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Chapter 2

THE CLINICAL FEATURES OF HUNTINGTON'S DISEASE

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ABSTRACT

Huntington's disease (HD) is a rare neurodegenerative condition with wide-ranging, slowly-evolving clinical features. A good clinician is aware of and knows how to assess these abnormalities, and understands how they impact on the daily lives of individuals with HD, and their loved ones.

Though psychiatric and cognitive problems are major components of HD, the disease is most known for its movement disorder, which dictates the timing of clinical diagnosis. Chorea predominates in early manifest disease, whereas features of poor voluntary motor control are more pronounced in later stages, and result in greater functional impairment.

Cognitive dysfunction in HD is of the subcortical type, which includes poor insight and personality changes. Features are present early and gradually develop to a more global dementia in late disease. Cognitive decline in HD is associated with reduced functional capacity, loss of work and worsening quality of life.

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The psychiatric features are amongst the first manifestations of HD. Features of mood disorders are common, and connected to the high suicidality seen in this population. Study findings have been contradictory regarding how psychiatric symptoms progress in relation to the course of HD.

Lesser-known characteristics of HD that also warrant discussion include weight loss and sleep dysfunction.

HD GENETICS

HD is a neurodegenerative condition caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the huntingtin gene. The presence of 40 or more CAG repeats establishes the disease. Alleles that are 36 to 39 CAG repeats in length have reduced penetrance, meaning that they may or may not lead to disease manifestation during the gene carrier's life span. Finally, expansions that are 27 to 35 trinucleotide repeats long are referred to as 'intermediate' in length, and carry the risk for expansion into the mutation range when passed to the next generation. The CAG repeat expansion length is inversely correlated with the age of onset of the disease (Duyao et al., 1993).

The discovery of the HD gene mutation has enabled for individuals at-risk for HD, (based on having a positive family history), to undergo predictive genetic testing. This makes HD one of the few neurodegenerative conditions which can be diagnosed prior to any overt clinical manifestations of the disease. Studying identified gene carriers has resulted in characterization of the subtle 'pre-motor' or 'pre-manifest' phenotype.

Despite being inherited in an autosomal dominant fashion, roughly 8 - 24% of patients report no known family history of HD (McCusker et al., 2000; Almqvist et al., 2002). Such cases may have arisen from an expansion in the intermediate allele. Alternatively, the affected parent was estranged or unknown (for example, in those who were adopted), or may not have manifest by the time of death. On questioning, sometimes these apparent probands do indeed have a family history that is suspicious for possible (undiagnosed) HD, for example, in that it includes psychiatric or 'balance problems' (Lipe et al., 2009). However, the majority of individuals with HD do have a known family history, and it is common to have HD patients who are related to one another.

HD CLINICAL PRESENTATION

Patients with a positive family history who present with features consistent with HD do not require genetic testing for confirmation of a diagnosis. Despite the prolonged 'pre-motor' period during which a variety of subtle clinical features insidiously develop, disease 'onset' is determined by the presence of (sufficient) motor abnormalities alone, (further discussed below, under UHDRS). Greater than half of HD patients present with clumsiness or choreic features, usually noticed by their loved ones (Foroud et al., 1999). This is typically around the age of 40 years, when patients have already had children of their own to pass the HD gene mutation on to (Stineet al., 1993; Roos et al., 2010). There is often already a long history of depression. Early 'subcortical' cognitive symptoms may be apparent at the time of presentation, or within the following few years (Ross et al., 2014; Vinther-Jensen et al., 2014).

HD MOVEMENT DISORDER

HD Movement Disorder Overview

The movement disorder of HD can be divided into two main components: excessive involuntary movements and impaired voluntary motor control (Ross et al., 2014). In early to mid HD, excessive choreic movements are typically the predominant motor feature. Whereas the later stages of disease are dominated by poor motor regulation, in terms of the speed, force and direction of intentional movements (Guo et al., 2012). The later stages also see more rigidity. It is the motor control problem, rather than the chorea, that correlates with functional impairment, (as measured by activities of daily living), and nursing home placement (Bylsma et al., 1993; Mahant et al., 2003; Rosenblatt et al., 2011). In regards to motor disability and functional decline, HD progression may be relatively faster in women compared to men (Zielonka et al., 2013). Finally, there is reportedly no connection between motor symptom severity in HD and quality of life (Eddy et al., 2013).

Chorea

HD most commonly presents with chorea (Foroud et al., 1999), which is considered a hyperkinetic motor abnormality. It consists of an excess of unpredictable, variable, involuntary movements. In the pre-motor stage, prior to overt clinical disease onset, subtle choreic movements are usually detectable (Kirkwood et al., 2000; Biglan et al., 2009). They begin in the peripheries. To best observe them on physical examination, it is ideal to have the patient seated on an examination table with his/her legs hanging freely, such that the patient's bare feet do not touch the floor. At the pre-motor stage, one may only appreciate some extra flexion/extension movements in the toes and possibly also in the fingers, (best observed with arms outstretched in prone position), and in the small muscles of the face, appearing as twitchiness. The patient may also exhibit some generalized, non-specific fidgetiness that could easily be mistaken for restlessness or nervousness.

Over time, the chorea gradually worsens, with the movements increasing in their frequency and amplitude. Likewise, the distribution increases, spreading proximally and generalizing to include the muscles of the axis, and sparing none. Though chorea is typically described as being random in terms of the distribution of affected muscles at a given time, there are some movement patterns that appear more characteristic than others, such as a transient widening of the eyes with frontalis contraction and head retropulsion. (Involvement of the muscles of the upper face (and an abnormal gait) may help to differentiate HD from cases of tardive dyskinesia, which rarely involve this area (Marsden et al., 1996)). Patients often appear unable to sit still, as they perform a continuous and quick succession of flowing, jerking, writhing movements. A shoulder elevates, a knee extends, the face grimaces, the back arches. These choreic movements sometimes appear semi-purposeful, a phenomenon known as "parakinesia." For example, an involuntarily arm jerk may morph into a seemingly intentional nose scratch.

