

A case report of juvenile Huntington disease

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Abstract

Huntington disease (HD) is a progressive neurodegenerative disorder, characterized by autosomal dominant inheritance, movement disorder, dementia, and behavioural disturbances. It is caused by a mutation in *IT15* gene on chromosome 4p16.3, which leads to unstable CAG trinucleotide repeat expansion. The onset of juvenile HD occurs before the 2nd decade of life and comprises approximately 10% of total HD patients. Juvenile HD differs in symptomatology and is usually transmitted from paternal side with genetic anticipation phenomenon. Magnetic resonance imaging (MRI) of the brain shows specific changes of early affection of caudate nucleus and putamen. Multidisciplinary approach with symptomatic treatment of specific symptoms is the current available management. Gene editing and gene silencing treatment are under trial. Hereby, we introduce a case of an 8-year-old boy, who presented with typical symptoms of juvenile HD, positive family history with genetic anticipation phenomenon and characteristic MRI findings.

Keywords

Huntington disease, juvenile, anticipation phenomenon.

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How to cite

Choudhary A, Minocha P, Sitaraman S. A case report of juvenile Huntington disease. J Pediatr Neonat Individual Med. 2017;6(2):e060217. doi: 10.7363/060217.

Introduction

Huntington disease (HD) was first described by George Huntington in 1872 as an established clinical entity. Three characteristics features, i.e. autosomal dominant transmission, psychiatric features and occurrence

in adult age, were described by him. With advancement in medical genetics, genetic basis of HD as mutation in *IT15* gene of chromosome 4p16.3 leading to unstable CAG trinucleotide repeat expansion was identified in 1993 [1].

HD can occur at any age but usual age of onset is midlife, i.e. 3rd-4th decade. Onset of juvenile HD occurs before 2nd decade of life and it comprises 10% of total HD patients. Chorea, a characteristic feature of HD in adults, is not common in juvenile onset disease and juvenile HD patients usually present with bradykinesia, rigidity, cognitive dysfunction and seizures.

Hereby, we introduce a case of an 8-year-old boy, who presented with typical family tree of HD and genetic anticipation phenomenon.

Case report

An 8-year-old boy, first in birth order, born to non-consanguineous couple out of normal vaginal delivery, presented to us with complaints of gradual worsening of school performance and tendency to fall while walking for the last 2 months. He had progressive deterioration of handwriting and difficulty in learning new things. There was also decline in concentration and attention span. He became clumsy in recent months. Parents noticed that child fell more often and was less coordinated than he used to be.

He didn't have any complaints of seizures, abnormal movements, hearing and vision loss, hallucination, delusion, illusion.

Family history revealed significant history of memory loss and dance like abnormal movements (chorea) in family members on paternal side, including great grandfather, sister of great grandfather, grandfather and father (Fig. 1). The onset of dementia in grandfather was in the 6th

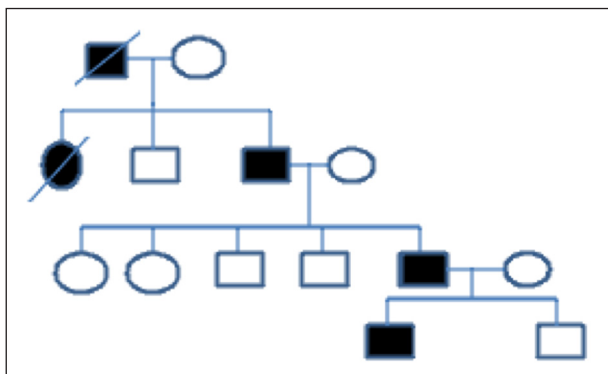


Figure 1. Pedigree.

decade, while in father it started in the 3rd decade. Neither of them consulted to doctor for this reason.

On clinical examination, the child had impaired cognitive function, IQ 70 and poor attention span. His gait was rigid and ataxic. Deep tendon reflexes were increased, slight hypertonia and bradykinesia were present. Fundus and extraocular muscles examination were normal.

The child was followed up after 3 and 6 months. He had gradual deterioration of cognitive function. He also had progressive decline of ability for swallow, chew, and speech. His speech became dysarthric and hypophonic. He started walking on toe tips with scissoring. Dystonic movements and rare choreatic movements were present in the upper limbs.

Magnetic resonance imaging (MRI) of the brain revealed an increase in signal intensity on T2-weighted images of the caudate nuclei and putamen. There was dilatation of frontal horn of lateral ventricle suggestive of caudate nuclei atrophy (Fig. 2).

The diagnosis of HD was confirmed by PCR study of trinucleotide (CAG) repeats, which showed 21 CAG repeats in one allele and 90 repeats in the other allele.

