some cases.

Table 2. Main symptoms reported

Initial symptom	Age of onset of symptoms	Number of patients	Signs and Symptoms during disease progression
Seizure	20 years	1	Choreic movements, gait disturbances, dysarthria, myoclonic seizures, irritability, sexual disinhibition, auditory hallucinations and poor impulse control.
Development delay and paroxysmal dyskinesia in the left lower limb	18 months	1	Development delay, paroxysmal dyskinesia, axial hypotonia, limb hypertonia and chorea.
Myoclonic seizure	6 years	1	Myoclonic seizure, dystonia, chorea, dysphagia, limb spasticity, growth delay.
4 patients started with decline in school performance, 2 patients with instability and 1 with behavior changes	7 patients manifested before 7 years old	29	Low weight gain, cerebellar ataxia, speech delay, motor delay, hypertonia of all 4 limbs, axial hypotonia , dysphagia and severe growth delay. Chorea during disease progression.
Absence seizure and "chattering"	3 years	1	Encephalopathy with epilepsy, ataxia, dysphagia, motor disorders, low weight and pyramidal signs.
Difficulty forming sentences, dysarthria	1 year	3	Dysarthria, ataxic gait, falls, parkinsonism, psychiatric disorders, rigidity, bradykinesia and dystonia.
Cognitive dysfunction	Between 4 and 14 years	12	Cognitive dysfunction, oropharyngeal dysphagia, impairment of fine motor skills, gait disturbances, behavioral disorders and seizures.
Generalized tonic-clonic seizure	7 weeks	1	Behavioral difficulties, cognitive dysfunction, athetosis, motor difficulties, dysarthria and chorea.
Bradykinesia, with 30% having seizures and 30% having psychiatric disorders	Between 2 and 13 years	4	Rigidity, bradykinesia, ataxia, dysarthria and pyramidal signs.
Most cases began with behavioral disorder. 2 presented cognitive decline and/or decline of school performance, 2 presented parkinsonism and 1 presented phobia, autism and seizures	Between 4 and 20 years	14	Behavioral and psychiatric disorders, cognitive decline, parkinsonism, dystonia, dysphagia, dysarthria, falls and postural instability.
Irritability	14 years	1	Irritability and emotional lability, choreic movements in upper limbs, ataxic gait.
Rigidity	2.5 years	1	Postural instability and falls, pyramidal signs and cognitive decline, myoclonic and complex partial seizures, hypomimia, upper limb postural tremor, limb rigidity, bradykinesia, gait disturbance. Dystonia at rest and loss of balance.
Abnormal movements	8 years	1	Motor tics, behavioral disorders and learning difficulties. Myoclonus, dystonia, dysarthria and dysphagia. Progressive impairment of cognitive function.
Loss of balance and progressive gait disturbance	17 and 20 years	2	Bradykinesia, rigidity with cogwheel phenomenom, choreic movements of trunk and limbs (at 24 years of age), dysarthria, hyperactive tendon reflexes and flexor plantar responses.
Memory impairment, frequent falls and first seizure episode	4 years	1	Tonic-clonic seizures, nasogastric tube feeding, clumsy, wide and unstable gait, oculomotor apraxia, hand dystonia, hyperactive tendon reflexes, increased leg muscle tone and involuntary spasms in the legs and hands.
Motor tics of the head	17 years	1	Involuntary movements in the shoulder, right upper limb and lower limbs, inattention and hyperactivity, night terrors, multifocal dystonia manifested through blinking, shaking head and shrugging, spasmodic torticollis, depression and anxiety.
Abnormal involuntary movements and behavioral decline	6 years	1	Regression in development, impairment fine and gross motor skills, unreadable writing and incomprehensible speech.
Frequent falls, ataxic gait, bradykinesia and seizures	8 years	1	Regression of developmental milestones to a developmental age of 1.5-2 years, regression of language milestones, monosyllable speech, bradykinesia, ataxic gait, oculomotor apraxia, rigidity and signs of cerebellar involvement.

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