Huntington's Disease

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History and Epidemiology

In his seminal 1872 paper, George Huntington provided a detailed description of a hereditary illness that emerges in mid-life, manifested by progressive chorea and clinical deterioration [1]. Subsequently, William Osler recognized the heredity of the illness as a clear example of an autosomal dominant Mendelian inheritance pattern [2]. George Huntington's precise, articulate, and crisp description of this illness led to its designation as Huntington's chorea and, subsequently, as Huntington's disease (HD). The responsible gene mutation was identified on the short arm of chromosome 4 in 1993 [3].

Although Huntington believed that the disease was restricted mainly to his native Long Island, today we know that HD is a globally widespread disorder with an approximate worldwide prevalence of 5–10 per 100,000 population, notwithstanding some regional and ethnic variability [4]. There is a notably lower prevalence of HD in Asia as compared to Europe, North America, and Australia [5], while some countries have distinctively low prevalence rates, such as Japan and Finland, with respective 0.1 and 0.5 HD cases per 100,000 population [6–8]. In the US, HD has been designated as an orphan disorder, with 25–35,000 individuals having clinical illness and 2–3 times as many pre-symptomatic gene carriers [4, 9].

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V. Demarin (ed.), *Mind and Brain*, https://doi.org/10.1007/978-3-030-38606-1_8

Natural History

Huntington's disease (HD) is a complex neurodegenerative disorder with a highly penetrant autosomal dominant inheritance pattern, with both sexes having a 50% chance of inheriting the genetic defect from the affected parent. The genetic defect consists of CAG trinucleotide expansion on the short arm of chromosome 4, which translates into polyglutamine chain expansion in the mutant huntingtin protein, resulting in abnormal protein aggregation and neurodegeneration. The illness usually emerges in mid-life, around the mean age of 40 years. The course is manifested by progressive motor, cognitive, and psychiatric deterioration. Juvenile-onset, before the age of 20 years, is seen in up to 10% of cases [10, 11].

In affected adults, chorea is the most notable feature and is often seen as the initial symptom of the disease. However, up to several years prior to the onset of chorea, subtle personality changes, psychological, and motor deficits can be identified on a detailed examination in individuals otherwise deemed asymptomatic [12, 13]. Neuroimaging studies have demonstrated subtle but definite structural changes in pre-symptomatic patients, particularly progressive atrophic changes in the striatum and caudate nuclei [14, 15]. The progression of motor symptoms is associated with intellectual decline and psychiatric disturbances, as a result of neurodegeneration. The rate of progression and duration of the illness may vary, but the majority of patients will survive 10–20 years after onset [16]. With the progression of HD, immobility and dystonia become more prominent, together with dysphagia, which directly contributes to weight loss and aspiration pneumonia, a common cause of death [17]. Terminally, pneumonia and cardiovascular disease are cited as common causes of death [18].

Juvenile HD usually presents with a hypokinetic form of the disease manifested primarily by bradykinesia, dystonia, and rigidity. Chorea is not a prominent feature, while myoclonus and epilepsy are more frequently seen than in the adult form [11, 19]. In affected children, initial symptoms may present as personality changes, attention and concentration disturbances, followed by a decline in cognitive function manifested by loss of previously achieved milestones and skills, as well as a steep decline in school performance and behavioral disturbances. Juvenile-onset HD has a higher risk of rapid progression and is more likely to be inherited from an affected father [19–21].

There is a clear relationship between the number of CAG repeats within the huntingtin gene and the expression of the disease. Individuals with 40 or more repeats will have a full expression of HD, with the progressive motor, cognitive, and psychiatric symptoms, while individuals carrying 36–39 repeats will have reduced penetrance, and attenuated or incomplete expression of the illness. Offspring in both of these groups carry a 50% risk of inheriting the illness. Individuals with 27–35 repeats will not develop HD, but their offspring will be at risk due to the phenomenon of meiotic instability [21, 22]. Individuals with less than 27 repeats will not develop HD, and their offspring will not be at risk. There is also a confirmed inverse correlation between age at onset of HD and CAG repeat length within the abnormal Huntingtin gene [23–27]. This correlation

accounts for only about 50% of the variance in age at onset. Therefore, CAG repeat length alone is not a sufficient predictor of onset [23]. There is also familial influence on age of onset which is independent of the effect of the CAG repeat expansion, suggesting a contribution from additional modifiers [28]. The relationship between CAG repeat length and the rate of clinical progression of illness remains unsettled.

