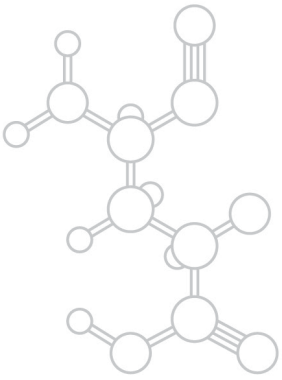
Juvenile Huntington Disease: towards better understanding its unique disease characteristics

Bakels, H.S.



CHAPTER 7

Summary and Discussion

SUMMARY

The aim of this thesis was to address several unresolved questions regarding the juvenile-onset HD (JHD) and Pediatric HD (PHD) populations through a translational approach. While numerous therapeutic trials are currently underway in the adult-onset HD (AHD) population,[1] focused on modifying disease progression, the JHD population, although part of the same HD continuum, presents with unique disease characteristics that necessitate a tailored approach distinct from that of the AHD population. Key issues related to the epidemiology of JHD and PHD, the capacity of these populations to participate in clinical trials, clinical disease characteristics of JHD, underlying pathophysiological mechanisms, and brain maturation in pediatric patients remain inadequately addressed. Resolving these questions is crucial to ensure that these patients are not excluded from future treatment options.

We have shown that the JHD and PHD populations in the Netherlands are even smaller than previously suggested, comprising less than 1% of the entire clinically manifest HD population (**Chapter 2**). Due to significant diagnostic delays in the JHD population, more than half of patients with JHD is not available for clinical trials under 18 years of age (PHD). Additionally, we have demonstrated that functional competence at the time of diagnosis is diminished in JHD patients, and that the CAP^{100} score, a measure of disease progression, is invalid for use in the JHD population. These findings highlight the need for alternative approaches in the design of interventional trials targeting these populations and novel inclusion criteria tailored to the JHD and PHD population.

We summarized clinical and neuropathological disease characteristics of JHD as reported in the literature and provided a pathophysiological perspective to explain differences with the prototypical AHD phenotype (**Chapter 3**). While toxic gain-of-function disease mechanisms in relation to CAG-repeat length explain age at disease onset and progression in HD, CAG-dependent modulation or loss of normal HTT function in neurodevelopment might explain some of the unique clinical disease characteristics that are seen in the JHD population, such as developmental delay, epilepsy, behavioral disorder and psychosis. Additionally, the pediatric age of onset in PHD cases may influence ongoing postnatal brain maturation processes. These potential differences in pathophysiology and brain development have important implications for future therapeutic strategies and underscore the need for a personalized approach to treatment in the JHD population.

We revealed that both the cJHD and aJHD populations exhibit distinct patterns in the prevalence, severity, and progression of clinical characteristics at onset and throughout the disease course, when compared to the prototypical AHD population (**Chapter 4**).

Specifically, the cJHD population demonstrated: (1) the highest prevalence of neurocognitive deficits at onset, and, during the disease course (2) the most severe and rapid progression of specified motor and neurocognitive subclusters, (3) the highest occurrence of irritability, violence, and aggressive behavior, and (4) the highest prevalence of epilepsy. In contrast, the aJHD population exhibited: (I) the highest prevalence of psychiatric disturbances at onset, and, during the disease course, (II) more severe and faster progression of motor and neurocognitive subclusters compared to AHD, (III) the highest prevalence of apathy and psychosis, and (IV) the highest prevalence of pain interference with daily life. These distinct patterns of clinical characteristics underscore the necessity of stratifying JHD subtypes separately when compared to AHD. Moreover, our findings suggest that many clinical features align with CAG-repeat length or age at onset, while others appear to be influenced by the age at which specific clinical characteristics emerge, indicating moderating effects of brain maturation.

We revealed the correlation between clinical, radiological and neuropathological disease characteristics in an aJHD brain donor who died mid-stage disease (**Chapter 5**). Our findings indicate that a moderate clinical and functional disease stage, along with a short disease duration of 4 years, correlates with mild to moderate radiological and neuropathological disease characteristics which were most prominent in the putamen. Additionally, we emphasized the importance of conducting a comprehensive neuropathological evaluation, rather than relying solely on Vonsattel grade, as our analysis revealed that neuropathological changes were more comprehensive than can be appreciated by the Vonsattel grading system.

