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Review

Irritability in Huntington's Disease

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Abstract. Huntington's disease (HD) is a heritable and fatal neurodegenerative disease characterized by a triad of motor, cognitive and neuropsychiatric symptoms. A common and particularly detrimental neuropsychiatric alteration in HD gene carriers is irritability, which frequently manifests as abrupt and unpredictable outbursts of anger. This symptom increases the burden of HD in multiple ways, such as jeopardizing employment and straining familial or caregiver support. Although irritability in HD is diagnosed by the administration of standardized rating scales and clinical expertise, measurement of severity and progression is complicated by several factors. Currently, individuals with HD who present with irritability may be managed with a variety of psychotropic medications, primarily antidepressants and antipsychotics. While these therapies offer relief to individuals suffering from irritability in HD, they are often not sufficient. Here, we review irritability in the context of HD and emphasize the need for treatments that are better tailored to mitigate this troublesome symptom. An expeditious strategy in pursuit of this goal involves evaluating the efficacy of approved medications that are used to treat similar neuropsychiatric symptoms.

Keywords: Huntington's disease, irritable mood, neuropsychiatry, behavioral symptoms, psychotropic drugs

INTRODUCTION

Huntington's disease (HD) is a completely penetrant autosomal dominant neurodegenerative disease caused by a trinucleotide repeat (CAG) expansion within the huntingtin gene (HTT) on chromosome 4 [1]. The disease is characterized by a triad of motor symptoms, progressive cognitive decline, and psychiatric disturbance [1]. These clinical manifestations are due to neuronal dysfunction arising first within striatal medium spiny neurons and then spreading to other regions of the brain, including the cortex [1]. To date, no disease modifying therapies are approved to treat HD, although novel approaches targeting the genetic underpinnings of the disease hold promise [2]. Given the current absence of curative therapy and the disruptive neuropsychiatric symptoms, improved symptomatic treatments are urgently needed.

The motor manifestations of HD, which are the symptoms that have historically informed a clinical diagnosis, typically arise during middle age [3, 4]. However, a variety of neuropsychiatric symptoms, including irritability, apathy, and depression, are known to affect HD gene carriers well before the onset of motor symptoms [4]. These neuropsychiatric alterations represent an underexplored area where novel treatments can be developed to benefit patients with HD. Here, we will review the current understanding, diagnosis, and treatment of irritability associated with HD—a common and pernicious aspect of the disease—and the prospect of future therapy.

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IRRITABILITY IN HD

In addition to motor and cognitive symptoms, individuals with HD may also experience a number of neuropsychiatric symptoms, several of which can begin years before the manifestation of motor symptoms [5, 6]. Psychiatric disturbances that occur in individuals with HD include apathy, depression, irritability, aggression, obsessive-compulsive behaviors and psychosis [7, 8]. Here, we will focus on irritability, which is most simply defined as possessing a proneness to anger [9]. A more expansive definition of irritability is a "mood that predisposes towards certain emotions (e.g., anger), certain cognition (e.g., hostile appraisals) and certain actions (e.g., aggression)" that is "subjectively unpleasant and objectively characterized by expressions of negative emotion in interpersonal relationships" [10].

In the context of HD, irritability is thought to result from the complex relationship between the primary neurobiological changes occurring as part of pathological progression and the secondary psychological effects, which constitute a reaction to the subjective changes patients experience [11]. For instance, the progressive cognitive decline caused by the disease may be experienced as a kind of cognitive overload, which contributes to the manifestation of irritability. In this sense, it can be distinguished from irritability in the general population. The clinical phenotype of irritability in HD is often reported by family, as they are usually the patient's primary caregivers and, unfortunately, are the target of the resulting aggression [12]. These aggressive episodes or outbursts have been described as being triggered by the slightest aggravation, which can incite angry or violent behavior that can last for hours to days [12]. HD gene carriers themselves sometimes, but not always, have insight into their experience of irritability, and may be surprised by the unpredictable and sudden onset of such atypical outbursts, which leaves them feeling guilty after the irritability resolves [12]. Alternatively, patients with HD may experience a lack of insight or awareness into many aspects of their disease, including irritability, which may further complicate treatment [13]. Regardless of the particular nature of an individual's irritability, such disruptive behaviors have major consequences for those living with HD and cause considerable functional disability [14]. This volatile behavior—often directed at familial caregivers—may also negatively impact quality of life in individuals with HD, as detrimental familial consequences are not uncommon [12]. For instance, divorce and even rejection by the family of the patient are risks associated with irritability in HD [12]. Additionally, irritability in HD can result in outbursts that may lead to incarceration [15]. Given the particularly devastating nature of these effects—that is, the potential dissolution of the patient's social support structure and the legal ramifications of criminal behavior—treatments that mitigate irritability can have substantial impact to reduce the disease burden of HD.

