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Juvenile-Onset Huntington Disease Pathophysiology and Neurodevelopment: A Review

Hannah S. Bakels, MD, MSc, Raymund A.C. Roos, MD, PhD, Willeke M.C. van Roon-Mom, PhD, and Susanne T. de Bot, MD, PhD

1Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
2Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

ABSTRACT: Huntington disease is an autosomal dominant inherited brain disorder that typically becomes manifest in adulthood. Juvenile-onset Huntington disease refers to approximately 5% of patients with symptom onset before the age of 21 years. The causal factor is a pathologically expanded CAG repeat in the Huntingtin gene. Age at onset is inversely correlated with CAG repeat length. Juvenile-onset patients have distinct symptoms and signs with more severe pathology of involved brain structures in comparison with disease onset in adulthood. The aim of this review is to compare clinical and pathological features in juvenile- and adult-onset Huntington disease and to explore which processes potentially contribute to the observed differences. A specific focus is placed on molecular mechanisms of mutant huntingtin in early neurodevelopment and the interaction of a neurodegenerative disease and postnatal brain maturation. The importance of a better understanding of pathophysiological differences between juvenile- and adult-onset Huntington disease lies in development and implementation of new therapeutic strategies. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: juvenile Huntington disease; pediatric Huntington disease; pediatric neurodegenerative disease; disease mechanisms; neurodevelopment

Huntington disease (HD) is an autosomal dominant progressive brain disorder caused by a pathological CAG repeat expansion coding for huntingtin (HTT gene), with an elongated polyglutamine tract. The length of the CAG repeat shows an inverse correlation with the age at onset. Symptoms become manifest at a mean age of 45 (range 2–87) years. All patients with symptom onset before the age of 21 years, irrespective of their present age, are referred to as juvenile-onset Huntington disease (JHD), which is seen in 4% to 10% of all HD cases. The term pediatric Huntington disease (PHD) is reserved for all patients with manifest disease who are still below the age of 18 years. Based on clinical signs, further distinction is made between childhood (<10 years) and adolescent onset (10–18 years). In approximately 50% of JHD cases the CAG expansion is ≥60, exceeding 80 repeats in childhood onset. About 80% of JHD patients inherit the repeat expansion via paternal transmission.

JHD patients are often difficult to diagnose. This is mainly due to psychiatric and cognitive complaints that are easily misdiagnosed. Apart from the atypical clinical presentation, disease progression in childhood-onset HD patients is faster and survival shorter compared to adult-onset HD (AHD). Furthermore, morphological changes in JHD brains are generally more severe than in AHD brains. These phenotypical and pathological differences raise the hypothesis of aberrant pathomechanisms. Detangling pathophysiological differences between JHD and AHD...
is important for the successful treatment of pediatric patients. Various treatments are currently under investigation in AHD patients, yet JHD patients are excluded from most therapeutic trials.

This review aims to highlight differences in clinical, neuropathological, and imaging features between JHD and AHD. Suggestions for further studies are made by explaining these differences in the light of HD pathophysiology and brain development.

**Clinical Features**

HD is characterized by motor and cognitive dysfunction and by psychiatric and behavioral changes, leading to loss of independence and eventually death. The median disease duration after motor onset in childhood JHD is 9 years, compared to 18 years in adolescent and adult HD.5,8

**Motor Symptoms**

Between 42% and 94% of JHD patients develop postural instability, bradykinesia, and rigidity, in combination with dystonia in the initial stages of motor onset.8,12,15-18 In contrast, motor onset with bradykinesia and rigidity is seen in only 20% of AHD patients, yet most AHD patients may become hypokinetic and rigid at the end of their disease.19,20 Chorea, which is the initial motor sign in 80% of AHD cases, is rarely seen in early JHD, but gradually evolves with disease progression in a subset of adolescent HD.8,18,21,22 Motor signs more often seen as initial signs in JHD include dysarthria and loss of dexterity, such as writing.8,12,21 Oral dyskinesias,8,11,18 tics,8,21,22 and myoclonus8,12,15,21 are more frequently seen in later stages of JHD. Of note are conflicting reports on the appearance of ataxia,8,15,21 which is probably a definition problem. Ataxia, imbalance, incoordination, and unsteady walking are words probably that refer to the same common early signs in JHD, which can also be seen in early stages of AHD.23

