Published in final edited form as:
Neurodegener Dis Manag. 2013 June 1; 3(3): . doi:10.2217/nmt.13.18.

Managing juvenile Huntington's disease

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SUMMARY

Huntington's disease (HD) is a well-recognized progressive neurodegenerative disorder that follows an autosomal dominant pattern of inheritance. Onset is insidious and can occur at almost any age, but most commonly the diagnosis is made between the ages of 35 and 55 years. Onset ≤20 years of age is classified as juvenile HD (JHD). This age-based definition is arbitrary but remains convenient. There is overlap between the clinical pathological and genetic features seen in JHD and more traditional adult-onset HD. Nonetheless, the frequent predominance of bradykinesia and dystonia early in the course of the illness, more frequent occurrence of epilepsy and myoclonus, more widespread pathology, and larger genetic lesion means that the distinction is still relevant. In addition, the relative rarity of JHD means that the clinician managing the patient is often doing so for the first time. Management is, at best, symptomatic and supportive with few or no evidence-based guidelines. In this article, the authors will review what is known of the condition and present some suggestions based on their experience.

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Financial & competing interest disclosure
OWJ Quarrell is lead facilitator for the Juvenile Huntington's Disease Working Group within the European Huntington's Disease Network (EHDN) and has been in receipt of seed fund grants supporting work on juvenile Huntington's disease. He has recently been appointed to the steering committee for the EHDN study called REGISTRY and is a member of the Scientific and Publication Review committee for the ENROLL-HD project. MA Nance served on an advisory board panel for Lundbeck Pharmaceuticals and Cure Huntington's Disease Initiative (CHDI); received honoraria from the Huntington Disease Society of America and WebMD; and receives or has received grant support from the Huntington Disease Society of America, National Parkinson Foundation, IMPax Pharmaceuticals, TEVA Pharmaceuticals, Prana Biotechnology, Schering–Plough Research Institute, Phytopharm, Biotie Therapies Inc., Neurosearch, Medivation/Pfizer, NIH/National Institute of Neurological Disorders and Stroke (NINDS), and National Center for Complimentary and Alternative Medicine (NCCAM). P Nopoulos receives research funding from CHDI and the NIH. JS Paulsen receives funding from the NIH (NS0040068), the Huntington Disease Society of America and CHDI. JA Smith has received funding from the EHDN. F Squitieri has recieved support from the patients' families organization Associazione Italiana Corea di Huntington (AICH), Neuromed, NeuroSearch and Telethon (grant number: GGP12218). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Historical note & prevalence

The first descriptions of Huntington's disease (HD) predate the succinct report by Huntington in 1872 [1]. Similarly, although juvenile HD (JHD) may have been described earlier, the first clear description is attributed to Hoffmann in 1888 [2]. In that article he described a family with HD, one of whom was a female aged 36 years. She had onset of epilepsy at the age of 2–3 years, but its relationship to HD is less clear. She developed abnormal movements before the end of her school years and lost the ability to do 'handicrafts' at the age of 22–23 years, at which time the epilepsy became more frequent. Hoffmann clearly described the poverty of movement in this patient. He also gave a briefer description of a female cousin who developed chorea at the age of 10 years and died in her twenties. Interestingly, in both cases the transmitting parent was the mother. An important point from this historical note is that the disease duration may be many years, well into young adulthood. The origin of the term JHD is obscure, but in 1968, Bruyn reviewed the published literature and accepted a definition of JHD as onset before 20 years [3]. A number of publications also include cases with onset at 20 years of age so the definition of ≤20 years will be used in this review; in addition, those with onset at ≤10 years will be described as having 'childhood-onset' HD.

The percentage of JHD in studies of HD prevalence varies; however, a recent meta-analysis of studies that used multiple methods of ascertainment from 1980 and were from countries described as high income by the World Bank gave a percentage of 4.81% (95% CI: 3.31–6.58%) [4]. This was contrasted with three studies from Venezuela and South Africa (that are described by the World Bank as high to middle income), which had a percentage of 9.95% (95% CI: 6.37–14.22%). The difference may be due to the different age structures in these populations. If there is a large elderly population then those with later ages of onset will present with the condition and as a consequence the percentage of JHD cases will be lower. Of the JHD cases in this meta-analysis, approximately 20% had childhood-onset HD. Prevalence figures vary between studies and populations, but a convenient figure is ten per 100,000, although in some populations it may be higher [5]; therefore, in a population of 50 million there should be approximately 250 cases of JHD, but it has to be remembered that at any point in time many will be over the age of 20 years.

Clinical features

Any patient with HD will experience a mixture of problems with both voluntary and involuntary movement. Classically, patients with adult HD (AHD) will demonstrate signs of chorea early in the course of the illness but, even at this stage, there can be slowing of rapid alternating movements, which can be demonstrated on clinical examination. As the disease progresses, the chorea becomes more prominent, but eventually plateaus or even declines. Meanwhile, problems with bradykinesia and dystonia become more prominent. In JHD, the pattern tends to be that the bradykinesia, dystonia and parkinsonian features are prominent at an early stage, while chorea, if present, is less prominent [6].

If cases of JHD are divided into predominantly choreic or predominantly dystonic and braykinetic, the proportion will be 40–50 and 50–60%, respectively [7–11]. There is less information available about myoclonus and epilepsy but this is reported in approximately 30–50% of cases [7–9,12].

