The prevalence of pain in Huntington's Disease in a large worldwide cohort

Sprenger, G.P.; Roos, R.A.C.; Zwet, E. van; Reijntjes, R.H.; Achterberg, W.P.; Bot, S.T. de

Parkinsonism and Related Disorders 89 (2021) 73–78

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The prevalence of pain in Huntington's disease in a large worldwide cohort

Gregory P. Sprenger [a,b,*], Raymund A.C. Roos [a], Erik van Zwet [c], Robert H. Reijntjes [a], Wilco P. Achterberg [d,e], Susanne T. de Bot [a]

[a] Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
[b] Amstelring, Huntington Center, Amsterdam, the Netherlands
[c] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
[d] Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands
[e] Topaz Huntington Center Overduin, Katwijk, the Netherlands

ARTICLE INFO

Keywords:
Huntington's disease
Pain
Pain interference
Analgesics
Painful conditions

ABSTRACT

Introduction: Pain could be an unknown non-motor symptom in Huntington's Disease (HD). The aim is therefore, to study the prevalence of pain interference, painful conditions and analgesic use across the different stages of HD and compare these levels to non-HD gene mutation carriers.

Methods: A cross-sectional analysis of the Enroll-HD study was conducted in premanifest, manifest HD gene mutation carriers (n = 3989 and n = 7,485, respectively) and in non-HD gene mutation carriers (n = 3719). To investigate group differences, multivariable logistic regression analysis was performed with pairwise comparisons.

Results: In the HD mutation carriers, the overall prevalence of pain interference was 34% (95% CI 31%–35%), of painful conditions 17% (95% CI 15%–19%) and analgesic use 13% (95% CI 11%–15%). Compared to non-mutation carriers, the prevalence of pain interference was significantly higher in the middle stage of HD (33% [95% CI 31%–35%] vs 42% [95% CI 39%–45%], $P = 0{,}02$), whereas the prevalence of painful conditions was significant lower in the late and middle stage of HD (17% [95% CI 16%–18%] vs 12% [95% CI 10%–14%], 15% [95% CI 13%–17%], $P < 0{,}01$]. No significant group difference was present in analgesic use.

Conclusions: The prevalence of pain interference increases as HD progresses, however, the prevalence of painful conditions and analgesics do not increase accordingly. Further studies are necessary to investigate the aetiology of pain in HD and the risk for undertreatment of pain.

1. Introduction

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease, caused by an increased CAG repeat in the gene which encodes the protein, Huntingtin [1]. The resulting abnormally long polyglutamine repeat in the Huntingtin protein causes neuronal loss in the brain, particularly in the basal ganglia [2], which subsequently leads to a variety of motor and non-motor symptoms, such as neurocognitive and neurobehavioral disturbances [3].

The basal ganglia are also involved in acute as well as chronic pain [4]. In Parkinson's Disease (PD), also a disease of the basal ganglia, pain is one of the four most prevalent complaints [5]. Moreover, pain in PD is significantly associated with a diminished Health-Related Quality of Life ((HR)-QoL) [6]. The prevalence of pain in PD can be as high as 80%, which is significantly higher than in the general population [7]. The compromised function of the basal ganglia in HD makes an alteration in pain processing and perception more than likely. In HD, the available experimental studies demonstrated a significant prolongation of processing painful stimuli at spinal cord level in the manifest stage, compared to healthy controls and individuals in the premanifest stage [8–10]. In addition, an abnormal subcortical and cortical activation of sensory information has been demonstrated in HD [11].

One study showed an increase in the prevalence of pain in HD from 32% in the premanifest stage to 50% in the late stage [12]. A recent meta-analysis estimated the overall mean prevalence of pain in HD to be around 41% (95% confidence interval: 36%–46%) [13]. It also revealed that the pain burden, measured in terms of pain intensity and interference with daily activities using the pain items of the SF-36, is lower in HD compared to that in the general population [13]. However, due to lack of studies, it is unclear whether the diminished pain burden applies

* Corresponding author. Leiden University Medical Center, Department of Neurology, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands.
E-mail address: G.Sprenger@lumc.nl (G.P. Sprenger).

https://doi.org/10.1016/j.parkreldis.2021.06.015
Received 12 December 2020; Received in revised form 5 June 2021; Accepted 17 June 2021
Available online 19 June 2021

to all stages of HD. Furthermore, the proportion of patients with HD reporting pain interference with daily activities is not yet known.

Another way to investigate the pain burden is to study the prevalence of painful conditions and the use of analgesics. No studies are available which investigated the prevalence of painful conditions in HD. One pilot study is available on the use of analgesics, demonstrating a 49% use in the premanifest stage [14]. Unfortunately, it is not clear whether the proportion of analgesic use changes as HD progresses, nor whether the usage is different from that in the general population.

Considering the findings of pain in PD and the limited studies about pain in HD, which might highly interfere with key symptoms like depression, irritability, and anxiety, systematic studies focusing on pain in HD are warranted. The aim of this study is to study the prevalence of pain interferences with daily activities, painful conditions and analgesic use in different stages of HD and compare these to the levels in non-HD gene mutation carriers.

