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Review

Clinical Review of Juvenile Huntington's Disease

Mayke Oosterloo[a,b,*], Alexiane Touze[c], Lauren M. Byrne[c], Jannis Achenbach[d], Hande Aksoy[e], Annabelle Coleman[c], Dawn Lammert[f], Martha Nance[g], Peggy Nopoulos[h], Ralf Reilmann[i,j], Carsten Saft[d], Helen Santini[k], Ferdinando Squitieri[l,m], Sarah Tabrizi[c] Jean-Marc Burgunder[n] and Oliver Quarrell[o,p] on behalf of the Pediatric Huntington Disease Working Group of the European Huntington Disease Network

[a]*Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands*
[b]*School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands*
[c]*Department of Neurodegenerative Disease, UCL Huntington's Disease Centre, UCL Queen Square Institute of Neurology, University College London, London, UK*
[d]*Department of Neurology, Huntington Centre NRW, Ruhr-University Bochum, St. Josef-Hospital, Bochum, Germany*
[e]*Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands*
[f]*Department of Neurology, Division of Child Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[g]*Struthers Parkinson's Center, Minneapolis, MN, USA*
[h]*Departments of Psychiatry, Pediatrics, & Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, USA*
[i]*George-Huntington-Institute & Department of Radiology, University of Muenster, Muenster, Germany*
[j]*Department for Neurodegeneration, Hertie Institute for Clinical, Brain Research, University of Tuebingen, Tuebingen, Germany*
[k]*Huntington's Disease Association, England and Wales*
[l]*Centre for Rare Neurological Diseases (CMRN), Italian League for Research on Huntington (LIRH) Foundation, Rome, Italy*
[m]*Huntington and Rare Diseases Unit, IRCCS Casa Sollievo Della Sofferenza Research Hospital, San Giovanni Rotondo, Italy*
[n]*Neurozentrum Siloah and Department of Neurology, Swiss HD Center, University of Bern, Bern, Switzerland*
[o]*Department of Clinical Genetics, Sheffield Children's Hospital, Sheffield, UK*
[p]*Department of Neurosciences University of Sheffield, Sheffield, UK*

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Abstract. Juvenile Huntington's disease (JHD) is rare. In the first decade of life speech difficulties, rigidity, and dystonia are common clinical motor symptoms, whereas onset in the second decade motor symptoms may sometimes resemble adult-onset Huntington's disease (AOHD). Cognitive decline is mostly detected by declining school performances. Behavioral

*Correspondence to: Mayke Oosterloo, MD, PhD, Department of Neurology, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, The Netherlands. Tel.: +31 43 387 50 62; Fax: +31 43 387 70 55; E-mail: mayke.oosterloo@mumc.nl.

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symptoms in general do not differ from AOHD but may be confused with autism spectrum disorder or attention deficit hyperactivity disorder and lead to misdiagnosis and/or diagnostic delay. JHD specific features are epilepsy, ataxia, spasticity, pain, itching, and possibly liver steatosis. Disease progression of JHD is faster compared to AOHD and the disease duration is shorter, particularly in case of higher CAG repeat lengths. The diagnosis is based on clinical judgement in combination with a positive family history and/or DNA analysis after careful consideration. Repeat length in JHD is usually > 55 and caused by anticipation, usually via paternal transmission. There are no pharmacological and multidisciplinary guidelines for JHD treatment. Future perspectives for earlier diagnosis are better diagnostic markers such as qualitative MRI and neurofilament light in serum.

Keywords: Juvenile Huntington's disease, pediatric Huntington's disease, early-onset Huntington's disease, juvenile-onset Huntington's disease, pediatric-onset Huntington's disease

INTRODUCTION

Huntington's disease (HD) is well recognized as an autosomal dominant inherited neurodegenerative disorder caused by an expansion of a CAG repeated sequence in the first exon of the *HTT* gene such that the abnormal protein product has an expanded polyglutamine sequence [1]. A CAG repeat size of ≥ 40 is invariably associated with HD. In most patients, symptoms and signs occur in adulthood. However, a small fraction of the patients develops the juvenile form of HD [2]. Juvenile HD (JHD) is historically defined as HD with an onset ≤ 20 years of age [3]. Our review aims to provide an overview of the clinical aspects of this subset of HD patients, based on the experience of members of the European Huntington Disease Network (EHDN) working group on JHD.

HISTORY AND NOMENCLATURE

The origins of the term JHD are obscure. The paper by Hoffmann (1888) is often given as the earliest detailed reference to JHD [4].

