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NEUROPATHOLOGICAL COMPARISON OF ADULT ONSET AND JUVENILE HUNTINGTON'S DISEASE WITH CEREBELLAR ATROPHY: A REPORT OF A FATHER AND SON

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Abstract

BACKGROUND—Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by a trinucleotide (CAG) repeat expansion in *huntingtin* (*HTT*) on chromosome 4. Anticipation can cause longer repeat expansions in children of HD patients. Juvenile Huntington's disease (JHD), defined as HD arising before age 20, accounts for 5-10% of HD cases, with cases arising in the first decade accounting for approximately 1%. Clinically, JHD differs from the predominately choreiform adult onset Huntington's disease (AOHD) with variable presentations, including symptoms such as myoclonus, seizures, Parkinsonism, and cognitive decline.

OBJECTIVE—The neuropathologic changes of AOHD are well characterized, but there are fewer reports that describe the neuropathology of JHD. Here we report a case of a six-year-old boy with paternally-inherited JHD caused by 169 CAG trinucleotide repeats who presented at age four with developmental delay, dysarthria, and seizures before dying at age 6. The boy's clinical presentation and neuropathological findings are directly compared to those of his father, who presented with AOHD and 54 repeats.

METHODS—A full autopsy was performed for the JHD case and a brain-only autopsy was performed for the AOHD case. Histochemically- and immunohistochemically-stained slides were prepared from formalin-fixed, paraffin-embedded tissue sections.

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RESULTS—Both cases had neuropathology corresponding to Vonsattel grade 3. The boy also had cerebellar atrophy with huntingtin-positive inclusions in the cerebellum, findings not present in the father.

CONCLUSIONS—Autopsies of father and son provide a unique opportunity to compare and contrast the neuropathologic findings of juvenile and adult onset HD while also providing the first immunohistochemical evidence of cerebellar involvement in JHD. Additionally this is the first known report to include findings from peripheral tissue in a case of JHD.

Keywords

Huntington's Disease; Juvenile Huntington Disease; Autopsy; Neuropathology; Huntingtin protein; Immunohistochemistry; Literature review

Introduction

Huntington's disease (HD) is a progressive, autosomal dominant neurodegenerative disease that is caused by an expansion of the CAG repeat in *HTT* located in the short arm of chromosome four. The CAG repeat results in polyglutamine expansions and production of a misfolded form of the huntingtin protein, which aggregates and accumulates in both the neuronal nucleus and cytoplasm throughout the brain. Although the precise mechanism is not clearly understood, the presence of this mutant *HTT* ultimately leads to neuronal dysfunction and death with associated reactive gliosis, most notably in the caudate nucleus, putamen, globus pallidus and cerebral cortex, but also in in many other brain regions, such as thalamus, hypothalamus, and hippocampus, particularly at later stages of the disease(1).

Two clinical subtypes of HD can be differentiated by age of onset. Adult onset Huntington's disease (AOHD) tends to present between the ages of 35 and 50 in individuals who usually harbor over 39 trinucleotide repeats in *HTT*, but rarely more than 60. Juvenile HD (JHD) is defined as presentation before the age of 20, and is usually due to the presence of greater than 60 CAG repeats in *HTT*, with the highest reported number of CAG repeats being 265 in a child of eighteen months (2).

While the underlying etiology is the same in both the juvenile and adult onset form, the presentation is often strikingly different. Adults typically exhibit choreiform movements, personality changes and cognitive decline, while children develop rigidity without chorea, seizures, and cognitive decline (3, 4). Additionally in children, cerebellar symptoms may be prominent, with gait disturbance and ataxia reported (5, 6). JHD progresses nearly twice as rapidly as the adult form.

JHD is uncommon, accounting for approximately 5-10% of HD cases, and patients presenting before age 10 make up only 1% (7). A review of the English speaking literature shows that few of these cases go to autopsy; as such, the neuropathologic features are relatively undefined. Notably, although cerebellar involvement is reported in 15–20% of cases found in the literature, only half of these include neuropathologic evaluations detailing the cerebellar pathology, and the majority of cases with autopsy findings report no immunohistochemical studies. Therefore, it is not well understood how neuropathology of

the juvenile form, which can have a drastically different clinical presentation, compares to the adult onset form. Complete autopsies are very rare but are essential in characterizing the systemic impact of the disease. This report of HD in a father with adult onset HD without cerebellar involvement, and his son with juvenile HD with cerebellar pathology, provides a unique opportunity to compare and contrast the neuropathologic features of the same neurodegenerative disease with two very different presentations within a family.

Materials and Methods

JHD (Case 1)

Consent for autopsy was obtained from the legal next of kin according to protocols approved by the UW Institutional Review Board. At the time of autopsy, the brain, spinal cord, and eyes were removed. The brain was bisected along the midsagittal plane and the left hemisphere was fixed in formalin. The right brainstem and cerebellum were removed from the right cerebrum by axial transection at the level of the midbrain and then sectioned axially. The right cerebrum was sectioned coronally. Right cerebrum, cerebellum, and brainstem sections were frozen for future studies. After fixation in 10% neutral buffered formalin, the left cerebrum was sectioned coronally and the brainstem and cerebellum were sectioned axially. Hematoxylin and eosin-stained slides were prepared from paraffin-embedded tissue sections of representative brain regions for microscopic analysis.