2. Methods

We applied the fourth periodic database of the Enroll-HD study (released March 2019) (see e-Methods). Enroll-HD is a global clinical research platform designed to facilitate clinical research in HD. Core datasets are collected annually from all research participants as part of this multi-center longitudinal observational study. Data are monitored for quality and accuracy using a risk-based approach. In the fourth release of Enroll-HD, standardized data of 15,301 participants are collected.

This study included all baseline assessments of individuals with genetically confirmed HD gene mutation and non-HD mutation carriers (family controls [spouses, partners, caregivers] and genotype-negatives). The baseline assessment gathered data on: age, gender, region, race, international standard classification of education [ICSED], marital status, CAG-repeat length, motor symptoms, stage of disease, comorbidities, medication use and indication, Short Form Health Survey-12-version 2 (SF-12v2) [15], Mini-Mental State Examination (MMSE) [16] and the Hospital Anxiety and Depression Scale (HADS) [17].

2.1. Outcomes

The degree of pain interference with daily activities was based on the bodily pain interference item of the SF-12v2 [15]. The version used in the Enroll-HD study was: 'During the *past week*, how much did pain *interfere* with your normal work, including both outside the home and housework?'. The possible answers were based on an ordinal five-point scale: 'Not at all', 'A little bit', 'Moderately', 'Quite a bit' and 'Extremely'. The presence of pain interference was defined as an individual score of "A little bit' or higher.

The comorbidities and medication use in the Enroll-HD database were classified according to the tenth edition of the International Classification of Diseases (ICD-10, version 2014) and the Anatomical Therapeutic Chemical (ATC) Classification System, respectively [18,19]. Inclusion criteria were postulated to identify painful conditions and analgesic use (see eMethods).

The prevalence of pain interference, painful conditions and analgesic use were investigated for each stage of the disease. HD mutation carrier status was defined as subjects with 36 or more CAG repeats in the Huntingtin gene. A Total Motor Score (TMS) of five or lower and a Diagnostic Confidence Level (DCL) of three or lower on the Unified Huntington's Disease Rating Scale (UHDRS), was defined as the premanifest stage of HD [20]. According to the TRACK-HD studies, the premanifest stage was divided at baseline group median (10.8 years) for predicted years to onset into PreHDA ($\geq$10.8 years from predicted onset) and PreHDB (<10.8 years), by using the Langebehn formula [21,22]. The manifest stage was divided into an early, middle and late stage, according to international standards, by using the Total Functional Capacity (TFC) score of the UHDRS [23,24]. A TFC score between 11 and 13 indicated the early stage, between 3 and 10 the middle stage, and a score between 0 and 2 the late stage [24]. Depression or anxiety symptoms were present if a participant scored an eight or higher on the HADS [17]. A score of 23 points or lower on the MMSE indicated the presence of cognitive disturbances [16].

2.2. Statistical analysis

The analyses were conducted using IBM SPSS statistics versions 26 and for more details regarding the analyses see e-Methods [25]. All outcomes (pain interference, painful conditions and analgesic use) were dichotomized in order to calculate the prevalence. Multivariable logistic regression analyses were performed, with a pairwise comparison (Bonferroni correction), to investigate differences in the prevalence of the pain outcomes between premanifest, manifest HD gene mutation carriers and in non-HD gene mutation carriers. These analyses were adjusted for age. Multiple imputations were carried out in order to assess the impact of the missing data on socio-demographic, clinical factors and the outcomes (see eMethods).

3. Results

3.1. Overall

The total sample size at baseline included 15,301 participants, 108 (0.7%) of whom were not categorized into subgroups due to missing data, like for example: diagnostic confidence score. The sample (n = 15,193) consisted of non-HD mutation carriers (n = 3719; 24%), PreHDA (n = 2556; 17%), PreHDB (n = 1433; 9%), early (n = 4867; 32%), middle (n = 1360; 9%) and late stage patients with HD (n = 1258; 8%) (Table 1).

3.2. Socio-demographic characteristics

At baseline, the proportion of females in the non-mutation carriers, premanifest and manifest mutation carriers was 61% (n = 2260), 58% (n = 2331) and 54% (n = 3852), respectively. The mean age was 47.2 (SD 14.7), 42.2 (SD 12.0) and 54.4 (SD 12.5). The mean age was lowest in the PreHDA (37.2 [SD 11.0]) and highest in the late stage (56.8 [SD 12.3]). Of the total sample, 61% of participants were from Europe, 35.0% from Northern America, 3.5% from Australasia and around 0.7% from Latin America (Table 1).

3.3. Pain interference with daily activities

From the 15,301 participants, 10,912 participants completed the pain interference item of the SF-12v2. The non-mutation carriers included 2998 (27%) participants, the PreHDA 2037 (19%), PreHDB 1099 (10%), early 3464 (32%), middle 810 (7%) and late stage HD 504 (5%). Data of the SF12v2 pain interference scale were absent in 4281 (28%) participants.

The overall mean prevalence of pain interference in HD mutation carriers (n = 7914) was 34% (95% confidence interval [CI] 31%–35%), with significant differences between the groups (χ^2 (5) = 130.34, $p <$ 0.01) (PreHDA 26%; PreHDB 29%; early 38%; middle 42%; late 38%; non-mutation carriers 33%) (Fig. 1). When adjusting for age, only a significant higher prevalence of pain interference was demonstrated in the middle stage of HD, compared to non-mutation carriers (42% [95% CI 39%–45%] vs 33% [95% CI 31%–35%], P = 0,02). For additional significant between group differences see supplemental data (eFig. 1). The prevalence of pain interference varied between the different demographic regions, with the greatest differences within the early and middle stage HD, with the highest pain interference reported in Latin America in both stages (eTable 1).

