

Review

Obsessive-Compulsive and Perseverative Behaviors in Huntington's Disease

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Abstract.

Background: Neuropsychiatric symptoms are highly prevalent in Huntington's disease (HD). However, little is known of the prevalence and course of obsessive-compulsive behaviors (OCBs) and perseverative behaviors (PBs) during the progression of the disease.

Objective: This review provides a summary of the literature on OCBs and PBs in HD gene expansion carriers (HDGECs).

Methods: Pubmed database was searched for articles on OCBs and PBs in HD up to 2017. We used search terms, all synonyms for HD, and various terms for OCBs and PBs.

Results: We found 5 case series and 11 original articles that describe a prevalence range of 5 to 52% for OCBs and up to 75% for PBs depending on disease stage and measurement scale used. Premanifest HDGECs report more OCBs compared to controls, and manifest HDGECs report a higher rate of OCBs compared to premanifest HDGECs. OCBs and PBs are associated with a longer disease duration and disease severity in manifest HDGECs, but decrease in the most advanced stages. When HDGECs come closer to estimated motor onset, the companion ratings on OCBs appear to be higher than the self-ratings of HDGECs.

Conclusions: Both OCBs and PBs are characteristic neuropsychiatric features of HD. Perseveration is probably best distinguished from OCBs as it occurs without the individual's full awareness or insight into their presence (and the behavior may not be distressing). Although these behaviors are seldom distinguished, we conclude that differentiating OCBs from PBs in HD is beneficial for the management and treatment of these symptoms in HDGECs.

Keywords: Huntington's disease, Huntington's disease gene expansion carriers, obsessive compulsive behavior, obsessive compulsive disorder, perseverative behavior, perseverations

INTRODUCTION

Neuropsychiatric symptoms, including depression, irritability, apathy, obsessive-compulsive behaviors (OCBs), and perseverative behaviors (PBs) are highly prevalent in Huntington's disease

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gene expansion carriers (HDGECs) [1]. Recently, the TRACK-HD study has shown that neuropsychiatric symptoms can already be present up to 11 years before motor onset [2]. These neuropsychiatric symptoms contribute to a decline in daily functioning and are often the most distressing aspects of HD for patients as well as their caregivers [3, 4]. Severe negative thoughts of guilt, or a feeling of worthlessness, increase the risk of HD patients to attempt suicide [5]. Together with impairment of mobility and cognitive deterioration, behavioral problems and neuropsychiatric symptoms play an important role in the admission to a nursing home [6]. Whereas studies on depression, irritability and apathy in HDGECs are quite common, published research on OCBs and PBs in HDGECs is limited [7].

OCBs are marked by recurrent intrusive and inappropriate thoughts (obsessions) and by repetitive behaviors (compulsions) such as checking and ordering, which the patient feels driven to perform in order to reduce distress [8]. A patient usually realizes that his obsessions or compulsions are excessive or unreasonable, but this is not always the case. In the general population, the weighted lifetime prevalence for obsessive-compulsive symptoms, without a formal diagnosis of obsessive-compulsive disorder (OCD), is 5.5% by the age of 30 [9]. To receive a formal OCD diagnosis, a person must meet the diagnostic criteria that are described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), e.g., the obsessions and compulsions need to be time-consuming and are not attributable to physiological effects of a substance and/or not better explained by the symptoms of another mental disorder [8].

Perseverative behavior (PB) is the uncontrolled repetition or continuation of a response (motor act, word, thought, activity, strategy, or emotion) that has persisted beyond the psychological context or rationale in which it arose. It occurs without the individual's full awareness or insight into their presence and the behavior may not be distressing [10]. There are other overlapping terms referring to repetitive behavior such as *punding* and *ruminating*, mainly used in Parkinson's disease and other neuropsychiatric disorders [11, 12]. Since OCBs and PBs have similarities in clinical presentation they are frequently not differentiated.

Our aim is to give an overview of the literature on the prevalence and course of OCBs and PBs in HDGECs. We aim to assess clinical criteria to differentiate OCBs from PBs, that may give guidance for

future research, and specific psychosocial and pharmacologic interventions for management of these symptoms.