In most cases of HD, the motor symptoms are less of a problem for the family than the cognitive and behavioral problems. In fact, not only are behavioral and cognitive problems more difficult for the family, they are the most common presenting symptoms [10,12]. It is well recognized that declining school performance can be a significant feature of JHD [13]. Speech and language problems may occur early in the course of the illness and can be a

pointer toward the diagnosis [14]. The evidence basis for the behavioral effects of JHD in relation to changes in puberty and sexual activity is limited. It is not possible to give specific advice; each case should to be managed by the multidisciplinary team described below.

HD is considered to be a disease of the nervous system, but there are some wider manifestations such as weight loss and cachexia [15] and, as may be expected, these also occur in JHD.

Pathology

There is similarity between the pathology seen in HD and JHD. Although the pathological process affects several areas of the brain, the initial brunt of the pathology occurs in the corpus striatum, with significant atrophy of the caudate and putamen nuclei, and globus pallidus, which is divided into internal and external nuclei. The pathology in JHD is likely to be more extensive and severe than in a more classical AHD case, provided the patient has not died prematurely [16,17]. In 20% of AHD cases the frontal lobe can appear normal, whereas in JHD the brains are small with prominent frontal and parietal atrophy. In contrast to AHD, the internal globus pallidus is grossly atrophic in JHD and this may account for some of the symptoms related to poverty of movement [16,17]. There have been reports that cerebellar atrophy occurs in JHD [18–24], but not in every case with very early onset [25,26]. It has been suggested that this could be related to hypoxic–ischemic changes secondary to epilepsy [15,16]; however, this is less likely as, more recently, cerebellar changes in AHD have been recognized as occurring early in the course of the disease, which were not correlated with the extent of the striatal atrophy, but may explain some of the features seen in HD [27].

HD results from an unstable expansion of a CAG repeat sequence in the first exon of the huntingtin gene such that the resulting protein (HTT), contains an expanded glutamine sequence [28]. The abnormal protein is widely expressed, but the neurodegenerative process is selective; therefore, within the caudate and putamen nuclei, the medium spiny neurons are especially sensitive to the neuropathological process. There has been a large number of studies trying to explain how the normal protein affects cellular processes and in turn explain how the abnormal protein subsequently results in the pathological changes seen in HD. HTT has a number of functions within the cell and, to date, there is not a coherent explanation of how the multifaceted functions of normal and abnormal HTT in cells results in the well-recognized clinical and pathological features.

Genetic issues

There is a consensus about the reporting of genetic testing results: under 27 CAG repeats is unequivocally normal; 27–35 CAG repeats has the potential to expand into the abnormal range in future generations; 36–39 CAG repeats is abnormal, but there may be reduced penetrance; and over 40 CAG repeats is considered unequivocally abnormal [29]. Soon after the gene was cloned it became clear that there was a negative correlation between the mean CAG repeat length and the age of onset [30–37]. Although this relationship has proved to be robust, there is such a large range around the mean that the specific CAG result does not provide reliable information regarding a predicted age of disease onset for an individual [38].

It is often stated that individuals with CAG repeat lengths >60 have JHD. However, it is not appropriate to define JHD based on >60 CAG repeats because approximately half of the cases have a CAG repeat length <60 and in some rare cases repeat length can be in the 40s [11–13,31]. In addition, there may be a few patients with repeat lengths >60 and an onset

just over 20 years [39]. The extent of the overlap of the CAG repeat lengths between AHD and JHD is often not fully appreciated [40].

Apart from man, no known natural animal develops HD. The cloning of the *HTT* gene led to the development of a number of mouse and other animal models of the condition. In order to drive the pathological process, most animal models of HD contain grossly abnormal CAG repeat lengths so, in a broad sense, they are more likely to model JHD rather than AHD. The mouse models have recapitulated a number of features of HD, including the presence of intra-neuronal inclusions, transcriptional and energetic deficits, as well as the development of progressive motor and cognitive defects, predictably leading to death [41].

It has been widely recognized that in the majority of JHD cases the transmitting parent is the father: this occurs in approximately 70–80% of those cases with an onset between 11 and 20 years of age and may be over 90% in those with childhood-onset HD [3,8–12,31,42–47]. This observation was originally made before the gene was cloned, but we now have an explanation in that there is instability in the CAG repeat length during spermatogenesis, which increases if the father has a longer CAG repeat length [31–33,48–50]. Care has to be taken with remarks about paternal transmission in JHD because families may have increased worry about their children. While it is true that in the majority of cases the transmitting parent is the father, it does not follow that fathers affected by HD will necessarily have offspring with JHD. In some families, specific reassurance on this point may be required, as in some notable cases the transmitting parent was the mother [2,25,26,51].

Disease duration & progression

Patients with AHD have a slowly progressive condition that lasts for many years. It is often said to last 15–20 years, but there is wide variation around this figure, with some patients having longer disease duration. Gusella and MacDonald reviewed the data presented in Persichetti *et al.* [52] and demonstrated that, while there was a correlation between CAG repeat length and age of onset, there was no correlation with disease duration [53]. The implication of this observation is that once the disease process starts it continues and factors other than the CAG repeat length determine progression of the pathological process. Unfortunately, there were only two to four cases with onset at ≤20 years of age in that dataset and no cases of childhood-onset HD.