Table 1
Characteristics of groups of participants from Enroll HD included in the present study.

		Socio-demographic factors			Clinical Variables					
Groups	N	Age Mean (SD)	Gender N^0 (%)	Region N^0 (%)	CAG-repeat Mean (SD)	UHDRS-TMS Mean (SD)	UHDRS-TFC Mean (SD)	MMSE Mean (SD)	HADS-depression Mean (SD)	HADS-anxiety Mean (SD)
Non-mutation carriers	3719	47,2 (14.7) Miss.: 4 (0,1%)	F: 2260 (60,8) M: 1459 (39,2)	E: 1718 (46,2) LA: 32 (0,9) NA: 1863 (50,1) AU: 106 (2,9)	20,2 (3.6)	1,7 (3.5) Miss.: 14 (0.4%)	12,9 (0.7) Miss.: 3 (0.1%)	28,9 (1.5) Miss.: 998 (26.8%)	3,5 (3.3) Miss.: 894 (24.0%)	5,2 (3.8) Miss.: 895 (24.1%)
PreHDA	2556	37,2 (11.0)	F: 1533 (60,0) M: 1023 (40,0)	E: 1505 (59,0) LA: 7 (0,3) NA: 910 (35,5) AU: 134 (5,2)	41,8 (2.4)	2,4 (3.9) Miss: 11 (0.4%)	12,7 (1.1) Miss.: 4 (0.2%)	28,8 (1.7) Miss.: 730 (28,6%)	3,6 (3.6) Miss.: 750 (29.3%)	5,8 (4.2) Miss.: 748 (29,3%)
PreHDB	1433	47,1 (12.3)	F: 798 (55,7) M: 635 (44,3)	E: 779 (54,4) NA: 564 (39,4) AU: 90(6,3)	43,8 (3.1)	7,4 (8.5) Miss.: 6 (0,4%)	12,1 (1.8) Miss.: 5 (0,4%)	28,0 (2.4) Miss.: 485 (33,8%)	4,3 (3.7) Miss.: 482 (33,9%)	5,6 (4.0) Miss.: 481 (33,6%)
Early	4867	52,0 (12.2) Miss.: 3 (0,1%)	F: 2393 (49,2) M: 2474 (50,8)	E: 3206 (65,9) LA: 41 (0,8) NA: 1484 (30,5) AU: 136 (2,8)	43,8 (3.6)	30,4 (14.0)	10,2 (2.0)	26,1 (3.0) Miss.: 1653 (34,0%)	5,7 (4.0) Miss.: 1860 (38,2%)	6,0 (4.2) Miss.: 1859 (38,2%)
Middle	1360	54,4 (12.9) Miss.: 1 (0.1%)	F: 728 (53,6) M: 632 (46,4)	E: 928 (68,2) LA: 15 (1,1) NA: 376 (27,6) AU: 41 (3,0)	44,5 (4.4)	48,2 (16.2)	5,1 (0.8)	22,9 (4.3) Miss.: 561 (41,3%)	7,3 (4.4) Miss.: 697 (51,3%)	6,2 (4.3) Miss.: 696 (51,2%)
Late	1258	56,8 (12.3)	F: 731 (58,1) M: 527 (41,9)	E: 1057 (84,0) LA: 11 (0,9) NA: 168 (13,4) AU: 22 (1,7)	44,8 (4.2)	70,5 (18.9)	1,7 (1.1)	18,1 (6.4) Miss.: 687 (54,6%)	8,0 (4.8) Miss.: 850 (67,6%)	5,8 (4.4) Miss.: 853 (67,8%)

Table 1. After multiple imputation of missing data, no significant differences were found compared to the original data set. Abbreviations: Australasia (AU), Cytosine-Adenine-Guanine repeat (CAG-repeat), European (E), Female (F), Hospital Anxiety and Depression scale (HADS), Latin-American (LA), Male (M), Mini-Mental State Examination (MMSE), Missing data (Miss.), Northern America (NA), Standard Deviation (SD), Unified Huntington Disease Rating Scale – Total Motor Score/Total Function Category (UHDRS- TMS/TFC).

