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Early-Onset Huntington's Disease with Maternal Anticipation A Case Report

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Abstract

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. This case report describes a 40-year-old female presenting with a one-year history of progressive chorea affecting her limbs and face, speech difficulties, gait instability, and behavioral changes. Neurological examination revealed a Mini-Mental State Examination (MMSE) score of 19/30 and generalized chorea with positive milkmaid's grip and piano key signs. Brain MRI showed bilateral caudate and putaminal atrophy, enlarged frontal horns, and globus pallidus mineralization. Genetic testing confirmed HD with 48 CAG repeats on one allele and 21 on the other. Notably, her mother had a later onset of similar symptoms in her 60s, suggesting maternal anticipation in this case. This observation, along with the patient's relatively early disease onset and severity, highlights the complex inheritance patterns and potential influence of maternal transmission, somatic mosaicism, or other modifying factors in HD. While paternal transmission is typically associated with anticipation, this case underscores the importance of considering non-canonical inheritance patterns and the limitations of CAG repeat length alone in predicting disease onset and severity. This case emphasizes the need for further research to fully elucidate the interplay of genetic and environmental factors in HD pathogenesis and phenotypic variability.

Keywords: Huntington's disease, Neurodegeneration, CAG repeat expansion.

Introduction

Huntington's disease (HD) is an autosomal dominant, neurodegenerative disorder characterized by a triad of motor, cognitive, and psychiatric symptoms (Walker, 2007; Cronin et al., 2019). Motor symptoms include chorea (involuntary jerky movements), bradykinesia, rigidity, and dystonia (Sun et al., 2017). Cognitive decline manifests as impaired executive function, memory problems, and dementia (Bates et al., 2015). Psychiatric disturbances cover depression, anxiety, irritability, and psychosis (Castilhos et al., 2019).

The global prevalence of HD is estimated at 4–10 cases per 100,000 individuals, with variations across different populations (Walker, 2007). In Asia, prevalence rates are generally lower compared to Western populations, and data from India suggests a prevalence of approximately 1–2 cases per 100,000 (Castilhos et al., 2019). Paternal transmission of HD is associated with an increased risk of earlier disease onset and more severe symptoms compared to maternal transmission, a phenomenon known as anticipation (Cronin et al., 2019; Monckton, 2021). Furthermore, a correlation exists between the length of the CAG repeat expansion in the huntingtin gene and the severity and age of onset of HD (Sun et al., 2017; Monckton, 2021).

In the present case, maternal anticipation is observed with the patient experiencing disease onset in her 40s, significantly earlier than her mother's onset in her 60s, and with more severe symptoms at an earlier age. This earlier onset and increased severity can be potentially associated with an increased number of CAG repeats in the patient compared to her mother (Sun et al., 2017; Cronin et al., 2019).

Case Presentation

A 40-year-old female presented to the outpatient department with a one-year history of progressive, uncontrollable abnormal movements affecting her bilateral upper and lower limbs, and face. The movements initially manifested in her right hand, gradually progressing to involve the left hand and subsequently both legs. Over the past six months, these involuntary movements extended to her face. She described the movements as jerky, continual, and exacerbated by activity, resolving only during sleep. She reported an inability to suppress the movements for any significant duration. Associated symptoms included speech difficulties characterized by unexpected pauses, gait instability with imbalance and variable stepping, and significant impairment in performing daily activities. Her husband also reported behavioral changes, including irritability and untidiness, over the past five months.

The patient denied focal weakness, seizures, sensory disturbances (numbness, tingling, or burning pain), bowel or bladder dysfunction, ptosis, diplopia, visual impairment, facial asymmetry, drooling, hearing loss, vertigo, dysphagia, nasal regurgitation, or falls. There was no history of preceding fever, head injury, toxin or drug exposure, or weight loss.

Her past medical history was unremarkable, with no history of diabetes mellitus, hypertension, tuberculosis, blood transfusions, thyroid disorders, or surgeries. Notably, her mother had a similar history of involuntary movements beginning around the age of 60 and died by suicide. The patient's family pedigree reveals this maternal history of similar movements. She has been married for 20 years, has four children, and has completed 8th grade education, belonging to a lower socioeconomic background. None of her children have reported any abnormal movements.