There is a perception that JHD patients have shorter disease duration, but there is conflicting evidence on this topic within the published literature [8,54–56]. There have been case reports of individuals with very high repeat lengths (95–240) of whom three have died: they had onsets at ages 2.5, 3.5 and 3 years, and their duration of illness was 13.5, 4 and 8 years, respectively. [23,25,26]. It is often difficult to draw conclusions from single case reports. It may be the case that disease duration is shorter in childhood-onset cases; however, they are much less common than those with onset in the second decade so a large international study is required to settle the question.

The view that the illness in JHD progresses at a faster rate is widely held [6]. The problem with a review of the literature is that some studies are cross-sectional whereas others are longitudinal; in addition, progression has been assessed with a variety of different clinical assessments or different imaging measurements [6]. Taken as a whole, there is probably a greater rate of disease progression in those with JHD, but given the relative rarity of JHD, the assessment of disease progression may require the collection of data as part of a multinational collaboration such as the European Huntington's Disease Network (EHDN) project REGISTRY [101]. The EHDN has established a working group on JHD and a

specific substudy for JHD [102]. This work will be developed further as part of a new study called ENROLL-HD [103].

The issue of disease progression is not wholly academic because parents will ask about how long the illness lasts and may themselves have come across comments that JHD is associated with shorter disease duration. As in any medical discussion, the clinical features of the young individual need to be considered but, in general, it may be wise to avoid categorical statements and still speak in terms of a duration measured in years, up to as much as a decade or two.

Issues with diagnosis

The diagnosis of HD, whether AHD or JHD, is based on a clinical judgment that unequivocal neurological signs are present. If a young individual comes from a family with HD and unequivocal neurological signs are present, then undertaking a genetic test to confirm the diagnosis is noncontroversial. Nance and the US Huntington Disease Genetic Testing Group have proposed that a clinical diagnosis of JHD can be made in those with onset aged under 10 years if the criteria in Box 1 are met [12]; identifying a similar set of diagnostic criteria for those with onset between 11 and 20 years of age proved more challenging.

Box 1

Diagnostic criteria for childhood-onset Huntington's disease (≤10 years)

- A family history of Huntington's disease (usually in the father) and two or more of:
  - Declining school performance
  - Seizures
  - Oral motor dysfunction
  - Rigidity
  - Gait disturbance

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Although symptomatic and supportive treatment is available for HD, there is no treatment that is disease modifying. For this reason, the genetic test is used cautiously and guidelines have been developed for undertaking predictive testing. The updated guidelines specify that predictive testing is not recommended for those aged under 18 years [37]. This poses a difficulty if a young individual presents with behavioral problems as it can lead to delays in diagnosis [11,57]. Quite reasonably, there is reluctance to undertake genetic testing in this scenario. If the CAG repeat length is >60 then JHD onset is very likely. If the result is in the normal range then it is clear that the problems are unrelated to HD. However, if the result is in the more usual abnormal range then it will have been established that the young individual has inherited the mutation, but whether the current symptoms are related to JHD will remain unclear. Moreover, it is possible that the current problems are unrelated to HD and the individual is due to start to have symptoms at a more distant time in the future. The delay in diagnosis may lead to frustration for the parents and care must be taken not to imply that the behavioral difficulties result from bad parenting [58].

In the circumstances of a child with exclusively behavioral symptoms, a baseline cognitive assessment and MRI scan may be considered, not because they are diagnostic in themselves,

but because they can be repeated at a future time to assess whether there has been decline. This, in turn, can help with the management of the young individual and their family.

It is possible for a young individual to present with HD before one parent, usually the father, is diagnosed; this has happened in cases with very long CAG repeats [22,25,49,59,60], but the extent to which it happens with teenage onset is less clear, although the authors have personal experience of this in at least one case. In this circumstance, managing the family requires additional care because the possibility of nonpaternity may arise or, if a history of HD is described in other relatives, the relevant parent may be reluctant to undergo genetic testing.

A further problem may arise if behavioral issues occur in a teenager and the parents do not want HD discussed in front of the young individual. This has to be handled sensitively and progress can only be made at a pace allowed by the family.

Management

Once a diagnosis of JHD has been established it is essential to consider a multiprofessional approach as outlined in Table 1. There is no disease-modifying treatment available and no specific evidence basis for interventions so the team needs to consider the symptoms and work together to provide effective symptomatic and supportive care. Given the progressive neurodegeneration, the role and relative importance of each team member will vary according to the stage of the illness. In the majority of cases, the individual professional may come across JHD for the first time so it is important to recognize this and not pretend to have knowledge. Families may prefer a response along the lines of: ‘I do not know the answer to your question but will find out’ [58]. Schooling is especially important and teachers may value an annual assessment of the cognitive decline so as to plan a relevant curriculum. Given that there is, as yet, no disease-modifying therapy, considerable emphasis needs to be placed on nonpharmacological interventions.