After examination of brain, spinal cord, and globes, a full autopsy was performed according to standard practices briefly described as follows. After an external examination, the body cavities were opened in the usual fashion and the mediastinal, abdominal, and pelvic organs removed en bloc in addition to samples of skin, skeletal muscle, and peripheral nerve. Gross pathologic examination was performed; samples from each organ and tissue were preserved by flash freezing in liquid nitrogen and storage at −80°C or fixation in 10% normal buffered formalin followed by paraffin embedding (FFPE). Hematoxylin and eosin-stained slides were prepared from standard FFPE tissue sections.

AOHD (Case 2)

Consent for autopsy was obtained from the legal next of kin according to protocols approved by the UW Institutional Review Board. A brain-only autopsy was performed; the entire brain was fixed in 10% neutral buffered formalin, after which the brainstem and cerebellum were removed from the cerebrum via axial transection through the midbrain. The cerebral hemispheres were then sectioned coronally and the brainstem and cerebellum sectioned axially. Hematoxylin and eosin-stained slides were prepared from paraffin-embedded tissue sections of representative brain regions for microscopic analysis.

Immunohistochemistry and special stains—A microtome was used to cut 4 μm thick tissue sections from FFPE tissue blocks. Immunohistochemistry was performed on multiple brain tissue sections in both cases, including cortex, striatum, and cerebellum, using standardized procedures. Primary antibodies included: anti mutant-huntingtin protein (HTT; Millipore; 1:100), GFAP (DAKO, 1:2500), and PHF-tau (Pierce, 1:4200). All three antibodies required initial antigen retrieval with incubation in boiling citrate buffer at pH

6.0. Appropriate positive controls were included for each antibody (a genetically and histologically confirmed HD case for HTT; an Alzheimer's disease case for PHF-tau, and a section of cerebral cortex for GFAP). Negative controls were also run and consisted of secondary antibodies of the appropriate species in the absence of primary antibody. In case 1, huntingtin immunohistochemistry was also performed on cervical, thoracic and lumbar spinal cord sections, as well as numerous peripheral tissues, including salivary gland, peripheral nerve, skeletal and cardiac muscle, globe, colon, small intestine, stomach, esophagus, pancreas, spleen, liver, gall bladder, kidney, prostate testis, bladder, thyroid, thymus, trachea, lung, and aorta. Additionally, a Bielschowsky silver stain was manually performed on 8 μm thick tissue sections of cerebellum in both cases.

Results

Clinical History

Juvenile (Case 1)—The patient, the son of case 2 (below), was born via an uncomplicated vaginal delivery to a 29-year-old G1P0 mother. Developmental milestones were met on time, including crawling and walking, but speech was slow to come and by two years of age he only spoke five to ten words. His comprehension appeared intact and he had a normal hearing test so speech therapy was initiated. At age 4 he was experiencing memory difficulties, frequent falls, and had his first witnessed seizure. The seizures progressed to generalized tonic-clonic and became medically intractable. By age five he could not walk or eat on his own, requiring nasogastric tube feedings. His gait was mildly wide-based and unsteady and he had oculomotor apraxia, dystonic posture of his hands, hyperactive tendon reflexes, sustained ankle clonus, increased tone in his legs and jerky involuntary movements of his legs and occasionally hands. Magnetic resonance imaging (MRI) of the brain showed diffuse volume loss involving the caudate nucleus with associated ventriculomegaly, as well as mild cerebellar volume loss (Fig. 1). Genetic testing for HD enumerated 169 CAG trinucleotide repeats in *HTT*, and a diagnosis of JHD was rendered. The boy's cognitive function worsened in step with increasing rigidity, dystonia, and dysphagia. A percutaneous endoscopic gastrostomy (PEG) tube was placed by age six for increased difficulty with feedings, including frequent choking, despite oropharynx suctioning to help prevent aspiration. He died at age six, approximately two years after initial presentation. The clinical impression for cause of death was aspiration pneumonia as a complication of HD. A full autopsy was performed.

Adult Onset (Case 2)—The patient, the father of case 1 (above), was a 44-year-old man who presented to the neurogenetics clinic at age 35 with a family history of Huntington's disease. His father died at age 52 from HD and his paternal grandmother died in her 40s of presumed HD (Fig 2). At presentation he had mild chorea in face, trunk, and arms, slowed eye movements, and hyperreflexia. Genetic testing enumerated 54 CAG trinucleotide repeats in *HTT*. By age 37 he had masked facies, bradykinesia, some dystonic posturing of trunk and arms, slowing of rapid alternating movements, difficulty with tandem walking and had begun having problems with swallowing. By age 39 he developed mild dysarthria and at age 40 he needed a PEG tube placed and was unable to walk without assistance. By the time he was age 44, he moved into long-term care. His chorea progressed in severity and was

challenging to treat. He became profoundly dysarthric and dysphagic, manifested perseverative thoughts but remained oriented. He was eventually transitioned to comfort care and died, nine years after initial diagnosis. Neuroimaging, if performed, was not available for evaluation. A neuropathologic examination was performed.

General Autopsy

JHD (Case 1)—Gross anatomic examination demonstrated hyperemic tracheal and bronchial mucosa with copious pink-red clear mucous. The lungs were heavy (right 180 grams; left 190 grams) and the cut surface demonstrated bilaterally congested parenchyma with diffuse edema, focal hemorrhage, and patchy consolidation, consistent with multifocal suppurative pneumonia. All other organs including the eyes were grossly normal.