MATERIAL AND METHODS

Data resource

We searched the Pubmed database for articles on OCBs and PBs in HD up to October 2017. We used a variety of search terms, all synonyms for HD, and various terms for OCBs and PBs. Where possible, these were mapped onto the following standard database terms (subject headings/MeSH terms): "Huntington's disease", "Huntington disease", "Huntington's chorea", "obsessive compulsive behavior", "obsessive compulsive disorder", "perseverative behavior", "perseveration", "repetitive behavior", "repetitive thinking", "preoccupation", "preoccupied behavior". All references of the included articles were hand-searched for further relevant literature. Articles not available in English and without full text availability were excluded, as were studies on pathophysiology and animal studies. Case reports, articles describing original research and/or intervention were included.

RESULTS

The literature search resulted in 18 articles: 6 case reports/series and 12 articles describing original research. No additional original articles could be retrieved from checking the references. One case report was excluded since the patient had no clinical signs or symptoms suggesting HD, DNA analysis was not available and he had a negative family history for HD [13]. One article did not use standardized or validated research instruments for OCBs or PBs, and was therefore excluded [14].

Case reports

The eight patients that were described in the five included case series were all diagnosed with OCD (Table 1). Six of them had genetically confirmed HD (4 manifest, 2 premanifest) [15–18], whereas case 1 and 2 had HD symptoms with a positive family history for HD without genetic confirmation [19].

Original research

We found 11 original studies on behavioral problems that included the assessment of OCBs or PBs

Table 1
Overview of case-reports

	Author	Age (y)	Gender	Symptoms	Diagnosis	Disease stage
1	Cummings [19]	58	M	Inappropriate cleaning up and removing trash	OCD	Manifest
2		55	M	Compulsive smoking (>5 packs/day)	OCD	Manifest
3	De Marchi [18]	59	F	compulsive hand washing up to 30 years prior to manifest HD	OCD	Manifest
4		37	F	ideas of contamination; checking rituals	OCD	Premanifest
5		29	M	Obsessive thoughts of harm/death of his son	OCD	Premanifest
6	Scicutella [17]	72	M	contamination with poison; repetitively washing hands; checking rituals	OCD	Manifest
7	Patzold [16]	42	F	obsession to kill neighbor, thoughts were unpleasant and intrusive	OCD	Manifest
8	Molano-Eslava [15]	45	F	anxiety about contamination, washing body parts repeatedly (20–30 times a day) and avoiding to touch objects	OCD	Manifest

Characteristics of HD case reports with obsessive compulsive behavior/disorder. y, years of age; M, male; F, female; OCD, obsessive compulsive disorder.

Table 2
Overview of original research on OCBs and PBs

Author	Year	N	OCB			P	Measure	Disease stage
			O	C	Total			
Duff [20]	2007	589	–	–	–	–	SCL-90-R	Premanifest
Beglinger [22]	2008	300	–	–	–	–	SCOPI	Premanifest
Epping [21]	2016	1,305	–	–	–	–	SCL-90-R	Premanifest
Beglinger [25]	2007	3,964	24%*	12%*	–	–	UHDRS	premanifest/manifest
van Duijn [23]	2008	140	–	–	6	–	CIDI	premanifest/manifest
Van Duijn [1]	2014	1,993	–	–	13.2%	–	UHDRS	premanifest/manifest
Anderson [26]	2001	27	52%	26%	–	–	Y-BOCS + UHDRS	Manifest
Craufurd [29]	2001	134	5%	10%	–	24%	PBA-HD	Manifest
Murgod [28]	2001	26	11,5%	15,3%	19,3%	–	UHDRS	Manifest
Anderson [27]	2010	1,642	24%	13,9%	27,2%	–	UHDRS	Manifest
Thompson [30]	2012	111	–	–	–	75%	PBA-HD	Manifest

Overview of included articles on obsessive compulsive and perseverative behavior in Huntington's disease. O, obsessive behavior; C, compulsive behavior; P, perseverative preoccupations; SCL-90-R, Symptom Checklist 90 Revised; SCOPI = Schedule of Compulsions, Obsessions, and Pathologic Impulses; CIDI, Composite International Diagnostic Review; UHDRS, Unified Huntington Disease Rating Scale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PBA-HD, Problem Behavior Assessment for Huntington's Disease; *probability in Shoulson and Fahn stage 4/5 of disease; –, not applicable.

in HD [1, 20–30]. Table 2 shows an overview of the articles on OCBs or PBs in HDGECs.

