Curr Psychiatry Rep (2017) 19: 9
DOI 10.1007/s11920-017-0759-9

COMPLEX MEDICAL-PSYCHIATRIC ISSUES (MB RIBA, SECTION EDITOR)

# Juvenile Huntington's Disease: Diagnostic and Treatment Considerations for the Psychiatrist

**Joanna Quigley** [1]

Published online: 7 February 2017


**Abstract** Juvenile Huntington's disease (JHD) is a neurodegenerative disease with onset prior to the age of 21. While it accounts for a relatively small proportion of Huntington's disease (HD) diagnoses, its impact is significant on the quality of life for those affected. Clinicians may be unaware that HD can present in childhood and adolescence, delaying diagnosis. HD develops due to an expanded CAG repeat in the huntington gene. Rigidity, dystonia, and seizures are more common in JHD. Cognitive changes such as executive function impairments and decline in school performance are common. The burden of psychiatric symptoms is considerable and includes depression, anxiety, impulsivity, and aggression. While novel approaches to treatment interventions are investigated, current care is limited to targeting symptoms rather than disease modification. Prompt diagnosis and symptomatic treatment can maximize quality of life for these patients.

**Keywords** Juvenile Huntington's disease · Neuropsychiatric · Neurodegenerative · Depression · Anxiety · Rigidity · Chorea

## Introduction

Huntington's disease (HD) is a progressive neurodegenerative disease. It is due to a trinucleotide expansion (CAG) following exon 1 in the huntington (HTT) gene [1]. This gene is located on chromosome 4p16.3 and is inherited in an autosomal dominant pattern [2, 3]. The gene encodes the huntington protein, and CAG expansion leads to expansion of the glutamine repeat within this protein [2, 4]. This leads to the progressive deterioration of neurons in the putamen, caudate nucleus, and cerebral cortex [5]. Approximately 5–10% of all HD cases present with juvenile onset [6, 7]. Prevalence estimates by one UK study cited an annual average prevalence of juvenile HD between 1990 and 2010 as 6.77/million (95% CI 5.60 to 8.12/million) [2]. Juvenile Huntington's disease (JHD) is defined as disease onset before age 21, with childhood disease defined as onset before age 10 (often characterized by greater than 60 CAG repeats [6]. A greater number of CAG repeats is typically correlated with younger age of disease onset [8]. It is very rare for JHD to present before 10 years of age, though cases, including disease presentation at 18 months of age, have been reported in the literature [9].

## Neurologic and Psychiatric Disease Presentation

Prodromal symptoms are often identified retrospectively in JHD, for example sleep changes, changes in executive function and academic performance, depression and anxiety, and movement disorders [2]. The literature describes initial identification of ADHD, anxiety, depression, psychosis, or seizures, for example, before motor symptoms become more apparent [7, 10]. One study identified a mean delay of diagnosis of 9 ± 6 years due to the relative rarity of this disease and the complex symptom presentation (0–21 years) [11].

Consideration of JHD in the differential diagnosis in the assessment of a child is difficult. Taking a careful family history can be very helpful to the clinician in determining whether the child presenting with ADHD symptoms and behavioral

This article is part of the Topical Collection on *Complex Medical-Psychiatric Issues*

✉ Joanna Quigley
joannaq@med.umich.edu

[1] Department of Psychiatry, University of Michigan, Rachel Upjohn Building, 4250 Plymouth Road, SPC 5766, Ann Arbor, MI 48109-2700, USA

**Table 1** Medications considered in the treatment of Huntington's disease symptomatology

| Type of medication | Potential indication | Potential cautions |
|---|---|---|
| Anti-depressant (SSRI, SNRI) | Depression, anxiety, obsessions, and compulsions | Disinhibition, activation, irritability, suicidality |
| Stimulant | Impairment in executive functioning, impulsivity, apathy | Increased irritability or agitation, worsening of sleep disruption |
| Alpha-Agonist | Impairment in executive functioning, impulsivity | Irritability, somnolence, hypotension, autonomic instability |
| Anti-psychotic | Irritability, aggression, mood lability, psychotic symptoms, anxiety | Metabolic side effects, somnolence, irritability, extra-pyramidal symptoms |
| Mood stabilizer | Irritability, aggression, mood lability | Further cognitive slowing |
| Sleep aid (e.g., melatonin, clonidine, quetiapine) | Sleep disruption, disturbance | Irritability, disinhibition, confusion |
| Benzodiazepine | Anxiety | Disinhibition, increased irritability |
| Tetrabenazine | Chorea | Depression, akathisia |
| Anti-Parkinsonian (e.g., sinemet, amantadine) | Parkinsonian symptoms including rigidity | Hallucinations |
| Anti-spasticity (e.g., baclofen) | Rigidity | Somnolence/sedation |
| Seizure medications | Seizure activity, as above mood stabilization | Sedation, irritability, gastrointestinal side effects |

changes should be assessed for a disease such as this. The differential diagnosis for the motor symptoms exhibited in JHD is brought could include for example Wilson's disease, juvenile Parkinson's disease, and neuroacanthocytosis [12, 13]. Neuroimaging and genetic testing can be helpful in identifying the diagnosis.

Rigidity is the distinguishing feature of JHD in contrast with adult-onset HD [11]. Dystonia and epilepsy are also more common in JHD than adult HD [2, 14, 15]. Patients will present with difficulties in both voluntary and involuntary movement [16].

Motor symptoms will also include bradykinesia, dysphagia, ataxia, speech changes and deficits, upper motor neuron signs, and, typically later on, chorea [4, 16]. There are both hyperkinetic and hypokinetic motor symptoms in HD involving malfunctions in the basal ganglia [17]. Changes in the caudate and putamen are a hallmark of the disease process, specifically striatal medium spiny neurons are impacted significantly [4, 18].