Chorea can temporarily worsen with heightened emotional states. In clinic, care-givers may comment that the obviously choreic patient "rarely moves this much at home." Chorea persists while awake and is thought to be dramatically reduced in sleep. HD patients are unable to temporarily suppress their involuntary movements, (which may help to differentiate them from patients with tics or other causes of chorea (Roos et al., 2010)). Overall, the chorea peaks during the middle phase of the disease. Even at this time, the movements are rarely bothersome, as most patients are not even aware of them (Jankovic et al., 2014). The chorea plateaus before ultimately diminishing with

further disease progression. By end-stage HD, patients exhibit a predominantly akinetic-rigid phenotype, with minimal chorea.

Gait and Falls

After chorea, HD's most common presenting motor symptoms are trouble walking and poor balance (both at 13.7%) (Foroud et al., 1999). Even during the pre-motor stage of disease, subtle gait deficits are detectable (Blanchet et al., 2014). Abnormalities include relatively reduced velocity and stride length, and greater stride length variability, both of which correspond with disease severity (Rao et al., 2008). These features worsen gradually, and are associated with falls in manifest HD (Grimbergen et al., 2008). Falls are also associated with worse bradykinesia, chorea and cognition, all of which are suggested to have a contributory role (Grimbergen et al., 2008). In a study on early to mid HD, 60% of patients reported 2 or more falls a year, with the majority falling weekly or monthly (Grimbergen et al., 2008). Few of these fallers reported any fear of falling, despite the fact that 73% of the falls resulted in injuries (Grimbergen et al., 2008).

Oculomotor Dysfunction

Impaired eye movement control may be one of the earliest motor abnormalities in pre-manifest individuals (Hicks et al., 2008). Patients exhibit delayed saccadic eye movements and anti-saccadic errors, (in inhibition control to novel visual stimuli) (Hicks et al., 2008; Antoniades et al., 2010; Blekher et al., 2006). These abnormalities correlate with the other subtle motor findings in pre-motor HD, and worsen with disease progression (Patel et al., 2012). In the manifest stage, saccades are not only delayed, but slow, (vertical more than horizontal), and hypometric, (meaning that they arrive short of their visual target) (Turner et al., 2011; Golding et al., 2006; Lasker et al., 1997). In addition, both fixation and smooth pursuits are disrupted by intrusive saccades, such that they have a jerky quality (Lasker et al., 1997). As the disease advances, patients will unconsciously use an insuppressible eye blink or head thrust to break fixation when trying to initiate a gaze shift (Paulson et al., 2011). These features can be seen on clinical examination. The patient is instructed to look straight ahead at the examiner's nose. Without turning their head, the patient is to then look to where the examiner has snapped his or her

fingers, which are outstretched to either side, thereby directing the desired, (in this case horizontal), gaze shift.

Dysarthria

Family members of individuals with HD reported dysarthria in 24% of patients within the first 5 years of disease onset; this increased to 88.5% for those with HD for over 10 years (Kirkwood, et al., 2001). On formal testing, 93% of manifest HD subjects were found to have imprecise vowel articulation and excess intensity variations (Rusz et al., 2014). Use of antipsychotic medications, which is common in HD, was associated with improved articulation, but appeared to contribute to dose-dependent variations in loudness and pitch (Rusz et al., 2014). Other common prosodic abnormalities in HD include altered speech timing and deviations in phonation (Hartelius et al., 2003). (Speech pattern and content are discussed below, in relation to cognitive impairment).

Dysphagia

The movement disorder of HD does not spare the muscles involved in the normally-coordinated mastication and swallowing processes. Individuals with HD may appear to impulsively gulp down large amounts of barely-chewed food boluses (Leopold et al., 1975). This can contribute to choking, which is typically first noted by care-givers around the middle stage of HD (Kalkhoven et al., 2014). Dysphagia worsens over time, with some patients ultimately opting for a feeding tube, which was present in a quarter of nursing home residents with HD, in an older study (Nance et al., 1996). Note that tube feeding does not circumvent the risk of choking on pooled saliva. The severity of dysphagia correlates with disease duration and other motor impairments, including dysarthria and bradykinesia (de Tommaso et al., 2015). The main consequence of dysphagia is aspiration pneumonia, which is the most common cause of hospitalization for HD patients (Dubinsky et al., 2005). It is also the leading cause of death in HD, accounting for 86.8% of cases in one recent study (Heemskerk et al., 2012).

Hypokinesia

The hypokinesia that dominates in advanced HD is also present in the earlier stages, though less severe and less obvious under the superimposed chorea (Rao et al., 2008). This somewhat counter-intuitive reduction of movement actually begins in pre-motor HD. One aspect of it is a delay in the initiation of voluntary movements. This has been extensively documented in relation to eye movements, (discussed above). Data from wrist-worn activity monitors have also shown that, despite the chorea, individuals with HD actually have a relative paucity of movement (van Vugt et al., 2001). This correlates with measures of impaired motor control and reduced functional capacity (van Vugt et al., 2001). Finally, slowing of voluntary movement is present as well; it also predicts functional inability, even in early HD (Sánchez-Pernaute et al., 2000). It is important to note that the antipsychotic medications that are commonly used in HD can contribute to the reduction, delay and slowing of movements.

On physical examination, besides for the delayed eye movements and slowness seen on finger to nose testing, hypokinesia can be evaluated by having the patient perform rapid alternating movements, such as a quick succession of supination/pronation turns at the wrist. Finger tapping is also commonly used. Motor arrests, varied amplitude and slowness are apparent. This hypokinesia is a component of HD's poor motor control.