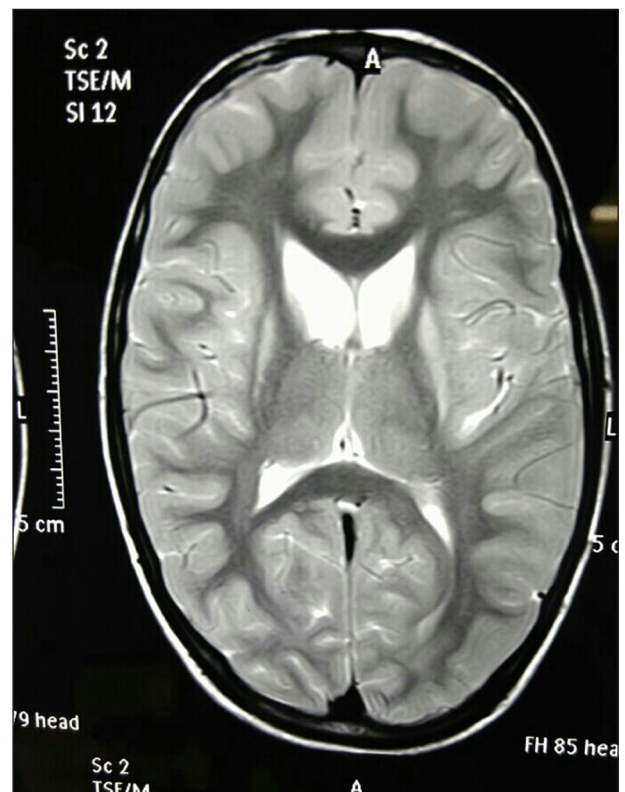


Figure 2. Magnetic resonance imaging (MRI) of the brain showing dilatation of frontal horn of lateral ventricle suggestive of caudate nuclei atrophy.

Discussion

HD is an autosomal dominant inherited neurodegenerative disorder, characterized by movement disorder, dementia, and behavioral disturbances. Diagnosis of HD is suspected in a person who presents with cognition changes, usually memory loss, chorea and behavioural or psychiatric problems such as depression, irritability, or mood swings, and usually with a positive family history of HD in a parent.

The presenting complaints of juvenile HD are different from adult onset HD and child usually presents with positive family history of HD, usually in the father, along with any 2 of the following features [2]:

- stiffness of the legs;
- clumsiness of arms and legs;
- decline in cognitive function;
- changes in behaviour;
- seizures;
- changes in oral motor function.

This child also presented with 2 features (declining school performance and gait disorder) and positive family history.

Pathology of HD is usually confined to brain and characterized by atrophy of basal ganglia usually caudate, putamen and cerebral cortex. Microscopically, prominent neuronal loss of medium spiny neurons in the caudate and putamen [3] and large neurons in layers III, IV, and V of the cortex [4] are seen. Intranuclear inclusion bodies, consisting of amyloid-like fibrils that contain mutant huntingtin, ubiquitin, synuclein, and other proteins, are characteristic findings [5, 6].

Diagnosis can be made by clinical features. MRI brain shows specific changes of early affection of the mainly caudate nucleus and putamen [7]. There is a decrease in striatal grey matter density of caudate, putamen, and globus pallidus. Reduction of hippocampal, entorhinal cortex, cerebellum and brainstem volume and neuro-degenerative changes in cortical grey-matter and cerebral white-matter regions are some recent findings described in literature [8-10]. Positron emission tomography (PET) scan shows a decrease of fluorodeoxyglucose (FDG) uptake in basal ganglia and frontal cortex due to hypometabolism [11]. These findings become evident even before noticeable caudate nucleus volume loss. MRI reveals decrease in NAA/creatinine ratio and elevation of lactate in the occipital cortex and basal ganglia [12].

Diagnosis can be confirmed by genetic testing of CAG repeats [13]. Most cases of juvenile HD are transmitted paternally with anticipation phenomenon. The number of CAG repeats in normal alleles ranges from 10 to 26. CAG repeats are very unstable during meiosis so a number of CAG repeats between 27-35 in a person develop risk of developing HD in their offspring. More than 60 CAG repeats in a symptomatic person confirms the diagnosis. Age of onset of disease symptoms is usually inversely proportional to CAG repeats. A higher number of repeats are associated with early onset disease; this happens usually for repeats exceeding 80. This explains the anticipation phenomenon, in which the age of presentation decreases in successive generation [14]. Sun et al. described the major role of the CAG triplet expansion variation along with many modifier genes for the occurrence and clinical manifestations of HD [15].

Differential diagnosis of HD are Dentatorubral-pallidoluysian atrophy, Huntington disease-like 2, Benign hereditary chorea, Fahr disease, Hereditary Creutzfeldt-Jakob disease, Spinocerebellar ataxia (SCA) 17, Neuronal ceroid lipofuscinoses, Pantothenate kinase-associated neurodegeneration, Wilson disease, etc.

Early onset HD is associated with short life span. Children deteriorate gradually and show signs of adult HD such as chorea, rigidity, memory loss. There is no specific therapy to halt this disease. A multidisciplinary treatment approach, including pediatrician, pediatric neurologist, psychiatrist, occupational therapist, speech therapist, physiotherapist, is the best and ideal for managing the person with HD. Tetrabenazine is the first drug approved by FDA to treat Huntington chorea. Antidepressants (including selective serotonin reuptake inhibitors [SSRI], tricyclic antidepressants [TCA]), mood stabilisers (such as carbamazepine, olanzapine, sodium valproate and lamotrigine) and medications to suppress the involuntary movements (such as benzodiazepines, tetrabenazine and olanzapine) are some medications which are used for specific symptoms. Occupational therapy, physiotherapy and speech therapy also provide some additional benefits to a person with HD. Recently, two novel treatment approaches of gene editing and gene silencing are under trial. The gene editing zinc finger protein works by targeting the mutant copies of the Huntingtin gene, repressing its ability to express and create harmful proteins [16]. IONIS-HTT, an antisense molecule, works on

principal of gene silencing. It is the mirror image of one of the DNA strands in the gene and binds to the Huntingtin gene. It prevents the formation of the mRNA molecule that acts as a mediator in the process of making a protein from the gene, so the abnormal protein formation is halted.

Declaration of interest

The Author declares that there is no conflict of interest.

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