**Cognitive Symptoms**

Cognitive deficits are reported as initial disease signs in 30%–83% of JHD patients, before motor onset is apparent.8,21,24,25 This wide range might be attributed to differences in description but emphasizes the notion that cognitive deficits are prominent in the initial stage of JHD. Similarly, in about one-third of AHD cases, early cognitive disturbance, typically related to psychomotor speed and deterioration of executive functions such as attention, planning, and flexibility of mind, are present years before the first motor symptoms appear.25,26 More specific for JHD is the prevalence of developmental delay. This feature is used to describe delays in cognitive, motor, language, and social development, thus referring to a broader range of neurological features than just cognition. An early cohort study reported that 6 of 33 JHD cases present with some form of developmental delay.18 An additional description of three unrelated JHD patients (CAG repeats of 93, 100, and 120) mentioned a developmental delay in speech and language, followed by a delay in social and motor skills.27 Several other publications confirmed the presence of developmental delay in the JHD population and showed that these delays are particularly seen in patients with childhood disease onset.8,21 Of note is the lack of data delineating the neurological base of the observed delays (eg, cognition, motor, and/or social) as well as comparative data with AHD.

**Psychiatric Symptoms**

About 30% of JHD patients present with some form of psychiatric or behavioral disturbances before motor onset, which increases to 75% during disease progression.8,12,15,21,22,25 These numbers largely resemble those in adult-onset disease.25,26,28 However, the nature of psychiatric complaints in JHD patients differs from those seen in AHD patients. Obsessive–compulsive behaviors are more common in adolescent onset (50%–73%) compared to AHD (26%). The prevalence of behavioral deficits is higher in adolescent-onset HD patients compared with childhood-onset HD.8,28,29 Psychotic symptoms are reported in 17% to 39% of JHD patients,8,22 and only in about 4% of AHD cases.28

**Other Symptoms**

The most remarkable difference in clinical appearance between JHD and AHD is the higher prevalence of epileptic seizures in the JHD population, estimated to be 30% to 35%. Observational studies show it is far more common in childhood-onset HD patients than in adolescent-onset HD.8,13,30 In AHD, the prevalence of epileptic seizures is comparable to population risk. Furthermore, sleep disturbance, pain, and itching are explicitly or more commonly mentioned in the juvenile population.22 Unintended weight loss and hyper-metabolic state is seen in both AHD and JHD cases, yet its severity correlates with an increase in CAG repeat length and thus is more severe in JHD patients.31,32

**Neuropathology and Imaging**

In HD pathology, various cell types and brain regions are affected, and although there are shared characteristics between JHD and AHD, subtle pathological differences between the two forms exist. There is a lack of systematic assessments of differences between JHD and AHD brains. What is known, mainly based on small sample sizes from either pathology or imaging studies, will be discussed here and illustrated in Fig. 1.
comparing to AHD brains (see Fig. 1). Thalamic and more often affected in post-mortem JHD brains when pallidus, the nucleus accumbens, and thalamus, are regions, such as the internal segment of the globus pallidus, aggregate and somatic CAG repeat mosaicism (see Box 2) are more severe in the neostriatum of JHD brains. The assignment of a grade is based on macroscopic and microscopic findings, the latter on three standardized coronal sections of the striatum.

**Grade 0:** no macro- and microscopic alterations are seen, yet subtle neuronal cell loss of the head of the caudate nucleus can be quantified when compared with non-neurological control brains; **grade 1:** there are no major macroscopic changes, but neuronal loss and astrogliosis can be reliably observed microscopically in the caudate nucleus and to a smaller extent in the putamen; **grade 2:** caudate nucleus volume loss can be observed macroscopically (medial outline into the lateral ventricle slightly convex); **grade 3:** gross caudate nucleus volume loss extents in a straight or concave line with the lateral ventricle; and **grade 4:** outline of caudate nucleus is concave, as is the anterior limb of the internal capsule, and 95% of neostriatal neurons are lost microscopically.

