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CLINICAL PRESENTATION OF JUVENILE HUNTINGTON DISEASE

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ABSTRACT - *Objective:* To describe the clinical presentation a group of patients with juvenile onset of Huntington disease. *Method:* All patients were interviewed following a structured clinical questioner. Patients were genotyped for the trinucleotide cytosine-adenine-guanine (CAG) repeat in the *Huntington Disease* gene. High resolution brain MRI was performed in all patients. *Results:* We identified 4 patients with juvenile onset of disease among 50 patients with Huntington disease followed prospectively in our Neurogenetics clinic. Age at onset varied from 3 to 13 years, there were 2 boys, and 3 patients had a paternal inheritance of the disease. Expanded Huntington disease allele sizes varied from 41 to 69 trinucleotide repeats. The early onset patients presented with rigidity, bradykinesia, dystonia, dysarthria, seizures and ataxia. MRI showed severe volume loss of caudate and putamen nuclei (p=0.001) and reduced cerebral and cerebellum volumes (p=0.01). *Conclusion:* 8% of Huntington disease patients seen in our clinic had juvenile onset of the disease. They did not present with typical chorea as seen in adult onset Huntington disease. There was a predominance of rigidity and bradykinesia. Two other important clinical features were seizures and ataxia, which related with the imaging findings of early cortical atrophy and cerebellum volume loss.

KEY WORDS: neurodegenerative disorder, dynamic mutations, genotype-phenotype correlation, basal ganglia, atrophy.

Apresentação clínica da forma juvenil da doença de Huntington

RESUMO - *Objetivo:* Descrever o quadro clínico de um grupo de pacientes com forma juvenil da doença de Huntington. *Método:* Os pacientes foram entrevistados seguindo um questionário clínico estruturado; genotipados para a repetição do trinucleotídeo citosina-adenina-guanina (CAG) no gene da doença de Huntington; e realizaram exame de RM de alta resolução. *Resultados:* Identificamos 4 pacientes com doença de Huntington de início juvenil dentre 50 pacientes com doença de Huntington seguidos prospectivamente em nosso ambulatório de neurogenética. A idade de início variou entre 3 e 13 anos (2 meninos e 2 meninas). Três pacientes tiveram herança paterna da doença. O tamanho do alelo expandido da doença de Huntington variou entre 41 a 69 repetições de trinucleotídeos. As principais manifestações clínicas no início da doença foram rigidez, bradicinesia, distonia, disartria, crises epilépticas e ataxia. A RM mostrou acentuada atrofia dos núcleos caudado e putamem (p=0.001) e redução do volume cerebral e cerebelar (p=0.01). *Conclusão:* 8% dos pacientes com doença de Huntington acompanhados em nosso ambulatório apresentaram início juvenil da doença. Estes pacientes não apresentaram a manifestação típica de coréia observada em adultos. Houve predomínio de rigidez, bradicinesia, crises epilépticas e ataxia, o que tem relação com a atrofia cortical e cerebelar precoce na RM.

PALAVRAS-CHAVE: doença neurodegenerativa, mutações dinâmicas, correlação genótipo-fenótipo, atrofia de núcleos da base.

Huntington disease is an adult onset disorder beginning typically in the fourth and fifth decades of life. Juvenile Huntington disease is an uncommon condition and it is believed that these patients have a somewhat different clinical presentation when compared to the typical adult onset form[1,2]. Therefore, the presentation of juvenile and childhood Huntington disease may lead to difficulties in diagnosis. With the development of molecular testing, diagnostic confirmation can now be achieved with certainty if clinical suspicion is raised.

In this study we aimed to characterize clinical presentation and MRI findings in patients with juvenile Huntington disease.

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METHOD

Subjects assessment – We identified 4 patients with juvenile form of Huntington disease among patients followed in our Huntington disease clinic (2 boys) with a mean age of 14.5 years (ranging from 4 to 21). Three patients had paternal inheritance and one had maternal inheritance. Age at onset varied between 2 to 13 years (mean age 6.75 years). All had clinical and molecular diagnosis of Huntington disease at the Neurogenetic clinic of our Hospital. The diagnosis of Huntington disease was made according to established, reliable criteria, including a positive family history, the presence of choreiform movements, dystonia or impaired voluntary motor function, and cognitive or emotional changes[3,4]. For each patient, the onset age of Huntington disease was determined by asking the patient and multiple unaffected family members to recollect the first occurrence of chorea, rigidity, irritability, sleep disturbance, frequent falls, loss of energy, altered social behavior, or failing memory that was not an isolated incident but heralded a progressive decline. Neurological exams were performed in all patients by the same investigator (HHR). All patients had known trinucleotide repeat expansion. The control group (8 men and 10 women), with ages ranging from 18 to 28 years (mean age 23 years), had no history of neurological and psychiatric illness. All subjects, or legal guardians, signed written informed consent to participate in this study, approved by Ethics Committee from our hospital.