Pathology and Pathophysiology

There is a selective pattern of neuronal vulnerability to huntingtin protein aggregation, with a particular susceptibility and loss of medium spiny neurons that use gamma-aminobutyric acid (GABA) as their neurotransmitter [29, 30]. In the early stages of HD, medium spiny neurons projecting into the external segment of the globus pallidus (GPe) are more prominently lost in comparison to those projecting into the internal segment of the globus pallidus (GPi) [31]. This differential loss of striatal projections has been postulated to result in imbalanced activity in the so-called direct and indirect pathways, causing chorea [31, 32]. More balanced loss of neurons projecting to both, GPi and GPe may result in a rigid-akinetic variant of HD, such as seen in juvenile cases [33]. Therefore, in the early stages, increased dopamine neurotransmission results in hyperkinetic movements, while, in the late stages, dopamine deficits produce hypokinesia [34]. During the long process of progression, several types of neurons vulnerable in HD undergo proliferative and degenerative alterations [35, 36]. At the point when neurons become unable to compensate for the ongoing cellular stress, they degenerate in a process similar to apoptosis, finally resulting in cell death [37].

The severity of atrophy in the striatum, as well as in the cortex and thalamus, correlates with the clinical progression of the disease [38, 39]. There is a 15–30% loss in brain weight that occurs in the course of HD [39, 40]. The most prominent pathological changes in HD are seen in the neostriatum, manifested particularly by atrophy of the caudate nucleus and putamen, with associated neuronal loss, astrogliosis, as well as reactive microgliosis [41, 42]. Neuropathological changes may precede clinical onset by several years and maybe manifested by huntingtin protein aggregation, striatal atrophy, neuronal loss, and oligodendrogliosis [43]. In the process of globus pallidus atrophy, GPi and GPe may lose more than 50% of volume and 40% of neurons, while glia increases in concentration, as well as in absolute number [40]. Atrophy and gliosis in HD have also been described in the substantia nigra, including both the pars compacta and pars reticulata, with a cross-sectional area loss up to 40% [36, 44]. Neuronal loss has also been found within the thalamic and subthalamic nuclei but has not been studied extensively [40, 45]. In the hypothalamus, the significant neuronal loss has been described in the supraoptic nucleus, lateral hypothalamic, and lateral tuberal nuclei, which has been postulated to play a role in cachexia in HD [46, 47]. Generalized cortical atrophy is often noted at autopsy, and accounts for most of the loss in brain mass associated with HD [39, 40]. The loss of neurons and volume is most prominent in

cortical layers III, V, and VI [48, 49]. The mean neuronal loss in the entire cortical hemisphere maybe as high as 33%, while astrocyte and oligodendrocyte concentrations may significantly increase, particularly in layers III–VI [50].

In the cells of individuals with Huntington's disease, both mutant and normal huntingtin proteins are present [51–53]. The function of normal, wild-type, huntingtin is not fully elucidated. Within the cell, normal huntingtin is associated with dendritic microtubules, as well as organelles such as mitochondria, transport vesicles, synaptic vesicles, and portions of the endocytic system [54–57]. Such associations and distribution allude to its role in the function of these organelles. The expanded CAG trinucleotide repeat sequence in the huntingtin gene translates into an elongated polyglutamine chain that results in an abnormal conformational change in the protein [51, 58]. In the process of misfolding, the polyglutamine sequence bonds within itself and with other molecules [59]. In addition, mutant huntingtin undergoes proteolytic cleavage producing fragments that form macromolecular aggregates among themselves and with other proteins, visible in the cytoplasm, processes and nuclei of neurons [54]. These aggregates can be found throughout the brain particularly in the cortical regions, and less so in the striatum [55, 60]. Relatively high concentrations of huntingtin aggregates are found in dendrites and axons, with lower concentrations in neural cell bodies and nuclei [55, 56].