**Subcortical Structures**

In HD, progressive neostriatal (e.g., putamen and caudate nucleus) loss of medium spiny projection neurons and concomitant reactive increase of astroglial cells (e.g., astrogliosis) are the most prominent neuropathological changes observed, and determine mainly the neuropathological grading (see Box 1). Neostriatal volume loss is generally more severe in JHD brains when compared with AHD brains and follows a linear correlation with CAG repeat length (see Table 1 and Fig. 1). Of note is the importance of disease severity and duration of illness at autopsy in the interpretation of volume loss between the two forms, which is only sporadically taken into account in pathological comparisons. Magnetic resonance imaging (MRI) studies confirm these findings by comparing neostriatal volume loss and disease severity between patient groups with varying CAG repeat lengths. Furthermore, other pathological hallmarks like mutant huntingtin (mHTT) aggregates and somatic CAG repeat mosaicism (see Box 2) are more severe in the neostriatum of JHD brains when compared to AHD brains (Fig. 1). In addition to neostriatal pathology, other subcortical regions, such as the internal segment of the globus pallidus, the nucleus accumbens, and thalamus, are more often affected in post-mortem JHD brains when compared to AHD brains (see Fig. 1). Thalamic and pallidal volume loss in JHD patients was also observed in a recent age-matched cross-sectional MRI study (N = 19). An inverse relationship between CAG repeat length and thalamic volume loss was found within this same cohort. Taken together, these findings show more severe pathology of subcortical structures in JHD patients.

**Neocortex**

Neocortical volume and pyramidal neuron loss is also found in AHD and PHD brains. In general, atrophy is most pronounced in frontal and parietal regions and is most often seen in Vonsattel grade 3 and 4 brains. Based on macroscopy, frontal and parietal atrophy is more commonly observed in post-mortem JHD brains when compared with AHD brains (see Fig. 1), like the higher Vonsattel grades in JHD brains. More widespread cortical volume loss and faster volume loss over time has also been observed in a longitudinal MRI analysis of 2 JHD patients who carried CAGs higher than 55, when compared with 34 AHD patients with repeat lengths between 40 and 55. However, cross-sectional analysis of cortical volume loss and CAG repeat length in the same cohort failed to replicate this result. In addition, structural brain MRI in 19 JHD patients showed relatively preserved cortical volumes when compared with age-matched controls, suggesting that cortical volume loss in JHD brains is related to end-stage disease. Other pathological hallmarks such as N-terminal mHTT-, exon 1-, and RAN protein aggregates and somatic CAG repeat mosaicism, are more highly expressed in the neocortex of JHD brains when compared with AHD brains, as shown in
The need for more refined comparison of JHD and AHD post-mortem brains, with extensive longitudinal MRI data, analyzing and comparing JHD and AHD patients, will be essential to clarify the relative involvement of cortical pathology in the two forms.

**Cerebellum**

The hypothesis of more pronounced cerebellar pathology in JHD brains remains a matter of controversy. Severe macroscopic cerebellar atrophy is described in a subset of neuropathological and MRI studies of JHD brains, all of them from childhood-onset cases (see Fig. 1).\(^{53-58}\) However, of concern is the cause of cerebellar atrophy in these JHD brains, since most of

<table>
<thead>
<tr>
<th>Vonsattel grading system</th>
<th>JHD brains ((N = 50))</th>
<th>AHD brains ((N = 1300))</th>
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<tr>
<td>Grade 0</td>
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<tr>
<td>Grade 1</td>
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<tr>
<td>Grade 2</td>
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<tr>
<td>Grade 3</td>
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<td>53%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>64%</td>
<td>28%</td>
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\(^a\) Ninety percent of grade 1 juvenile-onset Huntington disease (JHD) brains were from JHD patients who committed suicide and therefore do not reflect end-stage disease. For the adult-onset Huntington disease (AHD) brains, these percentages are unknown/not provided.
the examined cases (11 out of 13) were known to have epilepsy, which could potentially cause hypoxic-ischemic events in this area. In both JHD and AHD brains, subtle macroscopic cerebellar atrophy is seen together with extensive striatal degeneration (Vonsattel grades 3 and 4). Cross-sectional imaging studies of cerebellar volume loss in both JHD and AHD patients have failed to replicate group differences in the amount of cerebellar atrophy. Of particular interest are two recent in vivo MRI studies that revealed relative enlargement of anterior cerebellar compartments in AHD and JHD subjects when compared with age-matched controls. Additional functional investigations have suggested the cerebellum is a compensatory brain structure for pathological basal ganglia changes in early HD disease stages. Studies of the presence of mHTT and RAN protein aggregates in HD cerebells found evidence that such pathological hallmarks are selectively or more prominently found in JHD cerebells (Fig. 1). In particular, the higher expression of RAN protein species suggests that toxicological processes are more likely to take place in JHD cerebells when compared to AHD cerebells. Additional research into the role of the cerebellum in HD pathophysiology is needed to further clarify discrepant in vivo and post-mortem findings and to address its relation to JHD and AHD.

