CLINICAL VIGNETTE

Huntington Disease Presenting as Recurrent Falls

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A 63-year-old man reported recurrent falls during a routine primary care visit. His medical issues including type 2 diabetes with right lower limb amputation as well as prior ischemic stroke attributed to tobacco use and hypertension. He described falls occurring more frequently over the past several years and now occurring several times a week. He attributed the falls to poor balance and coordination related to involuntary limb movements which he recalled beginning sometime after his stroke. He denied any associated dizziness, loss of consciousness, auditory or visual changes, weakness, or decreased sensation. On examination, he was noted to have paroxysmal jerking and writhing movements involving his neck, torso, and all extremities though not simultaneously. He had chronic mild left hemiparesis since his prior stroke. His gait with a right leg prosthesis was wide-based, ataxic, and disrupted by these involuntary movements.

The patient had been followed by neurology after his stroke 6 years ago. He presented with acute left-sided hemiparesis and dysarthria with imaging showing multiple small ischemic infarcts involving the right brain including the frontotemporal cortex, posterior internal capsule, and basal ganglia. Brain imaging also incidentally revealed global volume loss out of proportion to age. The stroke was treated with systemic thrombolysis with significant improvement in his speech and strength. The stroke was suspected to be due to embolism potentially from a proximal atherosclerotic plaque. A review of records from that hospitalization and rehabilitation did not note involuntary movements or falls. Abnormal movements were first noted about 6 months after his stroke during a neurology visit, prompting repeat MRI which did not show any new ischemic disease. At the time, these movements were suspected to be related to his prior infarcts with a recommendation to continue physical therapy and monitor for changes of his movements.

Given his continued worsening movements and increased number of falls, the patient was referred to the movement disorder specialty clinic for evaluation. Their examination, described generalized bilateral chorea and athetosis. Laboratory tests including a comprehensive metabolic panel, thyroid, antinuclear antibodies, and anticardiolipin titers returned normal. Another MRI emphasized volume loss and gliosis affecting the bilateral basal ganglia. Due to concern for a possible genetic movement disorder, despite the absence of any known family history, he was referred for genetic testing which revealed a heterozygous CAG trinucleotide repeat expansion mutation of the huntingtin (HTT) gene with number of repeats in the low 40s. He was given a diagnosis of Huntington disease approximately 6 years after the onset of the involuntary movements and was referred for additional speech, swallow, and physical therapy as well as psychiatric consultation. He was advised to discuss his diagnosis with his family especially his adult children so that they could seek evaluation. The patient was provided a motorized wheelchair and had a home safety evaluation to help prevent additional falls.

Discussion

Huntington disease (HD) is a neurodegenerative disorder caused by the expansion of the trinucleotide (CAG) repeating sequence within the HTT gene on chromosome 4 resulting in motor, cognitive, and psychiatric symptoms.[1] The repeating sequence translates to excessive glutamine residues which result in misfolding and aggregation of the huntingtin protein.[1] The complete pathophysiology of the disease is not yet understood but the aggregation of huntingtin is thought to results in defects in neuronal transport and mitochondrial metabolism leading to dysfunction and cell death, particularly in medium spiny neurons (MSN) which are found in the basal ganglia and implicated in the motor features of the disease.[1,2]

Huntington disease has an estimated prevalence of approximately 10 per 100,000 though this has been shown to vary depending on the region studied.[2] The condition shows an autosomal dominant pattern of inheritance and demonstrates a genetic phenomenon known as “anticipation” whereby successive generations who inherit the mutation may develop disease at progressively younger ages.[2] This occurs due to the risk of further expansion of the nucleotide repeat sequence during DNA replication, as there is an inverse relationship between the number of CAG repeats and the age of onset.[1] Normally there are less than 25 repeats within the HTT gene; between 26-35 repeats does not cause disease but bears risk of sufficient expansion to have children who will develop disease.[2] Individuals with 36-39 repeats may develop disease (incomplete penetrance), while those with 40 or more repeats inevitably develop the disease (complete penetrance).[1,2] The disease typically manifests in third through fifth decade of life, but alleles with more than 60 repeats result in juvenile presentations.[2]