Clinical and molecular investigation – All patients and family members were seen in our Neurogenetic clinic and followed according to the same clinical protocol. Molecular testing was performed following international standard protocols for laboratory testing[5]. We further divided patients into three groups according to the age of onset of disease: patients who had early onset Huntington disease (4 patients, 2 males and 2 females, mean age of onset 8 years), those who had adult onset Huntington disease (24 patients, 8 males and 16 females, mean age of onset 30 years), and those had late onset Huntington disease (22 patients, 19 males and 3 females, mean age of onset 44 years).

MRI acquisition – MRI images were obtained in a 2 Tesla system (Elscint Prestige®, Haifa, Israel). Images were acquired in the coronal, sagittal, and axial planes. Our Huntington disease protocol consisted of: (1) sagittal T1 spin-echo, 6 mm thick (repetition time [TR]=430; echo time [TE]=12); (2) coronal T1 inversion recovery, 3 mm thick (flip angle=200°; repetition time=2700; echo time=14; T1, 840; matrix=130x256; field of view [FOV]=16x18 cm); (3) coronal T2-weighted fast spin-echo, 3 to 4 mm thick (flip angle=120°, repetition time= 4800; echo time=129; matrix=252x320; field of view= 18x18 cm); (4) axial images parallel to the long axis of the hippocampi; T1 gradient echo, 3 mm thick (flip angle=70°; repetition time=200; echo time=5; matrix=180x232; field of view=22x22 cm); (5) axial T2 fast spin-echo, 4 mm thick (flip angle=120°; repetition time=6800; echo time=129; matrix= 252x328; field of view=21x23 cm).

Volumetric studies – Measurements of basal ganglia and cerebral volumes were performed on coronal inversion recovery images and cerebellar volume measurement were performed on sagittal T1 spin-echo acquisition using the NIH Image program (http://rsb.info.nih.gov/nih-image), following anatomic guidelines. Caudate and putamen structures (Figure), total intracranial and cerebellar volumes were manually delineated using the NIH image program. The volume of each region was compared to the control group of 18 healthy volunteers. Values below two standard deviations from the mean of control group were considered abnormal.

Statistics analysis – We described the minimum, maximum, mean value and standard deviations for the volumes of the structures analyzed, and p values of less than 0.05 were accepted as statistically significant. These values were separated in. We used analyses of variance (ANOVA) to compare continuous variables among the three subgroups of Huntington disease subjects and in the control group. We used the Exact Mann-Whitney test to compare cerebellum and cerebral volumes between Huntington disease and control groups and Kruskal-Wallis test when these structures were compared with 3 subgroups of Huntington disease.

RESULTS

There were 4 patients with clinical and molecular diagnosis of juvenile or childhood Huntington disease (2 boys and 2 girls). Mean age was 14.5 years (ranging from 4 to 21). Age at onset varied between 2 and 13 years (mean age of 6.75 years), characterizing childhood onset. In the patients studied, the expanded trinucleotide cytosine-adenine-guanine repeat at the *Huntington disease* gene ranged from 41 to 69, mean 57.3 repeats (trinucleotide repeats of 53, 69, 41, and 66, respectively for each patient) and normal alleles varied from 18 to 26 trinucleotide cytosine-adenine-guanine repeats (mean=22 repeats).

All 4 juvenile-childhood Huntington disease patients presented marked reduction of the caudate and putamen nuclei, with a statistically significant difference when compared to the control group (p=0.0001) (Figure), as well as cerebral and cerebellar atrophy (p= 0.01).

When the juvenile group was compared to adult onset Huntington disease, there was no statistical difference in basal ganglia, cerebellum and intracerebral volumes (p=0.1, p=0.4 and p=0.3 respectively).

Clinically, early Huntington disease patients had more rigidity, bradykinesia, dystonia, dysarthria, seizures and ataxia when compared to adult onset Huntington disease patients, but chorea was more frequent in the adult onset group (Table).