The most comprehensive review of JHD was by the Dutch neurologist, Bruyn in 1968, with 150 cases with an onset of HD ≤ 20 years [3]. Bruyn also described the Westphal variant. This is a hypokinetic rigid form with onset early in the course of the illness of HD [5]. It is well established that hypokinesia and dystonia may be more common in cases with very early onset in life. However, adult-onset cases may also have prominent hypokinesia since the beginning of the illness. Thus, the Westphal variant is not specific for JHD exclusively and should therefore be avoided to address childhood-onset HD.

Up until 2019, the term used for those with HD ≤ 20 years was JHD [6]. Published papers vary a little, but patients with HD and an onset of symptoms ≤ 20 years were considered to have JHD. This cut-off age is probably introduced by Bruyn and related to the fact that until 1990 everyone ≤ 20 years of age was a minor in the Netherlands. Even though JHD cases may have started at childhood, most cases are appreciated and diagnosed in adulthood due to the atypical presentation and consequent clinical misinterpretation. The overall problem with the term JHD is that it makes no difference between patients who are currently children and those with a disease-onset in childhood, but who are currently adults. Therefore, this working group introduced the term Pediatric HD (PHD) for those who are currently affected and under the age of 18 years. Internationally, there is a common consensus and legal rule children become adults by the age of 18. Also, the working group proposed to rephrase JHD to Juvenile Onset HD (JOHD) including every person with JHD regardless their age [6].

Another issue is the diversity of JHD has been sub-divided in several ways. A common method is to divide JHD into those with onset 0–10 years and those with onset 11–20 years. Data on this subdivision is available from 42 of 62 studies on JHD, representing 475 cases ($n = 111$ (23.4%) with onset 0–10 years and $n = 364$ (76.6%) onset 11–20 years) [7]. Another suggested method is based on CAG repeat length which divides patients into low expansion (LE) (50–73 CAG repeats) and high expansion (HE) (>73 CAG repeats) [8].

EPIDEMIOLOGY

The proportion of JHD cases reported in studies of Huntington's disease (HD) varies. A meta-analysis of 62 studies reports proportions of JHD cases between 1–15% [7]. Also, other studies report comparable percentages [7, 9–16], with 14–16% being highest in a Middle Eastern and in a mixed-raced South African population [17, 18]. According to the Enroll-

HD database, the prevalence of JHD ranges between 0.14 and 0.66% [19]; however, this reflects the relative number of participants included at database cut but not the actual number of participants at that age and does not reflect the actual incidence in the general population. A sub-analysis of 11 studies which used multiple methods or ascertainment post 1980 and from high income countries gave a result of 4.81% JHD cases (95%CI 3.31–6.58), whereas three studies with the same criteria but from upper middle-income countries gave a result of 9.95% [7].

The problem with determining the prevalence and incidence of JHD is that most research papers do not differentiate between those who are already adults and those who are still under 18 years of age. Another problem is that if a population survives for a shorter period of time, they are less likely to be presented in a study. Or, such in the Enroll-HD database, the study is not explicitly designed as a study for children. This makes underestimation likely. The Huntington's Disease Youth Organization (HDYO) has recently developed a global web-based patient-led registry of JOHD cases which inter alia will give an indication of the number of PHD available for clinical studies (https://join-hd.org).

CLINICAL FEATURES

The classic presentation of AOHD is a triad of motor symptoms (e.g., chorea, motor coordination), cognitive decline and behavioral changes [2]. However, clinical presentation in children varies from that seen in adults. Also, symptoms in childhood ($\leq$10 years) and adolescence are usually different. Nance described diagnostic criteria for this presenting in the first years of life [20]: 1. A family history of HD and 2. two or more of the following features: a. Declining school performance; b. Seizures; c. Oral motor dysfunction; d. Rigidity; e. Slurred speech and gait disturbance starting in the first 2 years of life [21]. A systematic review of the onset of symptoms from 69 case reports and 10 case series had data on the onset for 285 cases with behavioral disturbance/personality change being the most common at 26%. Children with disease-onset between 0–10 years ($n = 127$) had significantly more gait disturbances/ataxia ($p = 0.0001$), dysarthria ($p = 0.008$), seizures ($p = 0.0008$) and developmental regression/delay ($p = 0.0001$) compared to those with an onset between 11–20 years ($n = 101$) [22]. Depression and suicidal ideation, obsessions and perseveration, however, were significantly higher in the group with an onset between 11–20 years compared to those with onset $\leq$10 years ($p = 0.003$) [8, 22]. The results are similar to the diagnostic criteria suggested by Nance.