OCBs and PBs in premanifest and prodromal HDCEGs versus controls

Three articles describe psychiatric symptoms in premanifest and prodromal HDGECs who participated in the PREDICT-HD study [20, 21]. Prodromal HD is defined as subtle motor and/or cognitive signs and symptoms with minor decline in premorbid

level of function [31]. In the first study [20], the Symptom Checklist 90 Revised (SCL-90-R) was used to measure psychiatric symptoms, including obsessive compulsive symptoms. Mean prevalence of obsessive compulsive symptoms was significantly higher in HDGECs compared to gene negative participants. The second study using PREDICT-HD data [21], showed significant differences between ratings of obsessive compulsive symptoms in prodromal HDGECs and controls at baseline and at follow-up.

The third study [22] also reports data from the PREDICT-HD study using another self-report measure of obsessive compulsive symptoms, the Schedule of Compulsions, Obsessions and Pathologic Impulses (SCOPI) in HDGECs compared to controls. Although HDGECs had more obsessive checking and pathologic impulses than controls, and OCBs increased as disease burden increased, those closest to onset had OCBs similar to controls

A cross-sectional study, using the Composite International Diagnostic Interview (CIDI), on prevalence of formal DSM-IV psychiatric disorders in presymptomatic and symptomatic HDGECs reported significantly more OCDs in HDGECs compared to the general population, but not compared to their gene-negative first degree relatives [23].

OCBs and PBs rating by premanifest HDCEGs and their companions

In several studies both HDGECs and companions were asked to rate the presence and severity of OCBs and PBs in HDGECs. The first PREDICT-HD study showed that the ratings of premanifest HDGECs and their companions were significantly correlated ($r = 0.52; p < 0.05$) [20]. Furthermore, in HDGECs closer to estimated motor onset, the ratings by their partner, family member or friend were significantly higher than those of the HDGECs, whereas HDGECs who were further from estimated motor onset, self-ratings of HDGECs did not differ from the rating by their companions [21].

OCBs and PBs and disease duration

In a large European REGISTRY cohort, the behavioral section of the Unified Huntington's Disease Rating Scale (UHDRS) was used to assess prevalence and correlates of neuropsychiatric symptoms [1]. This scale has two separate items for perseverative/obsessional thinking and compulsive behaviors. The combined prevalence of perseverative/obsessional thinking and compulsive behaviors increased significantly with disease stage: 4.5% in stage 1 to 25.8% in stages 4-5. HDGECs with OCBs and PBs had a longer disease duration and had more often a psychiatric history such as depression or psychosis, and more often used psychiatric medication [1]. Another study [25], measured the probability of having OCBs in persons at-risk for HD and manifest HDGECs across various disease stages using

the perseverative/obsessional thinking and compulsive behaviors items of the UHDRS. The probability of meeting the threshold for OCBs increased with advancing disease stage and was more than three times greater in clinically manifest patients than in the at-risk group. However, in the end stage of disease OCBs were less prevalent.

Two studies [26, 27] found that HDGECs with OCBs show significantly greater impairment in executive function, greater functional impairment and longer duration of disease. Two other studies assessed OCBs and PBs with the Problem Behaviors Assessment for HD (PBA-HD) [29, 30]. Craufurd et al. investigated behavioral changes in 134 manifest HDGECs with a mean disease duration of 9 years (SD 5) [29]. Ten percent of these patients showed compulsive behavior, 5% obsessions and 24% perseverative preoccupations. Perseverative preoccupations, obsessions and compulsive behavior occurred with roughly equal frequency at all stages of the illness. However, a longitudinal study using the PBA-HD found significantly worsening of perseveration over time with a prevalence of approximately 30% at baseline (mean duration of illness: 5.5 years; SD 4.7) and 75% after a mean follow-up time of 5 years (SD 2.6) [30].

Treatment of OCBs and PBs

There are no evidence-based guidelines how to treat OCBs in HD. Anderson et al. surveyed international HD experts on the treatment of OCBs in HD. This resulted in an expert-based guideline that recommends to start with selective serotonin reuptake inhibitors (SSRIs) as first choice, and the tricyclic antidepressant clomipramine as second most recommended treatment choice. Antipsychotics and anti-epileptic mood stabilizers were used as augmentation strategies by some of the experts. Half of the experts indicated cognitive behavioral therapy being useful in patients with mild cognitive impairment and 83% endorsed family education on OCBs [32].