Pharmacological treatment has a place in the management of JHD but as no current evidence exists. Box 2 summarizes the symptoms that may need to be managed over the course of the illness. A recent report of medications that are prescribed in JHD showed evidence of polypharmacy [61]; therefore, it may be wise to have periodic reassessment of the pharmacological treatments as the needs of patients vary over the course of the illness. Table 2 summarizes the drugs that were prescribed to 45 European patients [61]. The current authors emphasize that, to date, there is no evidence for the use of these medications in JHD so the fact that they have been mentioned in this review should not imply that we endorse any particular drug. In that study, the most commonly prescribed drugs were dopa blockers, antidepressants and dopa agonists [61]. Dopa blockers and dopa agonists (if parkinsonian features are present), muscle relaxants and benzodiazepines have been used to manage motor symptoms. Behavioral symptoms can be managed with the use of dopa blockers (antipsychotics are often used to quell aggression), antidepressants and mood-stabilizing agents. Antiepileptic medications may be used either as mood stabilizers or for the management of epilepsy. Treatment of cognitive problems, such as inattention, with stimulants can be useful; however, these should be used cautiously in the context of monitoring adverse effects on motor symptoms; therefore, nonstimulant treatments, such as atomoxetine, may be an important alternative. Parents or care providers may have contact with another family with JHD and may not understand why the medications that have been prescribed differ and may wonder if another clinician could suggest something more helpful. This requires a willingness to consider the suggestion proposed by the family while, at the same time, explaining that each patient’s symptoms vary and in certain circumstances why a particular medication is inappropriate for their child.

Box 2

Summary of Huntington's disease symptoms that require treatment

- Movement disorder:
  - Involuntary movements
  - Incoordination of voluntary movements
  - Rigidity/dystonia
  - Oral–motor dysfunction
- Cognitive disorder:
  - Progressive cognitive dysfunction (treated by repeated testing, and creation of appropriate school or vocational programs and goals)
- Psychological/behavioral disorder:
  - Depression
  - Anxiety
  - Obsessiveness
  - Inattention/ADHD
  - Apathy
  - Impulsiveness
  - Irritability
- Family issues:
  - Caregiver stress
  - School placement
  - Work placement
- Other:
  - Weight loss
  - Poor oral hygiene
  - Aspiration pneumonia (late)

The progressive dystonia may be difficult to treat and, depending on the individual concerned, there can be difficulty in managing the behavioral problems. This underscores the need for a multiprofessional approach and the importance of reinforcing the point that the disruptive behavior results from the underlying neurodegenerative process.

The progressive nature of the illness means that at some stage there has to be a discussion of end-of-life care, which, in the case of JHD, can be over a prolonged period of time. Weight loss and dysphagia with its attendant risk of aspiration pneumonia means that use of a percutaneous endoscopic gastrostomy feeding tube needs consideration; ideally, this should have been discussed earlier in the course of the illness so that its mention later does not come as a surprise. There is a limited literature of end-of-life care in JHD [62]. Nonetheless, palliative care clinicians can advise on symptomatic medication and management of pain, which may be associated with dystonic spasms.

Views of families

So far, this review has focused on JHD from the perspective of the clinician. There has been one account of JHD given by an individual with JHD in which he describes his losses and the progressive isolation from his friends, but he also describes those aspects of his life that are important to him [63]. Qualitative methods are valuable when attempting to understand the participant's perspective, especially when the phenomenon is rare. A British study employed such an approach to examine the experience of parents/primary carers of children with JHD [64].

When questioned about their experience, parents/care providers reported that they slowly became aware that something was wrong: at times, this could be based on nonspecific observations with small gradual changes often not noticed by others. Carers spoke about the physical symptoms and were distressed by falls, epilepsy and pain. Similarly, problems with communication and progressive isolation from friends caused distress for the parents. The behavioral problems were difficult for carers, especially when these occurred in public and resulted in perceived criticism from others. Carers also spoke of the slow and relentless nature of the condition. Aspects of helpful and unhelpful support and of feeling isolated were described in separate reports [58,65]. A study employing the same methodology to examine the experiences of parents in different European countries has recently been completed and reports similar findings [66].

Conclusion & future perspective

HD research has benefited from multicenter and international observational studies, such as REGISTRY [67,101], COHORT [68], PREDICT [69] and TRACK-HD [70]. The REGISTRY and COHORT studies are going to be merged into a global observational study called ENROLL-HD [103]. These studies will allow information on cases of JHD to be shared. This exposes a problem that the rating scale most often used to monitor disease progression in HD, the Unified Huntington's Disease Rating Scale (UHDRS), is not suitable for assessing younger patients [71]. New rating scales are being developed so that some specific questions related to JHD can be addressed [72].

The development of specific rating scales will allow a more rigorous assessment of the treatments currently used for JHD. At the same time, it is important to develop biomarkers to assess disease progression. Imaging studies provide the prospect of objectively measuring the rate of atrophy in the caudate and putamen nuclei, which can be used as an assessment of treatment in both AHD and JHD patients in future clinical trials.

Hopefully disease-modifying treatments will become available. Clinical trials of proposed therapies are likely to be undertaken on patients with AHD in the first instance. These could include treatments to prevent the abnormal protein from being produced (using RNA suppression or gene repair strategies) or the use of compounds to promote increased clearance of mutant HTT using the cell's own mechanisms. Experiments are being undertaken with stem cells, including induced pluripotent stem cell technology. There is an active research pipeline involving the identification of new treatment targets and testing these in cell cultures and model organisms, through to supporting the development of new outcome measures that can be used in clinical trials.

An effective treatment could be identified serendipitously but, short of that, an understanding of the multifaceted nature of HD, of which JHD is a part, is an essential prerequisite for developing effective disease-modifying treatments. There is now a greater prospect for therapies that alter the natural history of HD than ever before.

