A Case of Previously Undiscovered Huntington Disease Diagnosed at Autopsy

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ABSTRACT

Huntington disease (HD) is a neurodegenerative disorder with a worldwide prevalence of four to ten per 100 000. It is characterized by choreiform movements, behavioral/psychiatric disturbances, and eventual cognitive decline. Symptoms usually present between 30 and 50 years of age and the diagnosis is based on the combination of clinical symptoms, family history, and genetic testing. A variation of HD, juvenile Huntington disease (JHD), presents earlier, with more severe symptoms and with a worse prognosis. Symptoms are different in JHD, with personality changes and learning difficulties being the predominant presenting features. Seizures are common in JHD, and chorea is uncommon; movement disorders at presentation of JHD are predominantly nonchoreiform. The inheritance pattern for both HD and JHD is autosomal dominant and the disease is caused by an elongation of the CAG repeat in the huntingtin gene.

There are many published case reports of Huntington disease that were confirmed at autopsy, but to our knowledge, there are no reports in the literature where the diagnosis of Huntington disease was first made at autopsy. We present a case of a 28-year-old African-American male who was in a state of neglect due to a lifetime of abuse, cognitive difficulties, and seizures, whose cause of death was pneumonia.

The gross autopsy findings included bilateral caudate nucleus atrophy and lateral ventricular dilation. Microscopically, severe bilateral neuronal loss and gliosis of the caudate and putamen nuclei were seen. Genetic testing for the number of CAG repeats confirmed the diagnosis and was consistent with JHD. *Acad Forensic Pathol.* 2017 7(1): 136-144

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INTRODUCTION

Huntington disease (HD) is a progressive and fatal neurodegenerative disorder with a worldwide prevalence of four to ten per 100 000 persons and regional variations in prevalence, making it the most common single-gene neurodegenerative disorder (1-5). It is characterized by choreiform movements, behavioral/psychiatric disturbances, and eventual mental decline (2, 6). Symptoms usually present between the ages of 30 and 50 years, with death occurring within 15 to 20 years after the onset of symptoms (2).

The clinical diagnosis is made based on the combination of symptoms, family history, and genetic testing, and characteristic lesions (early striatal atrophy, particularly of the caudate nucleus, and potential cortical and/or cerebellar atrophy late in the course of the disease) may be detected while the patient is still living or at autopsy using magnetic resonance imaging (7-9). Classic pathologic findings at autopsy include lateral ventricle dilation and bilateral caudate atrophy; in severe cases, the atrophy may extend to the rest of the basal ganglia structures (3, 4).

The inheritance pattern is autosomal dominant with anticipation. The disease is caused by an elongation of the cytosine-adenine-guanine (CAG) repeat in the huntingtin gene (IT-15; "Interesting transcript 15") (5, 8). The locus of the CAG repeat in the huntingtin gene is on exon 1 and the gene itself is located on chromosome 4p16.3. The range of repeats in normal alleles is 6-26, with the most common allele lengths containing 17 and 19 repeats (5, 8). A definitive diagnosis of Huntington disease can be made in any patient with a repeat length equal to or greater than 40. The intermediate-ranges of 27-35 and 36-39 are considered to be the mutable normal allele range and the reduced penetrance range, respectively, and a repeat length of greater than 50-60 may be diagnostic of Juvenile HD (JHD) (2, 5, 8). It is thought that the huntingtin gene functions as a housekeeping gene, and that the mutation associated with increased repeats is a gain of function mutation. The result is increased production of the mutated, truncated huntingtin protein, which is insoluble and creates interfering, multimerized aggregates

inside the nuclei of the neocortical, neostriatal, and dentate neurons of Huntington patients, which may only be detected using immunohistochemical stains (2, 8).