A summary of clinical history and neurological follow up of the 4 patients with juvenile and childhood Huntington disease:

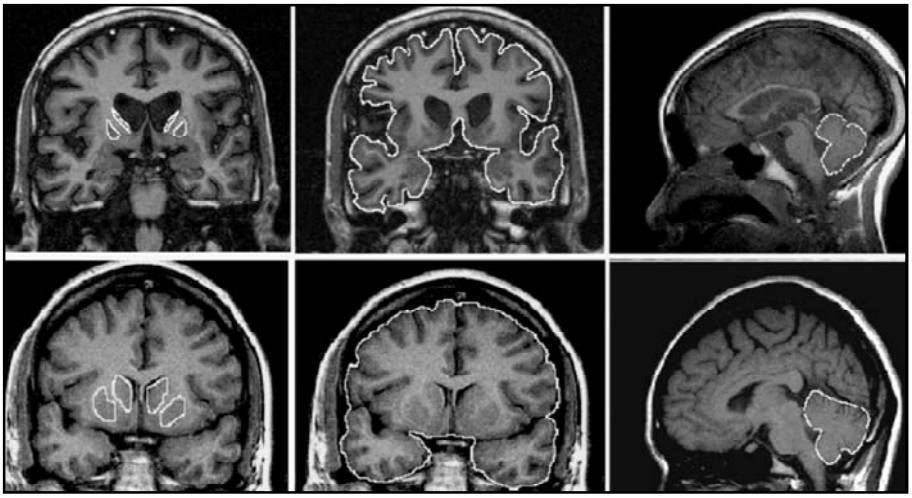

Figure. Samples of coronal and sagittal MR images showing outlines for caudate, putamen, cerebral and cerebellar volumes in a patient with Huntington's disease (top) and a normal control (bottom).

Table. Summary of clinical findings for Huntington's disease (HD) patients.

Clinical findings	Group HD	
	Juvenile and childhood onset (n=4)	Adult and late onset (n=46)
Rigidity	100%	86%
Bradykinesia	100%	33.5%
Ataxia	100%	67%
Dystonia	75%	48%
Chorea	75%	86%
Dysarthria	100%	76%
Pyramidal signs	100%	76%
Dysmetria	50%	38%

Patient 1 – A 4 years-old boy is the only son of a non-consanguineous couple with many affected family members with Huntington disease, including his father. He developed normally during the first 2 years of life and then he started with psychomotor deterioration, with unarticulated speech, progressive gait difficulties, and incoordination. At the age of 3, he developed myoclonic seizures which were controlled with valproate. EEG was normal at this time. By the age of 4, he had progressive deterioration of his ability for swallow, chew, and speech and developed urinary incontinence. On physical examination, speech was significantly dysarthric and hypophonic, almost incomprehensible, and he was unable to extend his tongue. Muscle tone was diffusely increased. Deep tendon reflexes were increased. His gait was wide-based, rigid, slow, and unsteady. Examination of extraocular movements revealed slow saccades and nystagmus. Rare choreic movements and bradykinesia were present in all limbs. He now feeds by a gastrectomy because he is unable to chew and swallow, due to tongue's dystonia.

Patient 2 – A 21 years-old woman is the only daughter of a non-consanguineous couple with family history for Huntington disease, with maternal inheritance. She presented history of dystonic movements of hands with difficulties in catching objects since 4 years of age. She started with gait ataxia at 6 years, and incoordination to write at age of 10 years. At 13 years, she had severe dysarthria, ataxia, rigidity and spasticity of limbs, bradykinesia, poor school development, and behavioral changes, followed by rapid disease progression with psychomotor and cognitive deterioration. By 15 years after onset, she developed chorea. On physical examination, speech was dysarthric and hypophonic, gait was rigid and ataxic. Deep tendon reflexes were increased. Examination of extraocular movements revealed impaired saccade initiation and velocity and nystagmus. Dystonic movements and rare choreatic movements were present in upper limbs. She had no seizures up to her last visit. She had severe dysphagia needing a gastric probe for feeding.

Patient 3 – A 12 years-old boy is the only son of a non-consanguineous couple with affected father for

Huntington disease. He began with febrile generalized tonic-clonic seizures at the age of 3 months, but his development was normal until 8 years of age, when he started with progressive gait difficulties. One year later, he started with cognitive deterioration dysarthria, and incoordination to write. His interictal EEG showed normal background activity, epileptiform discharges in the right anterior temporal region and generalized spike and wave discharges induced by photic stimulation. On exam, he was bedridden, had dysarthric and hypophonic speech, increased deep tendon reflexes, hypertonia with bradykinesia, slow saccades and nystagmus, choreic movements and dementia.