Impaired Motor Control

HD patients' impaired motor control also involves the direction and force of voluntary movements. HD subjects can begin a motor task on target, but instead of a smooth and efficient motion, they quickly deviate off their trajectory in an increasingly jerky manner, with frequent changes in direction (Smith et al., 2000). This motor impairment is detectable even in pre-motor HD, and worsens with disease progression (Smith et al., 2000). A similar phenomenon is seen with the force of HD patients' movements, which is quite variable as a result (Georgiou-Karistianis et al., 2004). Such inconsistencies in direction and force are thought to be related to dysfunctional feedback mechanisms (Bradshaw et al., 1992; Smith et al., 2000). This results in patients being unable to effectively monitor or check their own movements' direction and force, to compare it to that which is required for the task at hand (Bradshaw et al., 1992).

Motor Impersistence

Motor force variability clinically manifests as motor impersistence, which is the inability to maintain consistent power of a voluntary muscle contraction. Motor impersistence occurs independently of chorea and is linearly progressive in HD (Walker et al., 2007). On examination, impersistence can be visualized by having the patient try to keep his or her tongue fully outstretched. One may notice that the tongue's force of protrusion is variable; it partially relaxes intermittently. With disease progression, the protruded tongue may quickly jut in and out a few times; this was traditionally referred to as the 'harlequin sign'. (In more advanced disease, hypokinesia will cause a delayed and only partial (if at all) protrusion of the tongue). Impersistence can also be easily appreciated in hand grip, by asking the patient to tightly squeeze ones' fingers. As the force of the grip fluctuates, the sensation is supposedly comparable to milking a cow, hence the name 'milkmaid's grip'. Objective measures of this grip strength variability have been shown to correlate with functional capacity (Gordon et al., 2000).

Dystonia

Dystonia is another motor abnormality seen in HD. It is characterized by an involuntary increase in muscle tone with associated abnormal posturing, such as hyperextension of the digits or torticollis at the neck. In one HD study, dystonia was found to be present in 95% of subjects (Louis et al., 1999). Most subjects had dystonia involving a few different body parts, often mild to moderate in severity, and present roughly half of the time. It most commonly consisted of internal shoulder rotation (64%), fist clenching (47%), unwarranted knee flexion (43%), and foot inversion (43%) (Louis et al., 1999). Most patients are not bothered by their dystonia. It does not appear to be a sensitive marker of disease progression, and some consider it to be an irrelevant component of the motor assessment (Vaccarino et al., 2011).

SUBCORTICAL DEMENTIA

Cognitive Dysfunction Overview

Cognitive decline is a prominent feature of HD. As early as 10 to 15 years prior to overt disease onset, subtle deficits in multiple cognitive domains are detectable with formal testing (Paulsen et al., 2008; Paulsen et al., 2014). In a cohort of subjects with pre-motor HD, over a third of cases met the criteria for mild cognitive impairment (Duff et al., 2009; Duff et al., 2010). Cognitive signs typically become apparent to care-givers around the same time as motor features do, or within a year or 2 afterwards (Ross et al., 2014). These deficits worsen over time, corresponding in severity to disease progression (Tabrizi et al., 2013) and impaired functional capacity (Marder et al., 2000). Though ultimately leading to a global dementia by end-stage disease, the primary cognitive dysfunction in HD is 'subcortical' dementia. This includes executive dysfunction, slowed mentation, poor insight and bad judgement. It also includes personality changes that overlap with psychiatry, such as irritability and apathy.

Executive Dysfunction

Executive dysfunction includes deficits in multi-tasking and problem-solving. As these are commonly used skills in the work-place, job performance is often one of the first areas in which functional impairment is noted in HD; this may occur even prior to the development of motor signs (Paulsen et al., 2010; Beglinger et al., 2010; McCabe et al., 2008). Patients may be less productive, make errors, and require extra time to keep up with the usual demands. Similarly, management of personal finances also suffers, with patients over-spending or forgetting to pay bills (Paulsen et al., 2010; Beglinger et al., 2010).

In HD, there is also a deterioration in planning and goal-directed behavior, which are key executive functions that result from forward-thinking (Ho et al., 2003; Rodrigues et al., 2009; Gray et al., 2012). Evidence of such features is commonly seen: one HD patient reported taking her children on a peak-season holiday without reserving any hotel rooms in advance. Another patient arrived to clinic without knowing how to get back home.

Poor planning is often evident in those with poor attention, with patients' having difficulty in focusing on what's pertinent and ignoring what's

irrelevant (Snowden, 2001). An appropriate example here is of an HD patient who presented a letter in which she had highlighted every word!

Speech pattern and content

Speech allows for a convenient way of observing the cognitive deterioration of HD. Even in pre-motor subjects, formal testing can detect slower speech with longer pauses in between utterances (Vogel et al., 2012). These features persist into manifest disease and worsen over time, correlating with disease burden (Hartelius et al., 2003; Rohrer et al., 1999). In addition, patients' attempts at initiating communication become increasingly infrequent (Murray, 2000; Murray et al., 2001). Speech analysis reveals a speech pattern which uses relatively few words, has low syntactic complexity, and exhibits deficits in language production (Murray, 2000; Murray et al., 2001). In regards to speech content, family members complain of a 'lack of depth' (Hartelius et al., 2010). All of these features are routinely observed in clinic patients, especially those in late-stage disease. The overall limited verbal output can be prominent, (though some patients have intrusive vocalizations, such as frequently uttering a perseverative "yup", irrespective of the conversation's context). They may also take a very long time to respond to a question, though will typically expect their care-giver to answer for them. Findings from patient interviews have revealed that patients feel that they have insufficient time to think of what to say during a conversation, hence the long pauses (Hartelius et al., 2010). They described the act of talking as if it were work, demanding effort and concentration (Hartelius et al., 2010). Increasingly reduced verbal output may ultimately lead to mutism by end-stage HD (Roos et al., 2010).