Juvenile Huntington disease is a variation of classic HD that shows onset of symptoms in the first or second decade of life (10-12). It is thought that the worldwide prevalence of JHD is 4-9%, and that 5-10% of all HD sufferers are afflicted with JHD (10, 11). In 90% of JHD cases, the affected parent is the father (10). Classic HD is typically seen in adults, and JHD may not even be on the radar of a pediatrician evaluating a child for developmental delays or other symptoms. The rarity of the disease makes the diagnosis more challenging, and this is compounded by the fact that the presenting symptoms of JHD are dissimilar to the symptoms typically seen in classic HD. Juvenile Huntington disease typically presents with seizures (with which psychotic episodes may be associated) and early behavioral, cognitive, and speech/language problems manifesting as problems at school (indeed, these may be the presenting symptoms). Rigidity, dystonia, and bradykinesia are all more common movement disorders in this population than the choreiform movements seen in classic HD (10-13).

There are many published case reports of diagnoses of Huntington disease confirmed at autopsy in the literature, but to our knowledge there are no reports in the same literature where the diagnoses of Huntington disease was made initially at autopsy (1, 3-5, 7).

CASE REPORT

A 28-year-old male with a past medical history of cognitive difficulties and seizures, who was in a state of neglect due to a lifetime of abuse at the hands of his mother and her boyfriend, died of pneumonia. The patient was a ward of the state of Texas, and the whereabouts of his mother and biological father are unknown. The details of the patient's past medical history are not known.

The decedent was autopsied by the local medical examiner using standard autopsy procedures.

The brain and spinal cord were submitted for consultation to the autopsy service at our institution based on the medical examiner's concerns regarding the decedent's history of seizure and developmental delays.

The brain and spinal cord were fixed for two weeks in 20% formalin; gross and microscopic evaluations were performed on the brain, and only gross evaluation was performed on the spinal cord. The brain and spinal cord were examined by one of our institution's neuropathologists (GAC). The cerebrum was coronally sectioned at approximately 1.0 cm thickness per section after visually evaluating the cerebral vessels for atherosclerotic plaques and separating the cerebellum and brainstem from the cerebrum. The cerebellum was sectioned sagittally at approximately 0.5 cm thickness per section and the brainstem was transversely sectioned at approximately 0.5 cm thickness per section.

The following sections were submitted for histologic evaluation: frontal lobe (area 8), basal ganglia, hippocampus, thalamus, substantia nigra, cerebellum, and basilar artery. All sections are part of the standard neuropathology technique at our institution, with the exception of the thalamus, substantia nigra, and basilar artery. All slides were stained with hematoxylin and eosin (H&E) and Luxol fast blue/H&E (LFB/H&E). Sections of the hippocampus and basal ganglia were also stained with glial fibrillary acidic protein (GFAP), the basilar artery slide was additionally stained with pancytokeratin (AE1/3 monoclonal antibody cocktail) and epithelial membrane antigen (EMA), and both the hippocampus and basilar artery slides were additionally stained with periodic acid-Schiff (PAS). Additional staining for HD (e.g., ubiquitin, mutant-huntingtin protein) was not performed due to lack of stain availability, contrasted with availability and relative ease of genetic testing at our institution.

Blood cards obtained from the medical examiner's office were subjected to genetic testing. Capillary electrophoresis on an agarose gel method was used as a screening test for the patient's HD status. Confirmatory testing was performed using polymerase chain reaction (PCR) amplification with the GeneAmp 9700

Thermal Reaction Cycler (Thermo Fisher Scientific, Waltham, MA), and the results were analyzed using the GeneMapper Software 5 (Thermo Fisher Scientific, Waltham, MA) (13-15).

The gross autopsy findings were characteristic of HD and related neurodegenerative disorders (9, 16, 17). The brain weighed 1270 g (our institution's normal male brain weight range is 1200 – 1400 g). The cerebral gyri did not appear grossly atrophic. Coronal sectioning revealed moderate dilation of the cerebral ventricles bilaterally, and marked bilateral atrophy with flattening of the ventricular surfaces of the heads of the caudate nuclei as compared to a comparison (non-age-matched) normal brain (**Images 1 and 2**). The putamen and globus pallidus appeared grossly normal. The laminations of the hippocampi bilaterally were accentuated, raising the question of ischemia or atrophy, although microscopically there was no evidence of either ischemia or atrophy. Additionally, the hippocampi were neither grossly nor microscopically sclerotic, despite the patient's reported history of seizures. Microscopically, there was severe bilateral neuronal loss and marked reactive gliosis (increase in the number and size of astrocytes, and increase in the number of oligodendrocytes and rod-shaped microglial cells demonstrated by GFAP immunohistochemical stain of the corpus striatum (caudate and putamen nuclei [**Images 3, 4, and 5**]), corresponding to Vonsattel's grade 3 HD. Possible grades for a given brain using the Vonsattel grading system are 0, 1, 2, 3, and 4, and are based on both macroscopic and microscopic observations, in increasing order of disease severity; the Vonsattel grade closely corresponds to the extent of clinically observed disability (3, 4). The neocortical gray matter and other deep nuclei, including the globus pallidus, were less severely affected, which prevented a categorization of this disease process into Vonsattel's grade 4. The cerebral myelinated white matter was not significantly reduced, based on LFB staining. An incidental finding of a small, firm, thin, white-to-translucent plaque present in the leptomeninges on the ventral surface of the rostral basilar artery was also noted, and was diagnosed as a benign notochordal hamartoma (echordosis physiliphora). No evidence of recent or