New emerging drugs might represent future resources for JHD patients. One example is pridopidine, a dopamine stabilizer, recently tested in AHD; it did not achieve significance in its primary outcome measure but improved motor scores, particularly in those with dystonia [73]. Another potential pharmacological resource might be creatine, a food supplement expected to improve energy metabolism in HD. This is the subject of a current clinical trial and, for the first time, patients with an age as low as 18 years are currently under experimental treatment in a trial named the CREST-E study [104].

A question arises as to whether abnormal HTT has an effect on development. A recent study evaluated 20 asymptomatic children at risk of HD with basic morphometric measures of height, BMI, weight and head circumference, as well as a research laboratory assessment of CAG repeats in *HTT* (no genetic results were provided to subjects) [74]. The gene-expanded (CAG repeats >39) subset of asymptomatic children were compared with 138 healthy control children who did not have a family history of HD. The gene-expanded children had a significantly smaller mean head circumference and lower BMI compared with controls. Head circumference, a noninvasive proxy for brain size, was abnormally low even after correcting for height, suggesting a specific deficit in brain growth, rather than a global growth abnormality. These findings suggest that abnormal HTT may have a direct effect on brain development and led to the speculation that this phenomenon is more pronounced in JHD.

Acknowledgments

The authors would like to thank their patients and the European Huntington's Disease Network (EHDN) for establishing a working group on juvenile Huntington's disease, which has brought them together.

References

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1. Huntington G. On chorea. Medical and Surgical Reporter. 1872; 26:317–321.
2. Hoffmann J. On chronic progressive chorea (Huntington's chorea, hereditary chorea). Virchows Arch A Pathol Anat. 1888; 111:513–548.
3▪. Bruyn, GW. Huntington's chorea historical, clinical and laboratory synopsis. In: Vinken, PJ.; Bruyn, GW., editors. Handbook of Clinical Neurology. Vol. 16. Elsevier; Amsterdam, The Netherlands: 1968. p. 298-387.Summarizes the cases of juvenile Huntington's disease (JHD) reported in the literature up to 1968
4. Quarrell O, O'Donovan KL, Bandmann O, Strong M. The prevalence of Huntington's disease: a review of the literature and meta-analysis. PLoS Curr. 2012; 4:e4f8606b742ef3.
5. Rawlins M. Huntington's disease out of the closet. Lancet. 2010; 376(9750):1372–1373. [PubMed: 20594589]
6. Quarrell, OWJ. Juvenile Huntington's disease. In: Bates, G.; Jones, L.; Tabrizi, S., editors. Huntington's Disease. 4. Oxford University Press; NY, USA: 2014. (In Press)
7. Brackenridge CJ. Factors influencing dementia and epilepsy in Huntington's disease of early onset. Acta Neurol Scandinav. 1980; 62:305–311. [PubMed: 6451137]
8. Hayden, MR. Huntington's Chorea. Springer-Verlag; Berlin Heidelberg, NY, USA: 1981. p. 78-81.
9. van Dijk JG, van der Velde EA, Roos RA, Bruyn GW. Juvenile Huntington disease. Hum Genet. 1986; 73:235–239. [PubMed: 2942452]
10. Seisling S, Vegter-van der Vlis M, Roos RA. Juvenile Huntington's disease in the Netherlands. Pediatr Neurol. 1997; 17:37–43. [PubMed: 9308974]

11. Cannella M, Gellera C, Maglione M, et al. The gender effect in juvenile Huntington disease patients of Italian origin. Am J Med Genet Part B Neuropsychiatr Genet. 2004; 125B(1):92–98.

12▪▪. Ribbai P, Nguyen K, Hahn-Barma V, et al. Psychiatric and cognitive difficulties as indicators of juvenile Huntington's disease onset in 29 patients. Arch Neurol. 2007; 64:813–819. Outlines some of the delays that can occur in diagnosing JHD. [PubMed: 17562929]

13▪▪. Nance MA. US Huntington Disease Genetic Testing Group. Genetic testing of children at risk for Huntington's disease. Neurology. 1997; 49:1048–1053. Summarizes the clinical features of very young individuals with JHD. Diagnostic criteria were proposed to aid diagnosis for those cases with disease onset at ≤10 years. [PubMed: 9339688]

14. Yoon G, Kramer J, Zanko A, et al. Speech and language delay are early manifestations of juvenile-onset Huntington disease. Neurology. 2006; 67:1265–1267. [PubMed: 17030763]

15. van der Burg JM, Björkvist, Brundin P. Beyond the brain: widespread pathology in Huntington's disease. Lancet Neurol. 2009; 8:765–774. [PubMed: 19608102]

16. Vonsattel, JP.; Cortes, EP.; Keller, CE. Juvenile Huntington's disease: neuropathology. In: Quarrell, OWJ.; Brewer, HM.; Squitieri, F.; Barker, RA.; Nance, MA.; Landwehrmeyer, GB., editors. Juvenile Huntington's Disease and Other Trinucleotide Repeat Disorders. Oxford University Press; NY, USA: 2009. p. 51-78.