Three patients with OCBs described in the case reports (Table 1) were treated with medication: case 1 was treated with haloperidol to reduce chorea, which had no apparent effect on the compulsions [19]. Sertraline was prescribed at a daily dose of 150 mg in case 7 with a complete remission of obsessive ideas within 4 weeks of treatment [16]. In case 8 the patient was treated with olanzapine 2.5 mg and paroxetine

40 mg per day, resulting in a decrease of obsessional thoughts after 4 weeks [15].

DISCUSSION

Both OCBs and PBs are frequently reported by HDGECs. The prevalence ranges from 5 to 52% for OCBs and up to 75% for PBs depending on disease stage and measurement scale used. Premanifest HDGECs report more OCBs compared to gene-negative controls [20, 21], and manifest HDGECs report a higher rate of OCBs compared to premanifest HDGECs. Data on the prevalence of PBs in premanifest HDGECs are not available, however, both OCBs and PBs are associated with duration and severity of HD, but decrease in the most advanced stage. When HDGECs come closer to estimated motor onset, the companion ratings on OCBs appeared to be higher than the self-ratings of HDGECs [21]. This might suggest that HDGECs close to estimated onset of disease have diminished awareness of their symptoms, and the resulting reduction of the distress caused by the OCB changes the symptom into a PB.

Next to the neuropsychiatric features OCBs and PBs, formal psychiatric diagnosis OCD is also more prevalent among premanifest and manifest HDGECs than in the general population.

Obsessive compulsive and perseverative symptoms are more frequently observed in patients with orbital frontal lobe dysfunction, including frontal-striatal disturbances. OCBs are believed to be associated with impaired neuronal circuits between orbitofrontal cortex and striatum leading to this neuropsychiatric symptom. PBs are considered to be true cognitive symptom leading to impaired cognitive flexibility caused by a disruption of frontal-subcortical circuitry [32]. It seems that OCBs and PBs share a similar pathology in which the frontal lobe circuits are disrupted [33].

OCBs and PBs are typical features of neuropsychiatric disorders like HD. Neuropsychiatric symptoms of progressive neurodegenerative diseases are often strongly related with co-occurring cognitive, motor and physical symptoms [1, 29, 32]. Unlike OCD, these features are not classified as formal psychiatric disorders although OCBs can be classified as 'obsessive-compulsive and related disorders due to another medical condition' in DSM-5. In general, OCBs cause clinically significant distress or impairment in functioning. In most cases, PBs occur without the individual's full awareness or insight

into their presence, and are characterized by the uncontrolled repetition or continuation of a response (motor act, activity, thought or emotion) that has persisted beyond the psychological context or rationale in which it arose.

Limitations of this review are that some studies have small sample sizes and other studies combined pre-manifest and manifest HDGECs, making comparison difficult. Furthermore, different measures were used to assess OCBs, and only a few of these specifically assess PBs, which are not all validated scales in HD.

There is still a lack of evidence for the treatment of behavioral problems in HD. The first step to cope with this problem is to properly define the nature of its behavioral manifestations. According to an international expert-based guideline, treatment with SSRIs or clomipramine is preferred as first choice of OCBs [32]. Unfortunately, for PBs in HD there are no expert-based guidelines. For OCD a combination of an SSRI with behavioral and cognitive-behavioral psychotherapy (CBT) is considered first-line treatment [34]. Successful treatment will benefit patients' overall wellbeing and social functioning. There is limited evidence for the use of CBT in HD, in any stage of the disease. Cognitive impairments in memory and awareness may limit its effectiveness, especially as cognitive impairments increase with disease duration. Since some patients might subjectively suffer or have no insight into their behavior or suffer, they will probably be less motivated to engage in, or benefit from behavioral treatment. However, this needs to be studied to see if this theoretical concern actually limits benefits of CBT in patients and which cognitive impairment mediated the loss of benefit. Spouses and caregivers, however, often find these symptoms to be highly problematic and the presence of PBs in early HD patients is found to be associated with reduced quality of life in their partners [35]. It is more likely that family and caregivers will benefit from treatment focusing on the management of the symptoms. Therefore, family and caregiver education, skill development and support on management of behavioral symptoms is also recommended.

Differentiating OCBs from PBs can be challenging in clinical practice. In our opinion, differentiating OCBs from PBs in HD is beneficial for the management and treatment of these symptoms in HDGECs, and the instructions to and support of their family members and caregivers. Family psycho-education might give an opportunity to augment treatment

effects and reduce the suffering associated with medication resistant symptoms.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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