Clinically the disease is characterized by motor as well as cognitive and psychiatric symptoms. The motor feature most commonly associated with Huntington disease is chorea. Chorea is characterized by involuntary, nonrepetitive jerking

movements in the distal extremities as well as trunk.[2] However, as the disease progresses, most patients will exhibit hypokinetic motor changes including bradykinesia and rigidity which may leave them incapacitated and often bedbound.[1,2] In addition to these motor symptoms, the cognitive and psychiatric manifestations should not be underestimated as many patients will develop apathy, depression, and occasionally psychosis, with suicide being the second most common cause of death.[1] One scoring system called the Unified HD Rating Scale (UHDRS) has been used in specialty centers to grade disease activity over four major domains: motor, cognitive, psychiatric, and functional capacity.[3] Median survival is 15-18 years after symptom onset with the most common cause of death being pneumonia.[2,3] Imaging findings in early disease, which may precede symptom onset, include volume loss within the striatum (caudate, putamen, nucleus accumbens) as well as the white matter surrounding the striatum.[1] More advanced disease is associated with diffuse atrophy, particularly of the white matter.[1] Following clinical and radiographic assessments, genetic testing is necessary to confirm the diagnosis in those suspected of having the disorder. It is also necessary to confirm inheritance of the mutation in the offspring of those who have already been diagnosed. Genetic testing must include informed consent with pre- and post-test counseling. This is true in general for genetic testing but particularly in the case of Huntington disease as suicide risk has been shown to be increased in those undergoing testing.[2]

Management of Huntington disease is generally supportive, targeting manifestations and complications of the disease. Treatment of hyperkinetic motor symptoms includes physical and occupational therapy as well as dopamine-depleting vesicular monoamine transporter 2 (VMAT2) inhibitors such as tetrabenzene and deutetrabenzene or dopamine antagonizing neuroleptics (especially haloperidol, risperidone, and olanzapine).[2] Psychiatric treatment of the mood-related symptoms includes cognitive-behavioral therapy and usual first-line antidepressant agents such as SSRI/SNRIs.[1] There is active ongoing research to develop disease-modifying therapies targeting the expression and accumulation of mutant huntingtin including post-transcriptional RNA interference.[1]

This patient presented with motor symptoms including chorea and gait instability at an older age. His neurologic assessment was confounded by his history of lower limb amputation as well as prior stroke. While cortical strokes are typically associated with an upper motor neuron pattern of unilateral weakness, infarction of the basal ganglia can also result in hyperkinetic motor symptoms including chorea and ballismus. Overall however, movement disorders after stroke are rare, estimated to occur in about 1% of patients.[4] While these motor features may be difficult to distinguish from a neurodegenerative process such as Huntington disease, they will typically present with unilateral symptoms (i.e. hemiballismus and hemichorea) immediately or shortly after a stroke and may attenuate rather than progress over time.[4] Brain imaging would also be expected to show infarction of the relevant neuroanatomy.[4] This patient did indeed have some ischemic change of his right basal ganglia which resulted in initial attribution of his hyperkinetic symptoms to stroke. However, the relatively later development of motor symptoms after clinical stroke, their continued progression in the absence of further stroke, and bilateral distribution of his motor symptoms all pointed to another etiology and eventually prompted genetic testing.

Our patient's movement disorder presented later than most patients with HD. Comparisons of usual-onset HD (manifesting in third through fifth decade of life) to late-onset HD (age at onset at least 60) have shown that patients with late-onset HD are less likely to have a family history or psychiatric issues but more likely to have motor-predominant symptoms, gait unsteadiness, and faster progression of disease.[5,6] Our patient had no known family history of HD, minimal psychiatric symptoms, and prominent motor symptoms with gait impairment and associated functional decline. This patient also self-identified as African-American. One analysis of a large North American cohort of patients with HD, African-American patients were reported to receive a diagnosis one year later after symptom onset than their white counterparts.[7]

In summary, this case demonstrates the difficulty of successfully arriving at a rare diagnosis particularly when confounded by other more common pathologies. Careful monitoring of symptoms over time and correlation with other data including imaging showed disease progression and distribution not consistent with the original diagnosis of post-stroke sequelae. This prompted a broader diagnostic investigation years after his initial presentation, which allowed for the diagnosis of a typical presentation of a rare disorder instead of the initial assumption of a rare presentation of a common disease.

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