remote trauma was identified, despite the patient's reported history of abuse.

No gross or microscopic evidence of the reported history of abuse was noted in the brain or spinal cord, and the cerebellum, brain stem, and spinal cord were all grossly and microscopically without pathologic change.

Capillary electrophoresis confirmed that there was one expanded huntingtin allele and one normal allele present in this patient (18). The confirmatory PCR amplification testing also allowed for CAG repeat quantitation. The patient exhibited 19 repeats on his nonmutated allele and 64 repeats on his mutated allele, confirming the diagnosis of Huntington disease (**Figure 1**). Given the number of repeats and the early reported age (exact age unknown) or symptom onset, the authors are comfortable not only diagnosing the patient with HD, but further completing the diagnosis with a diagnosis of JHD.

Image 1: Frontal coronal slice showing severe symmetric atrophy of the caudate nuclei. The putamen nuclei are grossly normal.

DISCUSSION

Huntington disease is a rare, progressive, and fatal neurodegenerative disorder. There have been several cases of suspected HD reported in the literature that have been confirmed at autopsy, but to our knowledge, the case we present here is the first where the patient was initially diagnosed with HD at autopsy. Our decedent, a 28-year-old African-American male with a history of cognitive difficulties, seizure disorder, and physical abuse, was especially young for the onset of HD. This early onset possibly led to the failure of this diagnosis to be considered during his life. Very little is known about the patient's childhood, the status of the reported abuse, the circumstances that led to him being placed as a ward of the State of Texas, or the circumstances surrounding his death.

Although the worldwide prevalence of HD is estimated at four to ten cases per 100 000 persons, the majority of those cases occur in the Caucasian population

Image 2: Frontal coronal slice at a comparable level in a normal brain to illustrate normal caudate configuration.

Image 3: Corpus striatum of patient showing few neurons and increased glial cells (H&E, x40).

Image 4: Comparison normal corpus striatum (H&E, x40).

(1-5). It is thought that the prevalence of HD in the black or African-American population is considerably lower, on the order of 0.97 cases per 100 000 persons (19). The patient's cause of death was pneumonia, which is the most common cause of death in HD (1, 6, 20). Of course, other causes of death in HD, such as choking and suicidal causes, are also common, and may also be encountered in the forensic setting (6).

At autopsy, the caudate nuclei were grossly atrophic bilaterally, with associated moderate lateral ventricular dilation. Microscopy showed severe bilaterally symmetric caudate and putamen atrophy with marked reactive astrocytosis (gliosis), corresponding to Vonsattel's grade 3 HD (3, 4). The globus pallidus and nucleus accumbens were significantly less affected in our patient, which excluded advancement of the grade to 4. No neuronal inclusions were identified (although specific staining was not done), and there was not a significant loss of myelinated cerebral white matter, despite the enlargement of the lateral ventricles (en-

largement was therefore likely due mainly to atrophy of the corpus striatum). Frontoparietal cortical atrophy was also not identified in this case, although it has been shown that the degree of cortical atrophy in HD patients correlates with the number of CAG repeats, and may be more severe in later stages of the disease (21). The cerebellum, brain stem, and spinal cord were all without pathologic change. It also is worth noting that though HD-specific staining (i.e., ubiquitin, mutant huntingtin protein) was not performed before performing genetic testing on this patient due to lack of stain availability at our institution, at an institution where these stains are readily available, performing them would be a reasonable step between evaluation of H&E-stained slides and performance of genetic testing.