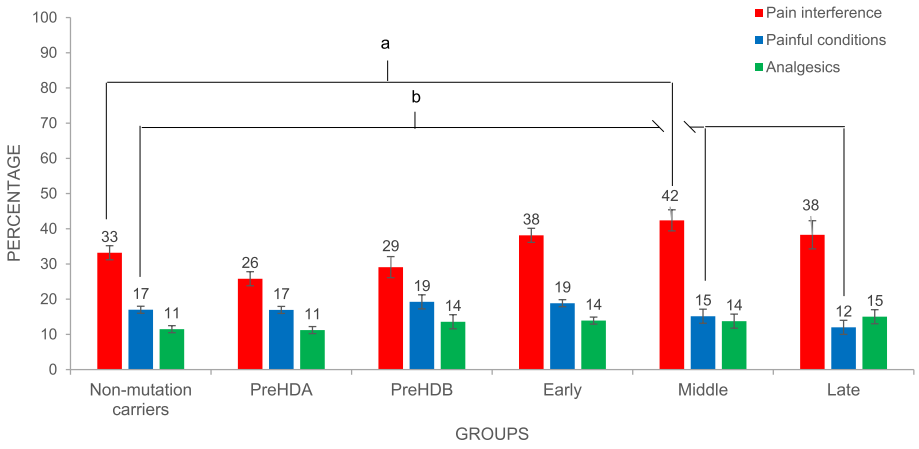

Fig. 1. The prevalence of pain interference[1], painful conditions and analgesic use across the different groups. [1]The cut-off for pain interference was set at a score of 'A little bit' or higher on the pain interference item of the SF12v2. Rounded to whole numbers. Error Bar (I), Total Sample Size (N). Pain interference: Non-mutation carriers (N = 2998), PreHDA (N = 2037), PreHDB (N = 1099), Early (N = 3464), Middle (N = 810), Late (N = 504). Painful conditions and analgesics: Non-mutation carriers (N = 3719), PreHDA (N = 2556), PreHDB (N = 1433), Early (N = 4867), Middle (N = 1360), Late (1,258). a. Middle vs Non-mutation carriers ($P = 0.02$); b Middle vs Non-mutation carriers ($P < 0.01$) AND Late vs Non-mutation carriers ($P < 0.01$).

3.4. Painful conditions

Overall, 17% (95% CI 15%–19%) of the HD gene mutation carriers (n = 11,474) reported a painful condition. A significant group difference was present (χ^2 (5) = 35.46, $p < 0.01$) (PreHDA 17%; PreHDB 19%; early 19%; middle 15%; late 12%; non-mutation carriers 17%) (Fig. 1). When adjusting for age, only a significantly lower prevalence of painful conditions was found in the middle or late stage of HD, compared to non-

mutation carriers (15% [95% CI 13%–17%.], 12% [95% CI 10%–14%] vs 17% [95% CI 16–18%], $P < 0.01$). For additional significant group differences, see supplemental data (eFig. 2). The prevalence of painful conditions varies slightly between the different demographic regions (eTable 2).

In the group reporting a painful condition, the proportion of the thirteen clusters of painful conditions, varies across the different stages (see eTable 3). Those reported most often were headache, limb, back, abdominal pain and pain due to fractures (Fig. 2). As HD progressed, reporting of abdominal pain and pain caused by fractures increased, while the number of reports of headache decreased. The majority of the patients with pain reported only one pain condition (around 78%). The proportion with two, three or more painful conditions varies between the groups (eTable 4). The proportion of painful conditions commonly associated with chronic pain decreased as HD progressed, while the proportion of acute painful conditions increased (eTable 5).

3.5. Analgesic use

The overall prevalence of analgesic use in the HD gene mutation carriers (n = 11,474) was 13% (95% CI 11%–15%). A significant prevalence difference was found between the groups (χ^2 (5) = 23,95, $p < 0,01$) (PreHDA 11%; PreHDB 14%; early 14%; middle 14%; late 15%; non-mutation carriers 11%) (Fig. 1). After controlling for age, no significant group differences were present. The prevalence of analgesic use was the highest in Europe in the middle and late stage of HD (eTable 6).

In the group reporting the use of analgesics, the top three most often used across the different stages of HD were Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), paracetamol, anti-epileptics. As HD progressed, the use of paracetamol (PreHDA 17%; Late stage 41%) and strong opioids (PreHDA 8%; Late stage 14%) increased, while the use of NSAIDs decreased (PreHDA 40%; Late stage 25%) (eTable 7). The majority of the patients reported the use of only one type of analgesic (around 71%) (eTable 8).

3.6. Other possible (co)factors affecting pain interference

In general, participants with a painful condition reported more pain interference, compared to those without a pain condition (Fig. 3). Also, the use of analgesics was greater in participants reporting a pain condition, compared to the group without a pain condition.

As HD progressed, the proportion of pain interference increased in both groups: with and without painful conditions. This is in contrast to the use of analgesics, which increased slightly in the group without a painful condition but remained the same in the group with a painful condition. The proportion of cognitive disturbances and depression increased equally in both groups as HD progressed. Finally, the proportion of participants reporting anxiety disturbances did not differ between the two groups, nor between the different HD stages.

4. Discussion

Based on the large worldwide Enroll-HD database, we found that in HD gene mutation carriers, the overall prevalence of pain interference was 34% (and even 39% in the manifest stage of HD), of painful conditions 17% and of analgesic use 13%. Compared to non-HD mutation carriers, the prevalence of pain interference was significant higher in the middle stage of HD (33% [95% CI 31%–35%] vs 42% [95% CI 39%–45%], respectively), whereas the prevalence of painful conditions was significant lower in the late and middle stage of HD (17% [95 CI% 16%–18%] vs 12% [95% CI 10%–14%], 15% [95% CI 13%–17%], respectively) (see Fig. 1). There were no significant group differences in the prevalence of analgesic use.