On general examination, the patient was conscious, cooperative, fairly built, and moderately nourished (BMI: 20 kg/m²). Vital signs were stable: temperature was normal on palpation, pulse rate was 82 bpm, regular, with normal volume and tension, respiratory rate was 16 breaths/min, abdomino-thoracic, and blood pressure was 116/80 mmHg. There was no evidence of pallor, icterus, cyanosis, clubbing, lymphadenopathy, or edema.

Neurological examination revealed a Mini-Mental State Examination (MMSE) score of 19/30, with significant impairment in attention (0/5) and recall (0/3). Orientation (10/10), registration (3/3), and language (6/9) were relatively preserved, although her speech was notable for unexpected pauses. Writing was affected by the involuntary movements, but reading was normal. Cranial nerve examination was normal. Motor examination revealed hypotonia in all four limbs, normal power (5/5) at all joints, and generalized chorea characterized by hyperkinetic, distal>proximal, jerky, non-rhythmic, multidirectional, continual movements flowing from one joint to another, increasing with activity. Milkmaid's grip and piano key sign were positive. Deep tendon reflexes were brisk (+3) with pendular reflexes at the knees. Plantar responses were flexor bilaterally. Sensory examination (superficial, deep, and cortical - stereognosis) was intact, but two-point discrimination and graphesthesia could not be reliably assessed due to the choreiform movements. Cerebellar examination was limited by the chorea; however, tone was hypotonic, and nystagmus was absent. Gait was choreic, with a variable stepping pattern and decreased walking velocity. Meningeal signs were absent, and examination of the back, spine, cardiovascular, respiratory, and abdominal systems was normal.

Laboratory investigations, including complete blood count, electrolytes, renal and liver function tests, thyroid function tests, and HIV testing, were within normal limits. MRI of the brain showed bilaterally symmetrical abnormal signal intensity lesions, hyperintense on T2 and FLAIR, barely visible on T1, in the bilateral caudate nuclei and Putamen, with significant volume loss and enlargement of the frontal horns. Measurements included a frontal horn width of 4.0 cm, a caudate distance of 3.1 cm, and an inner table width of 10.0 cm. These measurements resulted in a frontal horn intercaudate distance (FHCC) of 2.0 and an inner table width intercaudate distance (CCT) of 0.3 (high abnormal). The calculated frontal horn width to intercaudate distance ratio (FHCC) was 1.3, which is abnormal (low). Mineralization was noted in the bilateral Globus pallidum. Genetic testing revealed 21 CAG repeats on one allele and 48 CAG repeats on the other allele, confirming a diagnosis of Huntington's disease.

The patient was initiated on tetrabenazine, titrated gradually to 1 mg three times daily, and clonazepam 0.5 mg at bedtime. She was screened for depression and suicidal ideation, which were not significant at the time of presentation.

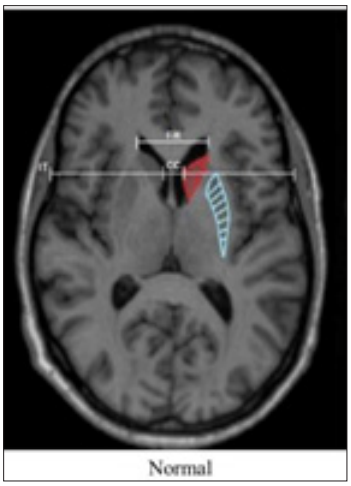

Figure 1: Normal MRI Brain Anatomy (Control Image)

This T1-weighted axial MRI scan demonstrates normal brain anatomy, highlighting the caudate head (red region) and putamen (blue region). The measurements include the frontal horn width (FH), intercaudate distance (CC), and inter-table width (IT). These landmarks represent the baseline anatomical structure for comparison.

