Chapter 1

Introduction
In his essay ‘On Chorea’, George Huntington (1850 - 1916) described three disease characteristics of what was then called Huntington’s chorea: the hereditary nature, the tendency to insanity and suicidal behavior, and the manifestation of the illness at adult age.\(^1\) Clearly, he was already aware that next to the observable motor symptoms, patients also suffer from psychiatric disorders.

**History**

In the early twentieth century, the Dutch psychiatrist Gerbrandus Jelgersma (1859 - 1942) portrayed ‘chorea hereditaria’ as an organic brain disease with severe psychiatric symptoms that occurred in specific families. In his ‘Leerboek der Psychiatrie’, he discussed all kinds of psychiatric symptoms which he had seen in patients with this disease: melancholia, dysphoria, irritability, anxiety, delusional thoughts, indifference, ignorant behavior, and at the end dementia.\(^7\) For a long period, patients with Huntington’s disease were hospitalized mainly in psychiatric hospitals, because of their severe psychiatric symptoms.

In 1983, the localization of a DNA polymorphism linked with the transmission of Huntington’s disease was reported.\(^2\) Genetic linkage analysis to assess the risk of developing the disease with 95% accuracy became available in 1986. Finally, the causal genetic mutation of Huntington’s disease was discovered in 1993.\(^3\) Since this discovery, predictive testing with a theoretical 100% accuracy became available. Although predictive testing is widely available in the Netherlands, only 25% of all persons at risk choose to be tested.

**Clinical features**

Huntington’s disease is characterized by a triad of psychiatric, motor, and cognitive symptoms.\(^5\) These symptoms commonly co-occur, though in clinical practice patients are typically only diagnosed with Huntington’s disease once motor symptoms appear.

**Psychiatric symptoms**

The occurrence of psychiatric symptoms can be the first sign of Huntington’s disease.\(^7\) A subtle, though progressive, personality change may herald the onset of the disease. Psychopathology in Huntington’s disease includes psychiatric disorders such as depression, as well as neuropsychiatric behavioral problems such as apathy and impulsivity.\(^7,10\)

Reported prevalences of different psychiatric disorders and behavioral problems vary widely, depending on the criteria used and disease stage examined. Also, major differences exist in applied measurements, study design being retrospective or prospective, sample sizes, use of informants, and the analyzed time period. Furthermore, assessment of psychopathology in Huntington’s disease is complicated due to co-morbid somatic and cognitive disturbances, and diminished disease awareness.\(^5,10\)

**Motor symptoms**

Early motor signs of Huntington’s disease include the gradual onset of clumsiness and balance difficulties, that might be unrecognized by the patient. Movement disorders are usually slowly progressive. The most prominent movement disorder in Huntington’s disease is chorea,
characterized by unwanted, jerky movements of head, trunk, and limbs. The gait is poorly coordinated and mimics a dance, and was therefore called chorea (Greek: to dance). As the disease progresses, chorea may become more pronounced, but other movement disorders also occur, such as dystonia, rigidity, bradykinesia, hypokinesia, and postural instability. Swallowing and speech dysfunction develop during the course of the illness and ultimately lead to dysphagia and an inability to communicate. In the most advanced stage of the disease, almost all patients are totally dependent on full time skilled nursing.

Cognitive symptoms
Cognitive disorders are also prevalent in Huntington’s disease, and can occur before motor symptoms are present. Severity and progression of cognitive disorders vary considerably, but many patients develop severe subcortical dementia in advanced disease stage. Cognitive assessment typically shows deficits predominantly in frontal executive functions, including abstract thinking, problem solving, attention, mental set shifting, sequencing, and mental generation of information. A loss of cognitive speed and flexibility may not be acknowledged as a disease symptom, and may subsequently cause problems in social relations.

Inheritance
Huntington’s disease is a neurodegenerative disorder with an autosomal dominant pattern of inheritance, resulting in an a-priori 50% risk of developing the disease for every child when one of the parents is affected. The causal genetic mutation of Huntington’s disease is localized on the short arm of chromosome 4 (4p16.3). This genetic modification is an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat coding for the protein huntingtin. A CAG expansion of 36 repeats or more is associated with Huntington’s disease, though a repeat between 36 to 39 repeats has a reduced penetrance and may not in all cases result in the clinical phenotype. Higher repeat length is associated with a younger age of onset, but the repeat length seems to determine the age of onset only partially (about 60%). Previous studies have shown that parental age of onset is an additional predictor of the age of onset, and presumably reflects genetic and/or environmental influences.

Epidemiology
The prevalence of Huntington’s disease varies widely, depending on the geographic region; in Europe and Northern-America the prevalence is approximately 7 - 9 per 100,000 inhabitants. The total number of symptomatic patients in The Netherlands is about 1,200 - 1,500. Another 6,000 to 5,000 persons have a 50% risk of developing Huntington’s disease.

The mean age of onset is difficult to estimate accurately, because onset symptoms differ widely. The age of onset of motor symptoms is usually between 30 and 50 years (range 2 - 80 years), but many patients experience psychiatric symptoms before the presence of motor symptoms. The mean duration of illness is approximately 16 years.