Juvenile HD typically progresses more rapidly than adult-onset HD [7]. The literature cites three general stages of JHD: behavioral disruption, learning impairments, gait changes and mild chorea, a subsequent phase of rapid cognitive changes, rigidity, speech deficits and seizures, and a last phase of hypotonia, increase in seizure activity and immobility [19•, 20]. There is a movement towards defining disease stages in order to establish clinical diagnostic criteria for HD [21]. Motor symptoms in juvenile HD are more often tremor, bradykinesia, and dystonia, rather than the chorea seen classically in adult HD. One study identified the most common seizure types as generalized tonic-clonic and found increased seizure risk the younger a child was at age of disease onset [3], and seizures have been reported to occur in 30% of patients with JHD [20].

Cognitive decline is known to occur in HD and also manifest in JHD. Executive function impairments are common. Retrospective review of clinical presentation in JHD patients finds several that previously received ADHD diagnoses [20]. Behavioral changes and difficulties are a hallmark of the disease and very impairing for both the patient and their family. Prevalence rates of up to 87% are documented in the literature [22]. Behavioral changes often precede the development of motor symptoms and may initially be quite subtle. Common behavioral problems JHD include impulsivity, aggression, and oppositional behaviors [4]. These symptoms and corresponding behavioral disinhibition become impairing both in the school and home setting, impacting relationships and socioemotional functioning.

Development of sleep disorders can also occur [4]. Behavioral disruption can become a significant safety issue for patients and their families, particularly when aggression escalates. This can lead to frequent emergency room evaluations as well as medical and psychiatric hospital admissions.

Neuropsychiatric symptoms include lack of insight, depression, anxiety, psychosis, inattention, memory impairment, irritability, aggression, and social withdrawal [10, 11]. Depression and suicidality are of significant concern in this population, particularly if they have witnessed the decline of a family member.

Language impairments may make it difficult for these patients to express the emotional distress they are experiencing. Cognitive changes and, at times, developmental regression further compound the challenges in helping patients with JHD manage their mental health symptoms.

## Assessment

Objective measures of functioning, symptom burden, and behavior can be difficult to perform regularly with these patients; however, scales do exist to measure important clinical components of this disease in adults. Several years ago, the Unified Huntington's Disease Rating Scale was developed by the Huntington Study Group [23]. It is validated for adults and has been less consistent in application to JHD patients [15]. This assesses four clinical domains: motor function, cognitive function, behavioral abnormalities, and functional capacity [11]. The Problem Behaviors Assessment for Huntington's Disease-Short Form (PBA-s) is also used to assess psychiatric symptoms in HD [24•]. In the review of pertinent assessment scales, clinically significant psychiatric domains over the course of HD are identified as irritability, anxiety, depression, apathy, obsessive-compulsive behaviors, psychosis, and suicidal ideation [24•]. There is a paucity of data in validation of existing scales in the JHD population, and general scales utilized to assess specific symptom domains are frequently used.

## Treatment

Care for patients with JHD requires a multi-disciplinary effort including the primary care providers, genetics, neurology, rehabilitation medicine, child and adolescent psychiatry, palliative care, speech therapy, occupational therapy, and the support staff at school. At present, there is no curative or disease-modifying treatment intervention for HD [16]. Behavioral interventions are very important in targeting functionally impairing symptoms. Generally speaking, treatment is targeted at symptom control and may include some of the agents listed in Table 1. No data exists to support specific treatments in the setting of psychiatric symptoms in JHD [16]. Review of treatment of JHD patients has identified that polypharmacy is common in targeting impairing symptoms [2, 4, 14].

### Novel Treatment Approaches

Researchers continue to work towards a better understanding of this disease process as well as the opportunity for novel therapeutic interventions. These generally focus on motor symptoms. There is discussion in the literature of use of deep brain stimulation to target motor symptoms in HD, specifically chorea movements [17]. The Huntington Study Group has recently published data on a trial of deutetrabenazine to target chorea symptoms in adults with Huntington's disease [25•]. Tetrabenzine is an existing FDA-approved treatment for chorea [25•]. It is very expensive and can be difficult to obtain [19•]. Chorea is typically a more prominent symptom in adult patients with HD. In this trial, total maximal chorea score improved at the 12-week point for those patients taking deutetrabenzine. As chorea is typically not as common in JHD, these therapies have less of an impact on symptom management in these younger patients.

Studies have reported lower levels of brain-derived neurotrophic factor (BDNF) in HD, and trials have been proposed to use genetically engineered mesenchymal stem cells to produce supplemental BDNF [5, 19•]. Even if these move forward in clinical trials, it is difficult to know whether this will have a role in treatment for JHD patients.

## Conclusions

There is still a need to better understand the underlying mechanism of disease pathogenesis in HD and JHD in order to develop targeted treatments that can significantly modify disease course. The neuropsychiatric symptom burden of JHD is considerable and for many patients and families as impairing as the motor disease of this illness. Due to the relative rarity of JHD, it is important that clinicians and researchers utilize the available registries and databases to continue building on data that allows for more robust treatment guidelines. The sooner the diagnosis of JHD is made, the better prepared the patient, family, and providers can be to provide appropriate care. Gene therapy likely has a role in the future of HD treatment.

However, it is important to refer families to genetic counselors who are knowledgeable about this disease prior to considering testing of asymptomatic family members, particularly of children who are considered to be at risk.

**Acknowledgements** The editors would like to thank Dr. Harrison Levine for taking time to review this manuscript.

**Compliance with Ethical Standards**

**Conflict of Interest** The author declares that she has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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