In general, the presenting symptoms in the second decade are more likely to correspond in with symptoms in AOHD [8, 23]. Psychiatric symptoms may precede motor symptoms [24, 25]. Eventually, most JHD patients will develop motor, cognitive as well as behavioral symptoms [24]. In the end stage of the disease, JHD patients are usually bed-bound, have tube feeding and are dependent on others for all their care needs [23]. Causes of death may be cardiac arrest, pneumonia or neurovegetative crisis (with hyperthermia and hypertonic posture) [24]. HE-PHD patients also show a life span significantly shorter than AOHD and LE-JOHD [8].

Motor symptoms

A third of the JHD patients present with motor symptoms as the first sign of HD [24, 26]. The motor manifestation in JHD is in many cases the opposite of AOHD. First of all, chorea is uncommon in the first decade of life, but may become manifest in the second decade [8, 20]. Speech difficulties, deficits in fine motor coordination and gait disturbances are the most common presenting motor features, especially in early childhood [8, 21, 26, 27]. Speech and language delay may precede other obvious motor symptoms in JHD if the onset is in the first decade of life [27].

Rigidity, axial bradykinesia, and dystonia are other frequently reported features, also predominant in disease-onset $\leq$ 10 years [8, 10, 26, 28]. Abnormalities of saccadic eye movements in JHD patients have been only slightly explored [29].

Although some of the listed symptoms may be less frequent in AOHD, they are not unique features of JHD. Cerebellar ataxia, however, mainly presents in JHD and may be manifest in up to 35% of the cases [8, 20, 24, 25]. Tics are a less known motor symptom in JHD [28, 30]. Blinking and sniffing are the most common tics in children with HD [30]. They were reported in at least 75% of the cases in an online survey. Patients and caregivers indicated tics to be mildly-to-moderately present on a daily basis in 50% [30]. Upper motor neuron signs, such as spasticity, is another motor symptom predominantly seen in JHD and may be present in > 70% of the cases [26]. Finally, tremor has been described in JHD in 20–40% of cases [20, 25, 26].

Cognitive symptoms

Decline of cognitive function is the presenting symptom in a third of all JHD cases [24]. In several case series it was the most prevalent clinical feature at presentation [10, 24, 26]. Surprisingly, cognition is better preserved in patients with JHD compared to AOHD [31]. Such an observation is in line with a recent *ex vivo* study performed in autoptic brains from HE-PHD children who showed a relatively preserved neuronal loss in the brain cortex, anticipated by glucose transporter and mitochondrial machinery dysfunction [32]. Examples of cognitive decline include regression in language skills, significant changes in school performances, and inability to properly develop reading skills [20, 26, 33]. Declining school performances may have other (medical or non-medical) causes which are not JHD specific. They may, for example, be the effect of social and domestic problems, such as taking care of a sick parent [23]. Therefore, neuropsychological assessment can be helpful in documenting the presence of and mapping the course of cognitive decline [23].

Behavioral symptoms

Additionally, behavioral changes may be the first symptoms arising in JHD in one third of the cases [24, 25]. Behavioral changes include irritability, aggression, obsessive-compulsive behaviors, and depressive mood [20, 28]. Severe problems, such as drugs and alcohol abuse, sexually aggressiveness, and suicidal ideation may be present in adolescents [20, 23, 24]. Psychosis was reported in over a third of cases in a series of 33 patients. The range of severity is wide, but most patients suffer from mild psychosis. The most common manifestations are visual hallucinations followed by auditory hallucinations [30]. In general, these symptoms do not differ from AOHD behavioral changes [34]. They may precede motor symptoms, and, therefore, be confused with more common childhood disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).

Epilepsy

Unlike AOHD, in which the prevalence of epilepsy is approximately equal to that of the general population (∼1%), at least 50% of patients with JHD will develop epilepsy during their disease course; the prevalence may be even higher in patients with younger onset (<10 years of age) [35–37]. These observations suggest that seizures represent a biomarker for early disease, although the mechanism(s) underlying this dramatic age-related difference is not known.

In JHD, seizures are one of the most common causes of hospitalization and can engender significant distress for the family and caregivers [38, 39]. Seizures are most often generalized tonic-clonic, myoclonic, or absence, and a child may have multiple seizure types [35, 37]. Electroencephalogram (EEG) may show generalized, focal, or multifocal epileptiform discharges, commonly with a disorganized background and spike, poly-spike, and spike-and-wave discharges [16, 40–42]. Over the course of the disease, the EEG may progress to diffuse slowing with resolution of epileptiform discharges [43, 44]. Continuous video EEG monitoring can be particularly useful in differentiating movement disorders, sleep disturbance, and seizure [45].

