Defining Pediatric Huntington Disease: Time to Abandon the Term *Juvenile Huntington Disease*?

Huntington disease (HD) is a progressive neurodegenerative disorder for which no disease-modifying treatment is available. Numerous novel approaches for treatments in HD are in development. Several clinical trials have already been conducted, and further trials are under way.[1] Onset may be at almost any age, but it is most common in mid-life. Traditionally, those with an onset age ≤20 years are said to have juvenile Huntington disease (JHD).[2] Recently, the European Medicines Agency (EMA) removed a class waiver that allowed sponsors to exclude children and adolescents from clinical studies for a number of conditions, including HD (EMA decision CW/0001/2015).[3] The EMA justified its decision as follows: "According to recent data (Roos 2011), Huntington disease may occur in the paediatric population in a juvenile form. It is reported to be about 6% of the cases of Huntington disease (which itself has a prevalence of 1/10,000) and is characterised in paediatric and adult populations by a similar molecular aberration in the HTT (huntingtin) gene."[3,4]

We would like to address problems arising from terminology because JHD more accurately means juvenile-onset HD and refers to all those who meet the criteria for the onset of signs and symptoms before the age of 21 years, the majority of whom are now adults (Fig. 1). The prevalence of those affected by HD who are still aged younger than 18 years is unknown. In the context of the removal of the class waiver, the use of the term *JHD* and the 6% figure is misleading. The point of removing the waiver is to force sponsors to submit a pediatric investigation plan early in the drug development process. This is meant to make them consider providing data (which could include modelling and simulation data) relevant to the pediatric cohort, although they may still apply for an individual waiver or deferral. Sponsors and regulatory agencies would benefit from a more defined terminology to refer specifically to children and young teenagers with an HD diagnosis. We propose phasing out the term *JHD* (there may be some studies that report findings prior to this change) and introducing the term *pediatric HD*. This term is simpler to understand and means young people affected by HD who are currently aged <18 years.

Although the EMA and U.S. Food and Drug Administration have similar regulations, there are subtle differences between them.[5] In the case of pediatric waivers, the statutory instruments that established the EMA and U.S. Food and Drug Administration have slightly different criteria for considering them. The U.S. Food and Drug Administration continues to include HD in the list of adult-related conditions that qualify for a waiver because they never or rarely occur in children.[6]

We agree with the EMA that those in the pediatric HD group have unmet needs, but both sponsors and regulators need to recognize that obtaining observational data following an intervention for this small, widely dispersed, cohort will be challenging.

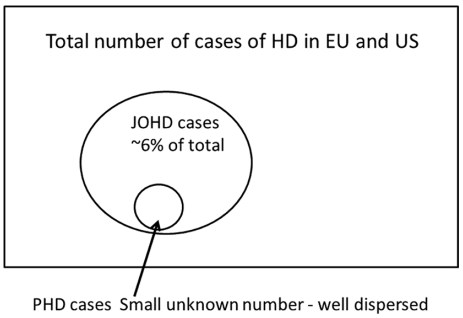

FIG. 1. The rectangle represents all the cases of Huntington disease (HD) in Europe (EU) and the United States (US). Of these, approximately 6% have an onset ≤20 years and meet the current definition of juvenile-onset HD (JOHD). Most of these cases are now adults. The number of patients meeting the definition of pediatric HD (PHD), that is, currently affected and <18 years of age, is small and unknown.

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Relevant conflicts of interests/financial disclosures: The majority of authors have been involved with clinical trials of HD.

Funding agency: The European Huntington Disease Network funded a meeting of the authors.

Received: 11 January 2019; **Revised:** 18 January 2019; **Accepted:** 15 January 2019

Published online 20 February 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27640

References

1. Rodrigues FB, Wild EJ. Clinical trials corner: September 2017. J Huntington Dis 2017;6:255-263.
2. Quarrell OWJ, Nanace MA, Nopoulos P, Paulsen JS, Smith JA Squitieri F. Managing juvenile Huntington's disease. Neurodegener Dis Manage 2013;3:267-276.
3. European Medicines Agency decision CW/0001/2015. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190385.pdf. Accessed December 21, 2018.
4. Roos, R., 2011. Juvenile Huntington disease. http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=19562. Accessed December 21, 2018.
5. Bhati S, Sanders C. Regulations: US and EU. http://www.samedanltd.com/magazine/11/issue/149/article/2893. Accessed September 2, 2018.
6. Adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM531157.pdf. Accessed January 11, 2019.