The lack of coherence between the prevalence of pain interference, painful conditions and the use of analgesics is interesting. This could be due to several factors. First of all, HD on its own may induce pain, which could be an aspect of which physicians might be insufficiently aware, resulting in a low analgesic use and prescription. The present study demonstrates that, as HD progressed, the increase in pain interference could not be explained fully by the included painful conditions (Figs. 1 and 3). This was also supported by a slight increase in analgesic use in the group without a painful condition as HD progressed (Fig. 3). Even when a stricter cut-off score for pain interference was used or the analysis was conducted only within the group with available pain interference data, the incoherence between the outcomes remained in the manifest stage of HD (eFig. 3 and eFig. 4, respectively). Systematic studies are, however, necessary to explore this speculation. Secondly, the lack of coherence might be explained by dysfunction of the basal ganglia, causing on the one hand an increase in the severity of pain (interference) as HD progresses, but on the other, resulting in an inadequate pain behavior, possibly due to the disturbances in the sensory, affective and/or cognitive dimensions of pain [4]. Thirdly, the neurocognitive disturbances in HD might also contribute to the lack of coherence. In particular the diminished awareness of deficits (loss of insight) in HD makes it challenging and less reliable to collect data using self-reported pain scales. In the majority of the literature, a minimum score of 18 on the MMSE is recommended for using a self-assessment pain scale [26]. Fourthly, depression and anxiety are important factors associated with pain interference in the general population [27]. As demonstrated in this study, depression and anxiety are most prevalent in the manifest stages of HD. The association between mood, cognitive disturbances, HD and pain is, however, complex, as illustrated by a network (see eFig. 5). Finally, the incoherence in the prevalence could also be caused by the in- and exclusion criteria applied for painful condition and analgesics. In practice, there are more painful conditions, as well as pharmacological and non-pharmacological treatments, than

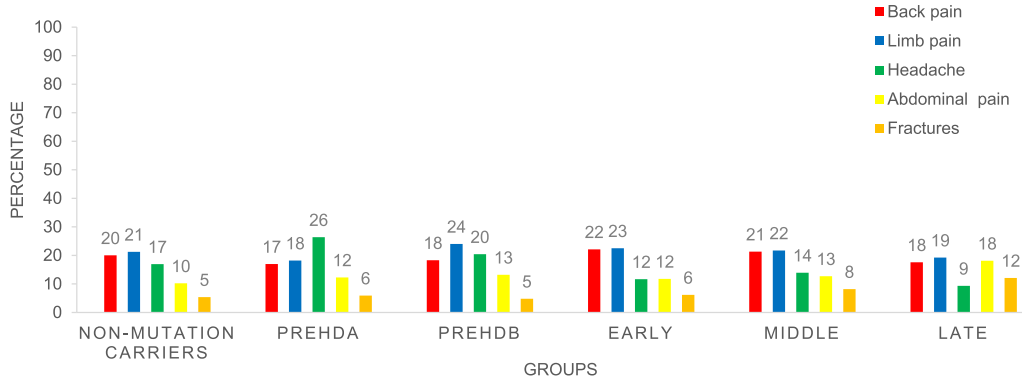

Fig. 2. The proportion of the five most-reported conditions causing pain across the different groups. No correction was carried out if patients reported two or more painful conditions. Rounded to whole numbers. For group size, see eTable 3 in Supplement 1.