Poor Insight

An important characteristic of patients with HD is their lack of insight regarding their deficits, (anosognosia) (Wallace et al., 1996). This unawareness starts in the pre-motor stage, and is progressive (McCusker et al., 2013; Duff et al., 2010a; Epping et al., 2016). Fifty percent of HD gene carriers deny having any motor symptoms at the time of clinical diagnosis, (which requires the presence of convincing motor abnormalities) (McCusker et al., 2013). However, even patients in middle-stage disease with moderate chorea, (whose writhing body and flinging, jerking limbs are obvious to the

casual observer), will often deny the presence of any involuntary movements. This notion can be quite alarming to those who are unfamiliar with HD. When patients do admit to movement symptoms, they nearly always underestimate their severity (Justo et al., 2013).

The anosognosia in HD is also in relation to issues with mood, (such as depression, apathy and irritability), cognition and functional capacity (Sitek et al., 2011; Chatterjee et al., 2005; Hoth et al., 2007; Duff et al., 2010a; Ho et al., 2006; Epping et al., 2016). This results in patients overestimating their wellness, temperament and competency, and is associated with deficits in global cognition, executive functioning and memory (Hoth et al., 2007). Of interest, those with poor awareness of their motor and functional deficits have relatively less depression than patients with retained insight (Hoth et al., 2007; McCusker et al., 2013).

Along with the lack of insight in HD, there is often a profound indifference to deficits (anosodiaphoria) (McCusker et al., 2014). In clinic, the early-stage HD patient is often jolly and care-free, glibly reporting that they are 'fine' or 'great', regardless of reality and their worried loved ones' concerns. In fact, on history-taking, it is not uncommon for the patient and care-giver to provide contrasting information. For example, on questioning, the patient may deny ever falling, while the care-giver in the background holds up a few fingers to indicate the actual fall count. The patient's poor insight can interfere with his or her care. By not recognizing the need for any intervention or assistance, the patient may refuse or even argue against it (McCusker et al., 2014; Killoran et al., 2012).

Driving Impairment

One of the concerns regarding anosognosia (and anosodiaphoria) in HD is the potential for motor vehicle accidents, when patients do not recognize (or care) that their driving is impaired. In pre-motor HD, when insight is still somewhat preserved, driving ability is one of the first areas of functional decline that patients actually report (Beglinger et al., 2010). However, after diagnosis, the majority of individuals with HD still continue to drive (Rebok et al., 1995). At only roughly 2 years into the disease, HD patients were found to have a 50% failure rate on Fitness to Drive evaluations (Devos et al., 2012). Not surprisingly, the reported rate of motor vehicle accidents is much higher for HD patients than for unaffected individuals (58% vs 11% over a 2-year period). Despite this difference, HD subjects' self-claimed driving ability was

similar to that of healthy control subjects (Rebok et al., 1995). Interestingly, the poor driving skills in HD are not associated with primary motor impairment, but with cognitive performance, (based on scores on the Symbol Digit Modalities Test, Stroop word reading, and the Trail Making Test B) (Devos et al., 2012).

Poor Judgment

The continued driving of bad motorists is also a feature of HD patients' poor judgement, and their tendency to participate in risky behaviors. These, in turn, may partly stem from HD patients' lack of fear, (according to testing in which subjects were exposed to frightening stimuli (Eddy et al., 2012)). For example, one petite clinic patient casually mentioned her sexual encounters with men whom she met online. She had no recognition of the potential risks involved. Another individual with HD was caught stealing a pair of jeans while a salesperson was standing directly behind him (Paulsen, 1999). Ethical issues aside, in this type of scenario, most people fear getting caught. This last example also underscores the impulsivity that is typical of the dysexecutive persona. Somewhat like children, people with HD are often driven by instant gratification without consideration or concern for the potential negative consequences of their actions (Snowden, 2001).

Legal Issues and Alcohol

In some cases, as with the man whimsically stealing the jeans, poor judgement can lead to legal difficulties (Jensen et al., 1998). A history of criminal behavior was reported in 20% of subjects in one HD study (Liljegren et al., 2015). It was more commonly seen in men with HD, whose crimes mostly involved misdemeanors, such as driving under the influence of alcohol (Jensen et al., 1998).

Heavy drinkers made up 29% of one study's HD population (Ehret et al., 2007). However, even when sober, people with HD in public places are often mistaken for being intoxicated. This is presumably because of their motor abnormalities, (such as chorea, gait dysfunction and dysarthria), in addition to possible social inappropriateness, short temper and/or impulsive behavior. Such misunderstandings often lead to interactions with law enforcement,

which in these mistaken circumstances can be quite unpleasant (Georgandis, 2015; Narain, 2008; Reporter, 2014).

Apathy

Apathy, a feature of subcortical dementia, is characterized by reduced energy and activity, lack of motivation, and impaired performance of everyday tasks. Studies on the behavioral abnormalities of HD have found that symptoms of apathy are the most prevalent, varying between 84% and 99% (Thompson et al., 2012; Tabrizi et al., 2009; Craufurd et al., 2001; Baudic et al., 2006). Apathy is detectable even in the prodromal period (Duff et al., 2010; Tabrizi et al., 2009), and it progresses with the disease, (alongside motor and cognitive dysfunction), strongly correlating with disease duration (Thompson et al., 2012; Van Duijn et al., 2010; Baudic et al., 2006; Craufurd et al., 2001). Patients become increasingly less interactive, and are often misinterpreted as being depressed, which they usually deny (Nopoulos, 2016). Apathy can be quite prominent in advanced HD (van Duijn et al., 2014), when patients may barely speak any more, but spend much of their time in bed or in front of the TV, often not even bothering to change the channel.

Apathy correlates with deficits in attention, executive functioning and episodic memory (Baudic et al., 2006), and is associated with the use of antipsychotics and benzodiazepines, which may be a contributing factor (van Duijn et al., 2014). It is more frequently seen in male patients, and those with a history of depression, obsessive compulsive behaviors or a previous suicide attempt (van Duijn et al., 2014). Finally, apathy is strongly related to poor quality of life in HD (Eddy et al., 2013), and more than any other psychiatric feature is associated with functional impairment (Baudic et al., 2006; van Duijn et al., 2014).