Successful Spinal Cord Stimulation for Severe Medication-Refractory Restless Legs Syndrome

Restless legs syndrome (RLS) is characterized by an urge to move the legs, classically accompanied by uncomfortable sensations. Symptoms typically worsen during rest and at night.[1,2] Pharmacotherapy includes levodopa/dopamine agonists, anticonvulsants (alpha-2-delta ligands), opioids, and iron supplementation.[2,3] Nonpharmacologic approaches involve pneumatic compression, near-infrared spectroscopy, or transcranial magnetic stimulation.[3]

One patient who underwent spinal cord stimulation (SCS) for neuropathic pain experienced improvement of concomitant RLS.[4] Analogously, spinal transcutaneous direct current stimulation and limb transcutaneous electrical nerve stimulation may improve RLS.[1,5]

Currently, SCS to specifically treat RLS has not yet been reported.

We present an otherwise healthy 24-year-old student suffering nonfamilial RLS. Symptoms started at age 12 and gradually progressed. He reported a crawling leg sensation at rest, alleviated by mobilizing, maximum at night, but eventually present throughout the day. He slept only 4 to 5 hours nightly and had prolonged sleep latency.

Besides repetitive voluntary leg movements, neurological examination was normal. Polysomnography performed elsewhere excluded sleep disordered breathing (apnea hypopnea index 2.1 without significant oxygen desaturation) and demonstrated periodic limb movement arousals (indices unavailable).

Serum markers measuring iron status (total iron = 20 μmol/L [9-32], ferritin = 170 μg/L [22-275], transferrin saturation = 33% [20-50]) and thyroid and renal function were normal. He was on zolpidem 10 mg, clonazepam 0.25 mg, and medical marijuana with limited benefit. Levodopa/carbidopa, pramipexole, and ropirinole initially improved RLS but subsequently contributed to augmentation. Rotigotine, retigabine, gabapentin, pregabalin, loprazolam, zolpidem, melatonin, venlafaxine, morphine, oxycodone, codeine, nabilone, oral iron supplementation, cognitive behavioral therapy, and compression socks were ineffective. Ferric carboxymaltose was unavailable in Canada. He refused methadone. Transcutaneous electrical nerve stimulation only helped partially and was cumbersome.

After a multidisciplinary review, institutional approval, and detailed consenting, a spinal epidural paddle electrode was implanted at T7-9 under general anesthesia (Fig. 1B). Following a 1-week inpatient trial period, confirming good leg coverage and symptom improvement, an internal pulse generator (IPG) was implanted and programmed (Fig. 1C).

Subjectively, his legs were instantaneously less restless with SCS on, even in the absence of SCS-induced paresthesia, for example, with stimulation in certain positions or at lower amplitudes. Six months postoperatively, the International RLS Study Group rating scale and RLS 6-item questionnaire scores were reduced by 44% and 25%, respectively. This translated into a 33% improvement in RLS-Quality of Life questionnaire score (Fig. 1A). Subjectively and polysomnographically, sleep quality (no more periodic limb movement arousals) and duration (6-8 hours) improved, with some remaining sleep onset insomnia. Medication was gradually tapered to exclusively zolpidem 5 mg occasionally.

This benefit is sustained at 33 months, with gradual worsening upon IPG depletion and instantaneous improvement after IPG replacement (Fig. 1A).

SCS was considered on experimental[1,5] and theoretical grounds. Theoretically, SCS-induced paresthesia may override uncomfortable ascending sensations, similar to one postulated mechanism in neuropathic pain. Indirect action via modulation of sensory cortices and/or cerebellum[6] is also possible.

SCS may substantially improve RLS severity and quality of life. Although this is a single case and SCS-induced paresthesia renders blinding difficult, symptom recurrence/improvement upon IPG depletion/replacement, respectively, is encouraging. However, a placebo response, common in RLS,[7] cannot be excluded. Further study is warranted to define the role of SCS in medication-refractory RLS.

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Relevant conflicts of interests/financial disclosures: P.D.V. has received grants for education and traveling from Medtronic. He is supported by the 2016 Research Grant of the European Society for Stereotactic and Functional Neurosurgery and the Helaers Foundation. A.F. has received consultancies, honoraria, and research support from Medtronic. A.E.L. has received honoraria from Medtronic. S.K.K. has received speaker's fees from Medtronic. M.L., D.P., G.D.R., N.R., F.S., B.J.M., and R.P.M. report no disclosures.

Received: 1 November 2018; **Revised:** 17 December 2018; **Accepted:** 23 January 2019

Published online 15 February 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27644

Acknowledgment: We thank Alicia Triantafilou for administrative support.