Neuropathology
So far, the neuropathology of Huntington’s disease is not understood. A regional selectivity of atrophy and neuronal loss in the caudate nucleus and putamen of the striatum is common, but other regions may also be affected. Some neurons contain intranuclear inclusions that are characteristic for Huntington’s disease, though their role in the pathogenesis of the disease is not known.

Disease stage
The period before the onset of symptoms is called the presymptomatic or premanifest period. The appearance of one of the characteristic motor, psychiatric or cognitive symptoms is the start of the disease, and – if one has not been tested – reveals the carriership of the disease.

The progression of the disease can be defined by the duration of illness, the presence and severity of symptoms, or the level of functional impairment. So far, no objective criterion for disease stage (e.g., atrophy of the striatum) is available. In this study, a conservative approach is applied to differentiate presymptomatic and symptomatic mutation carriers. A neurologist expressed his level of confidence that the presence of motor symptoms in a study subject is a sign of clinically manifest Huntington’s disease. This confidence level is an item of the widely used motor section of the Unified Huntington’s Disease Rating Scale (UHDRS), and ranges from 0 to 4. All mutation carriers with confidence level score 0 (normal) or score 1 (nonspecific motor abnormalities; < 50% confidence) were classified as presymptomatic. The remaining mutation carriers with score 2 (motor abnormalities that may be signs of Huntington’s disease; 50% - 89% confidence), score 3 (likely signs of Huntington’s disease; 90% - 98% confidence), or score 4 (unequivocal signs of Huntington’s disease; ≥ 99% confidence) were considered symptomatic.

Focus of this thesis: Psychopathology in Huntington’s disease
During the course of Huntington’s disease, most patients will develop psychiatric disorders or behavioral problems that have an important negative impact on their quality of life and add greatly to their suffering and the burden of caregivers. Therefore, it is important to gain insight in the prevalence and characteristics of psychopathology. However, diagnosis of psychopathology in Huntington’s disease is complicated by the presence of co-morbid disorders, overlapping symptoms, and a diminished insight. Apathy, for example, may be a symptom of depression, but can also occur independently as a syndrome in its own right, and is more often a complain of caregivers rather than of patients themselves.

An important previous study describing psychopathology in Huntington’s disease showed that behavioral problems can be divided in three symptom clusters: depression, apathy and irritability. This study also showed that psychopathology in Huntington’s disease may have disease specific features, that fluctuate during the progression of the disease.

No association has been found between psychopathology in Huntington’s disease and the expanded CAG repeat length. Furthermore, it is unknown to what extend alternative genetic, biologic or environmental factors contribute to the presence of psychopathology. For example, exposure to potential stressful life circumstances, e.g., growing up in stressful family circumstances and being at risk for Huntington’s disease, can result in an increase of stress hormones by hyperactivity of the hypothalamic-pituitary adrenal axis. This increased level of stress hormones may be one of the biological factors that contribute to the manifestation of the first subtle symptoms of Huntington’s disease, including psychiatric symptoms.
Aims of the study

Primary aim

The primary aim of this thesis was to assess the prevalence of both formal psychiatric disorders and behavioral problems. We assumed that members of families with Huntington’s disease, regardless of their genetic status, would all show an increased prevalence of psychiatric disorders and behavioral problems compared to the general population.

We started with a review of the literature, that was used to guide the design of the study, to identify psychiatric disorders and behavioral problems in Huntington’s disease, and to obtain a set of reference data (Chapter 2). Since differences in study population and measurement tools used, resulted in widely variable prevalences, we assessed psychopathology both conservatively with diagnostic criteria according to the Diagnostic and Statistical Manual of mental disorders, Version IV (DSM-IV) (Chapter 3), and with the recently developed Problem Behaviors Assessment scale (Chapter 4).

Secondary aims

We hypothesized that measurement tools using caregiver information are more appropriate to detect psychopathology in advanced stages of Huntington’s disease. Therefore, we assessed the concurrent validity of two rating scales using caregiver information, that were specifically designed for the assessment of psychopathology in Huntington’s disease, in comparison with a categorical assessment of psychiatric disorders as defined by criteria of the DSM-IV (Chapter 5). Since apathy showed to be a frequent neuropsychiatric symptom in Huntington’s disease, we aimed to assess the prevalence as well as the sociodemographic, clinical, and neuropsychiatric correlates of apathy in Huntington’s disease (Chapter 6). Furthermore, we aimed to investigate the function of the hypothalamic-pituitary-adrenal axis as one of the potential biological markers in relation to symptoms of Huntington’s disease in an exploratory way (Chapter 7).

In the general discussion the results of this thesis are put into a wider perspective together with recommendations for future research (Chapter 8).

References

20. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S: Inclusion body formation reduces levels of...
Chorea

Degeneration and atrophy of caudate nucleus and cerebral cortex, with resulting enlargement of ventricles

CT scan of brain: atrophy of caudate nucleus and enlargement of ventricles

Young woman exhibiting choreiform movements:
- Sydenham chorea
- Lupus erythematosus
- Chorea gravidarum
- Drug effects

Huntington’s disease

Middle-aged person: mental deterioration, grimacing, choreiform movements

Chorea

Differential diagnosis

Sydenham chorea
Lupus erythematosus
Chorea gravidarum
Drug effects

Genetic chart (example)

Degeneration and atrophy of caudate nucleus and cerebral cortex, with resulting enlargement of ventricles