Lastly, we demonstrated diminished RNA and protein expression of glucose transporters and mitochondrial complexes in high-expansion cJHD brains and fibroblasts, compared to aJHD, AHD patient and healthy control material (**Chapter 6**). These findings suggest that glucose metabolism is impaired in high-expansion cJHD, a pattern that contrasts partially with aJHD and AHD. This indicates that distinct pathophysiological mechanisms may be at play in the high-expansion cJHD subtype, but not in other HD subtypes. Furthermore, patients with mutations in glucose transporter genes (e.g. GLUT1) exhibit disease characteristics like those of the cJHD population, such as developmental delay and epilepsy, which may help explain the atypical clinical features observed in the cJHD phenotype.

In the next part we will discuss these results in a broader overarching perspective and provide recommendations and future perspectives on (1) the definition of the JHD and PHD population, (2) practical implementations and (3) the pathophysiological framework and neurodevelopment.

DISCUSSION

Juvenile-onset and Pediatric Huntington Disease nomenclature and selection criteria

As mentioned in the introduction of this thesis, the definition of "JHD" is rather arbitrary and not bound to any obvious criteria such as unique disease characteristics or onset on pediatric (≤17) or adult (≥18) age. The additional definition "PHD" for cases between 0-17 years with clinically manifest HD was introduced to resolve regulatory issues in clinical trial design relating to manifest HD on pediatric vs adult age.[2] Our finding relating to the extremely low prevalence of PHD (**Chapter 2**) drives the awareness that conventional clinical trial design is not feasible in such a small patient population and urges regulatory authorities to the use of alternative trial designs.

Yet both the term JHD and PHD do not tell us anything concerning unique clinical characteristics in (part of) these populations, which troubles the selection of homogeneous patient populations and getting insight in pathophysiological differences between HD subtypes. There is no straightforward answer to how to optimally define JHD nomenclature and selection criteria. By dividing JHD patients into a childhood-onset (cJHD) and adolescent-onset (aJHD) phenotype, we have shown that both cJHD and aJHD as compared to AHD have distinct patterns in the occurrence, severity and progression of disease characteristics (**Chapter 4**). Age at onset is an useful measure to distinguish JHD subpopulations from AHD, as it relates to developmental stages relevant to disease expression. However, defining JHD based on age of onset is complicated by the different types of onsets (motor, psychiatric, neurocognitive). Relying on motor onset alone, as is often done in clinical trial designs, may exclude JHD cases where isolated non-motor symptoms appear first, which is seen in approximately 50% of JHD cases (**Chapter 4**). The introduction of the HD-ISS,[1] which includes neurocognitive assessments, partially addresses this issue, though up to now it is only validated for AHD cases. Also other selection criteria have been used to refer to sub-JHD populations sharing unique disease patterns. For instance "Highly-Expanded JHD" (HE-JHD, CAG-repeats ≥80), which progresses more rapidly with resulting shorter survival and prevalent epileptic seizures compared to "Low-Expansion" JHD cases (LE-JHD, CAG-repeats <80).[3] Additionally, we have shown that glucose transporters and mitochondrial complexes are selectively diminished in HE-JHD brain material compared to LE-JHD and AHD (**Chapter 6**). CAG-repeat length can explain much of the variability in

motor onset age,[4] but considerable overlap exists between cJHD, aJHD, and AHD, limiting its usability as a sole criterion for unique JHD subpopulations.

These studies reveal the need for accurate and internationally approved JHD subtype selection criteria to ensure valid methodology and reliable study results in the different JHD subtypes. Our study results suggest stratification is needed between JHD cases with (1) high expansions (≥80) or onset in childhood with (2) JHD cases that have lower expansions or onset in adolescence. To establish a both sensitive and specific stratification of JHD subtypes, all types of clinical onset should be considered, as well as the conditional and combined use of clinical severity markers (e.g. age onset, rate of progression), unique disease characteristics (e.g. epileptic seizures) and molecular disease markers (e.g. CAG-repeat length, somatic expansion index). International agreement and implementation of such selection criteria can be harbored via the established international JHD working group of the EHDN.

Practical implementations

Our findings of an extremely small PHD population (**Chapter 2**) and clinically distinct JHD population (**Chapter 2 and 4**), reveals the need for a tailored clinical and research approach, differing from standard HD practices. The practical implementation of this tailored approach influences types of research designs, collaborations, the validation and use of (clinical) assessment tools, and prediction models and, ultimately, the type of clinical care that is offered and implementation of therapeutic strategies. In the paragraph below several directives are offered in light of these practical implementations for future research.