Microscopically, the lungs showed diffuse, marked vascular congestion with focal intra-alveolar hemorrhage and focal intra-alveolar suppurative inflammation associated with intrabronchiolar suppurative infiltrates and scattered clusters of coccal and rod-shaped bacteria, consistent with multifocal bacterial pneumonia. Microscopic examination of the other organs and salivary gland, sural nerve, femoral nerve, vastus lateralis, gastrocnemius, and eye globe, were unremarkable. Huntingtin-immunopositive inclusions were not identified in peripheral organs, peripheral nervous system, including sections from the femoral and sural nerves, or the retina or other orbital contents.

AOHD (Case 2)—This case was limited to a brain-only examination and therefore there are no general autopsy findings.

Gross Neuropathologic findings

JHD (Case 1)—The 1,425 gram (fresh) brain had mild cortical atrophy involving frontal lobes without significant temporal, parietal, or occipital cortical atrophy. There was also no significant edema or evidence of herniation or mass lesions. There was enlargement of the lateral ventricles, with a maximal cross section of 2.3 cm at the level of the temporal tips. Atrophy of the caudate and putamen was mild to mostly moderate, appropriate for grade 3 neostriatal atrophy using the Vonsattel criteria (1) (Fig. 3A). Mild cerebellar atrophy, primarily involving the midline/vermis, was present (Fig. 3B, C).

AOHD (Case 2)—The 1,240 gram (fixed) brain had mild frontal cortical atrophy without significant atrophy of the frontal, parietal, or occipital lobes. Atrophy of the caudate and putamen was moderate and assigned a Vonsattel grade of 3 (Fig. 2D). The cerebellum was grossly unremarkable (Fig. 2E,F).

Microscopic Neuropathologic findings

JHD (Case 1)—Cerebral cortex had normal hexalaminar architecture with no definite neuron loss (Fig. 4A) and unremarkable white matter. There was mild diffuse gliosis of the cerebral cortex (confirmed with GFAP IHC; Fig. 4B). The caudate nucleus, putamen, and globus pallidus had gliotic gray matter with moderate neuron loss corresponding to histologic Vonsattel grade 3 HD (Fig. 4G,H). Prominent intranuclear huntingtin-immunopositive inclusions were identified by immunohistochemistry in cerebral cortical and

striatal neurons (Fig. 4 C, I). Thalamus was less involved. There was also marked atrophy of cerebellar cortex characterized by severe thinning of the molecular layer and prominent loss of Purkinje cells with associated Bergmann gliosis (Fig. 5A–E). Immunohistochemical staining with GFAP in particular highlighted the increased gliosis (Fig. 5C). Granule neurons were relatively preserved. Of the remaining Purkinje cells, many were small with irregular cytoplasmic borders and pyknotic nuclei with rare huntingtin-immunopositive intranuclear inclusions (Fig. 5F). Lewy bodies were not identified in the sections examined. Hippocampus was well-formed without significant neuron loss or gliosis. Spinal cord architecture was normal without definite neuronal loss, gliosis or inflammatory infiltrates, and no evidence of huntingtin-immunopositive intranuclear or cytoplasmic inclusions at the cervical, thoracic, or lumbar levels. Immunohistochemical staining for PHF-tau was negative in all sections examined.

AOHD (Case 2)—Cerebral cortex had normal hexalaminar architecture with mild to focally moderate neuron loss (Fig. 4D) and patchy gliosis of the cerebral cortex (confirmed with GFAP immunostains; Fig. 5E). There was moderate to focally severe astrogliosis in association with moderate to focally severe neuron loss in the caudate nucleus and putamen (Fig. 4 J, K) as well as globus pallidus. The thalamus was mildly gliotic. The cerebellum was relatively uninvolved; Purkinje neurons were intact and significant Bergmann gliosis was not noted (Fig. 5 G–K). Hippocampus and brainstem were intact without evidence of significant neuron loss or astrogliosis. Huntingtin-positive intranuclear and cytoplasmic inclusions as well as scattered extracellular inclusions were confirmed by immunohistochemistry in the frontal cortex and striatum (Fig. 4F,L); intranuclear and cytoplasmic inclusions were not identified in cerebellum (Fig 5 L). Immunohistochemical staining for PHF-tau was negative in all sections examined. Lewy bodies were not identified in sampled brainstem, limbic, or neocortical regions.

Discussion

There are relatively few cases of JHD in the literature that include neuropathologic findings, particularly with cerebellar pathology, and even fewer with a full autopsy. This report provides both a neuropathologic evaluation and a full autopsy of a 6-year-old child with genetically confirmed HD in comparison with neuropathologic examination of his father, enabling a direct neuropathologic comparison between two family members with very different presentations of the same disease.

Father and son were diagnosed within a year of each other but with very different symptoms. The father presented first, at age 35, with classic symptoms of AOHD, including chorea. Genetic testing revealed 54 CAG trinucleotide repeats in *HTT*. His son developed seizures at age 4 with progressive cerebellar symptoms, including ataxia, and cerebellar and cortical atrophy on MRI. His *HTT* CAG repeat length was more than triple that of his father at 169, a dramatic example of anticipation. The clinical course for the father was rapid with only a ten-year disease course while his son had an even more rapid decline, with progression to death within two years of his diagnosis.

This is most likely due, in large part, to dramatic differences in CAG repeat length in each patient (8). The phenomenon of anticipation is often reported in cases of paternal inheritance, as in this case (2, 9).