Autonomic dysfunction

Autonomic nerve system dysfunction is a known feature in HD [46, 47]. This feature may also display within JHD. Significant elevations resting heart rate and lower mean diastolic blood pressure are reported in JHD patients compared to healthy controls [48].

Weight loss

Unintended weight loss occurs frequently in AOHD patients, especially in the late stages of the disease. Decrease of caloric intake due to swallowing difficulties might play a role, but hypermetabolic state is likely the main cause of weight loss [49]. It is also known that weight loss increases with higher CAG repeat numbers, which is the case in JHD [49, 50]. Weight and body mass index (BMI) tend to be lower in PHD compared to healthy controls, but low BMI in PHD is similar to the findings in AOHD [50].

Sleep and circadian rhythm disturbances

Disturbance of sleep and circadian rhythm is present in 90% of HD patients. The probable cause is atrophy of the hypothalamic area [51]. Sleep disruption is reported in 87% of a case series of 33 JHD patients. They range from problems falling asleep to maintaining sleep or both [21]. Sleeping problems are severe in nearly half of these cases. Sleeping prob-

lems may precede the diagnosis in 50% of the patients by up to seven years [30].

Pain and itching

Pain and itching are both quite unique symptoms in JHD. They have not consequently been reported in JHD individual case studies and may easily be overlooked [52]. Pain, however, occurs in 69% of patients in a case series of 33 JHD patients. Although, the pain is moderate in most cases, 50% of the patients experience pain on a daily basis [30]. The pain may be located in every part of the body but is most reported in the legs. It is unknown what the cause of pain in JHD is, but dystonia, rigidity and spasticity may play a large role [53].

Itching may occur in JHD patients without a preceding skin irritation [30, 53]. So, it seems that the sensation of itching is not caused by a dermatological problem, but instead a sensory abnormality. Itching is reported as a moderate-to-severe problem in 60% of patients before diagnosis. The legs are a common site (40%), but abdomen and back itching occur as well [30]. There is a significant relation between the CAG repeat size and the presence of itching. This means that the longer the repeat size, the higher the chance of experiencing itching.

Liver steatosis

One study reports liver steatosis and increased liver volume in three, longitudinally followed-up, PHD patients (onset < 5 years) on ultrasound (US) and/or Acoustic Radiation Force Impulse (ARFI); ARFI is a non-invasive elasto-graphic based, US modality investigating liver stiffness [54]. Liver function tests were normal and patients were not treated with hepatotoxic medication. Although the cause of steatosis is not completely clear, increased CAG mosaicism [55] and mitochondrial dysfunction are documented in HD livers [56]. In addition, the liver is a key contributor to glucose homeostasis, which is impaired in HD brain [57]. It is too early to conclude liver steatosis in children with JHD is disease related.

DISEASE DURATION AND PROGRESSION

Median survival in AOHD patients is 15–20 years with usual disease-onset between 30 and 50 years [2]. The age of onset in JHD ranges from 2 to 20 years in various case series [8, 10, 20, 24, 26, 28, 29, 50]. Unfortunately, there are not many longitudinal studies of JHD patients. Those who describe disease duration, indicate the years from onset but not the age of death [24, 25, 29]. It may also be hard for clinicians to estimate age of onset exactly, since the first symptoms may be non-specific at first and there is a high chance of diagnostic delay [26, 58]. This makes it hard to indicate disease duration. It seems, however, that disease duration in JHD patients is significantly shorter compared to AOHD patients, indicating faster disease progression [8]. This is demonstrated by the fact that JHD patients show significantly faster striatal degeneration and quicker worsening of motor functions compared to AOHD [59]. Furthermore, duration of illness in patients with rigidity tends to be shorter compared to those with chorea as main feature [25]. Since rigidity is more likely to be a symptom presenting in childhood, it seems earlier onset leads to shorter survival and may be related to the length of the repeat size. Compared to JHD patients with higher repeat expansions (>80) median survival is higher in patients with lower repeat expansions (60–73). Survival time in patients with lower repeat expansions does not differ from those with AOHD. The conclusion is that patients with JHD and larger repeat expansions (>80) have a more severe pathogenic process compared to those with repeat expansions between 60 and 73 [8].

DIAGNOSIS

The diagnosis of PHD is based on clinical judgement frequently in combination with a positive family history, similar to the diagnosis of AOHD. The diagnostic criteria for childhood onset HD are mentioned in the clinical section paragraph of this review [20]. For adolescence onset the criteria are less specific. There are however some important issues to keep in mind.

