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Case Report

A Rare Case of Juvenile Huntington Disease in Dizygotic Twins in Saudi Arabia

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Abstract

Background: Huntington disease (HD) is a neurodegenerative disorder inherited in an autosomal dominant pattern. Huntington disease results as a consequence of accentuation of cytosine-adenine-guanine (CAG) trinucleotide sequence repeats which range from 10 - 35 in the normal population. Although adult-onset Huntington disease is well studied and a well-recognized entity, Juvenile Huntington disease, which presents in an atypical manner before the age of 20 years has yet to receive the deserved attention.

Case Presentation: Here we present the cases of dizygotic twins who presented with similar symptoms within the lapse of one year, at ages 6 and 7, with sudden onset tonic seizures and dystonia with multiple episodes over the course of 24 hours. While their past medical, surgical, psychiatric and developmental histories were non-contributory, significant family history of HD existed in their older brother, paternal uncle and, grandmother. Both patients had unremarkable physical examination and investigations. Both were diagnosed with Juvenile Huntington disease by molecular genetic analysis showing one normal allele and one allele with repeat CAG expansions. The patients received supportive management with regular outpatient monitoring.

Conclusion: To the best of our knowledge, this is the first case report to present Juvenile Huntington Disease with an unusually low number of CAG repeats (53 and 58) and with such early age of symptom onset (6 and 7 years). With this case report, we also intend to enhance awareness among health care professionals and parents of children to be cognizant of this fatal and untreatable neurological disease to allow earlier diagnosis and limit suffering with an earlier resort to supportive care.

Keywords: *Juvenile Huntington Disease; Early Onset Huntington Disease; Neurodegenerative Disorder; Autosomal Dominant; Monozygotic and Dizygotic Twins With Huntington Disease*

Introduction

Huntington disease (HD) is a well-recognized, progressive neurodegenerative disorder that is inherited as an autosomal dominant genetic abnormality resulting from repeated expansions of cytosine-adenine-guanine (CAG) trinucleotide bases [1]. Huntington disease usually has a mean age of onset between 35 - 55 years, and commonly presents with a triad of symptoms, including psychiatric changes, chorea and, dementia [2]. Although it usually affects adults, it can also be seen in children in up to 10% of the cases, where it is termed as Juvenile Huntington disease. Juvenile Huntington disease is known to have different presentations and illness course than adult-onset HD [3]. Here, we present the case of non-identical twins who were diagnosed with Juvenile Huntington disease presenting at the ages of 6 and 7.

Case Presentation

The first patient was a 6 years old girl, fifth by birth order, born from a non-consanguineous marriage, who was developmentally normal till 6 years of age and achieved all her developmental milestones on time. She presented to the emergency department of our hospital due to the sudden onset of tonic seizure of upper limbs, up rolling ¬of eyes, drooling of saliva, and urinary incontinence that lasted for less than 30 seconds, followed by postictal drowsiness lasting for one hour. She had 4 similar episodes over a 24 hours period. Also, there was one attack of dystonic posturing of the upper limps and trunk last for seconds and resolved spontaneously. The patient had no prior history of seizures and had a non-contributory past medical, surgical, and psychiatric history.

On physical examination the patient was alert, oriented to time person and place, emotionally stable, with intact long- and short-term memory. Neurological examination revealed preserved cranial nerves functions, with normal muscle tone, power, and deep tendon reflexes in all limbs. Well-coordinated eye movements were observed with a steady gait. Rest of the physical examination was non-contributory with no chorea, facial dysmorphism, ataxia and/or rigidity.

There is family history of huntingtin disease in the older brother, father, uncle from paternal side and grandmother from father's side (Figure 1).

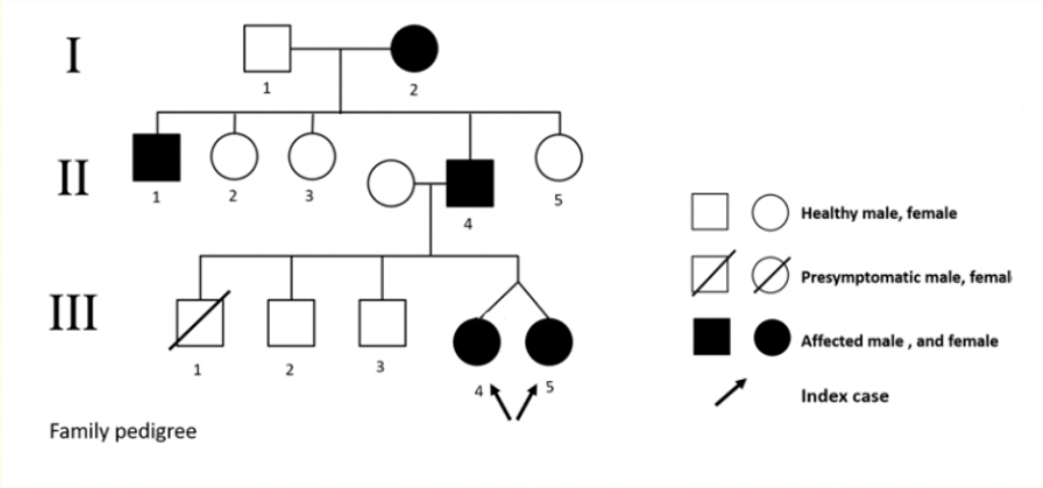

Figure 1

An electroencephalogram and Magnetic resonance imaging (MRI) were requested both of which had unremarkable findings. Molecular genetic analysis revealed one allele with an expansion of 53 (+3) CAG repeats and one normal allele with 15 (+1) CAG, detected in the (CAG) n repetitive region of the HTT gene. The patient was diagnosed with Juvenile Huntington disease on the basis of genetic analysis. Management consisted of regular observation and monitoring of disease progression over time through out-patient neurology clinic visits with possible prescription of long-term anticonvulsant medications.