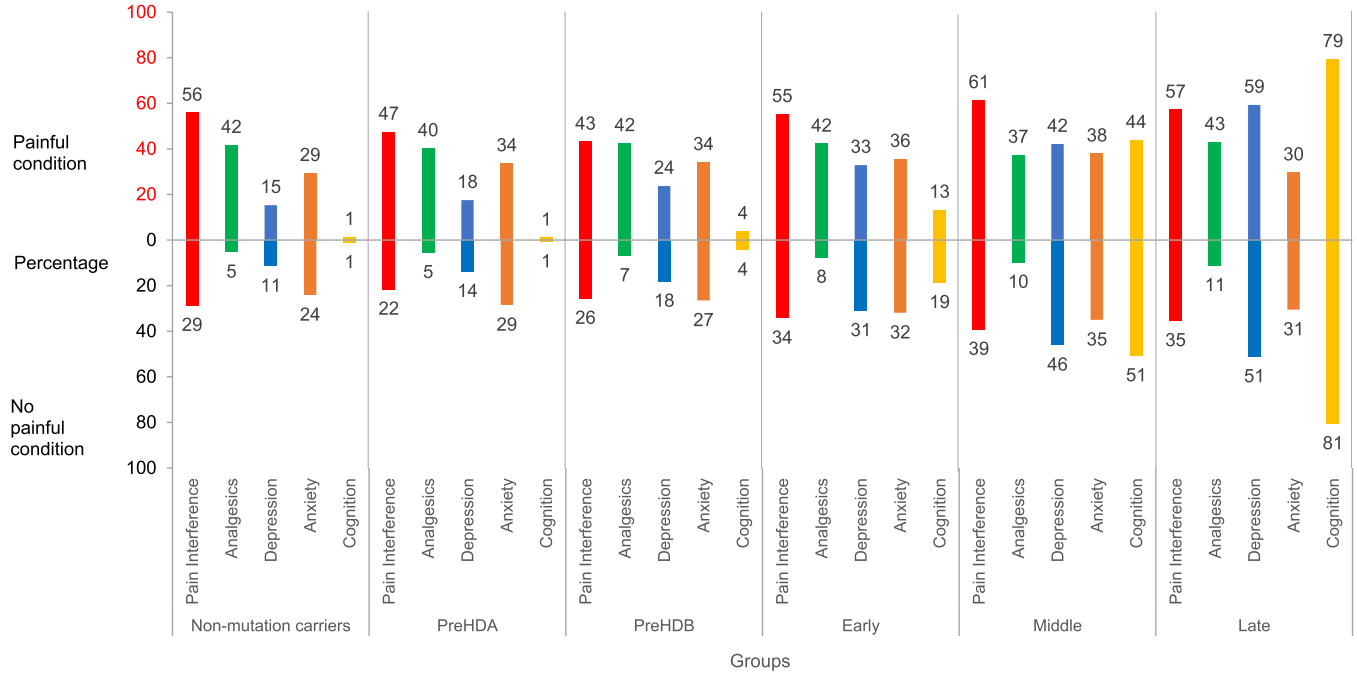

Fig. 3. The proportion of pain interference[1], analgesic use and the presence of mood[2] and cognitive[3] disturbances demonstrated in two different groups (with/without a painful condition). [1]Pain interference was stated as a score of 'A little bit' or higher on the pain interference item of the SF12v2. [2] HADS score of eight or higher indicated depressive or anxiety symptoms. [3]Cognition: MMSE score of 23 points or lower was defined as presence of cognitive disturbance. Rounded to whole numbers. The frequencies are reported in eTable 9.

those adopted in this study. For instance, specific -sometimes painful-dystonia was not included as a painful condition, while this symptom may be present in the manifest stage of HD and well-known in inducing pain [28]. This might have resulted in a lower prevalence of painful conditions as well analgesic use.

The present study revealed some interesting findings with regard to the prevalence of specific painful conditions and analgesic use. In the final stage of HD, abdominal pain and pain caused by fractures were more frequently reported, while the proportion of headache decreased as HD progressed. The increase in abdominal pain could be explained by the high prevalence of a variety of upper and lower gastrointestinal dysfunctions in patients with HD [29]. Furthermore, the increase in the report of pain caused by fractures, might be related to falls and lower bone density in patients with late stage HD [30]. The decrease in the proportion of headache (migraine) as HD progressed, corresponds with that in PD, where, after disease onset, it seems to be reported less frequently [31]. With regard to analgesics, the use of paracetamol and strong opioids seems to increase as HD progresses, while this study found a tendency for the use of NSAIDs to decrease. This is compliant with the recommendations about the use of NSAIDs in vulnerable and older patient groups and demonstrates the robustness of our data.

A limitation of the present study, is that only patients who were motivated and capable of participating in the Enroll-HD study were included. In addition, 28% of the data of the SF12v2 pain interference scale was missing. Multiple imputation did not lead, however, to different conclusions compared to the complete case analysis. Nevertheless, there is a risk of selection bias. The use of only one ordinal scale for assessing the degree of pain interference is too limited to understand the effect of pain on performing different daily activities and also enhances the risk of scale attenuation effects (including ceiling and floor effects). The significant group differences found in this study, does not always imply clinical relevance, in particular for the group differences concerning the prevalence of painful conditions. Finally, the scope of this study did not allow inclusion of potential mediators and moderators, such as social demographic variables, neurocognitive and mood disturbances in the analysis.

The strengths of the present study are the use of a large, high quality, world-wide database of genetically confirmed (non-) HD gene mutation carriers, increasing the generalizability of the findings. The approach to investigating prevalence of painful conditions and analgesic use was objective and conservative.

The effect of HD on pain and its aetiology should be further investigated. A proposed framework for investigating the different causes of pain in PD may be helpful for future HD studies [32]. Despite the similarities between the compromised function of the basal ganglia in HD and PD, the motor and non-motor symptoms differ significantly. The manifestation of pain in HD might be different and unique compared to PD. Future studies should also take into account the clinical observations of patients with HD with (severe) painful conditions, however, not complaining about it or vice versa. In addition, future studies could also use a more recent formula (PIN score) to differentiate between PreHDA and PreHDB. In our study, however, the use of the PIN score did not result in different findings [33]. Finally, especially for the final stages of HD, validation of pain assessments, including observational pain instruments, is required.

Authors' Roles

1) Research project

A. Conception and Design: Gregory P. Sprenger; Wilco P. Achterberg; Susanne T. de Bot; Raymund A.C. Roos.
B. Organization: Gregory P. Sprenger.
C. Execution: Gregory P. Sprenger.

2) Acquisition and analysis of the data

A. Acquisition data from Dataset: Gregory P. Sprenger; Robert H. Reijntjes.
B. Statistical Design: Erik van Zwet.

B. Execution: Gregory P. Sprenger.
C. Review analysis and Critique: Erik van Zwet.

3) Manuscript

A. Writing the first draft: Gregory P. Sprenger.
B. Review and Critique: Raymund A.C. Roos; Erik van Zwet; Robert H. Reijntjes; Wilco P. Achterberg; Susanne T. de Bot.

Financial disclosures

Susanne T. de Bot: The LUMC institution receives grants from the European Huntington's Disease Network (EHDN), Cure Huntington's Disease Initiative (CHDI) and participates in a clinical trial sponsored by Hoffmann-La Roche. The other authors have nothing to disclosure.