**White Matter**

While substantial evidence suggests (microstructural) white matter changes in HD, the relative involvement of white matter pathology in JHD as compared to AHD is as yet unknown. In JHD patients, scarce quantitative data of white matter involvement are available and diffusion tensor imaging (DTI) measures have never been published. Hedjoudje and others showed subtle cerebral white matter volume decrease in three JHD siblings with childhood onset of disease, carrying CAG repeats >120, when compared to age-matched controls. Tereshchenko and others replicated this finding in a sample of 19 JHD patients (CAG repeat range 54 to 96) and revealed more pronounced white matter volume decrease in JHD patients with longer repeats, suggesting a CAG-dependent relation. More comparative imaging data in both JHD and AHD patients is needed to reliably interpret possible differences in white matter involvement between the two forms.

**Differences in Clinicopathology and Causal Factors**

Summarizing the previous paragraphs, JHD shows a faster disease progression and a shorter survival, as compared to AHD, with some distinct clinical symptoms and signs, like hypokinetic- and rigid syndrome, developmental delay, behavioral disorder, epilepsy, and psychosis. This is accompanied by increased pathological hallmarks, such as subcortical volume loss and gliosis and selective or higher number of mHTT aggregates, exon 1 and RAN proteins, and somatic CAG repeat mosaicism (Fig. 1). Differences in these clinico-pathological measures can be explained by environmental, biological, and pathophysiological factors. Although the upbringing of JHD patients in a family with an affected HD parent might well affect certain cognitive and psychiatric measures, differences in biological and pathophysiological factors are important to consider in the light of treatment opportunities.

General HD pathophysiology involves both cell dysfunction and cell loss, with clinical symptoms and signs as a result. Contributing factors to cell dysfunction and loss are a gain of toxic mHTT protein function and a loss of normal huntingtin protein function, and include RNA toxicity, transcriptional dysregulation, mitochondrial dysfunction, excitotoxicity, and inflammation. Neurodegenerative pathomechanisms in HD follow a linear correlation with CAG repeat length and age at disease onset and are an important contributor to the clinicopathological differences between JHD and AHD patients. Apart from neurodegeneration, aberrant neuropsychological and behavioral factors. Although the upbringing of JHD patients in a family with an affected HD parent might well affect certain cognitive and psychiatric measures, differences in biological and pathophysiological factors are important to consider in the light of treatment opportunities.

Neurodevelopmental Defects

Brain development involves overlapping processes of: (1) neurogenesis and cell differentiation; (2) neuronal migration; (3) synaptogenesis; (4) neural circuitry
formation; and (5) synaptic pruning and myelination (see Fig. 2). The first two processes are mainly established before birth (prenatal neurodevelopment), and the latter three continue to change well into early adulthood (postnatal brain maturation). As mentioned earlier, various preclinical studies have revealed aberrant neurogenesis and cell differentiation in relation to pathologically expanded CAG repeat lengths, as is nicely reviewed by Wiatr and others. Two such studies, using HD stem cells with increasing CAG repeat lengths, have revealed defective progenitor cell differentiation, abnormal multinucleated neuron morphology, chromosomal instability, and changes in cytokinesis in a CAG-dependent manner. This suggests greater neurogenesis and cell differentiation defects in JHD when compared with AHD. Greater defects in early developmental processes can cause distinct clinical characteristics in the JHD population, such as developmental delay (see pink, green, and blue lines in Fig. 2), as is similarly seen in a large heterogeneous group of neurodevelopmental disorders. Another study in R6/2 mice highlighted changes in neuronal migration and arborization (see green and blue lines in Fig. 2) that are similar to those found in focal cortical dysplasia (FCD) type 1. Changes in cortical development are a common etiology of developmental delay and epileptic seizures in a variety of neurodevelopmental disorders. Future studies should determine if there are FCD-like changes in JHD and AHD patient material.