Firstly, PHD is very rare and the likelihood that it is not recognized by clinicians without specific knowledge of HD is high. Most children will be seen by general physicians and pediatricians rather than by a HD specialist. Thus, there is a significant chance of misdiagnosis. The variable and non-specific clinical presentation, such as declining school performances and behavioral disturbance, may be confused with disorders such as ADHD and ASD. Also, the effects of disrupted social and home environments in HD families significantly increases the chance of misdiagnosis and/or diagnostic delay of PHD [2]. Diagnostic delay may vary between 0 and 21 years [24, 26]. Some parents report that diag-

nostic delay helped them growing slowly towards the realization of their child being affected by PHD [58].

Secondly, the chance of a child being affected by HD in a case of a negative family history, is very small. If the family history is negative, most reported cases are adopted or orphaned children [10, 20, 24, 26, 28]. There have also been a few rare cases in which the child becomes manifest before the parent or the parent is misdiagnosed [24, 42, 43, 60, 61].

Thirdly, currently there are no additional tests besides DNA analysis, which will help to make the diagnosis definite. Neuropsychological assessment may help to detect cognitive problems, which of course should not exist in healthy children. Brain magnetic resonance imaging (MRI) may show caudate atrophy, increased T2 weighted signal in the basal ganglia and/or white matter changes [24, 26, 62]. Also, lower intracranial volumes and lower volumes of grey and white matter compared to gene negative controls have been described [59], but may be difficult to interpret in specific cases without longitudinal observations.

Therefore, in the context of clinical assessment of a person at risk for PHD whose parent is concerned they are showing symptoms, the most important assessment is that of change over time. Any one-time assessment of a clinic component—motor, cognitive, or MRI—is not nearly as useful as showing change. For the neurologist, a motor feature at one visit may seem too subtle to consider significant, but may be easier to characterize if, on the next visit, those symptoms have worsened (or new ones have emerged). In regard to cognitive testing, having standardized testing for children at risk should be considered a standard of care assessment if JHD is being considered. More importantly, showing cognitive tests in which scores are declining over time should signal significant concern. Like in the diagnosis of AOHD, utilizing not just motor, but other features of the disease such as cognitive decline should be considered when making the diagnosis of JHD.

Finally, although DNA analysis provides the most efficient way to make the diagnosis, careful consideration is recommended [23]. Genetic testing below the age of 18 for persons at risk for HD is strongly discouraged or forbidden in some countries [20, 33, 63]. The diagnosis of HD is a clinical one, and DNA analysis can only confirm the diagnosis. However, if there is not complete confidence that the signs and symptoms shown by a child from a HD family are caused by HD, DNA analysis may be counterproductive and the child may have unintentionally had testing for later onset, including adult HD [33, 64, 65]. In many cases, the recommendation would be to consider the diagnosis of JHD after ruling out alternative causes and careful follow up. Behavioral and motor symptoms can be treated equally well symptomatically before genetic testing has been considered. It will not change the genetic outcome. However, it may harm the child since they will not receive disease specific care, follow up and/or treatment [20]. Some children, presenting with dystonia, may be diagnosed following investigation using a panel of DNA tests.

GENETICS AND INHERITANCE

There is an inverse correlation between the length of the CAG repeat and the age of onset. The longer the repeat, the earlier the disease-associated symptoms start [66, 67]. In JHD, the median CAG repeat length is approximately 60, with the longest reported expansion being 250 [11, 20, 43, 67, 68]. However, cases are reported with lower CAG repeats, with 45 being the lowest reported repeat length [10, 20, 24]. It is important to notice that reported JHD cases with a repeat length below 50 had an age >21 when they were diagnosed with their first motor symptoms [24]. Discussion remains if these cases are pure JHD cases. It is important to notice that most alleles are detected with polymerase chain reaction (PCR)-based assays. However, if alleles are larger than 100 CAG repeats, in the past they may have only been detected by Southern blot analysis of genomic DNA, due to poor PCR amplification of very large alleles [20, 43]. Recent technologies such as the Triplet-Primed PCR assay may overcome such an issue and detect HE alleles [69].

The occurrence of disease-onset at a younger age in the next generation is called anticipation. There is a higher chance for JHD to occur via paternal transmission than maternal transmission [3, 68]. Intergenerational CAG changes in paternally transmitted JHD are usually larger than in maternally transmitted JHD [11, 70]. This, however, does not lead to earlier disease onset in paternally inherited JHD [11, 71].