Approximately one year later, the aforementioned patient's twin presented in a similar manner. She was a 7 years old girl, 5th by birth order, born from a nonconsanguineous marriage, who was developmentally normal till 7 years of age with insignificant past medical, surgical and psychiatric histories, when she presented to the emergency department with sudden onset of generalized tonic seizure, up rolling ¬of eyes, drooling of saliva from mouth, and urinary incontinence that lasted for less than 1 minute, followed by postictal drowsiness lasting for one hour. She had 3 similar episodes in 24 hours period.

On physical examination the patient had a normal mental state; she was alert and oriented to time person and place, emotionally stable, with preserved long- and short-term memory. She had preserved cranial nerves functions, with normal muscle tone, power, and normal reflexes in limbs, coordinated eye movements and, a steady gait. Rest of the physical examination was non-contributory with no chorea, facial dysmorphism, ataxia and/or rigidity.

On investigations, an electroencephalogram and MRI came back as normal. Molecular genetic analysis revealed one allele with an expansion of 58 (+3) CAG repeats and one normal allele with 15 (+1) CAG, detected in the (CAG) n repetitive region of the HTT gene.

Based on the genetic analysis of the two siblings, a detailed family history was obtained, and a family pedigree was constructed. It was revealed that the patient's twin, older brother, paternal grandmother, and paternal uncle were all positive for Huntington disease based on PCR-based genetic analysis. The family pedigree is shown in figure 1.

This patient was managed in the same manner as her twin, with neurology outpatient regular visits and the possible start of anticonvulsant medications.

Discussion

Huntington disease is a genetically inherited disease caused by the expansion of the cytosine-adenine-guanin (CAG) trinucleotide repeats in the Huntington gene (also known as IT15 gene) [1]. This autosomal dominant mutation results in the synthesis of an altered protein known as Huntington protein which contains an expanded tract of glutamine domain. The number of repeats is usually more than 40 in HD patients, and below 30 in the normal population. The age of onset is determined by the number of repeat sequences with a negative correlation existing between the age of onset and the number of repeats [4].

Huntington disease is commonly seen in adults, but up to 10% of cases can be seen before the age of 21 years called Juvenile Huntington disease. Juvenile onset describes patients with disease onset prior to 10 years, which constitute only 1-2% of the total reported cases [1]. Juvenile Huntington disease has different presentations and disease course than adult-onset HD. The juvenile disease is marked by bradykinesia, dystonia and parkinsonism features, with chorea being less prominent [2,3].

Diagnostic criteria for juvenile-onset HD (≤ 10 years) requires family history of HD (usually seen in the father) and two or more of the following:

- Declining school performance
- Seizures
- Oral-motor dysfunction
- Rigidity
- Gait disturbance.

The patients in this report meet the criteria for juvenile HD given their age of presentation, significant paternal family history and, presentations of seizure and dystonia.

Juvenile HD frequently presents with behavioral and cognitive changes, which is in contrast to our patients, who presented with dystonia and seizure as initial complains [5]. In a large multicenter cohort study on Juvenile Huntington disease, seizures were seen in about 38% of the total study group, with generalized tonic-clonic being the most common type, followed by tonic, myoclonic, and staring spells in descending order [6].

The twins had different ages of presentation which can be explained by different penetration of gene expression and the different number of CAG repeats. Huntington Disease is known to become more aggressive with subsequent generations and produce more se-

vere consequences [7]. Huntington Disease has a strong genetic component with little known environmental influence. Several cases of juvenile HD have been described in monozygotic twins with similar ages and symptoms at the time of the onset with comparable motor and behavioral abnormalities and disease progression [8-10]. The genetic component is further strengthened by a study conducted by Georgiou et al., who observed similar ages and symptoms of onset of HD, even if monozygotic and dizygotic twins were raised in separate households from birth, minimizing environmental component in the occurrence and development of HD [11].

Early-onset of HD as in before 10 years of age usually requires a higher number of repeats exceeding 80 [12]. This case revealed paternal transmission in dizygotic twins with onset below 10 years of age with a significantly lower number (53 and 58) of CAG repeats. This is considerably less than the number of CAG repeats in previously published reports such as in a report published on a 6 year old boy in Korea who had 140 number of CAG repeats [1] and another in a 10 year old girl who had 94 CAG repeats as determined by PCR [13].

Most of the previously reported cases of juvenile HD, present a number of CAG repeats of at least 80 or more, and to the best of our knowledge, this is the only reported case with a relatively small number of expansions (53 repeats). This is also among the first reported cases of HD presenting with the previously mentioned symptoms at very young ages of 6 and 7.

The imaging studies in both cases were unremarkable which is expected in this age group and can progress at a later age to neostriatal atrophy [7]. Treatment is mainly supportive by controlling seizures, chorea, dystonia and other abnormal movements with medications and physical therapy as there is no definitive treatment [14].

Conclusion

This case report is one of the few cases of Huntington disease in the region of Saudi Arabia with such early age of symptom onset and with such low number of CAG repeats. We also conclude that it is mandatory to raise awareness among pediatricians and parents to be aware of this neurological disease to allow earlier and prompt diagnosis, since juvenile HD is not as commonly seen as adult onset HD and may not be readily recognized. This also calls for additional research to further enlighten the field of this yet, untreatable, fatal neurological disease.

Declarations

Patient Consent and Ethical approval: Consent to write and publish the case report was duly obtained from the parents of the two patients. No identifying or personal information of either of the two patients has been revealed.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Conflict of Interest

The authors declared that they do not have anything to disclose regarding financial conflict of interest with respect to this manuscript for publication.

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