Since the identification of the HTT gene in 1993,[5] substantial progress has been made in our understanding of HD disease characteristics and pathophysiology, with contributions from research organizations and patient advocacy groups driving funding, collaborations, and standardized tools. While JHD has benefited some of these advancements, the fundamental differences between JHD and AHD has been overlooked in key areas, particularly in the applicability of the Unified Huntington Disease Rating Scale (UHDRS). The UHDRS,[6,7] developed in 1996, is widely used to assess motor, neurocognitive, psychiatric, and functional symptoms of HD. Concerns about its applicability to JHD and PHD populations were raised over a decade ago,[8] yet no real advances have been made to modify and validate UHDRS scales to include the juvenile subtype. As our data reveals, the neurocognitive and

functional assessments in the UHDRS lack validity for JHD (**Chapter 2 and 4)**, hindering insights into affected cognitive domains and functional decline. Amongst other strategies, digital neurocognitive assessments and age-independent functional measures hold the promise of bridging this gap. A suitable UHDRS for the entire HD population – including JHD – is crucial to the necessity of including JHD patients in comparative studies alongside AHD, which in turn offers deeper insight into pathophysiological differences that may inform more tailored clinical care and therapeutic strategies.

Another overlooked topic in the JHD population is the use of prediction models for disease stage and progression (e.g., PIN,[9] CAP,[10] HD-ISS[1]). These models rely on a combination of clinical, functional, biomarker and molecular disease characteristics and are designed to properly identify candidates for clinical trials or patient materials for pre-clinical studies. So far, these prediction models are not validated for the JHD population, as is also demonstrated in this thesis by the CAP^{100} outcomes (**Chapter 2**). The lack of valid disease stage and progression markers in the JHD population hampers our insight into possible pathophysiological differences in AO-HD subtypes. Redesigning prediction models to include a somatic expansion index, quadratic CAG terms, interaction terms with smaller allele CAGs, and incorporating revised neurocognitive and functional assessments could improve their relevance and accuracy for the entire HD population.

In contrast to the invalidity of clinical and prediction markers for the JHD population, is the common use of HD disease models resembling a juvenile phenotype. To ensure early and prominent phenotypic disease, many insights in HD molecular mechanisms are based on mouse models carrying CAG-repeats in the extremely high range (CAG-repeats >100). Although useful to the JHD population, it remains to be seen if the same mechanisms are relevant to the entire HD spectrum or only to a small proportion of it, being HE-JHD. To substantiate the relevance of these molecular findings, comparison between CAG-repeat lengths in the mild (40-50), moderate (50-80) and severe (>80) range are needed. In turn this structural comparison between CAG-HD subtype models will benefit our understanding of pathomechanisms both in the classical adult-onset and JHD phenotypes.

Because of its rarity, broad international collaboration is another key aspect in moving the JHD research field forward. In this regard, significant progress has already been made by the sharing of knowledge and resources in JHD working

groups and by the foundation of the HDYO JOIN-HD registry.[11] However, there is still considerable potential to deepen and expand these efforts. For example, by standardizing clinical care assessments and adding these in multinational datasets, by allocating and sharing JHD patient materials and by sharing interim research findings on a larger scale. This way researchers have access to more diverse and larger JHD patient populations, which is crucial for improving the generalizability and robustness of study results. The exchange of interim findings between international teams can help accelerate the making of new research protocols and speed up the translation of new insights into clinical practice or therapeutic strategies.

A last topic worth addressing is clinical trial design and therapeutic strategies. With the extremely small number of PHD and JHD patients (**Chapter 2**), the design of conventional interventional trials is unrealistic. In our opinion, adopting flexible personalized approaches such as N=1 cross over designs and compassionate use programs with therapeutic agents tested in the AHD population should be strongly considered. Lastly, it may be worth reconsidering treatments that were unsuccessful in AHD trials but could potentially offer benefits for some JHD patients due to the different clinical course of the juvenile form. Re-testing these therapies in the JHD population might yield promising results, especially if the mechanisms of the disease in younger patients differ from those seen in adults.