Father and son each had complete neuropathologic evaluations; grossly both brains were mildly atrophic with moderate neostriatal atrophy and associated ventricular enlargement as expected in HD. There was moderate diffuse neuron loss throughout the striatum in association with gliosis and huntingtin immunopositive intranuclear and cytoplasmic striatal neuronal inclusions identified in both cases. However, there were also striking differences. The cerebellar injury/dysfunction suggested on clinical presentation/exam was confirmed with antemortem imaging and postmortem examination in the case of JHD while the adult brain did not show any Purkinje cell loss or significant gliosis in the cerebellum. In the JHD case, injury patterns were similar in the cerebellum as the neostriatum, including gliosis and significant loss of neurons. Interestingly, huntingtin-positive neuronal intranuclear inclusions were also identified in rare Purkinje cells, a finding neither seen in the adult onset case nor often reported in the literature (10). There are approximately ninety reported detailed cases of JHD dating back to the mid twentieth century. Of those cases, fifteen report cerebellar involvement, half of which include neuropathology (table 1). The majority of cases with neuropathology are from older reports, prior to the use of immunohistochemical stains for the identification of the neuronal intranuclear inclusions (11–15), and none have described the immunohistopathological features of the cerebellum in JHD. Cerebellar neurodegeneration has been reported AOHD, but it is much less common. In a study of eight genetically confirmed adult HD patients, severe loss of Purkinje cells and huntingtin-positive intranuclear inclusions within rare, scattered Purkinje cells was noted (16). Here we report for the first time similar findings of huntingtin-positive intranuclear inclusions in the cerebellum of a JHD case, which is not seen in the AOHD case, despite the two cases being genetically related.

It is not well understood why JHD is generally both clinically and neuropathologically distinct from AOHD. Most mouse models of HD have traditionally recapitulated the neuropathologic hallmarks of AOHD, often lacking features more typical of JHD, such as significant cerebellar involvement (17); however, more recent models using much larger CAG repeats of *HTT* have highlighted cerebellar pathology (18), which may indicate that features more common to JHD, such as cerebellar involvement, may at least in part be dependent on greater repeat length. Additionally, a mouse model in which loss of normal huntingtin protein was targeted specifically to the period of neural development showed characteristic features of JHD, such as hindlimb stiffness, seizures, and cerebellar involvement, suggesting that the effects of loss of normal huntingtin function may be somewhat related to neurodevelopmental processes (19). Indeed, huntingtin is known to interact with a number of different proteins involved in a variety of processes important for neurodevelopment, such as transcription, trafficking and endocytosis, signaling, and metabolism (20). It has been hypothesized that in JHD there is a more severe disruption in the interactions between huntingtin and its protein partners due to both a loss of function of the pathologic allele as well as a gain of toxic function against the functioning of the normal allele due to the marked trinucleotide expansion (19). This could ultimately lead to more developmentally important pathways affected in JHD than in AOHD, which may, in part,

explain the variable presentation seen in this case of a father and a son with HD. Because these two patients were related, the differences in the neuropathologic findings are manifesting on relatively similar (although not identical) genetic backgrounds. This limits the effects of genetic heterogeneity and supports the notion that differences between JHD and AOHD are fundamental to the disease process itself, such as a consequence of differing repeat length and the effects on the developing brain in the juvenile case compared to the mature brain in the adult case.

In addition to the neuropathologic evaluation, we report results of a complete autopsy in a patient with JHD, including an evaluation of the peripheral nervous system. In Parkinson's disease, some of the clinical symptoms are due to involvement of the peripheral nervous system by the underlying disease process (21); we find no evidence of diagnostic pathologic changes of JHD in the peripheral nervous system, including no intranuclear or intracytoplasmic inclusions.

This is a unique case comparison of adult onset and juvenile HD in a father and son. The findings support experimental data suggesting that the disease affects neurodevelopmental processes, resulting in differential effects on the developing brain of a child compared to those seen in the mature brain of an adult, which may in part be dependent on CAG repeat length.

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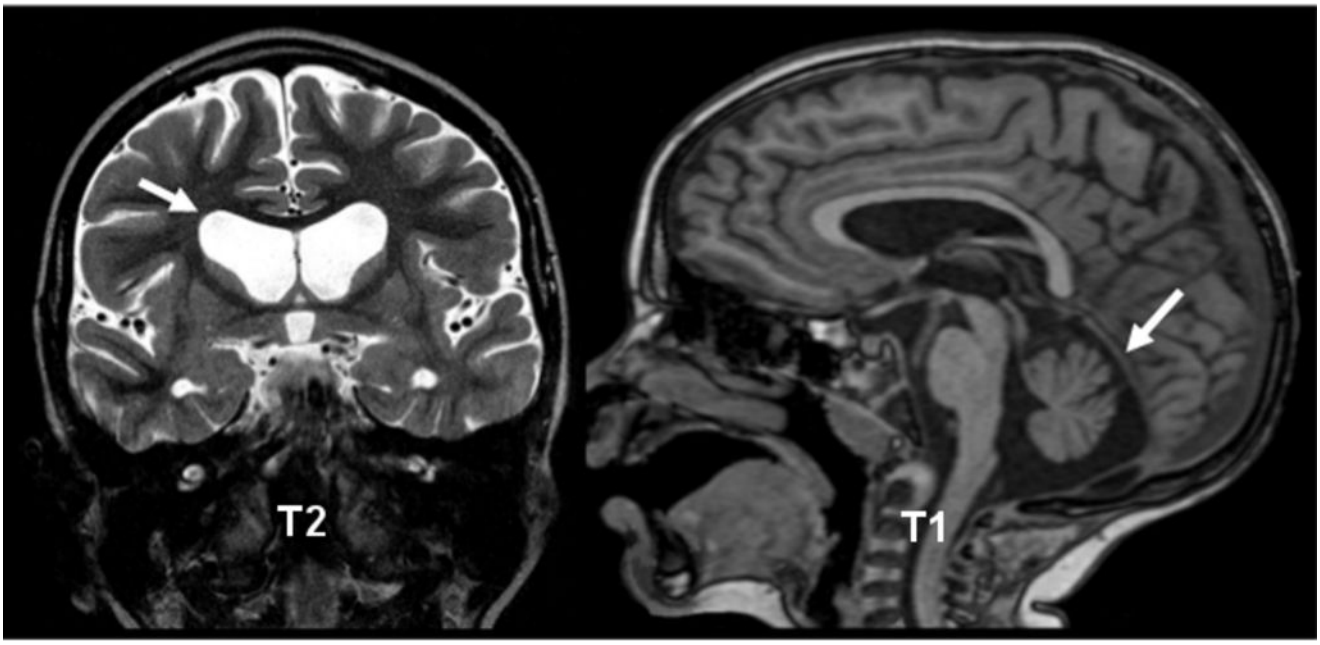