FAMILY PERSPECTIVES

The psychosocial impact of parenting a child with PHD is enormous. Parents describe denial at first, and then becoming aware that something is wrong with their offspring [39, 58, 72, 73]. Despite increasing

awareness of JHD among healthcare professionals, the wider psychosocial impact on families remains overlooked. Variance in age of onset and disease progression create unique challenges for these patients. Moreover, it may give rise to school struggles in childhood, peer problems in adolescence and reproductive considerations in adulthood. These are distressing for both the child and parental figures who witness the child missing out on typical experiences and milestones of that age group [39, 73, 74]. Behavioral, motor and communication difficulties further strain household dynamics and familial relationships [39, 73].

Navigating the aforementioned problems at home and coordinating complex healthcare for the child, often result in families becoming experts through experience [74]. Their observations become valuable in distinguishing early symptoms from normal child or adolescent behavior [39, 58, 74]. Importantly, the extent or manner these are relayed to the physician also indicate their insight and ability to cope with a diagnosis [58]. The grief of an incurable illness can be compounded with a sense of isolation, stemming from the rarity of JHD [39, 74]. Active listening, along with the adaptation of consultations and follow-ups accordingly, can be a helpful way of providing support and gauging the appropriate timing of diagnosis [58, 72]. Overall, identifying effects on families, who are often primary caregivers, is vital in forming a more complete understanding of JHD and in improving the quality of life of all affected. The JOIN-HD registry will also gather evidence from family and caregivers' experiences with JHD to consolidate our understanding of the disease and how best treat it.

PHARMACOLOGICAL MANAGEMENT

There are no evidence-based guidelines for the treatment of symptoms in JHD. All published data are on the basis of expert opinion. Antipsychotics, antidepressants, antiparkinsonian medication and anti-epileptics are commonly prescribed medications among HD clinicians treating PHD patients [75, 76]. Antipsychotics are the most prescribed to treat agitation, behavioral problems and psychiatric disturbances [75]. Recent evidence of biological changes that are specific of HE-PHD may open to new possible nutritional approaches such as the ketogenic diet [32].

Motor symptoms

Although chorea may not be the most prominent motor symptom in JHD, treatment options are equal to AOHD cases; tetrabenazine, deutetrabenazine, tiapride or other antipsychotics [53, 77]. However, if a patient also has prominent hypokinesia and/or dystonia, the effect of these medications will probably be contra-productive.

Rigidity may be treated with antiparkinsonian medication such as levodopa and dopamine receptor agonists. Doses of levodopa up to 600 mg/day have been described to improve hypokinesia, rigidity and speech in isolated cases [78]. It is important to keep in mind that levodopa may induce chorea and lower the threshold for psychosis. Tremors may respond to clonazepam [53].

Muscle relaxants such as baclofen, dantrolene or tizanidine can improve spasticity and dystonia; but benzodiazepines may also be useful [53]. There is also evidence for the effect of medicinal cannabinoids in dystonia in a case series with JHD (4 of the 7 patients) patients [79]. Botulinum toxin injections may be indicated in case of focal dystonia or spasticity, pain or need for bracing [53]. Finally, there is also some evidence for the use of cannabinoids for the treatment of dystonia [79].

Behavioral symptoms

Treatment of behavioral symptoms in children with HD resembles that of AOHD. Irritability and agitation are recommended to be treated with a Selective Serotonin Receptor Inhibitor (SSRI) or atypical antipsychotics [53, 80]. However, before the start of medication it is important to rule out other causes that may cause irritation or agitation such as pain or infections. Depressed mood is most likely to respond to antidepressants such as fluoxetine, mirtazapine, citalopram or sertraline or antipsychotics [75]. Benzodiazepines help to alleviate anxiety complaints, but antidepressants may also be a good choice, especially if the patient also suffers from depression. In case of a psychosis, antipsychotics are the first-choice medication.

Epilepsy

The most commonly and likely most effective anti-seizure medication reported is valproic acid [16, 81–86]. It is not clear why this broad-spectrum anti-seizure medicine may be particularly beneficial in

children with HD, but it could be related to valproate's GABAergic effect. Furthermore, it could be efficacious against myoclonus and chorea and against irritability and impulsion. Historically, carbamazepine and phenytoin were used, but they are now less favored due to their side-effect profile. Other anti-seizure medications reported include levetiracetam, topiramate, clobazam, clonazepam, and lamotrigine [16, 37, 40, 81, 84, 87]. While there is less data regarding these newer generation anti-seizure medications, it is reasonable to consider them for seizures that are not responsive to valproic acid. Seizures initially may be controlled with monotherapy, but they often become medication refractory [40, 81, 85, 87]. The choice of anti-seizure medication may be influenced by comorbid movement, psychiatric, and sleep disorders.