JHD pathophysiology

HD pathophysiological framework

Since the recognition in 1993 that HD pathophysiology in general is triggered by a germline expansion of the CAG-repeat (≥36) in the *HTT* gene,[5] it has become evident in recent years that further somatic expansion of the CAG-repeat in mainly neuronal cells of the HD brain plays an important mediating factor in the disease mechanism.[12] This somatic expansion is influenced by the length of the germline CAG-repeat itself, as well as *cis*-acting loss of mHTT CAA interruption and *trans*-acting SNPs in DNA-repair genes.[13-15] Eventually, this process enters into a cascade of multi -spatial and -cellular degenerative and reactive processes, with the medium spiny neurons (MSNs) of the caudolateral basal ganglia to be the earliest and most severely affected.[16,17] Another emerged extension on this pathophysiological framework are the more recently acquired insights in neurodevelopmental alterations, which have been observed in several HD models, materials and even patient *in vivo* studies.[18-21]

Although not fully elucidated, HTT's role in neurodevelopment suggests that these aberrations might be caused by dominant-negative loss-of-function mechanisms. Hypotheses exist regarding how neurodevelopmental defects may contribute to the clinical picture in HD,[22] however, much remains to be understood in this regard.

Neurodevelopmental context

The recognition that JHD patients exhibit a distinct clinical phenotype compared to prototypical AHD – and how this relates to the pathophysiological framework outlined above – formed the foundation of this thesis. The prevailing hypothesis that HD pathophysiology, driven by the HTT-CAG-repeat expansion, follows one continuum, was challenged in this thesis by an alternative hypothesis: are there specific pathomechanisms that contribute differently or more significantly in the JHD population? An important consideration when analyzing differences between AO-HD subtypes, is the different neurodevelopmental context that patients are in when they experience HD symptoms (**Chapter 3**). Postnatal brain maturation is a physiological process that continues well into early adulthood. Whereas AHD patients generally have a fully matured brain when HD pathomechanisms succumb, in JHD patients' neurodevelopmental changes are still ongoing when pathomechanisms occur and are therefore prone to interaction. This interaction is likely contributing to distinct clinical disease outcomes when compared to AHD. In this context we speculated on contributing pathomechanisms and interacting processes on certain highly prevalent symptoms in JHD, being developmental alterations, epileptic seizures and psychosis/behavioral disorder **(Chapter 3**). In the following subparagraph we will draw hypotheses regarding contributing disease mechanisms and neurodevelopmental interaction based on some of our own study results, and offer future directions for research. Furthermore, we will highlight some opportunities for future studies based on others' work.

Hypotheses and future directions

Based on longitudinal clinical data in the 3 defined AO-HD subtypes, we predicted distinct patterns of severity and progression across sub-motor and neurocognitive domains in the AO-HD subtypes (**Chapter 4**). For the submotor domains parkinsonism and dystonia we visualized a pattern of early occurrence and more severe changes in early-onset phenotypes compared to AHD, but a similar rate of progression over time in the 3 AO-HD subtypes. In contrast, in submotor domains dysarthria, oculomotor and gait and balance specifically a faster rate of progression

was associated with early onset phenotypes. In the neurocognitive domain, the aJHD population was predicted to have a better initial performance, but both JHD subtypes were associated with a faster decline over time in psychomotor speed function compared to AHD. The predicted differences in severity and progression rates suggest that the predictors 'age at onset' and 'age at measurement' have a differential impact on sub-motor and neurocognitive clusters. Based on these predictions, one can hypothesize that an early and more severe clinical phenotype of parkinsonism and dystonia with similar progression rates is more likely to be influenced by early neurodevelopmental defects, whereas a faster progression over time of dysarthria, oculomotor, gait and balance and psychomotor speed is more likely to be caused by neurodegenerative pathomechanisms. Although it is a difficult task of answering such hypotheses in small patient populations, the value of post-mortem HD neuropathology studies may prove insightful in untangling the contribution of neurodegenerative vs neurodevelopmental pathomechanisms on certain predominant clinical features.

Another interesting area for future research is the underlying pathomechanism of psychosis. We showed that this disease characteristic is specifically more common in aJHD patients compared to cJHD and AHD (**Chapter 4**). Notably, the same age-prevalence distribution is seen for the onset of psychosis (DSM-5: Schizophrenia Spectrum and Other Psychotic Disorders) in the general population, with a primary psychotic episode often occurring during adolescence. As is suggested by this age predilection, the pathogenesis of psychotic disorders is thought to relate to a lack of physiological synaptic pruning on adolescent age causing overabundance of synaptic connections in the post pubertal brain.[23] Given this, one could speculate about potential common pathways underlying the onset of psychosis in HD. In particular the suggested interaction between HD pathomechanisms in JHD and ongoing neurodevelopmental processes, such as synaptic pruning, provides an interesting hypothetical framework for future studies. Morphological and quantitative analysis of cell populations in post-mortem brain tissue from different AO-HD subtypes at various ages may offer insights into these mechanisms.