Figure 1.
Brain MRI in juvenile Huntington's disease (case 1). Neuroimaging demonstrates diffuse volume loss involving the caudate nucleus with associated ventriculomegaly (T2) as well as mild cerebellar volume loss, particularly of the vermis (T1).

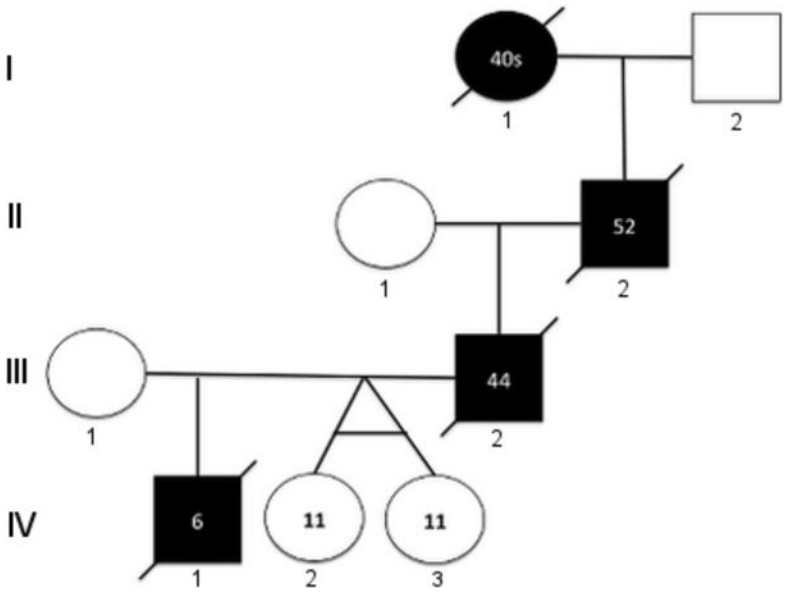

Figure 2.

Four-generation pedigree. Case 1 (IV-1) is the affected son of case 2 (III-2). Family history indicates that members of earlier generations also had Huntington's disease, including the father and paternal grandmother of case 2.