Aggregation of huntingtin fragments is dependent on the length of its glutamine repeats, occurring when 39 or more molecules in the polyglutamine chain are present [58, 61, 62]. However, the role of aggregation directly causing neurodegeneration has been questioned due to findings of a relatively low concentration of aggregates in the striatum compared to other areas of the brain [55, 56]. In addition, the vulnerable medium spiny neurons are less prone to have huntingtin aggregates than the resistant striatal interneurons [63]. There is a broader agreement that the effects of mutant huntingtin are the result of its abnormal interactions with proteins involved in signal transduction and metabolism, endocytosis and endosome transport, as well as proteins involved in intracellular transport of organelles [64–72]. Additionally, mutant huntingtin protein interacts with proteins associated with gene transcription, as well as proteolytic enzymes, such as caspases and calpains, which have been implicated in the production of toxic fragments of the mutant protein [73].

In addition to the above-mentioned protein aggregation, cleavage and degradation, there are multiple pathways proposed to play a role in the etiology of neurotoxicity in HD. These include transcriptional dysregulation [74], mitochondrial energy dysfunction [75], glutamate and dopamine excitotoxicity [76, 77], brain-derived neurotrophic factor (BDNF) deficit [78], axonal transport impairment [79], autophagy, and immune system-mediated neuroinflammation [80–82]. Despite significant gains in the understanding of the underlying pathophysiological mechanisms in HD, we still have not materialized these advancements into the development of viable disease-modifying therapies.

Neuroimaging

Neuroimaging is not routinely used in the diagnosis of HD, as it has been rendered obsolete by genetic testing. However, novel imaging techniques provide new opportunities in HD research, as they enable us to study brain changes in vivo and follow morphological changes that take place as the disease progresses. High-resolution Magnetic Resonance Imaging (MRI) has been used to obtain accurate measurements of brain atrophy. In addition to atrophy and volume loss in the striatum and basal ganglia, more recent studies have demonstrated regional cortical thinning in the frontal, parietal, posterior temporal, parahippocampal, and occipital regions, some of which have been found even in pre-symptomatic individuals [83–85]. Selective atrophic changes have been shown to correlate with total functional capacity and duration of symptoms [85].

Besides striatal dysfunction, functional MRI imaging studies have reported a variable pattern of increased and decreased activation in cortical regions in both pre-clinical and clinically manifest HD gene mutation carriers. Beyond regional brain activation changes, evidence from functional and diffusion-weighted MRI further suggests disrupted connectivity between corticocortical and corticostriatal areas. However, substantial inconsistencies with respect to structural and functional changes have been reported [86].

Use of Positron Emission Tomography (PET) imaging for evaluation of brain metabolism, postsynaptic dopaminergic function and phosphodiesterase 10A has shown promise in assessing disease progression. However, no single technique may be currently considered an optimal biomarker, and an integrative multimodal imaging approach, combining different techniques, may be needed for monitoring potential neuroprotective and preventive treatment in HD [87].

Clinical Features

Although HD is the result of a single-gene mutation, with a well-defined pathogenic protein, its clinical picture is strikingly complex, manifested by a unique combination of motor, cognitive, and psychiatric symptoms in each individual case. Therefore, each patient should be evaluated in a comprehensive manner to define their specific needs and treatment plan. However, for the purposes of this chapter, we will discuss the features of each symptom set separately.

Motor Symptoms

Movement disorders are the hallmark of HD, with chorea being its most recognizable symptom. Although the term "chorea" is derived from the Greek verb meaning "to dance," there is very little compatibility with this term in Huntington's chorea, as its clinical appearance lacks any symmetry, rhythmicity or graciousness. Chorea in HD is manifested by involuntary movements which are sudden, irregular, asynchronous, purposeless, but frequently "masked up" into semi-purposeful movements. It usually emerges in the distal muscles of the extremities, but with the progression of the disease, it gradually spreads to involve more proximal muscles in the extremities, face, neck, and paraspinal muscles. With further progression, chorea increases in frequency, duration, and amplitude, sometimes to ballistic proportions [88]. Although chorea is the most dramatic symptom, the affected individual may be able to function quite well, even with relatively prominent movements [89]. Nonetheless, in very advanced cases, chorea will interfere with self-care and activities of daily living. Finally, in the later stages of the disease, chorea settles down and gradually yields to dystonia, rigidity, and contractures [90].