Acknowledgments

The authors thank the research platform Enroll-HD. Biosamples and data used in this work were generously provided by the participants in the Enroll-HD study and made available by CHDI Foundation, Inc. Enroll-HD is a clinical research platform and longitudinal observational study for Huntington's disease families intended to accelerate progress towards therapeutics; it is sponsored by CHDI Foundation, a nonprofit biomedical research organization exclusively dedicated to collaboratively developing therapeutics for HD. Enroll-HD would not be possible without the vital contribution of the research participants and their families. In addition, we would like to acknowledge all the listed individuals who contributed to the collection of the Enroll-HD data (see, https://www.enroll-hd.org/acknowledgments/). Finally, we would like to acknowledge Amstelring, a specialized Huntington Center in Amsterdam, for the financial support to conduct this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.06.015.

References

[1] M.E. MacDonald, C.M. Ambrose, M.P. Duyao, R.H. Myers, C. Lin, L. Srinidhi, G. Barnes, S.A. Taylor, M. James, N. Groot, H. MacFarlane, B. Jenkins, M. A. Anderson, N.S. Wexler, J.F. Gusella, G.P. Bates, S. Baxendale, H. Hummerich, S. Kirby, M. North, S. Youngman, R. Mott, G. Zehetner, Z. Sedlacek, A. Poustka, A. M. Frischauf, H. Lehrach, A.J. Buckler, D. Church, L. Doucette-Stamm, M. C. O'Donovan, L. Riba-Ramirez, M. Shah, V.P. Stanton, S.A. Strobel, K.M. Draths, J. L. Wales, P. Dervan, D.E. Housman, M. Altherr, R. Shiang, L. Thompson, T. Fielder, J.J. Wasmuth, D. Tagle, J. Valdes, L. Elmer, M. Allard, L. Castilla, M. Swaroop, K. Blanchard, F.S. Collins, R. Snell, T. Holloway, K. Gillespie, N. Datson, D. Shaw, P.S. Harper, A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes, Cell 72 (1993) 971–983, https://doi.org/10.1016/0092-8674(93)90585-E.

[2] S.J. Tabrizi, D.R. Langbehn, B.R. Leavitt, R.A.C. Roos, A. Durr, D. Craufurd, C. Kennard, S.L. Hicks, N.C. Fox, R.I. Scahill, A.J. Tobin, H.D. Rosas, H. Johnson, R. Reilmann, Biological and clinical manifestations of Huntington's Disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data, Lancet Neurol. 8 (2013) 791–801, https://doi.org/10.1016/S1474-4422(09)70170-X. Biological.

[3] M.J.U. Novak, S.J. Tabrizi, Huntington's Disease: clinical presentation and treatment, Int. Rev. Neurobiol. 98 (2011) 297–323, https://doi.org/10.1016/B978-0-12-381328-2.00013-4.

[4] D. Borsook, J. Upadhyay, E.H. Chudler, L. Becerra, A key role of the basal ganglia in pain and analgesia - insights gained through human functional imaging, Mol. Pain 6 (2010) 1–17.

[5] M. Politis, K. Wu, S. Molloy, P.G. Bain, K.R. Chaudhuri, P. Piccini, Parkinson' s disease Symptoms : the patient' s perspective, Mov. Disord. 25 (2010) 1646–1651, https://doi.org/10.1002/mds.23135.

[6] S. Choi, B.C. Kim, H. Jung, G. Yoon, K. Wook, K. Choi, J. Kim, S. Lee, M. Park, M. Kim, K. Cho, Impact of pain and pain subtypes on the quality of life of patients with Parkinson' s disease, J. Clin. Neurosci. 45 (2017) 105–109, https://doi.org/10.1016/j.jocn.2017.08.002.

[7] A.G. Beiske, J.H. Loge, A. Rønningen, E. Svensson, Pain in Parkinson ' s disease : prevalence and characteristics, Pain 141 (2009) 173–177, https://doi.org/10.1016/j.pain.2008.12.004.

[8] M.C. De Tommaso, C. Serpino, C. Difruscolo, C. Cormio, V. Sciruicchio, I. Franco, I. Farella, P. Livrea, Nociceptive inputs transmission in Huntington ' s disease: a study by laser evoked potentials, Acta Neurol. Belg. 111 (2011) 33–40. https://pdfs.semanticscholar.org/76f0/c4ef1b84782f56fd9520565114184d7f1335.pdf.

[9] M. De Tommaso, G. Franco, K. Ricci, A. Montemurno, V. Sciruicchio, Laser evoked potentials in early and presymptomatic Huntington's disease, Behav. Neurol. (2016) 1–8, https://doi.org/10.1155/2016/8613729.

[10] A. Perrotta, C. Serpino, C. Cormio, M. Serrao, G. Sandrini, F. Pierelli, M. de Tommaso, Abnormal spinal cord pain processing in Huntington's disease. The role of the diffuse noxious inhibitory control, Clin. Neurophysiol. 123 (2012) 1624–1630, https://doi.org/10.1016/j.clinph.2012.01.012.

[11] H. Boecker, A. Ceballos-Baumann, P. Bartenstein, A. Weindl, H.R. Siebner, T. Fassbender, F. Munz, M. Schwaiger, B. Conrad, Sensory processing in Parkinson's and Huntington's disease. Investigations with 3D H215O-PET, Brain 122 (1999) 1651–1665, https://doi.org/10.1093/brain/122.9.1651.