PREVALENCE

The prevalence of irritability has been measured in multiple studies using a variety of detection methods, which has led to a range of results, specifically from 38% to 73% by one account [16]. Two early and relatively small ($N < 100$) studies assessing the neuropsychiatric profile of HD, using either the neuropsychiatric inventory (NPI) or the present state examination (PSE), found irritability rates of 65.4% and 64%, respectively, in patients with manifest HD [6, 17]. A later study ($N = 134$) used the problem behavior assessment for HD (PBA-HD) and found three prominent neuropsychiatric features of the disease, apathy, depression, and irritability, the latter of which was present (severity score > 2) in 44% of subjects [18]. A follow-up longitudinal study conducted by the same group in 2012 found that 49% of manifest HD patients were irritable at baseline while 83% were irritable during any assessment [19]. This study also found that irritability progressed in severity in the early stages of disease. Another study in 2012 compared rates of irritability in both HD gene carriers (N = 130) and confirmed healthy controls (N = 43) using the irritability scale (IS), detecting irritability ($IS \geq 14$) in 35% of subjects with HD versus 9% in healthy controls [20]. Findings from the TRACK-HD study indicate that the irritability scores on the PBA short version (PBA-s) are sensitive before and after diagnosis, with significant differences between premanifest HD and controls and between premanifest HD and manifest HD. The adjusted between-group differences were of 1.50 and 2.38, respectively [5]. Additionally, in patients with manifest HD, increased irritability was significantly correlated with worse total functional capacity (TFC) scores, suggesting the progressive nature of irritability in HD. The REGISTRY observational study (N = 1,993), which specifically assessed the neuropsychiatric features of HD, used the behavior component of the Unified

Huntington's Disease Rating Scale (UHDRS) to measure a moderate to severe irritability/aggression rate of 13.9% in HD gene carriers at various stages of disease [21]. This was lower than measured rates of moderate to severe apathy (28.1%), but higher than the prevalence of moderate to severe depression (12.7%), obsessive-compulsive behavior (13.2%) and psychosis (1.2%). Furthermore, The REGISTRY study found that irritability/aggression was positively correlated with being male, young, and having a history of depression, psychosis, and suicide attempt. Drawbacks of this study, as stated by the authors, include that the selected cohort may have been relatively healthy compared to the general HD population, which could have caused underestimation of symptom prevalence. A recent scoping review that identified studies comparing the prevalence of irritability in HD gene carriers versus healthy controls determined that 66% (8/12) of these reports found significantly higher irritability in subjects afflicted with HD [11]. The discrepancies between these studies may be due to the use of differing irritability measurement scales, which have arbitrary cut-off scores that cause variable sensitivity [11].

DIAGNOSIS

Irritability in the context of HD is diagnosed by clinical expertise and the administration of standardized rating scales. Precise and definitive diagnosis, including the characterization of severity and progression, is confounded by several factors, such as the co-occurrence of other neuropsychiatric symptoms alongside irritability, the distinctive characteristics of irritability in HD that are not entirely analogous to the symptom in the generation population, and the cognitive difficulties or lack of insight HD patients may possess [22]. Due to these challenges, a common diagnostic standard has yet to be fully adopted by the field, though some rating scales are used more than others.

Additionally, several efforts have been made to determine whether the number of CAG repeats, which is positively correlated with certain aspects of HD (e.g., age of onset), is related to the severity or presence of irritability in gene carriers, with mixed results [18, 23–25]. Several studies have failed to detect a significant association between CAG repeat number and irritability [18, 24, 25], while a study in 2016 conducted on a Chinese cohort found a positive correlation ($r = 0.449$) [23]. Thus, given that the majority of the evidence suggests no correlation, CAG repeat number cannot currently be relied on as a predictive diagnostic tool to judge risk of irritability in HD.