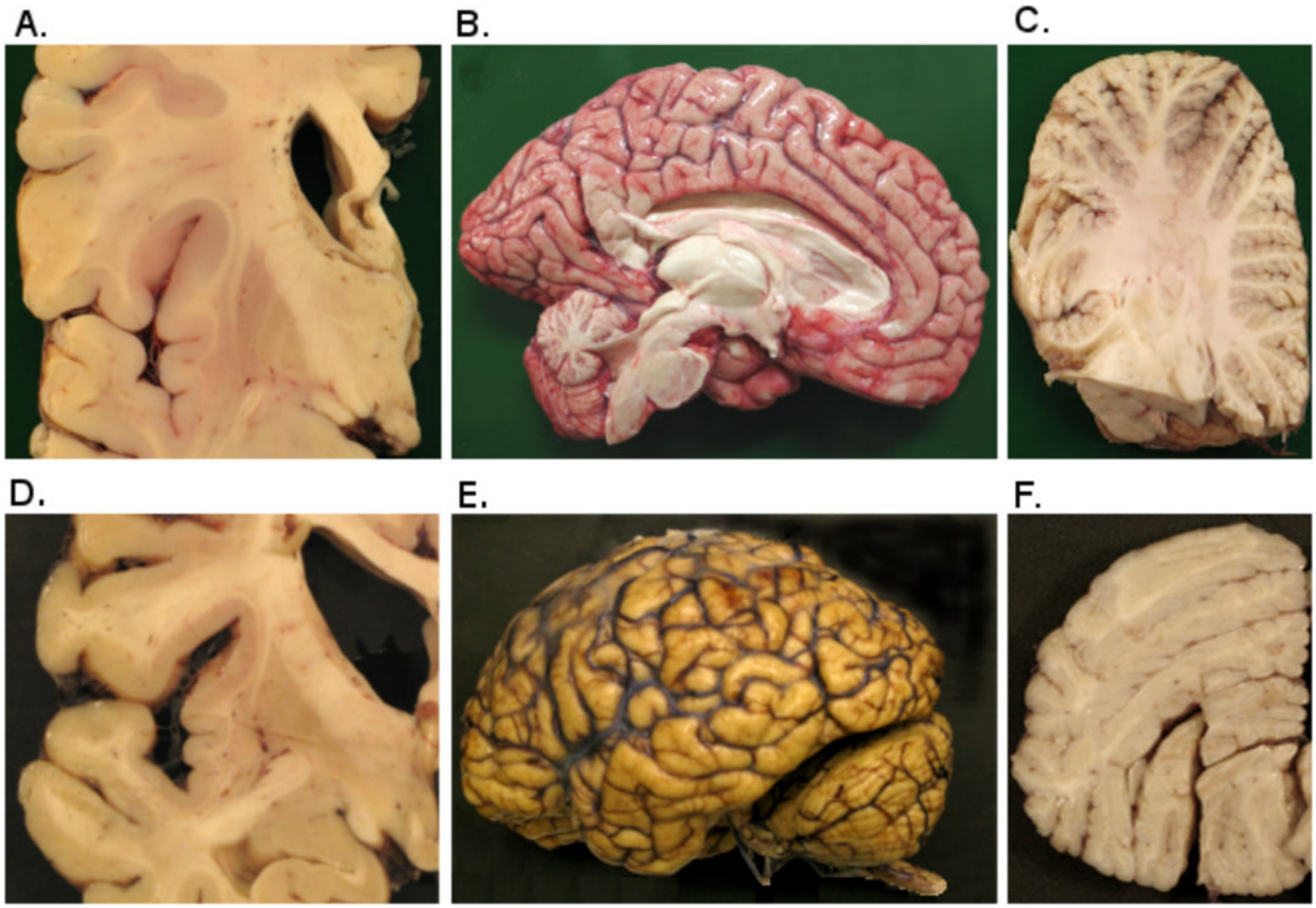

Figure 3.

Gross pathology. The juvenile (A) and the adult onset (D) case both demonstrate moderate atrophy of the caudate nucleus and putamen (Vonsattel grade 3). Sagittal sections of the cerebellum in the juvenile case also highlight the mild medial, predominantly vermian, atrophy (B) with thinning of the folia (C). In contrast, the cerebellum in the late onset case lacks significant cerebellar atrophy (E, F).

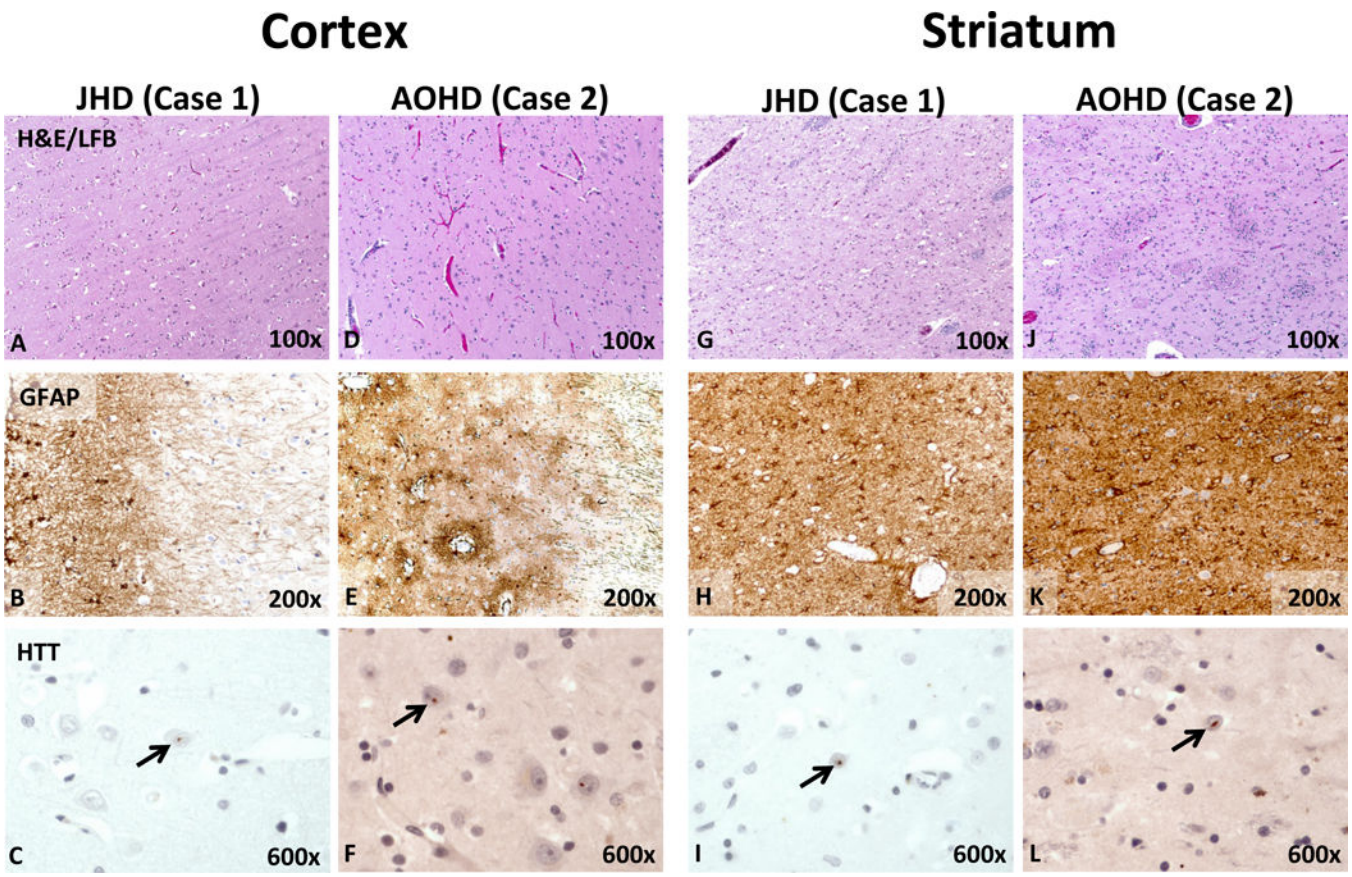

Figure 4.