Pain and itching

Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the first-choice medication to start in case of pain. However, it is important to get insight in the location and possible cause of the pain. If there is dystonia, rigidity or spasticity is the cause of the pain, it is recommended to treat the cause rather than the pain itself. Gabapentin for neuropathic pain can be very helpful for the widespread non-specific pain symptoms that commonly occur. Last resort pain medications are opioids, which are frequently reported in JHD patients [75, 88].

Itching seems difficult to treat [53]. Hydroxyzine, an antihistaminic drug, has been reported as treatment in JHD patients [75]. However, one case report describes no significant effect of antihistaminic drugs and recommends the use of gabapentin [53].

Insomnia

Melatonin, clonidine and quetiapine are mentioned as sleep aids [89]. Benzodiazepines such as diazepam are also mentioned [88]. Additionally, non-pharmacological interventions may be useful such as soft music and blue lighting [53].

MULTIDISCIPLINARY TREATMENT AND CARE

There are no guidelines nor expert opinions published on multidisciplinary treatment (MDT) and care in PHD. The clinical care pathway from pediatric to adult services for JHD is not well defined. A child will be seen in pediatric services whilst the needs of a teenager differ and there will be a need of transition to adult services. Adult JHD patients will also have different needs and potentially could have offspring of their own. Therefore, shared care between adult neurologists and pediatricians is very important.

As in AOHD, we recommend including a physiotherapist, occupational therapist, speech and language therapist and dietician in the MDT to treat rigidity and/or spasticity, swallowing problems and weight loss respectively. Dental management of JHD patients also requires a multidisciplinary approach to address the specific set of challenges faced by these patients (e.g., involuntary head and tongue movements make procedures in the oral cavity particularly difficult) [90]. Physical restraints or sedatives may be useful in the management of these patients, but their physician should always be consulted first to advise on the safest pharmacological agent to use to avoid harmful drug interactions with the patient's current medications. The patient's carers may also be helpful in providing information on stress reduction for the patient during a dental procedure (e.g., playing the patient's favorite music). In general, it is advised to keep dental treatments basic in JHD patients and the use of dentures and appliances is contraindicated.

Furthermore, it may be valuable to consult a pain specialist or palliative care specialists if general pain medication is not sufficient [88].

It is important not only to support the child but also other family members. In this difficult and devastating situation, a family-centered approach is needed. Therefore, we would recommend a case manager, nurse or social worker or care advisor from the local HD association as well as the option to visit a psychologist with knowledge of HD.

FUTURE PERSPECTIVES

Nomenclature

The nomenclature on JHD is still somewhat unclear and may be confusing especially regarding cut-off age and the differentiation between those who are currently adults and those whose are not. Clearer definitions are needed. In the future, this may also help to get better insight in the exact number of patients with JHD.

Assessment of clinical features

Results on clinical features in PHD vary since there are no official or validated clinical rating scales or assessment tools for children with HD. For example, the Total Motor Score (TMS) of the Unified Huntington Disease Ratings Scale (UHDRS) omits items on ataxia. A Rasch analysis on the TMS showed a significant overall misfit. Furthermore, all items relating to chorea displayed significant misfit due to underdiscrimination [91]. This analysis highlights the need of development of new rating scales and assessment tools specifically designed for children in order to provide better follow-up options in clinical care (e.g., change over time) as well as research (e.g., trials).

Diagnostic tools

There is a clear need for additional disease specific tests besides DNA analysis, which will help to make the diagnosis of JHD definite. A recent report of subjects with long CAG repeats (>50) who participated in a study of children at-risk for HD showed that early in life, and far from symptom onset, striatal volume is significantly larger than normal [92]. Importantly, the MRI scans from this study were research scans that generated quantitative volumes of striatum and were not clinical MRI scans. In fact, at the time of clinical diagnosis, a clinical MRI scan was read as normal despite the fact that the striatum was already substantially below a group of normal children matched to her age and sex. Given that there are advances in clinical MRI imaging such that quantitative measures of striatum may be possible in the near future, getting annual MRI scans (with quantitative measures of the striatum) on patients being assessed for JHD may be a sensitive marker for change over time, and useful information for clinical diagnosis. The recently developed HD-Integrated Staging System (ISS) may be of help to characterize disease progression [93].

Another future diagnostic tool for disease onset in children may be neurofilament light (NfL). Byrne et al. demonstrated that plasma NfL concentrations in JHD children were significantly higher compared to healthy age-matched controls [94]. The elevations were similar or higher than manifest AOHD compared to the subtle elevations in blood NfL thought to start around 20 years from predicted onset in premanifest HD mutation carriers. NfL elevations indicate an ongoing neurodegenerative process. In the future, high NfL in a child displaying ambiguous symptoms could aid the decision process for clinicians considering to genetically test a minor. A marked increase in NfL could increase the likelihood that the symptoms are indeed due to neurodegenerative JHD rather than another neurodevelopmental condition that would not have elevations in NfL.