Hygiene

Apathy includes a lack of interest in self-care. Consequently, appearance and personal hygiene are commonly neglected in HD. There is little research on hygiene in HD, other than one study on dental care, which revealed relatively high rates of tooth decay and plaques (Saft et al., 2013). (In addition to poor dental hygiene, this may be partly related to the high-sugar diet that is often seen in HD). Motor dysfunction may be a contributing factor to poor

hygiene in middle or late stage HD, if patients do not have the physical help that they require for their activities of daily living. However, many individuals with HD actually seem to have an aversion to bathing or showering, often refusing to do so (Ferrini, 2009). This is commonly a point of contention in the household; family members spend time and energy trying to coax patients to wash. In turn, patients may feel resentment for being "nagged," particularly as they might not recognize the need to bathe.

A lack of awareness regarding one's hygiene is probable in HD, given patients' poor self-awareness into their other deficits. In addition, a lack of social awareness may play a role. HD patients do not appreciate that their habits may be socially unacceptable, nor do they experience the shame or embarrassment that normally keeps people motivated to maintain a certain standard of self-care (Creative B., 2016).

Social Cognition

People with HD do not read people well, and they do poorly on formal tests of social cognition (Larsen et al., 2016). Individuals with HD are unable to decipher different emotions (Emre et al., 2016), particularly negative ones, such as disgust or anger. These deficits start in the pre-motor stage, and appear to be progressive (Emre et al., 2016). This impairment can have a negative impact on relationships, by limiting meaningful communication, and contributing to misunderstandings (Ille et al., 2011). It is also associated with behavioral problems (Philpott et al., 2016).

Likewise, HD patients seem to have limited ability in interpreting social situations and appropriately adapting their behavior (Snowden, 2001). This has been reported in nearly half of HD subjects of 5 years' disease duration (Thompson et al., 2012). People with early HD especially can be socially inappropriate, as it having no social barriers. Even in the clinic setting, they can be disinhibited and gregarious, as if they are at a social gathering, instead of at a doctor's appointment. Indeed, some have impulsively invited their neurologist "to party" or "go fishing" at the first clinic encounter, being completely out of tune with the setting's context.

Some HD patients' behavior may seem socially immature or juvenile. One pre-motor individual sent her doctor a letter that, despite being typed, was disarmingly child-like in that it was covered with stickers of bright flowers. The letter revealed a behavior that was somewhat socially incongruent with that of a middle aged woman. Other HD women in their forties and fifties have

been known to dye their hair bright red or even purple, conduct that is more typically seen in rebellious teenagers.

PSYCHIATRIC DISTURBANCES

Psychiatric Disturbances Overview

Psychiatric problems are a component of the classical clinical triad of HD. They are often considered to be the most distressing features of the disease for both patients and their loved ones alike. Psychiatric symptoms are amongst the first manifestations of the disease, beginning as early as 20 years before the onset of motor abnormalities (Marshall et al., 2007; Paulsen et al., 2008; Duff et al., 2007; Thompson et al., 2007). Study findings demonstrate a wide range of prevalences (van Duijn et al., 2007). Based on the results of formal testing in one large observational study, psychiatric disturbances were present in 87% of HD subjects, with 39% having a lifetime history of 'severe psychiatric signs' (Orth et al., 2011). Such manifestations appear to increase throughout the pre-motor period (Epping et al., 2016), but whether or not they continue to worsen with disease progression is unclear, due to conflicting study findings (van Duijn et al., 2014; Paulsen et al., 2005; Craufurd et al., 2001). Based on reports of clustering of psychiatric symptoms, it appears that some HD families may have a genetic predisposition towards mood disorders and psychotic features (Epping et al., 2011; Folstein et al., 1983a; Folstein et al., 1983b; Baxter et al., 1992; Tsuang et al., 2000). The most frequently and consistently reported psychiatric symptoms in HD are depression, irritability and anxiety. Less commonly occurring are obsessive-compulsive behaviors, and psychotic features even less so (van Duijn et al., 2007). Closely connected to depression is suicidality, which is an important cause of death in HD.

Depression

Depression is twice more common in HD than in the general population (Paulsen et al., 2005), with prevalence rates ranging from 33% to 69% (van Duijn et al., 2007). It is more frequently reported in females than in males (Zielonka et al., 2013; van Duijn et al., 2014). Depression often starts in the pre-motor period, during which its severity correlates with worsening cognition (Julien et al., 2007; Smith et al., 2012). Some studies have suggested

that depression does not worsen over the course of the disease (Craufurd et al., 2001; Kingma et al., 2008). However, the REGISTRY study of nearly 2000 HD gene mutation carriers, recently reported the opposite, that depression does indeed worsen with disease progression (Dale et al., 2016; van Duijn et al., 2014). Results from the PREDICT study, with close to 3000 HD subjects, suggest yet a different pattern. The prevalence of depression in this cohort increased only in early disease to peak at stage 2 (of 5), and subsequently diminish (Paulsen et al., 2005). Stage 2 of HD is significant in that it corresponds to functional decline that typically leads to loss of independence and job termination. The study authors suggested that the mid-stage decline in depression was possibly a consequence of worsening insight related to cognitive impairment (Paulsen et al., 2005). Symptoms of depression correlate with worsening quality of life for HD patients, as well as for their families and care-givers (Brugger et al., 2015; Banaszkiewicz et al., 2012; Ho et al., 2009).