As mentioned previously, a litany of neuropsychiatric rating scales has been employed to diagnose and score irritability in HD. These include the following: the NPI, the problem behavior assessment and its variants (PBA, PBA-HD, PBA-s), the irritability, depression and anxiety scale (IDA), the behavior component of the Unified Huntington's Disease Rating Scale (UHDRS), the irritability portion of the Irritability-Apathy Scale (IAS), the irritability scale (IS), and several others [22]. A study aimed at critiquing all of the commonly used scales employed to measure the neuropsychiatric elements of HD found that only one rating instrument, the IS, was recommended as a screening tool to identify the presence of irritability [22]. [Note: To avoid any confusion with previous literature, the IS was originally referred to as the John Hopkins Irritability Questionnaire in early publications [26, 27]]. The same study could only suggest, but not recommend, the IS, the irritability portion of the IAS, and the irritability portion of the IDA (also known as the Snaith's Irritability Self-Assessment Scale (SIS)) as measures of the severity of irritability in HD [22]. A possible strength of the two former scales is that they utilize information from the patient's caregiver, which may be a more objective measure of irritability, especially when the patient has lack of insight. Specifically, the IS surveys 14 items related to irritability from both the patient and the informant, while the irritability portion of the IAS only obtains information from the informant [11]. Ideally, a composite of multiple scales, especially when evaluating in the context of a clinical trial, may be used to diagnose and track irritability over time.

TREATMENT

Although there are currently no medications approved specifically to treat irritability in HD, there is consensus regarding therapeutic options amongst clinicians who treat the disease [12, 28, 29]. Before any pharmacological agents are considered, irritability secondary to a more proximal cause—such as pain or akathisia—should be considered and addressed if possible [29]. Indeed, the identification and removal of triggers that predispose patients with HD to irritability and associated behaviors are often very effective [12]. To this end, family members and caregivers of HD patients should be counseled on the best

strategies to mitigate irritability [12]. Furthermore, family therapy may be useful to alleviate the interpersonal conflict that may arise due to irritability in HD [30]. Non-pharmacologic therapy can also be used to directly manage the behaviors resulting from irritability. Both operant and classical conditioning are effective strategies to achieve behavioral modification, especially in more advanced disease [14, 30]. In practice, this may take the form of explicitly reinforcing appropriate behaviors with rewards and avoiding the inadvertent reinforcement of problematic behaviors. Other strategies, including implementation of structured routines, advantageous sequencing of an activity regimen (i.e., desirable activities are to follow unpleasant activities), and minimization of upsetting surprises may be effective non-pharmacologic treatments of irritability as well [31].

As HD progresses, irritability may worsen, at which time pharmacological therapy likely will be required to mitigate symptoms. A survey of clinicians (N = 55) who treat HD in North America, Europe and Australia revealed that a range of pharmaceuticals are used depending on the stage of therapy [28, 29]. In the study, a majority of clinicians (57%) reported use of selective serotonin reuptake inhibitors (SSRIs) as the preferred first line agents, while the most favored alternative monotherapy, at 37%, were antipsychotic drugs (APDs) [28]. However, if manifestations of acute irritability were present, such as aggression and impulsivity, the same clinicians preferred APDs (e.g., olanzapine, risperidone and quetiapine) as a first line choice [28, 29]. Likewise, a more recent expert review suggested that atypical APDs, namely olanzapine, should be used when both chorea and irritability/aggression are present [32]. However, potential side effects include weight gain, metabolic syndrome and tardive dyskinesia. The next most popular alternative monotherapy agents in the international survey, in order of descending frequency of use, were mirtazapine (28%), antiepileptic drugs (27%), SSRIs (23%), BZDs (16%), tricyclic antidepressants (16%), propranolol (12%), clomipramine (12%), and buspirone (6%) [28]. By far the most popular adjunctive therapy were benzodiazepines (BZDs), with 72% of clinicians utilizing this drug class, especially in the setting of comorbid anxiety [28, 29]. Although BZDs are widely used in this capacity, their use has been called into question due to concerns regarding dependency, tolerance, overuse as a long-term agent, increased risk of falls, and, most concerning in this context, one report that correlated BZD use with irritability in HD [20, 29, 33, 34]. Nevertheless, causality was not established in the latter study and it remains possible that irritability leads to BZD treatment, as opposed to the opposite [12].

A more recent effort by a task force commissioned by the European Huntington's Disease Network (EHDN) endeavored to provide evidence-based recommendations for the treatment of HD, including irritability [35]. While the task force endorsed several of the treatments for irritability alluded to above, all individual recommendations received a "Grade C", which indicates a low level of scientific proof [35]. Mirroring the findings of the aforementioned clinician survey, SSRIs were suggested as first line therapy, with mirtazapine and mianserine used in combination, especially with comorbid sleep disorder [35]. Efficacy of SSRIs to treat irritability in HD is supported by multiple case reports and a small (N = 30) randomly controlled trial (RCT) that achieved a modest reduction in agitation with fluoxetine treatment [36–38]. In cases of irritability characterized by overt aggression, the EHDN report also recommended APDs and mood stabilizers as first and second line therapies, respectively [35]. Indeed, with respect to specific APDs, olanzapine reduced behavior symptoms, including irritability, as measured by UHDRS, in two small (N = 11 in both studies) trials [39, 40]. Furthermore, another atypical antipsychotic, quetiapine, successfully treated irritability in a small report comprised of five HD patients [41]. As for mood stabilizers, valproate and carbamazepine are the most commonly used and a series of case reports in the literature suggest benefit for HD patients with irritability—though such treatment may be complicated by negative side effects or worsening of movement symptoms [28, 29, 42–44]. Additionally, several case reports suggest that lithium provides benefit to both motor and behavioral symptoms when used in combination with other psychiatric medications [29, 45, 46].