We can conclude that quantitative MRI and NfL concentrations may contribute to an earlier diagnosis in JHD but have no place in clinical settings yet. There are, however, no disease specific biomarkers for disease-onset, so further research is necessary on both qualitative MRI, NfL as well as disease specific biomarkers such as mutant Huntingtin (mHTT). More natural history studies in JHD, including studies involving lumbar punctures to explore the potential of CSF biomarkers that have yet to be studied in JHD, is strongly recommended.

CONCLUSION

JHD is a rare form of HD, although numbers in populations vary. The first case of JHD goes back to 1888. Since then, there have been several definitions for childhood-onset HD. These definitions may be confusing, and clarification is needed if the patient is already an adult or not. Therefore, we need clearer nomenclature to separate adult JHD from JHD patients < 18 years of age.

In the first decade of life speech difficulties, rigidity and dystonia are common clinical motor symptoms, whereas onset in the second decade motor symptoms may sometimes resemble AOHD. Cognitive decline is mostly detected by declining school performances. Behavioral symptoms in general do not differ from AOHD but may be confused with autism spectrum disorder or attention deficit hyperactivity disorder and lead to misdiagnosis and/or diagnostic delay. JHD specific features are epilepsy, ataxia, spasticity, pain, itching and rarely liver steatosis. Disease progression of JHD is faster compared to AOHD and the disease duration is shorter, particularly in case of higher CAG repeat lengths. The diagnosis is based on clinical judgement in combination with a positive family history. DNA analysis confirms the diagnosis; however, genetic testing is only recommended after careful consideration, exclusion of alternative causes, and careful follow up. Repeat length in JHD is usually > 55 and caused by anticipation, usually via paternal transmission. There are no evidence-based pharmacological and multidisciplinary guidelines for JHD treatment. Future perspectives for earlier diag-

nosis are better diagnostic markers such as qualitative MRI and neurofilament light in serum.

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CONFLICT OF INTEREST

During the past year, Mayke Oosterloo has received research grant funding from NWA-ORC (NWA.1389.20.244) and a pending patent (EP23197746.3). Mayke Oosterloo is on the scientific advisory board of the European Huntington Disease Network.

Martha Nance's institution, Health Partners, receives program funding from Parkinson's Foundation and for research activities from BIAL. Her institution, Hennepin HealthCare Institute, receives support from the Huntington Disease Society of America. In the last year, she has been compensated for consulting activities by F. Hoffman-La Roche, Neurocrine, Novartis, Sage Therapeutics, Uniqure Biopharma, and for service on Steering Committees for research studies funded by Neurocrine, BIAL, and Parkinson's Foundation. She is a member of the Executive Membership Committee of the Huntington Study Group.

Peggy Nopoulos receives funds from the National Institute of Health (NIH) to prospectively study subjects with JHD in a natural history program (no intervention). She is also a paid consultant for the companies Annexon, Prilenia, and Unicure.

Ralf Reilmann is founding director and owner of the George-Huntington-Institute, a private research institute focused on clinical and preclinical research in Huntington's disease, and QuantiMedis, a clinical research organization providing Q-Motor (quantitative motor) services in clinical trials and research. Dr. Reilmann has provided consulting services, advisory board functions, clinical trial services, quantitative motor analyses, and/or lectures for Actelion, Alnylam, Amarin, AOP Orphan Pharmaceuticals, AskBio, Cure Huntington Disease Initiative Foundation (CHDI), Desitin, Hoffmann-La Roche, IONIS, Ipsen, Lundbeck, MEDA Pharma, Medivation, Mitoconix, Neurocrine, Neurosearch, Novartis, Omeros, Pfizer, Prana Biotechnology, Prilenia, PTC Therapeutics, Raptor, Sage, Siena Biotech, Solaxa, Temmler Pharma, Teva, uniQure, Vaccinex, Voyager, Wave Life Sciences, and Zevra. He has received grant support from the Bundesministerium für Bildung und Forschung (BMBF), the Cure Huntington Disease Initiative Foundation (CHDI), the Deutsche Forschungsgemeinschaft (DFG), the Deutsches Zentrum für Neurodegeneration und Entzündung (DZNE), the European Union's 7th Framework Program (EU-FP7) and Horizon2020 Innovative Medicine Initiative 2 program (IMI2), the European Huntington Disease Network (EHDN), the High-Q-Foundation, the National Institute of Health (NIH), and the National Science Foundation (NSF).

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DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

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