Suicidality

Depression is closely connected with suicidality. Studies on suicidal ideation in HD, (both pre-motor and manifest), put its prevalence at roughly 20% (Orth et al., 2010; Paulsen et al., 2012; Wetzel et al., 2011). However, it was reported as 75% in one cohort (Booij et al., 2014). Interestingly, the questionnaire used in this study also asked HD respondents if they thought about euthanasia or physician-assisted suicide. The answer was affirmative in 64%, notably amongst those with early HD and a relatively higher education level (Booij et al., 2014). In terms of timing, the prevalence of suicidal ideation has 2 high points during the disease course. The first, (at 20%), occurs in people who are at-risk for HD and are starting to show mild motor abnormalities, (Wetzel et al., 2011). This would be just prior to becoming clinically diagnosed with HD, possibly with some recognition that they are likely affected, and what that entails. A second peak (at 22%) occurs at stage 2 of HD, when there is a drop in functional ability and independence. After this period, suicidal ideation subsequently diminishes (Wetzel et al., 2011). As suspected with depression, this may possibly be related to increasing cognitive decline and reduced insight. Suicidal ideation is prominently associated with depression, even in the pre-motor stage (Wetzel et al., 2011; Hubers et al., 2013, Hubers et al., 2012; Fiedorowicz et al., 2011). It is also more commonly seen in those with impulsivity, anxiety, and irritability or aggression (Zouk et al., 2006; Hubers et al., 2013; Wetzel et al., 2011).

Actual suicide attempts occur in 5-28% of HD patients, more commonly in females than in males (Fiedorowicz et al., 2011; Robins Wahlin et al., 2000; Larsson et al., 2006; Paulsen et al., 2005; Di Maio et al., 1993, Farrer et al., 1986; Hayden et al., 1980). Of interest, both suicidal ideation and suicide attempts are increased, (compared to controls), amongst individuals carrying an intermediate repeat allele of the HD gene (Killoran et al., 2013; Ha et al., 2011). Traditionally, people with this range of CAG repeat expansion length were thought to be safe from the manifestations of the disease, but now it appears that they may be at risk after all.

Suicides in HD are four- to eight-fold higher than in of the general population, being the cause of death in 6% of HD patients, according to one study (Schoenfeld et al., 1984; Farrer et al., 1986). They are more common in males than in females, those with no (or fewer) children, and those who are unemployed (Di Maio et al., 1993; Baliko et al., 2004; Lipe et al., 1993; Almqvist et al., 1999). Alcohol abuse also appears to play a role (Wetzel et al., 2011). In addition, those who are familiar with HD from their affected family members are more likely to commit suicide (Booij et al., 2014).

Irritability

HD patients often display signs of irritability, which include surges of anger and aggressive behaviors. These manifestations occur at all stages of HD (van Duijn et al., 2014), even pre-manifest disease (Tabrizi et al., 2009). In one longitudinal HD study, poor temper control was reported in approximately 80%, verbal outbursts in roughly 75%, and physical aggression in half (Thompson et al., 2012). Such occurrences are not commonly seen in clinic, but are described by care-givers, who may be at risk for physical harm. Sometimes law enforcement is called to the home to assist in trying to subdue an aggressive patient. It is possibly for these reasons that aggression in HD is associated with nursing home placement (Wheelock et al., 2003).

In HD, both irritability and aggression are seen more often in young males, and those with a history of depression, psychosis or a prior suicide attempt (van Duijn et al., 2014). They also inversely correlate with Total Functional Capacity scores (van Duijn et al., 2014). Studies are contradictory as to whether or not irritability and aggression increase with disease progression (van Duijn et al., 2014). Experience dictates that these features seem to decline with increasing apathy in the setting of dementia (Nopoulos, 2016) However, this apparent improvement may be secondary to the stabilizing effect of medications in well-managed patients.

Anxiety

A systematic review identified the prevalence of anxiety among HD cases at roughly 40%, with little difference between the pre-motor and manifest stages (van Duijn et al., 2007). One study reported a peak in anxiety around stage 2 (of 5) of the disease, which often coincides with the termination of employment (Paulsen et al., 2005). Anxiety does not seem to worsen with measures of disease progression, (such as cognitive decline or motor dysfunction) (Thompson et al., 2012; Orth et al., 2011; Dale et al., 2016). However, anxiety symptoms were found to be associated with other psychiatric symptoms, including depression, suicide and irritability, as well as with coping styles and quality of life (Dale et al., 2015).

Obsessive Compulsive Behaviors

Approximately 25% of HD patients have obsessive compulsive behaviors, with obsessive symptoms, (unwelcome or distressing thoughts or images), being twice as common as compulsive ones, (compelling feelings to perform an act) (Marder et al., 2000; Anderson et al., 2010; van Duijn et al., 2007; van Duijn et al., 2014; Anderson et al., 2001; Beglinger et al., 2007). These features are prevalent in all stages of HD. Their severity and prevalence appear to increase with disease progression (van Duijn et al., 2014; Beglinger et al., 2007; Anderson et al., 2010). Obsessive compulsive symptoms are associated with greater motor and functional impairment, depression, suicidal ideation, aggression and worse performance on the Stroop task, a measure of executive function (Anderson et al., 2010; van Duijn et al., 2014).

Preoccupation and Perseveration

Obsessive compulsive behaviors include symptoms of preoccupation and perseveration, which were present in close to 30% in one HD cohort (Thompson et al., 2012). In conversation, some patients will keep returning to the same topic, and appear to be incapable of discussing anything else. Such fixations, as well as idiosyncratic tendencies, are frequently seen in clinic. For example, one patient was preoccupied with yogurt, supposedly consuming upwards of 20 per day, every day, and little else. A different patient seemingly required having a clock visible at all times. Yet another patient seemed fixated on always getting his haircut, even after it was just clipped. Patients can be

quite inflexible in this regard, and may become agitated when their wants are not met.

Psychotic Features

Psychotic features are not particularly common in HD. Some patients become suspicious or paranoid, as was the case in approximately 13% of a cohort of HD patients who were (in their first 10 years of disease (Kirkwood, et al., 2001). Sometimes these features occur in the context of delusions, which were present in roughly 5% (Marder et al., 2000; van Duijn et al., 2014). Hallucinations are far less common, with a prevalence of only around 1% (Marder et al., 2000; van Duijn et al., 2014). When HD patients do become delusional and paranoid, they can quickly get aggressive and act out (Guttman et al., 2002). This explosive type of behavior from a distrustful patient is clearly unhelpful to the family dynamic, and adds stress to the home environment. Sometimes care-givers are unable to calm down the patient, who may need to be temporarily admitted to an inpatient psychiatric facility. Actual psychosis was found to be most common in Stage 3 (of 5), with a prevalence of 2.5%, in the large observational REGISTRY study (van Duijn et al., 2014). Interestingly, psychosis is more likely to occur in HD patients who have a first-degree relative with psychosis, suggesting a genetic predisposition (Tsuang et al., 2000).

