Psychopathology in Huntington's disease
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Chapter 8

General discussion and future perspectives
This thesis confirms that psychiatric disorders and behavioral problems are major constituents of the clinical spectrum of Huntington’s disease. The prevalence of the different psychiatric disorders and behavioral problems vary, but overall mutation carriers are at major risk of developing psychiatric disorders and behavioral problems in all disease stages. This is an important finding because the presence of psychopathology has a substantial negative impact on quality of life and daily functioning of patients, possibly even more so than motor and cognitive symptoms.1

Assessment
In our review, we demonstrated that prevalences of psychiatric disorders and behavioral problems in Huntington’s disease depend on definition of the disease stages and the measurement tools applied.

Definition of disease stages
In this thesis, the motor section of the Unified Huntington’s Disease Rating Scale (UHDRS-m) was used for the definition of disease stages.2 Although the motor score does not correlate perfectly with disease stage, the use of a functional assessment (e.g., the Total Functional Capacity (TFC)3 scale of the UHDRS) for disease staging was not preferable in our study, as it is directly influenced by the presence of psychiatric disorders and behavioral problems. For that reason, we assume that the assessment of motor function by a blinded experienced neurologist is the most objective and reliable method of disease staging for psychiatric research in Huntington’s disease.

Measurement tools
Diagnostic classification according to the Diagnostic Statistical Manual of mental disorders, Version IV (DSM-IV),4 is currently the gold standard for assessing psychiatric disorders in general psychiatry. Yet, this diagnostic classification insufficiently takes into account co-morbid and overlapping physical symptoms of Huntington’s disease. Furthermore, cognitive impairments may complicate the assessment of a psychiatric diagnosis. Particularly in an advanced stage of Huntington’s disease, when communication and insight may become so impaired that patients are no longer able to express their emotions or to judge their symptoms correctly. Therefore, a structured interview using formal DSM-IV criteria seems less applicable in an advanced stage, since it will result in an underestimation of the prevalences of psychiatric disorders.4 In this stage, dimensional measures of neuropsychiatric symptoms are necessary to capture the full range of psychopathology in Huntington’s disease. The semi-structured Problem Behaviors Assessment (PBA) is especially useful, since other diagnostic information sources such as clinician’s observation of behavior and caregivers’ information are being used.5

Symptomatology
Both with the Composite International Diagnostic Interview (CIDI),6 assessing DSM-IV diagnoses, and the PBA, assessing neuropsychiatric behavioral problems, an increased prevalence of depression was found in mutation carriers. Despite a threefold increase of formal depression in the group of mutation carriers (18%) compared to the general population (6%), this prevalence is considerably lower than the 33% to 69% prevalences reported in earlier studies in Huntington’s
disease.\textsuperscript{9-14} This can be explained by the fact that most earlier studies measured symptoms of depression such as ‘low mood’ or ‘dysphoria’, and not major depressive disorder meeting formal DSM-IV criteria. Also, some studies assessed the prevalence of psychiatric symptoms during a longer time period, e.g., prevalence since the occurrence of motor symptoms or life time prevalence.

Depression is equally present in presymptomatic and symptomatic disease stages, as assessed with the CIDI, as well as with the PBA. The difference in prevalence of depression between presymptomatic mutation carriers and non-carriers did not reach statistical significance when formal DSM-IV criteria were used. However, using the PBA, we found a significant increase of depression in presymptomatic carriers compared to non-carriers. This could be a reflection of higher sensitivity of the PBA for depression in Huntington’s disease, but may also be due to increased power as the PBA is a continuous measure whereas the CIDI is not.

Apathy is also a common neuropsychiatric behavioral problem in Huntington’s disease, with prevalences varying from 34% to 76%.\textsuperscript{9,10,14} Of all psychiatric symptoms, only apathy consistently appears to be positively related to disease progression.\textsuperscript{9} In our study, using the Apathy Scale, 32% of all mutation carriers showed apathy in the previous two weeks, compared to none of the non-carriers. We found that male sex was independently associated with apathy, together with higher use of both antidepressants and neuroleptics, and the presence of depression. As apathy may be an expression of depression, we excluded all subjects with depression (n = 10). Then, male sex, higher use of neuroleptics, higher use of benzodiazepines, and a decline of everyday functioning – that was quantified with the TFC scale – were independently associated with apathy. Since this study has a cross-sectional design, we cannot conclude whether the use of psychotropic medication is a cause or a consequence of apathy, but it is plausible that the use of psychotropic medication may at least worsen apathy.