Patient 4 – A 21 years-old woman is the second daughter of a non-consanguineous couple with five members affected for Huntington disease, with paternal inheritance. Her symptoms began with visual hallucination at 13 years (she saw beasts) followed by aggressiveness. Two years later, she presented chorea. By age 16 years, she had developed urinary incontinence. By age 18 years, she began gait disturbances and anarthria, followed by progressive intellectual decline with psychiatric disturbance and dysphagia. Generalized seizures began at 20 years of age. On physical examination, she had generalized rigidity, increased deep tendon reflexes, bradykinesia, choreic movements, anarthria, and dementia.

DISCUSSION

The term juvenile Huntington's disease is usually applied to Huntington disease patients with onset before 20 years of age. This group has been estimated to make up between 1% to 10% of all Huntington disease patients[6,7]. In juvenile Huntington disease there is a predominance of paternal inheritance[8], and clinical features are often far from typical, giving rise to diagnostic difficulties. Huntington disease with onset under 10 years of age is rare, probably representing no more than 0.5% of all Huntington disease patients[6]. Usually, larger trinucleotide cytosine-adenine-guanine repeats are associated with earlier onset, and 70% of Huntington disease-affected individuals who have onset in the first two decades have an affected father[9]. Trinucleotide expansions in juvenile Huntington disease are in the range of 80 to 100 repeats[8]. The largest trinucleotide repeat described contained approximately 250 units[9] followed by an expansion of 180 trinucleotides[10]. The 130-150 CAG units represent the third longest repeat described so far[11]. Curiously, in our patients, the trinucleotide expansions were not superior to 69 units, but the clinical manifestations were as severe as the largest trinucleotide repeat described in the literature. Therefore, it is clear that the length of expanded cytosine-adenine-guanine alone does not explain the wide spectrum in age of onset and clinical symptoms of Huntington disease patients. There are most likely modifying factors, in addition to the trinucleotide expansion, that control the kinetic of neuronal degeneration at the various stages of Huntington disease[12].

Rigidity is a prominent feature in most patients with juvenile onset[6] and was present in all our juvenile patients. It has been suggested that overactivity of reciprocal thalamocortical projection pathways secondary to degeneration of striatal efferents may be responsible for syndromes of rigidity[13]. Bradykinesia, like rigidity, commonly develops during the course of typical Huntington disease[14,15]. Our study shows that bradykinesia may be present also at the onset of the disease, without concomitant choreic movements (patient 2). Moreover, seizures of a variety of types are common in juvenile Huntington disease, occurring in around 30%, in contrast to the low frequency (about 2%) in adults[16,17]. Our patients illustrate that seizures can be frequent in the early stages of disease, but not in later stages of Huntington disease. Nonetheless, the pathophysiologic mechanism underlying epileptic seizures in juvenile Huntington disease remains unclear. It is possible that this has to do with the early neuronal degeneration in the cortex, which usually occurs in association with neuronal loss in the neostriatum[18].

Prominent psychiatric symptoms are the first manifestation of Huntington disease in 31% of the patients and almost always in association with progressive cognitive deterioration[19]. Paranoid psychotic symptoms occur in 23% these patients[19]. It is possible that genetic factors influencing age at onset also impact on phenotype, so that mechanisms influencing earlier onset also increase the probability of psychosis[20]. This aspect is illustrated by our patient 4, in whom initial symptoms were visual hallucinations followed by aggressiveness.

In adults with Huntington disease, the most important areas of degeneration are confined to the caudate and putamen[21]. In children with Huntington disease, changes occur in the same areas, but are more severe and widespread. In addition, unlike the adult Huntington disease form, the cerebellum is also involved in early stages of disease[1,22-24]. The length

of cytosine-adenine-guanine expansion alone does not explain the wide spectrum of age of onset and clinical symptoms in Huntington disease[25].

Our study showed that severe volume loss of caudate and putamen nuclei and cerebral and cerebellar atrophy occur in childhood and juvenile Huntington disease, and is associated with wide phenotypic variability. Patients with juvenile Huntington disease had more rigidity, bradykinesia, dystonia, dysarthria, seizures and ataxia when compared to patients with adult onset Huntington disease.

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