LESSER-KNOWN HD FEATURES

Weight Loss

Being underweight is a common feature in HD. The underlying defect is thought to be metabolic in nature, rather than being related to energy expenditure from the chorea (Mochel et al., 2007). Indeed, even asymptomatic, gene-positive children, decades prior to developing motor abnormalities, were found to have relatively low weights and body mass indices, as well as small head circumferences (Lee et al., 2012). In pre-motor adulthood, low body weight persists, despite patients' higher caloric intake compared to healthy control subjects (Marder et al., 2009; Mochel et al., 2007). Those with manifest disease weigh less than comparative control cases by an average of 10 kg, (22 pounds) (Hamilton et al., 2004). This is despite the

fact that patients (backed by their care-givers) often claim to have a hearty appetite and an unrestricted diet, typically guided by an indulgent sweet tooth. Regardless, by advanced HD, patients are typically very thin, if not cachexic (Kremer et al., 1992; Stoy et al., 2000). At this late stage, in addition to the metabolic abnormalities, part of the low weight problem may be related to poor motor control hampering self-feeding, in addition to possible dysphagia contributing to feeding limitations. Being underweight puts patients at risk for nutritional deficiencies, and their related consequences, (such as susceptibility towards breaking bones from a fall). In addition, a lower body mass index at the time of clinical onset was found to be associated with a faster disease progression in HD (Myers et al., 1991).

Sleep Disturbances

Sleep disturbances are almost twice as common in HD patients compared to healthy control subjects (Aziz et al., 2010), and they are considered to be severe in 27%, vs only 3% in the control group (Goodman et al., 2010). Even in the pre-motor stage, individuals with HD report more sleep disruptions and daytime sleepiness, compared to healthy subjects (Lazar et al., 2015). Polysomnographic studies reveal that pre-motor patients have a fragmented sleep, with a shortened rapid eye movement (REM) sleep stage (Lazar et al., 2015). Compared to healthy subjects, manifest patients also have reduced REM sleep, in addition to increased periodic leg movements, more nighttime awakenings and a less satisfactory sleep with lower sleep efficiency. They also have a delayed sleep onset which, in HD, is associated with depression, as well as a decline in cognitive and functional performance (Arnulf et al., 2008; Goodman et al., 2010; Hansotia et al., 1985; Wiegand et al., 1991; Videnovic et al., 2009; Silvestri et al., 1995; Aziz et al., 2010). According to polysomnographic studies, the sleep dysfunction in both pre-motor and manifest HD progressively worsens over time, associating with disease burden (Hansotia et al., 1985; Lazar et al., 2015).

The sleep disturbances in HD seem to affect patients in different ways. Many HD patients report spending much of their time in bed, for example, they might sleep 12 hours a night in addition to having a daytime nap. While others claim to be up wandering through the house or watching TV in the middle of the night, apparently with an inverted circadian rhythm. The sleep dysfunction is thought to be related to the fact that HD patients have reduced

and delayed nighttime secretion of the sleep hormone, melatonin (Kalliolia et al., 2014; Aziz et al., 2009).

Sexuality

There has not been a great deal of research on sexuality in HD. It is known that in early disease, hyper-sexuality can be problematic, as patients become disinhibited and have challenges with impulse control. Even back in 1872, George Huntington wrote of "two married men with HD who are constantly making love to some ladies, not seeming to be aware that there is any impropriety in it and they never let out an opportunity to flirt with a girl" (Huntington, 1872). Paraphilia, such as exhibitionism, has been reported in some HD patients with an overactive sex drive (Fedoroff et al., 1994; Mondon et al., 2008; Rich et al., 1994). In clinic, one sometimes sees sexual deviance in HD, such as a patient unabashedly talking about his regular visits to prostitutes. Hyper-sexuality was seen in 6% of 134 HD subjects in one study, in which it was associated with irritability, mental inflexibility and obsessive-compulsive or perseverative behavior (Craufurd et al., 2001).

As HD progresses, testosterone levels decline (Saleh et al., 2009), and clinical experience suggests that sex drive typically does as well. However, one must keep in mind that poor libido and sexual dysfunction can occur secondary to medications, such as neuroleptics and antidepressants, which are commonly used in HD patients (Novak et al., 2011). An older HD study of 39 participants reported that 63% of men and 75% of women had poor libido, and 56% of men and 42% of women claimed to have inhibited orgasm (Fedoroff et al., 1994).

Bladder and Bowel Dysfunction

Urinary issues are also a feature of HD, notably symptoms of bladder overactivity, which are present in close to half of patients (Kolenc et al., 2014). Study findings report that roughly a third of HD patients claim to have urinary incontinence in middle-stage disease. This increases to 73% in late HD (Nance et al., 1996). By advanced disease, loss of bowel control may also occur, with a reported prevalence of 23% (Kirkwood, et al., 2001).

END-STAGE HD

In advanced HD, patients become functionally incapacitated with severe limitations in voluntary movement. Many patients reside in long term care facilities, as they are dependent on care-givers for all activities of daily living. Demented, mute and incontinent, they most commonly perish from aspiration pneumonia, in the setting of immobility and cachexia. It is the cause of death in 86.8% (Heemskerk et al., 2012). Cardiovascular disease is the second most common cause of mortality in HD (Lanska et al., 1988; Heemskerk et al., 2012). Death usually occurs in the mid-50s, on average approximately 15 to 20 years after disease onset (Warby et al., 2016; Bates et al., 2002).