Histopathology of the cortex and neostriatum (caudate nucleus). There is no significant loss of neocortical neurons in the juvenile case (A) compared to mild to focally moderate neuron loss in the adult onset case (D) (H&E) associated with increased astrogliosis in both cases (B, E) (GFAP). Huntingtin-positive intranuclear and cytoplasmic neuronal inclusions are present in the cerebral cortex of both cases (C, F). There is significant neostriatal neuron loss (G, J) (H&E) and associated astrogliosis (H, K) (GFAP). Striatal Huntingtin-positive neuronal intranuclear and cytoplasmic inclusions are present in both cases (I, L).

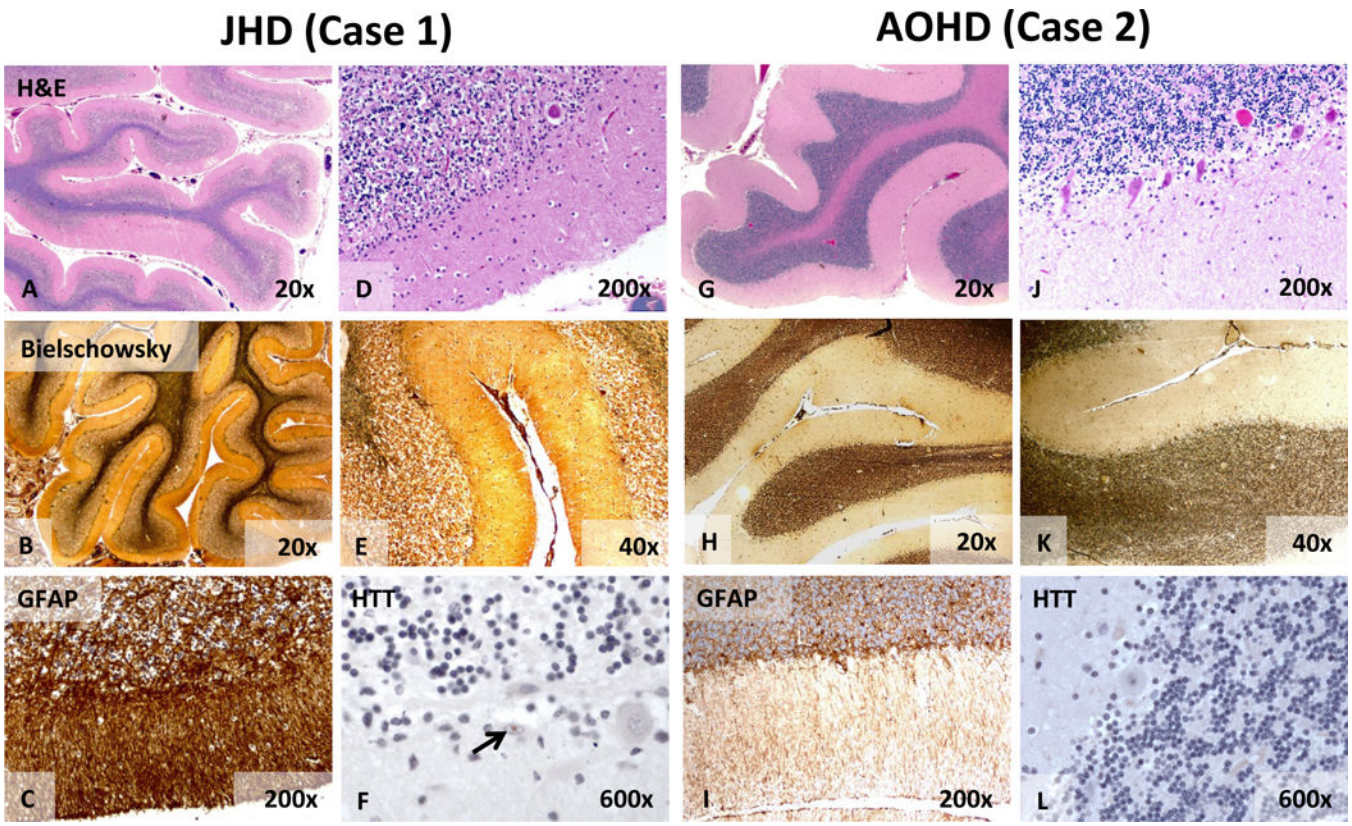

Figure 5.

Histopathology of the cerebellum. Marked atrophy of cerebellar cortex with associated severe gliosis is evident in H&E, Bielschowsky, and GFAP-stained sections in JHD (A-E) but not in the adult onset case (G-K). Rare huntingtin-positive intranuclear inclusions are identified in the cerebellum of the JHD brain (F) that are not identified in the AOHD case (L).