17▪▪. Vonsattel, JPG.; Keller, C.; Ramirez, EPC. Huntington's disease – neuropathology. In: Weiner, WJ.; Tolosa, E., editors. Hyperkinetic Movement Disorders. Handbook of Clinical Neurology. Elsevier, Amsterdam: The Netherlands; 2011. p. 83-100.Apart from summarizing pathology in Huntington's disease (HD), this chapter also provides a summary of the more extensive pathology in JHD

18. Jervis GA. Huntington's chorea in childhood. Arch Neurol. 1963; 9:244–257. [PubMed: 14049398]

19. Markham CH, Knox JW. Observations on Huntington's chorea in childhood. J Pediatr. 1965; 67:46–57. [PubMed: 14301558]

20. Byers RK, Gilles FH, Fung C. Huntington's disease in children. Neurology. 1973; 23:561–569. [PubMed: 4267989]

21. Squitieri F, Pustorino G, Cannella M, et al. Highly disabling cerebellar presentation in Huntington disease. Eur J Neurol. 2003; 10:443–444. [PubMed: 12823498]

22. Senaca S, Fagnart D, Keymolen K, et al. Early onset Huntington's disease: a neuronal degeneration syndrome. Eur J Pediatr. 2004; 16:717–721.

23. Wojaczynska-Stanek K, Adamek D, Marszal E, Hoffman-Zacharska D. Huntington disease in a 9-year-old boy: clinical course and neuropathologic examination. J Child Neurol. 2006; 21:1068–1073. [PubMed: 17156701]

24. Nicolas G, Devys D, Goldenberg A, et al. Juvenile Huntington disease in an 18-month-old boy revealed by global developmental delay and reduced cerebellar volume. Am J Med Genet A. 2011; 155A:815–818. [PubMed: 21412977]

25. Nance MA, Mathias-Hagen V, Breningstall G, Wick MJ, McGlennen RC. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. Neurology. 1999; 52:392–394. [PubMed: 9932964]

26. Nahhas FA, Garbern J, Krajeweski KM, Roa BB, Feldman GL. Juvenile onset Huntington's disease resulting from a maternal expansion. Am J Med Genet. 2005; 137A:328–331. [PubMed: 16096998]

27. Rüb U, Hoche F, Brunt ER, et al. Degeneration of the cerebellum in Huntington's disease (HD): possible relevance for the clinical picture and potential gateway to pathological mechanisms of the disease process. Brain Pathol. 2013; 23:165–177. [PubMed: 22925167]

28▪▪. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72:971–983. Describes the nature of the mutation in HD. [PubMed: 8458085]

29▪. The American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group. ACMG/ASHG Statement. Laboratory guidelines for Huntington's disease genetic testing. Am J Hum Genet. 1998; 62:1243–1247. Guidelines for reporting results that are still in use today. [PubMed: 9545416]

30. Andrew SE, Goldberg P, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet. 1993; 4:398–403. [PubMed: 8401589]
31. Telenius H, Kremer HPH, Theilmann J, et al. Molecular analysis of juvenile Huntington disease: the major influence on $(CAG)_n$ repeat length is the sex of the affected parent. Hum Mol Genet. 1993; 2:1535–1540. [PubMed: 8268906]
32. Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet. 1993; 4:387–392. [PubMed: 8401587]
33. Zühlke C, Reiss O, Bockel B, Lange H, Thies U. Mitotic stability and meiotic variability of the $(CAG)_n$ repeat in the Huntington disease gene. Hum Mol Genet. 1993; 2:2063–2067. [PubMed: 8111374]
34. MacMillan JC, Snell RG, Tyler A, et al. Molecular and clinical correlates of the Huntington's disease mutation. Lancet. 1993; 342:954–958. [PubMed: 8105214]
35. Snell RG, MacMillan JC, Cheadle JP, et al. Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nat Genet. 1993; 4:393–397. [PubMed: 8401588]
36. Nørremølle A, Riess O, Epplen JT, Fenger K, Hasholt L, Sørensen SA. Trinucleotide repeat elongation in huntingtin gene in Huntington's disease patients from 71 Danish families. Hum Mol Genet. 1993; 2:1475–1476. [PubMed: 8242074]
37. Claes S, Zand KV, Legius E, et al. Correlations between triplet repeat expansion and clinical features in Huntington's disease. Arch Neurol. 1995; 52:749–753. [PubMed: 7639626]
38▪. MacLeod R, Tibben A, Frontali M, et al. Recommendations for the predictive genetic test in Huntington's disease. Clin Genet. 2013; 83:221–231. Recommendations that guide the use of predictive testing for HD. [PubMed: 22642570]
39. Squitieri F, Frati L, Ciamiello A, Lastoria S, Quarrell O. Juvenile Huntington disease: does a dosage-effect pathogenic mechanism differ from the classical adult disease? Mech Ageing Dev. 2006; 127:208–212. [PubMed: 16274727]
40. Quarrell, OWJ.; Nance, MA. The diagnostic challenge. In: Quarrell, OWJ.; Brewer, HM.; Squitieri, F.; Barker, RA.; Nance, MA.; Landwehrmeyer, GB., editors. Juvenile Huntington's Disease and Other Trinucleotide Repeat Disorders. Oxford University Press; NY, USA: 2009. p. 135-149.
41. Bates, GP.; Woodman, B. Juvenile Huntington's disease and mouse models of Huntington's disease. In: Quarrell, OWJ.; Brewer, HM.; Squitieri, F.; Barker, RA.; Nance, MA.; Landwehrmeyer, GB., editors. Juvenile Huntington's Disease and Other Trinucleotide Repeat Disorders. Oxford University Press; NY, USA: 2009. p. 101-106.
42. Merritt, DA.; Conneally, PM.; Rahman, NF.; Drew, AL. Juvenile Huntington's chorea. In: Barbeau, A.; Burnette, JR., editors. Progress in Neurogenetics. Excerta Medica Foundation; Amsterdam, The Netherlands: 1969. p. 645-650.
43. Barbeau A. Parental ascent in the juvenile form of Huntington's chorea. Lancet. 1970; 2(7679): 937. [PubMed: 4097325]
44. Went LN, Vegter-van der Vlis M, Bruyn GW. Parental transmission in Huntington's disease. Lancet. 1984; 323(8386):1100–1102. [PubMed: 6144830]
45. Ho VB, Chuang HS, Rovira MJ, Koo B. Juvenile Huntington's disease: CT and MR features. Am J Neuoradiol. 1995; 16:1405–1412.
46. Rasmussen A, Macias R, Yescas P, Ochoa A, Davila G, Alonso E. Huntington disease in children: genotype–phenotype correlation. Neuropediatrics. 2000; 31:190–194. [PubMed: 11071143]
47. Nance MA, Myers RH. Juvenile onset Huntington's disease – clinical and research perspectives. Ment Retard Dev Disabil Res Rev. 2001; 7:153–157. [PubMed: 11553930]
48. MacDonald ME, Barnes G, Srindhi J, et al. Gametic but not somatic instability of CAG repeat length in Huntington's disease. J Med Genet. 1993; 30:982–986. [PubMed: 8133508]
49. Leeflang EP, Tavare S, Marjoram P, et al. Analysis of germline mutation spectra at the Huntington's disease loculs support a mitotic mutation mechanism. Hum Mol Genet. 1999; 8:173–183. [PubMed: 9931325]