Changes in postnatal brain maturation could also contribute to the clinical picture in JHD. Neural circuitry formation by dendrite branching and formation of new synapses starts during prenatal neurodevelopment but continues to expand into childhood.
(see brown line in Fig. 2). A longitudinal imaging study in asymptomatic children carrying an HTT gene expansion showed an incremental effect of CAG repeat length on functional circuitry adaptations. Resilience of brain regions such as the cerebellum is thought to functionally compensate for early developmental changes, with symptoms occurring as soon as this resilience cannot overcome the accumulating toxic effects of mHTT. A higher burden of toxic RAN and mHTT protein species in JHD cerebella could explain early loss of resilience and symptom onset, as well as the early occurrence of clinical characteristics, such as postural instability, ataxia, dystonia, hand dexterity, and dystonia. Furthermore, significant changes in neurotransmitter systems and ion channels during neural circuitry formation render the immature brain more prone to an imbalance between neuronal (GABA-ergic) inhibition and (glutamergic) excitation, in favor of the latter. This imbalance is an important contributor to the higher incidence of epileptic seizures in childhood neurodevelopmental disorders. The simultaneous dysfunction and loss of GABA-ergic medium spiny neurons of the striatum as well as prefrontal neurons in JHD patients with childhood-onset of disease renders these patients prone to such an imbalance. This could provide another explanation for selective occurrence of epileptic seizures in JHD patients. Changes in synapse abundance and pruning could also be involved in JHD pathophysiology (blue line in Fig. 2). By the age of 2 years, infant brain contains about 150% of synaptic connections compared to adult brain. During adolescence, a steep decline in synaptic connections is determined by the amount and timing of neural activity, which is further regulated by elements of the immune system such as microglial and complement function. Changes in synapse abundance play an important role in the pathogenesis of neurodevelopmental disorders such as schizophrenia, obsessive-compulsive disorder, and autism. As mentioned earlier, functional circuitries are known to be altered in HD patients. Furthermore, reactive and cell-autonomous effects of HD microglia induce a pro-inflammatory transcription profile and reduced fractalkine expression. The latter protein plays an important role in microglial capacity for synaptic pruning. Since psychosis and obsessive-compulsive disorder are far more prevalent in adolescent-onset HD, aberrant synaptic pruning is an interesting target for future studies.

Discussion and Future Directions

Clinicopathological differences between JHD and AHD exist and can be explained by pathological, biological, and environmental factors. A dosage effect of CAG repeat length on neurodegenerative and neurodevelopmental defects, as well as interaction of pathology with ongoing brain maturational processes in JHD patients, may be responsible for the observed difference. Due to the low prevalence of JHD there is still a huge lack of data linking CAG repeat length or age at disease onset with the underlying pathophysiology. In addition, many (pre)clinical studies focus on JHD or AHD and fail to structurally compare the two forms. Unraveling possible pathophysiological differences between JHD and AHD is important for the development of therapeutics designed to reduce symptoms or alter disease progression. For instance, due to differences in symptoms that affect brain areas and pathomechanisms, JHD patients might benefit from therapeutics which have been shown to be ineffective in adult patients. Conversely, therapeutics that target mutant huntingtin might be disproportionately damaging in JHD patients due to its effect on concurrent brain maturation. Furthermore, neurodevelopmental pathomechanisms largely take place in utero and are more difficult to influence once symptoms present themselves. Patients with a complex disorder such as HD might therefore benefit from a combination of therapies in a personalized way rather than a generalized one. Although the severity of JHD will lead clinicians to treat JHD patients as soon as viable therapeutic options are identified in the adult population, lack of well-established and reliable outcome measures in the pediatric population will further complicate successful implementation of therapeutic strategies. Therefore, future studies should focus on inclusion of both JHD and AHD patients, longitudinal study designs, structural comparison of CAG repeat lengths, or age at disease onset, the specification of JHD read-out parameters and possible interactions with postnatal brain development. Furthermore, international collaboration is necessary due to the rarity of JHD, and ethical and legal issues in pediatric studies must be overcome. Finally, the implementation of highly standard translational research methods will greatly enhance our knowledge of JHD.

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Data Availability Statement

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research

References


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