In earlier studies increased prevalences of anxiety (34% - 61%) have been reported,\textsuperscript{9,10,12-14} with higher prevalences in studies that used general questions about anxiety, worrying, and tensed feelings. In this thesis, we report a non-significant trend of an increased prevalence of generalized anxiety disorder in Huntington’s disease. We also found a twofold increased prevalence of panic disorder in mutation carriers, compared to the general population, but this difference was – presumably due to small numbers – non-significant. Factor analysis of the PBA revealed that anxiety and tensed feelings often co-occur with depressed mood, depressed cognitions and suicidal ideation, and may therefore be a symptom of an affective syndrome in Huntington’s disease, that is not covered by one DSM-IV diagnosis. Since no other studies are known that systematically investigated the prevalence of anxiety disorders in Huntington’s disease, this should be an important focus for future research.

Many patients with Huntington’s disease show personality changes with obsessive-like mental inflexibility in an early disease stage,\textsuperscript{15} though only a minority will get a formal diagnosis of obsessive-compulsive disorder. The few studies investigating obsessions and compulsions in verified mutation carriers, reported prevalences of 10% to 52% for the presence of obsessive or compulsive symptoms.\textsuperscript{13-15} We found a significantly increased prevalence of formal obsessive-compulsive disorder in mutation carriers compared to the general population, both in presymptomatic (6%) and in symptomatic (4%) mutation carriers, although their numbers were small.

Irritability occurs in most patients with Huntington’s disease, and may also precede motor symptoms.\textsuperscript{9,10,12,14} We found an increased prevalence of irritability according to the PBA in mutation carriers, compared to non-carriers, whereas no significant differences were found between disease stages. Given that irritability is a frequent neuropsychiatric symptom, consensus on a distinct definition is warranted for the assessment and clinical follow-up during treatments.

Prevalences of psychotic symptoms in verified mutation carriers vary from 3% to 11%.\textsuperscript{9,10,12,14} However, we found only two mutation carriers (1%) with psychosis. Although it may be delicate to draw conclusions from this small number of affected patients, the prevalence of psychosis may have been overestimated in earlier days when psychosis was considered to be a more prevalent psychiatric feature of Huntington’s disease. Next to the use of strict DSM-IV criteria, this can be explained by the relatively advanced disease stage at the time of diagnosis before genetic testing became available. In fact, our two psychotic patients were also advanced symptomatic patients.

Environmental and biological factors

Although family members with a prior 50% risk of Huntington’s disease, who were not genetically compromised, had a shared environment during two to three decades of their lives, they had no more psychiatric disorders than the general population. In contrast to our assumption, the presence of a familial disease burden, did not make them more susceptible to psychiatric disorders than the general population.

It is unlikely that the mutation on its own has a full penetrance for the presence of psychiatric disorders; other factors probably contribute to the risk of developing psychopathology. Future research should focus on the contribution of both environmental and biological factors to the presence of psychopathology, that may enable early (preventive) interventions.

In this thesis, we examined the function of the hypothalamic-pituitary-adrenal axis in mutation carriers and controls. The hypothalamic-pituitary-adrenal axis function was measured through salivary cortisol in a day curve and after a dexamethasone suppression test. We found an increased salivary cortisol concentration in pre-motor symptomatic mutation carriers, indicating a hyperactivation of the hypothalamic-pituitary-adrenal axis in mutation carriers before the onset of motor symptoms. Increased cortisol concentrations may in turn contribute to an increased susceptibility for emotional disturbances, but we could not demonstrate this in our cross-sectional study.

Strengths and weaknesses

The strengths of this study are the rather large study population with Huntington’s disease, the use of a control group consisting of mutation-negative first-degree relatives, and the use of
specific, reliable and validated measurement tools in a standardized interview setting.

Some potential sources of variation in test results as found in our study, such as low incidence
of Huntington’s disease with resulting small sample sizes and self-selection for testing and
research, were difficult to avoid. Also, since this is a cross-sectional and first assessment of a
follow-up study, no conclusions can be drawn on changes in time or causal relations.

A weakness of our study is that many patients in mid and advanced disease stages used psycho-
tropic medications. A medication-free population would have been better for the assessment of
psychopathology, though it is nearly impossible to include patients in these disease stages who
do not use psychotropic medications. This may have confounded our results, with most likely
an overestimation of apathy due to the use of neuroleptics and benzodiazepines, and an under-
estimation of other psychopathology.

Final remarks
This thesis confirms the observation of George Huntington that there is ‘a tendency to insanity’
in Huntington’s disease,\textsuperscript{16} characterized by a variety of psychopathology, already before the
onset of motor symptoms. These psychiatric manifestations of Huntington’s disease have major
influences on the daily functioning of patients and the lives of caregivers.

Since recognition and treatment of psychopathology is often complicated by co-morbid cognitive
and motor symptoms, a multidisciplinary approach is recommended to provide the optimal
patient care. Then, collaboration between clinical and pre-clinical researchers is needed for
further research involving multiple disciplines, to bridge the gap between promising basic
research and solutions for clinical manifestations of Huntington’s disease.

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