Table 1

Literature Review of Early-Onset Huntington's Disease Cases

Reference	Gender	Age of onset	CAG repeat in patient	Presenting symptoms	Transmission	CAG repeat in parent	Imaging findings	Autopsy findings
Patra et al (2015)(1)	Male	8 years	83	Signs of cerebellar involvement, frequent falls, ataxic gait, bradykinesia, intractable tonic-clonic seizures	sporadic	NA	atrophy and volume loss of the caudate and putamen	Not reported
Nicolas et al (2011) (2)	Male	18 months	210-250	Delayed motor and language skills	Paternal	43	Severe isolated reduced cerebellar volume, especially the vermis	Not reported
Sunwoo et al (2010) (3)	Male	6 years	140	Developmental regression and seizures	Paternal	55	Atrophy of putamen, caudate nucleus, cerebral cortex and cerebellum with ventriculomegaly	Not reported
Sakazume et al (2008)(4)	Female	3 years	160	Rigidity, ataxia, cognitive failure, seizure, speech impairment	Maternal	60	Severe cerebellar atrophy in the vermis and cortex; atrophy in the caudate nuclei, putamen, and globus pallidus	Not reported
Wojaczyńska-Stanek et al (2006)(5)	Male	3 years	95	Regression in speech and seizures	Sporadic	NA	Cerebral and cerebellar atrophy; ventriculomegaly	Significant striatal atrophy; Vonsattel grade 3; ubiquitin-positive inclusions in the striatum and cerebral cortex; marked gliosis
Gonzalez-Algere et al (2006)(6)	12 patients 7 male 5 female	4-14 years	66-130	Oropharyngeal dysfunction, fine motor problems, gait disorder, cognitive complaints, behavioral disorder, seizures	4 maternal 8 paternal	Not reported	Varying degrees of striatal atrophy; mild cerebellar atrophy (1 patient)	Not reported
Ruocco et al (2006) (7)	1. Male 2. Female 3. Male 4. Female	1. 2 years 2. 4 years 3. 8 years 4. 13 years	1. 53 2. 69 3. 41 4. 66	1. speech and gait difficulties 2. incoordination and gait ataxia 3. gait difficulties 4. visual hallucinations	1. Paternal 2. Maternal 3. Paternal 4. Paternal	Not reported	severe volume loss of caudate and putamen nuclei and cerebral and cerebellar atrophy	Not reported
Ullrich et al (2004) (8); Milunsky et al (2003)(9)	Female	18 months	265	Abrupt neuro-developmental regression	Paternal	54	Significant cerebellar atrophy	Not reported
Squitieri et al (2003) (10)	Male	3 years	120	Dysarthria and gait difficulties	Paternal	Not reported	Remarkable cerebellar atrophy with no atrophy in the basal ganglia	Not reported
Seneca et al (2004) (11)	Female	3 years	214	Seizure, psychomotor regression, diplegia	Paternal	54	Cortical atrophy with dilated ventricles and severe cerebellar atrophy	Not reported

Reference	Gender	Age of onset	CAG repeat in patient	Presenting symptoms	Transmission	CAG repeat in parent	Imaging findings	Autopsy findings
Haslam et al (1983) (12)	Male	20 months	Not reported	Seizures and behavioral disturbances	Unknown	NA	“findings consistent with HD”; mild ventricular enlargement suggestive of cerebral atrophy	Neuron loss and astrogliosis of basal ganglia; marked subpial and molecular layer gliosis; myelin loss of internal capsule and cerebellar hemispheres
Hattori et al (1983) (13)	Female	4 years	Not reported	Psychomotor deterioration	Paternal	Not reported	Dilatation of cortical subarachnoid space, atrophy of the caudate nuclei, enlargement of the cerebellar sulci and cerebellar cisterns	Not reported
Rodda (1980)(14)	Male	3 years	Not reported	Cerebellar ataxia	Paternal	Not reported	Not reported	Diffuse atrophy of cerebellum, caudate, putamen, globus pallidus; neuron loss in cortex, hippocampus, striatum with gliosis; cerebellum showed thinning of the molecular layer, loss of purkinje cells and Bergmann gliosis and neuron and myelin loss and gliosis of the dentate nucleus.
Byers et al (1973) (15)	4 cases, gender not reported	3-6 years	Not reported	Rigidity and seizures	Not reported	Not reported	Not reported	Cortical atrophy; hippocampal sclerosis; severe atrophy of the striatum with neuron loss and astrogliosis; astrogliosis of globus pallidus without neuron loss; neuron loss and gliosis of thalamus; severe atrophy of cerebellum with narrowing of molecular layer, loss of purkinje cells, and neuron loss of the dentate

Reference	Gender	Age of onset	CAG repeat in patient	Presenting symptoms	Transmission	CAG repeat in parent	Imaging findings	Autopsy findings
Markham (1965)(16)	7 cases 2 Male 5 Female	4-9 years	Not reported	Rigidity, cerebellar symptoms, choreoathetosis	6 Paternal 1 Maternal	Not reported	Not reported	1 case had autopsy (Female, paternal transmission, presented at age 5 with behavioral disturbances and gait difficulty): mild cortical atrophy; normal cerebellum; severely atrophic caudate and putamen; neuron loss and gliosis of caudate, putamen, globus pallidus; loss of purkinje cells and Bergmann gliosis; neuron loss of the dentate nucleus with some astrogliosis; neuron loss of inferior olives
Jervis (1963)(17)	1. Male 2. Male 3. Female 4. Male	1. 5 years 2. 9 years 3. 7 years 4. 5 years	Not reported	1. Speech delay; clumsiness 2. seizures 3. cognitive impairment and seizures 4. cognitive impairment, seizures, gait disorder	Paternal	Not reported	Not reported	1. atrophy of caudate and putamen; neuron loss and gliosis; loss of purkinje cells in cerebellum 2. Not reported 3. typical findings plus almost complete absence of Purkinje cells and considerable gliosis in the cerebellum 4. marked cerebral and cerebellar atrophy; loss of purkinje cells in cerebellum and neuron loss with gliosis in the dentate