50. Wheeler VC, Persichetti F, McNeil SM, et al. Factors associated with *HD* CAG repeat instability in Huntington's disease. J Med Genet. 2007; 44:695–701. [PubMed: 17660463]
51. Holinski-Feder E, Jedele KB, Hörtnaagel K, Albert A, Meindl A. Large intergenerational variation in age of onset in two young patients with Huntington's disease presenting as dyskinesia. Pediatrics. 1997; 100:896–898. [PubMed: 9346994]
52. Persichetti F, Carlee L, Faber PW, et al. Huntington's disease CAG trinucleotide repeats in pathologically confirmed postmortem brains. Neurobiol Dis. 1994; 1:159–166. [PubMed: 9173995]
53. Gusella J, MacDonald M. No post-genetics era in human disease research. Nat Rev Genet. 2002; 3:72–79. [PubMed: 11823793]
54. Foroud T, Gray J, Ivashina J, Conneally PM. Differences in duration of Huntington's disease based on age at onset. J Neurol Neurosurg Psychiat. 1999; 66:52–56. [PubMed: 9886451]
55. Roos RA, Hermans J, Vegter-van der Vlis M, van Ommen GJ, Bruyn GW. Duration of illness in Huntington's disease is not related to age at onset. J Neurol Neurosurg Psychiat. 1993; 56:98–100. [PubMed: 8429330]
56. Newcombe R, Walker DA, Harper PS. Factors influencing age of onset and survival in Huntington's chorea. Ann Hum Genet. 1981; 45:387–396. [PubMed: 6211129]
57. Jongen PJ, Renier WO, Gabreëls FJ. Seven cases of Huntington's disease in childhood and levadopa induced improvement in the hypokinetic-rigid form. Clin Neurol Neurosurg. 1980; 82:251–261. [PubMed: 6165509]
58. Brewer HM, Smith JA, Eatough V, Stanley CA, Glendinning NW, Quarrell OWJ. Caring for a child with juvenile Huntington's disease: helpful and unhelpful support. J Child Health Care. 2007; 11:40–52. [PubMed: 17287223]
59. Gencik M, Hammans C, Strehl H, Wagner M, Epplen JT. Chorea Huntington: a rare case with childhood onset. Neuropediatrics. 2002; 33:90–92. [PubMed: 12075490]
60. Gambadella A, Muglia M, Labati A, et al. Juvenile Huntington's disease presenting as progressive myoclonic epilepsy. Neurology. 2001; 57:708–711. [PubMed: 11524486]
61▪. Robertson L, Santini H, O'Donovan K, et al. Current pharmacological management in juvenile Huntington's disease. PLoS Curr. 2012; 4:RRN1304. Summarizes some of the pharmacological interventions in JHD. [PubMed: 22474619]
62. King N. Palliative care management of a child with juvenile onset Huntington's disease. Int J Palliative Nursing. 2005; 11:278–283.
63. Brewer, HM.; McGill, M. Family experiences: part I, diagnosis and early stages. In: Quarrell, OWJ.; Brewer, HM.; Squitieri, F.; Barker, RA.; Nance, MA.; Landwehrmeyer, GB., editors. Juvenile Huntington's Disease and Other Trinucleotide Repeat Disorders. Oxford University Press; NY, USA: 2009. p. 1-18.
64. Smith JA, Brewer HM, Eatough V, Stanley CA, Glendinning NW, Quarrell OWJ. The personal experience of juvenile Huntington's disease: an interpretative phenomenological analysis of parents' accounts of the primary features of a rare genetic condition. Clin Genet. 2006; 69:486–496. [PubMed: 16712700]
65. Brewer HM, Eatough V, Smith JA, Stanley CA, Glendinning NW, Quarrell OWJ. The impact of juvenile Huntington's disease on the family. J Health Psychol. 2008; 13:5–16. [PubMed: 18086713]
66. Eatough V, Santini H, Eiser C, et al. The personal experience of parenting a child with juvenile Huntington's disease: perceptions across Europe. Eur J Hum Genet. 2013 Epub ahead of print. 10.1038/ejhg.15
67. Orth M, Handley O, Schwenke C, et al. Observing Huntington's disease: the European Huntington's Disease Networks REGISTRY. PLoS Curr. 2010; 2:RRN1184. [PubMed: 20890398]
68. Dorsey ER. the Huntington Study Group COHORT Investigators. Characterization of a large group of individuals with Huntington disease and their relatives enrolled in the COHORT study. PLoS One. 2012; 7(2):e29522. [PubMed: 22359536]
69. Paulsen JS, Hayden M, Stout JC, et al. Preparing for preventive clinical trials: the Predict-HD study. Arch Neurol. 2006; 63:833–890. [PubMed: 16769864]

70. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol. 2009; 8:791–801. [PubMed: 19646924]

71. Huntington Study Group. Unified Huntington's disease rating scale: reliability and consistency. Mov Disord. 1996; 11:136–142. [PubMed: 8684382]

72. Brewer, HM.; Barker, RA.; Quarrell, OWJ. Challenges in assessment. In: Quarrell, OWJ.; Brewer, HM.; Squitieri, F.; Barker, RA.; Nance, MA.; Landwehrmeyer, GB., editors. Juvenile Huntington's Disease and Other Trinucleotide Repeat Disorders. Oxford University Press; NY, USA: 2009. p. 181-188.

73. de Yebenes JG, Landwehrmeyer B, Squitieri F, et al. Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a Phase 3, randomised, double blind, placebo-controlled study. Lancet Neurol. 2011; 10:1049–1057. [PubMed: 22071279]

74. Lee JK, Matthews K, Schlagger B, et al. Measures of growth in children at risk for Huntington's disease. Neurology. 2012; 79:668–674. [PubMed: 22815549]

Websites

101. European Huntington's Disease Network. [Accessed 29 October 2012] REGISTRY. www.euro-hd.net/html/network

102. European Huntington's Disease Network. [Accessed 29 October 2012] Huntington's Disease Working Group. www.euro-hd.net/html/network/groups/jhd

103. ENROLL-HD. [Accessed 14 October 2012] Enroll-HD – Working Groups – Protocol Development Committee. www.enroll-hd.org/html/wg/protocol/docs

104. ClinicalTrials.gov. [Accessed 19 February 2013] Creatine Safety, Tolerability, and Efficacy in Huntington's Disease (CREST-E). www.clinicaltrials.gov/ct2/show/NCT00712426?term=crest+E&rank=1

Practice Points

- Juvenile Huntington's disease (JHD) is defined as Huntington's disease (HD) with an age of onset ≤20 years and accounts for approximately 5% of all HD cases.
- Individuals with a CAG repeat length of >60 usually have JHD, but a significant proportion of JHD cases (~50%) have <60 CAG repeats.
- The transmitting parent is frequently the father (~70–80% of cases), but this is not an absolute even in those cases with very large CAG repeat lengths.
- Issues of disease duration and disease progression are contested, and it is wise to avoid categorical statements when talking to families.
- If a young individual from a HD family has behavioral problems, it is important for clinicians to avoid implying that these result from 'poor parenting skills'.
- The disease duration is prolonged; therefore, a multiprofessional approach is required for management.
- Pharmacological treatment is aimed at symptomatic and supportive care.
- End-of-life issues have to be considered on an individual basis.

Table 1

Professionals involved in the care of patients with juvenile Huntington's disease.

Professional	Potential role
General pediatrician/community pediatrician	Address general health needs and act as a focal point for specialist input
Pediatric neurologist possibly supplemented by a clinician (neurologist, psychiatrist or geneticist) with a specific interest in HD	Advice on pharmacological management and assessment of the disease stage
Child psychiatrist	Advise on management of the family and pharmacotherapy for behavioral disorders
Child psychologist or neuropsychologist	Assess cognition, provide strengths and weaknesses, assist with educational curriculum and recommend compensatory strategies for cognitive losses
Dietician	Manage the weight loss that is associated with HD
Nonclinical case manager able to coordinate non-medical services for the family (could be a social worker or nurse)	Relate to school teachers, arrange respite care, provide support for the family and arrange for adaptations to the house if necessary
Dentist	Dental hygiene may become a challenge given the problems with movement and behavior
Speech therapist	Advise on aspects of communication and swallowing difficulties
Physiotherapist and occupational therapist	Important for maintaining independence for as long as possible
Palliative care specialist	Important for the end stage of illness, which may last for many years

HD: Huntington's disease.

Table 2

Examples of pharmacological management data for Huntington's disease.

Class of drug	Examples
Dopa blockers or dopa-depleting agents	Tiapride Haloperidol Tetrabenazine
Antidepressant	Mirtazapine Citalopram Fluoxetine Sertraline
Dopa agonist	L-dopa Amantadine
Antiepileptic	Valproic acid Clonazepam
Vitamin preparations	Tocopherol Ascorbic acid Coenzyme Q10
Anxiolytic	Lorazepam Diazepam Hydroxyzine Alprazolam
Antidementia	Memantine hydrochloride
Muscle relaxant	Baclofen Tizanidine

Data taken from [61].