[12] M. Underwood, S. Bonas, M. Dale, Huntington's disease: prevalence and psychological indicators of pain, Mov Disord Clin. Pr. 4 (2016) 198–204, https://doi.org/10.1002/mdc3.12376.

[13] G.P. Sprenger, K.F. van der Zwaan, R.A.C. Roos, W.P. Achterberg, The prevalence and the burden of pain in patients with Huntington's disease, Pain 160 (2019) 773–783, https://doi.org/10.1097/j.pain.0000000000001472.

[14] N.A. Killoran, K. Biglan, E. Julian-Baros, N. Yoritomo, C. Ross, Analysis of analgesic use in premanifest huntingont disease, Neurol. 80 (2013). http://n.neurology.org/content/80/7_Supplement/P07.208.

[15] J.E. Ware, M. Kosinski, S.D. Keller, I. QualityMetric, H. New England Medical Center, L. Health Assessment, SF-12 : How to Score the SF-12 Physical and Mental Health Summary Scales, 1998.

[16] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198, https://doi.org/10.1016/0022-3956(75)90026-6.

[17] I. Bjelland, A.A. Dahl, T. Tangen, D. Neckelmann, The validity of the Hospital Anxiety and Depression Scale. An updated literature review, J. Psychosom. Res. 52 (2002) 69–77, https://doi.org/10.1016/S0022-3999(01)00296-3.

[18] The World Health Organization, The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). https://www.whocc.no/atc_ddd_index/, 2003.

[19] World Health Organization, International classification of diseases for mortality and morbidity stastics, 10th revision, https://icd.who.int/browse10/2014/en#!/XIV, 2014.

[20] S.J. Tabrizi, R.I. Scahill, G. Owen, A. Durr, B.R. Leavitt, R.A. Roos, B. Borowsky, B. Landwehrmeyer, C. Frost, H. Johnson, D. Craufurd, R. Reilmann, J.C. Stout, D. R. Langbehn, Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data, Lancet Neurol. 12 (2013) 637–649, https://doi.org/10.1016/S1474-4422(13)70088-7.

[21] D.R. Langbehn, R.R. Brinkman, D. Falush, J.S. Paulsen, M.R. Hayden, A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length, Clin. Genet. 65 (2004) 267–277, https://doi.org/10.1111/j.1399-0004.2004.00241.x.

[22] S.J. Tabrizi, R.I. Scahill, G. Owen, A. Durr, B.R. Leavitt, R.A. Roos, B. Borowsky, B. Landwehrmeyer, C. Frost, H. Johnson, D. Craufurd, R. Reilmann, J.C. Stout, D. R. Langbehn, Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data, Lancet Neurol. 12 (2013) 637–649, https://doi.org/10.1016/S1474-4422(13)70088-7.

[23] K. Kieburtz, Unified Huntington's disease rating scale: reliability and consistency, Mov. Disord. 11 (1996) 136–142, https://doi.org/10.1002/mds.870110204.

[24] G.P. Bates, S.J. Tabreizi, L. Jones, Huntington's Disease, 2014, pp. 1–512, 4th Edition.

[25] IBM SPSS Statistics for Windows, IBM Corporation, Armonk, New York, USA, 2018 version 26.

[26] J.T. Chibnall, R.C. Tait, Pain assessment in cognitively impaired and unimpaired older adults: a comparison of four scales, Pain 92 (2001) 173–186, https://doi.org/10.1016/S0304-3959(00)00485-1.

[27] H.M. Arola, E. Nicholls, C. Mallen, E. Thomas, Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: can a temporal relationship be determined? Eur. J. Pain 14 (2010) 966–971, https://doi.org/10.1016/j.ejpain.2010.02.012.

[28] B. Ford, Pain in Parkinson ' s disease, Mov. Disord. 25 (2010) 98–103, https://doi.org/10.1002/mds.22716.

[29] J.E. Andrich, M. Wobben, P. Klotz, O. Goetze, C. Saft, Upper gastrointestinal findings in Huntington's disease: patients suffer but do not complain, J. Neural. Transm. 116 (2009) 1607–1611, https://doi.org/10.1007/s00702-009-0310-1.

[30] J.B. Carroll, G.P. Bates, J. Steffan, C. Saft, S.J. Tabrizi, Treating the whole body in Huntington's disease, Lancet Neurol. 14 (2015) 1135–1142, https://doi.org/10.1016/S1474-4422(15)00177-5.

[31] P. Barbanti, G. Fabbrini, N. Vanacore, A. Rum, G. Lenzi, G. Meco, R. Cerbo, Dopamine and migraine: does Parkinson's disease modify migraine course? Cephalalgia 20 (2000) 720–723, https://doi.org/10.1046/j.1468-2982.2000.00123.x.

[32] G. Wasner, G. Deuschl, Pains in Parkinson disease — many syndromes, Nat. Rev. Neurol. 8 (2012) 284–294, https://doi.org/10.1038/nrneurol.2012.54.

[33] Jeffrey Long D., Douglas Langbehn R., Sarah Tabrizi J., Bernhard Landwehrmeyer G., Jane Paulsen S., John Warner, Cristina Sampaio, Validation of a prognostic index for Huntington's disease, Movement Disorders 32 (2018) 256–263, 33, https://doi.org/10.1002/mds.26838. In this issue.