Though the gross and microscopic findings of the patient's brain at autopsy led to the suspicion of HD, the patient's clinical picture was complicated by his cognitive impairment, seizures, and a history of phys-

Image 5: Corpus striatum of the patient showing severe reactive astrocytosis (GFAP, x100).

ical abuse. The patient's cognitive impairment could have been the result or the cause of the physical abuse the patient reportedly suffered as a child. However, cognitive impairment and seizures (from which the patient also suffered) are common presenting and often predominant symptoms in JHD. These symptoms, with the added factors of an abusive home life, the patient's young age, and the patient's race are all circumstances, which when taken in combination, would have made the diagnosis of JHD extremely difficult for a treating physician.

Additionally, the patient's general picture of cognitive impairment and seizures, coupled with the findings of bilateral caudate and putamen atrophy, provides a postmortem differential for the diagnosis of other neurodegenerative disorders that affect the basal ganglia. These disorders include but are not limited to chorea-acanthocytosis, McLeod syndrome, Huntington disease-like 1, 2, and 3 (HDL1, HDL2, HDL3), multiple system atrophy (MSA), and pantothenate

kinase-associated neurodegeneration (PKAN). They may be inherited in an autosomal dominant (as in HD), X-linked (McLeod syndrome), or autosomal recessive (chorea-acanthocytosis) pattern, with some diseases in this category showing unusual inheritance patterns, potential founder effects, and potential ubiquitin-positive intranuclear staining due to their natures as tripeptide repeat diseases (e.g., HLD2). These diseases are not trinucleotide repeat disorders, but instead are each caused by specific mutated genes on a variety of chromosomes (9, 16, 17). These diseases, although they should be considered by any evaluating neuropathologist presented with a case such as ours, are exceedingly rare. The evaluating neuropathologist may not wish to pursue them as a line of inquiry until genetic testing has effectively ruled out the more common diagnosis of HD or JHD.

As stated previously, the brain findings at autopsy led to the suspicion of HD and genetic testing confirmed the diagnosis.

Figure 1: Electropherogram result of the patient sample showing peaks at the normal (19 repeats) and affected (64 repeats) alleles. The screening electropherogram shows allele binning of stutter peaks generated from polymerase chain reaction amplicons using genomic DNA extracted from the patient sample. The vertical lines (y-axis) represent stutter peaks within each of the specific CAG bins separating along the horizontal line (x-axis) starting from the fifth CAG repeat as described (15). CAG repeats of normal, mutable, reduced penetrance allele, and affected alleles are marked at the top of the screen. The prominent peaks of the patient sample, located in the center of the stutter pattern, correspond to allele sizes of 19 and 64 repeats.

CONCLUSION

Huntington disease is inherited via an autosomal dominant mechanism, is considered to be fully penetrant at CAG repeat lengths greater than 40, and shows anticipation. Our patient was heterozygous for the huntingtin gene mutation, and his mutated allele showed a repeat length of 64. Repeat lengths of greater than 60 show increased likelihood of early onset of symptoms of HD (juvenile Huntington disease), which is likely what happened in this patient. Almost nothing is known about the patient's family, but from the results of our testing, it is highly likely that one of the patient's parents (most likely the father, as 90% of JHD cases are inherited via paternal meiotic instability) is likewise affected (10).

This case illustrates the importance of having good clinical and family information available at the time of autopsy and also the importance of an open mind and thorough examination in each autopsy performed. The autopsy pathologist must always be cognizant of the potential for an unexpected discovery of a neurodegenerative disorder, and must be willing to seek the help of a knowledgeable neuropathologist when confronted with a case that is suspicious. The ability to perform postmortem genetic testing on patients with potential neurodegenerative disorders is paramount to diagnosis, and may be of crucial importance to the family of the deceased. Huntington disease, in particular, is seen as a death sentence by many of its sufferers and proper diagnosis or confirmation of the disease in a decedent at autopsy is critical for family members when deciding to be tested themselves.

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