The UHDRS and UHDRS-FAP assessments in Huntington's disease

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CHAPTER 1

Introduction

Huntington's disease

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by motor disturbances, cognitive decline, psychiatric symptoms, and functional disability. It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin gene on chromosome 4.[1] A CAG expansion of 36 repeats or more is associated with HD, although only a CAG repeat length of 40 or more is considered fully penetrant and will cause HD inevitably.[2] The mean age of disease onset is 30-50 years, with a mean disease duration of 17-20 years.[3] Age of onset is inversely correlated to CAG repeat length.[4,5] Brain atrophy is most pronounced in the caudate nucleus and putamen of the striatum.[6] Atrophy is already detectable before disease onset and progresses throughout the course of the disease.[7]

HD is a rare disorder with a prevalence of 5-10 per 100,000 in the Caucasian population.[3] In the Netherlands, the total number of HD patients is approximately 1,700. About 6,000 to 9,000 people are at risk for developing HD. Genetic testing is available for individuals at risk. This test can identify premanifest gene carriers, who do not show symptoms or signs of HD yet, but will develop HD in the future. After disease onset, patients are referred to as manifest. Severity of HD progresses from early stage HD to late stage HD over time.[8]

Clinical features

HD is clinically characterized by a triad of motor, cognitive, and behavioral symptoms. The most distinctive motor symptom of HD is chorea; involuntary, irregular movements of the face, trunk, and limbs. Other motor symptoms include bradykinesia, dystonia, impairment of oculomotor function, and gait/balance problems. As the disease progresses, chorea tend to decline, while dystonia, bradykinesia, dysarthria and dysphagia become more prominent.[3,9] Cognitive decline is another sign of HD. Typically, impairment in executive functioning, memory, and psychomotor speed arise in HD.[10] The third main clinical feature of HD is behavioral change. Frequently reported psychiatric symptoms are depression, anxiety, irritability, and apathy.[11] Depression and anxiety are common in the mild-to-moderate disease severity stages, while apathy is especially prevalent in more advanced severity stages.[12-15]

HD is presently incurable and it is not possible to delay either onset or progression of the disease. Due to the progressive nature of the disease, the clinical features ultimately lead to functional decline and loss of independency. As a result, it becomes more difficult for care to be provided at home, which may lead to nursing home admission.

Assessment scales

Multiple rating scales and instruments to detect and monitor the severity and progression of clinical features in HD have been developed over the years. Some assessment scales, such as the Unified Huntington's Disease Rating Scale (UHDRS) and the Unified Huntington's Disease Rating Scale-For Advanced Patients (UHDRS-FAP), have a categorical and semi-quantitative design.[16,17] Other measurement instruments, such as eye-tracking equipment, tongue force analysis, and quantitative-motor (Q-Motor) assessments, have a continuous, quantitative, and more objective design.[18-20]

The clinical assessment of symptoms and signs in HD is usually performed with the UHDRS, developed by the Huntington Study Group (HSG).[16] The UHDRS is divided into four domains: motor performance, cognitive function, behavioral abnormalities, and functional abilities. The motor section assesses chorea, dystonia, eye movements, bradykinesia/rigidity, and gait/balance. Cognitive function is measured by the Verbal Fluency test, the Symbol Digit Modalities test, and the Stroop test (color naming, word reading, and interference).[21-23] The behavioral domain comprises depression, anxiety, irritability/aggression, obsessive-compulsive behaviors, psychosis, and apathy. Functional ability is assessed by the Total Functional Capacity (TFC), the Functional Assessment Scale (FAS), and the Independence Scale (IS). The UHDRS has been developed to follow individual patients systematically over time, and monitor disease progression for both research purposes and for use in clinical practice. The motor, cognitive, and functional domains of the UHDRS have demonstrated to be sensitive to detect longitudinal changes in manifest HD patients.[16,24-28]

In late stage HD, ceiling and floor effects of the UHDRS hamper the detection of changes and, therefore, disease progression is difficult to measure in patients with advanced HD.[28,29] For this reason, the UHDRS-FAP has been developed.[17] This scale consists of four sections, which are a motor, cognitive, somatic, and behavioral section. The items of the domains are adjusted for more severely affected patients.

This thesis

The main aim of this thesis was to investigate different measurement properties of the UHDRS and UHDRS-FAP in various severity stages of HD. The UHDRS is widely used in therapeutic clinical trials in HD and the motor domain, which is also called the Total Motor Score (TMS), often serves as primary endpoint to assess efficacy of interventions. Therefore, a high interrater reliability is desirable to determine the course of the motor

symptoms over time. A teaching video has been developed by the European Huntington's Disease Network (EHDN), in collaboration with the HSG, and an annual online certification has been implemented for this purpose in 2009.[30] In **chapter 2**, we aimed to investigate the interrater reliability of the UHDRS-TMS and of its subitems, using the ratings of the online certification. We also examined the impact of the annual certification on rater performance. In **chapter 3**, we focus on the oculomotor items of the UHDRS-TMS. The aim was to find out which of these items were affected in premanifest gene carriers compared to healthy controls and might be useful for detecting early clinical signs of HD.

In advanced stages of HD, knowledge is limited about the course of the clinical manifestations. Hardly any information on sensitive disease outcome measures to track disease progression is available and guidelines for management and care in long-term care facilities are limited.[31] Therefore, we aimed to explore the properties of the UHDRS-FAP and UHDRS in patients with advanced HD residing in a nursing home or receiving day-care. We investigated the capacity of the scales to differentiate between patients in the later stages of the disease using our cross-sectional data (**chapter 4**). Internal consistency and interrater reliability of both scales are also reported. The rating scales were administered again after six months. With our longitudinal data, we examined if the UHDRS-FAP and UHDRS could detect disease progression in patients with late stage HD (**chapter 5**). In **chapter 6**, we aimed to identify predictors for institutionalization by examining differences between nursing home residents and day-care patients with HD. Identification of predictors may lead to interventions and treatment strategies that can postpone the need for nursing home admission. In the final chapter (**chapter 7**), we discuss our conclusions and make recommendations for future research.

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