Furthermore, we have shown that the glucose receptor GLUT1 and mitochondrial complexes are specifically downregulated in high-expansion cJHD brains when compared to lower expansion aJHD and AHD brains (**Chapter 6**). These findings suggest that high-expansion cJHD patients may suffer brain glucose hypometabolism, which makes an interesting new investigational target for future

studies. The notion that the clinical phenotype cJHD partially overlaps with GLUT1-deficiency syndrome may imply an effect of glucose hypometabolism on symptoms like epilepsy. Analyzing glucose in blood and CSF and or ^{18}F-FDG PET imaging in cJHD patients can offer insight in the relation between epilepsy and brain glucose metabolism.

A particularly informative study in the context of developmental neural circuitry characteristics formation is the KIDS-HD study, which, among other outcomes, investigates fMRI-based functional circuitries in HD-Expanded Gene Carrier (HDEGC) minors who are decades removed from disease onset.[20,24] Their findings have provided valuable insights in spatial remodeling of functional circuitries that may compensate for early disease mechanisms in the brains of children and adolescent who are destined to develop HD clinical characteristics later in life. Although functional circuitry alterations can also relate to the presence of clinical symptoms, up to now, these results do not teach us anything on the relationship between AO-HD subtypes and manifest clinical characteristics. Yet it holds promise for an alternative study design in which manifest JHD and AHD patients are compared in relation to the occurrence of specific symptoms, such as epileptic seizures. This way it could address questions related to neural circuitry functionality across different AO-HD subtypes and in relation to clinical symptoms.

Finally, another avenue of future research would be the relationship between the HTT interactome and age. In many Mendelian inherited disorders, complex genotype-phenotype relationships are likely to involve abnormal multi-omic interactions between the disease-causing gene and other genes. While several studies have investigated perturbed interactions of (m)HTT in relation to various pathophysiological aspects of HD,[25-27] the relationship between the multi-omic HTT interactome and age has not yet been explored. Investigating this relationship could provide valuable information regarding age-related phenotypes in HD. Open-access resources, such as the Allen Brain Atlas, offer valuable data on the transcriptome of the developing brain, which could help address these questions.

CRITICAL LIMITATIONS

While this thesis provides novel insights into the clinical, molecular, and pathophysiological characteristics of JHD and PHD, several limitations must be acknowledged. The extreme rarity of these populations resulted in small sample

sizes, limiting statistical power and generalizability. The retrospective and cross-sectional study designs introduce potential biases due to incomplete longitudinal data and the limited validity of assessment tools such as the UHDRS in juvenile populations. A further limitation concerns the insufficient consideration of disease progression as a mediating factor in the analysis of AO-HD subtypes, potentially obscuring dynamic interactions between age at onset, CAG-repeat length, and evolving clinical phenotypes. Lastly, methodological variability between institutions and registries may have introduced inconsistencies in data collection and classification. Future studies in JHD and PHD research will continue to face challenges related to population size, data harmonization, and model validity. Overcoming these will require international collaboration, standardized diagnostic and assessment frameworks, longitudinal study designs, and the development of age-appropriate clinical and molecular markers to ensure reproducibility and translational relevance.

CONCLUDING REMARKS

The findings of this thesis emphasize the need for a tailored approach to conduct research in JHD and PHD, which differs from the standard practices for AHD. Several factors support this conclusion. First, the JHD and PHD populations are small and clinically distinct. The small population size makes traditional clinical trials difficult, while the unique clinical characteristics of JHD require a more personalized approach. Second, current assessment tools and prediction models are not validated for JHD and PHD, hampering the accurate assessment of disease progression. Third, the interaction between HD pathophysiology and the ongoing brain development in JHD and PHD requires special attention. The disease affects a developing brain, which likely contributes to the distinct clinical presentation compared to AHD. Future research should focus on (1) re-developing and validating assessment tools and prediction models to include the JHD and PHD populations, thereby enabling structural comparison of AO-HD subtypes, (2) further investigating the different pathophysiological mechanisms in JHD, particularly in the cJHD subgroup, (3) Studying the interaction between HD pathophysiology and brain development in JHD and PHD, and (4) considering flexible, personalized treatment approaches, such as N=1 cross-over designs and compassionate use programs. By following these recommendations, we can improve the care of JHD and PHD patients and hopefully pave the way for more effective treatments.

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