A less popular alternative is buspirone, an anxiolytic that successfully ameliorated HD-associated irritability in several case reports, including in a juvenile patient [47–49]. Likewise, some clinicians reportedly use propranolol, but the limited literature available on this agent is mixed [28, 29]. While not commonly used, case reports and a small pilot RCT have found that the synthetic cannabinoid, nabilone, may effectively reduce irritability in HD patients as well [50, 51].

While the aforementioned treatments provide some therapeutic benefit to patients and families burdened with irritability associated with HD, the need

for more effective treatment persists. To this end, results are pending for a phase II RCT (ClinicalTrials.gov Identifier: NCT02507284) testing the safety and tolerability of a first-in-class vasopressin 1A receptor (V1AR) antagonist (SRX246). The basis for targeting V1AR relies upon the role vasopressin is thought to play in social behavior and emotional regulation [52, 53]. Bolstering the case that vasopressin may be involved in mediating the neuropsychiatric symptoms present in HD, one report found that, in humans, hypothalamic vasopressin-releasing neurons were reduced in early stages of the disease [54]. Despite these early leads, a definitive link between HD-associated behavioral symptoms, including irritability, and vasopressin signaling has yet to be firmly established [52]. Phase III trials with agents such as SRX246 should provide clarity on this subject.

An alternative strategy is to consider pharmaceuticals already approved by the FDA, such as those employed to treat similar neuropsychiatric symptoms in other neurodegenerative diseases. A promising candidate in this regard is Nuedexta®, which is an oral combination formula of dextromethorphan hydrobromide (20 mg) and quinidine sulfate (10 mg) that was approved by the FDA in 2011 to treat pseudobulbar affect [55–57]. Pseudobulbar affect, though poorly understood on the neurobiological level, is characterized by the abrupt onset of uncontrollable laughter or crying that may occur in a number of different neurological diseases [55]. First shown to treat pseudobulbar affect in patients with amyotrophic lateral sclerosis and multiple sclerosis [58, 59], dextromethorphan/quinidine (DM/Q) has more recently proved to palliate pseudobulbar affect secondary to dementia, stroke, or traumatic brain injury [57, 60]. Given that DM/Q effectively treats pseudobulbar affect, the therapy may also lessen the severity of emotional and behavioral disturbances present in many neurological diseases, including the irritability associated with HD. Indeed, there is evidence that the ability of DM/Q to reduce such disturbances may generalize beyond pseudobulbar affect. For example, a RCT examining the effectiveness of DM/Q to reduce agitation in Alzheimer's disease found that the treatment improved measures on the agitation/aggression portion of the NPI [61]. Furthermore, with respect to the safety of long-term use of DM/Q, a 52-week open-label study comprised of patients afflicted with PBA secondary to a wide range of neurological conditions, including HD (N = 1), concluded that the therapy was generally well tolerated [62]. In light of this encouraging accumulation of data, a phase III RCT (ClinicalTrials.gov Identifier: NCT03854019) is currently ongoing to determine whether DM/Q reduces irritability in HD gene carriers.

CONCLUSION

Among the many challenges HD gene carriers and their families endure, irritability is particularly deleterious given both its prevalence and early onset in premanifest patients along with the negative externalities the resulting behavior may cause, including irreparable damage to social support systems, difficulty maintaining a livelihood, and legal problems [4, 12, 15]. To mitigate these issues, clinical expertise and a number of small studies have provided some guidance regarding which pharmaceutical agents are best used to treat irritability in HD in a variety of different contexts [28, 29, 35].

However, while case reports abound, few sufficiently powered RCTs have been conducted that provide definitive evidence of irritability reduction in patients with HD. In addition to establishing evidence-based practices pertaining to the pharmaceutical inventions currently used, greater investment should be directed towards finding new therapies to treat irritability in HD. As mentioned above, new treatments need not be developed from scratch. Given the availability of FDA-approved medications that already effectively treat neuropsychiatric disturbances such as PBA, the opportunity to evaluate such agents in the context of HD-associated irritability should be considered to address this most troublesome symptom.

CONFLICT OF INTEREST

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