AGE-VARIANTS

Juvenile HD

In roughly 5% of cases, HD presents under the age of 20 years and is considered 'juvenile-onset' (Quarrell et al., 2012). This variant is typically caused by a relatively long CAG repeat expansion inherited from the father (Telenius et al., 1993). Juvenile HD (JHD) often presents with cognitive and/or psychiatric difficulties, which can be especially problematic (Ribaï et al., 2007). Behavioral disturbances may include personality changes with aggressive, anti-social behavior. Depression and apathy are also common (Ribaï et al., 2007). The first notable feature may be a decline in school performance, sometimes with speech and language difficulties (Nance et al., 1997; Yoon et al., 2006). Motorically, JHD manifests as a hypokinetic–rigid syndrome, with bradykinesia, dystonia and rigidity, often referred to as the Westphal variant (Ribaï et al., 2007; Rasmussen et al., 2000; Nance et al, 2001). Chorea is not prominent and may only arise later in the disease (Ribaï et al., 2007). Seizures occur in roughly a third of cases, and are more likely in those with a particularly young onset (Ribaï et al., 2007; Cloud et al., 2012). Cerebellar features may also be seen (Byers et al., 1973; Ribaï et al., 2007). As with adult HD, the disease leads to death within 15-20 years (Roos et al., 1993; Foroud et al., 1999).

Late-onset HD

Patients presenting with symptoms starting after the age of 60 years are considered to have 'late-onset' HD. They make up roughly 8% of all HD patients (James et al., 1994; Koutsis et al., 2014; Sumathipala et al., 2013; Cornejo-Olivas et al., 2015). Note that some sources use a less stringent cut-off of 50 years, but this amounts to roughly a quarter of all HD cases (Foroud et al., 1999; Myers et al., 1985). Individuals with late onset HD typically have a relatively smaller CAG repeat expansion length, often in the reduced penetrance range, (36 - 39 repeats). This is in keeping with the age of HD onset being inversely correlated with the CAG expansion length (Duyao et al., 1993). In many late-onset patients, there is no known family history of HD. The absence of a family history in combination with the relatively late presentation may be the reason why many late-onset cases go undiagnosed (Teodorczuk et al., 2007).

Presentation is much the same as with regular HD, typically featuring mild chorea and incoordination (Lipe et al., 2009; James et al., 1994). In 2 studies on late-onset HD, concomitant cognitive decline was seen in roughly a third of cases, and psychiatric disturbances in roughly a quarter (Lipe et al., 2009; James et al., 1994). Late-onset HD is generally thought to have a relatively benign course with less functional impairment. However, disease duration is somewhat shorter than in regular HD, at around 12.5 years (Lipe et al., 2009). Death appears to be mostly secondary to unrelated comorbidities in the setting of patients' relatively older ages (Lipe et al., 2009).

CLINICAL ASSESSMENT

Unified Huntington Disease Rating Scale

For research purposes, clinical assessment of HD is performed with the Unified Huntington Disease Rating Scale (UHDRS). The UHDRS is a collection of subscales designed to assess manifest HD subjects for psychiatric abnormalities, cognitive and motor performance, and functional capacity (Huntington Study Group, 1996). The behavioral assessment evaluates both the severity and frequency of various psychiatric symptoms, from low self-esteem to delusions. The cognitive component of the UHDRS includes verbal fluency, the Stroop test and the Symbol Digit Modalities Test, (SDMT) (Benton et al., 1978; Stroop et al., 1935; Smith, 1973), which is one of the

most sensitive clinical assessments for monitoring pre-manifest HD progression (Paulsen et al., 2013).

The UHDRS motor scale is the most useful from a neurologist's perspective. It allows for subjective quantification of oculomotor abnormalities, chorea, dystonia, bradykinesia and rigidity. It also includes Diagnostic Confidence Level Criteria, which are used to denote the point of clinical diagnosis, or 'onset' of HD. This designation requires the patient to exhibit sufficient motor dysfunction, such that the examiner is 99% confident that the individual has clinical HD. This subjectively defined dichotomous 'disease onset' is somewhat arbitrary and motor-centric, given that it is preceded by several years of insidiously developing motor, cognitive and psychiatric abnormalities (Huntington Study Group et al., 2006; Craufurd et al., 2001). Some have suggested that the criteria for clinical diagnosis should include cognitive and psychiatric features (Loy et al., 2013), which would likely yield an earlier diagnosis for many patients. Currently, those who have tested gene-positive for HD, yet who have not reached the motor criteria for disease onset, are variably referred to as pre-motor, pre-manifest, pre-diagnostic, prodromal or asymptomatic HD gene-carriers, amongst other designations. For these individuals, with their subtle motor changes, the UHDRS may not be sufficiently sensitive (Biglan et al., 2009). Because of this, there has been a push to find surrogate, objective markers for which to measure early disease progression (Killoran et al., 2016).

Staging

For purely descriptive purposes, patients pass through early, middle and late stages, that are each roughly 5-years in duration. Research studies often utilize a 5 stage system that is based on scores of the Total Functional Capacity scale. In this framework, stage 1 is the earliest, when patients are still high functioning. At the other end is stage 5, which marks advanced disease.

CONCLUSION

HD is a complex and surprising condition. The movement disorder features excessive choreic activity. However, it is the understated, hypokinetic impaired motor control that correlates with functional decline in HD. This

combination of deficits gradually changes over time, as the chorea gradually burns itself out, leaving the patient rigid and still.

The complex cognitive phenotype that encompasses various neuropsychiatric features also morphs with disease progression. The initially impulsive and disinhibited early HD patient becomes the irritable, unkempt, unemployable, middle-aged individual unable to plan ahead, who subsequently develops into the abulic demented mute in late stages. And all the while, with little recognition of the profound deficits that he or she possesses. The reportedly high frequency of mood disorders and suicide in HD add to the tragic nature of this multifaceted neurodegenerative condition.

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