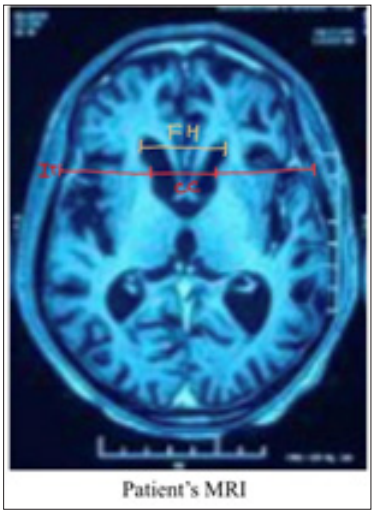

Figure 2: Patient's MRI Brain

This T1-weighted axial MRI scan of the patient reveals significant atrophy of the caudate nuclei and putamen with an increased frontal horn width (FH) and intercaudate distance (CC), along with reduced caudate to intercaudate ratio. These findings are consistent with Huntington's disease-related neurodegeneration. Measurements were annotated for direct comparison with normal anatomy.

Discussion

This case presents a 40-year-old female with progressive chorea, behavioral changes, and a positive family history, ultimately diagnosed with HD based on genetic testing revealing 48 CAG repeats. The clinical presentation, including the insidious onset of choreiform movements progressing from distal to proximal and involving the face, along with gait instability and speech difficulties, is consistent with the typical phenotype of HD. The presence of behavioral changes, such as irritability and untidiness, further supports the diagnosis, as these neuropsychiatric symptoms are common in HD and can precede motor manifestations (Monckton, 2021).

The patient's MMSE score of 19/30, with significant deficits in attention and recall, highlights the cognitive decline associated with HD. This decline, along with the motor impairments, significantly impacts daily functioning and quality of life. The MRI findings of bilateral caudate and putaminal atrophy with increased frontal horn width and mineralization in the globus pallidus are characteristic neuroimaging features of HD, reflecting the preferential neurodegeneration in the basal ganglia (Castilhos et al., 2019). The reduced frontal horn intercaudate distance ratio (FHCC) observed in our patient further strengthens the imaging findings suggestive of HD.

Despite the classical association of paternal transmission with greater CAG repeat expansion and anticipation, some studies highlight maternal anticipation leading to similar intergenerational differences. Although less common, maternal anticipation has been observed to result in earlier disease onset and more severe symptoms in certain cases, as exemplified in our patient (Talukder et al., 2021). While paternal inheritance is predominantly associated with instability and longer repeat expansions, maternal transmission may occasionally contribute to significant somatic mosaicism or unidentified modifiers that influence disease progression (Trottier et al., 1994; Pringsheim et al., 2017).

Adding to this complexity, CAG repeat length, while a cornerstone marker for disease onset and progression, does not fully account for all variability in HD presentation. Studies suggest that intermediate CAG repeat ranges can exhibit relative stability across maternal transmissions, complicating predictive models of disease onset and progression (Castilhos et al., 2019). Additionally, environmental factors and lifestyle may act as secondary influences modulating disease severity, even among individuals with similar repeat lengths (Monckton, 2021). These findings underscore the interplay between genetic and non-genetic factors in shaping HD phenotypes.

Furthermore, contradictory reports question whether intergenerational instability is uniformly predictive. While repeat expansion is commonly linked to earlier onset in successive generations, some research highlights that variability in expansion rates between paternal and maternal transmission complicates direct prediction models. For instance, Talukder et al. (2021), emphasized that the mechanisms underlying these variances might extend beyond simple genetic replication errors and involve epigenetic or cellular-level influences.

Conclusion

While this case aligns with classical features of HD, including neurodegeneration driven by expanded CAG repeats, it also illustrates the nuances of maternal anticipation. These findings highlight the necessity of considering non-canonical inheritance patterns, somatic instability, and modifier effects when evaluating intergenerational transmission dynamics in HD. Further research integrating genetic, molecular, and environmental factors is critical to refining our understanding and management of HD.

Conflicts of Interest

The authors have no competing interests to declare.

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