Although not as noticeable as chorea, dystonia also presents as a relatively early motor feature of HD, adding to the choreoathetoid and writhing appearance of the involuntary movements. Dystonia is frequently manifested by repetitive, abnormal muscle contraction, sometimes with a twisting component. With subsequent progression, dystonia involves the limbs, neck, and trunk resulting in abnormal and prolonged posturing. In the terminal stages of the disease, dystonia, bradykinesia, rigidity, and contractures dominate the clinical picture [90]. Particularly in juvenile-onset HD (Westphal variant), dystonia, rigidity, and bradykinesia are prominent from the onset of the disease and dominate throughout the course of the illness, while chorea is not as prominent [19, 91]. In general, dystonia may have a more detrimental effect on daily functioning than chorea does, as it contributes to postural instability, dysarthria, and dysphagia resulting in falls, communication difficulties, and aspiration pneumonia. Myoclonus maybe seen in the adult-onset form, but it is much more frequently encountered in the juvenile variant of HD [91]. Additionally, some HD patients may exhibit utterances, vocalizations and tics akin to Tourette's syndrome [92].

In addition to involuntary movements, progressive impairment of voluntary motor control is a core feature of HD, occurring relatively early in the disease. Particularly, voluntary eye movement abnormalities are some of the earliest signs of HD. Interrupted smooth pursuit, slow initiation, and impaired coordination of voluntary saccades are typical features, together with restrictions in the range of eye movements, particularly in a vertical plane. Even in presumably pre-symptomatic gene carriers, a detailed exam may reveal significantly more abnormalities of ocular function than in gene negative individuals [93]. Worsening in manual dexterity is another early sign of HD, manifested in the examination as slowness in finger tapping and rapid alternating movements of the hands. Motor

impersistence is manifested by the inability to maintain voluntary motor contraction, which further contributes to difficulties with manual tasks. Clinical exam for motor impersistence reveals an inability to maintain prolonged tongue protrusion and "milk-maid's grip." It has been proposed that depressed synaptic transmission plays a role in motor impersistence [94]. Upper motor neuron signs also may occur in the course of HD, such as spasticity, clonus, and extensor plantar responses. Impairment of voluntary motor control correlates with a disability and functional decline perhaps even more so than involuntary movement disorder [89]. Unfortunately, there are no effective medications to improve voluntary motor control.

The compounding effects of involuntary movements and impaired voluntary motor control result in a multi-faceted gait disorder in more advanced stages of HD. Progressive worsening of dystonia, ballistic chorea, motor impersistence, and voluntary eye movements all contribute to incoordination, impaired ambulation with a propensity towards falls and injuries, resulting in wheelchair dependence [95].

Cognitive Disorder

Although movement disorders and chorea are the most recognized symptoms of HD, cognitive impairment is a much more disabling and distressing manifestation of the disease and presents the greatest burden to the patients and their families [96]. Dementia in HD is classified as "subcortical," as it lacks typical cortical deficits such as aphasia, amnesia, and agnosia, typically seen in Alzheimer's disease [97, 98]. The cognitive disorder in HD consists of bradyphrenia, impairments in attention, sequencing, executive function, perceptual skills, as well as learning and memory impairments [97, 99, 100]. Registration and immediate recall are relatively spared, while retrieval of recent and remote memories are impaired [97, 99, 100]. Explicit sequence learning appears to be more affected than implicit, both in pre-manifest and manifest individuals [101]. For routine monitoring of cognitive status, most HD clinics utilize the Unified Huntington Disease Rating Scale (UHDRS), which, in addition to motor and behavioral scales, also incorporates reliable indicators of cognitive decline including the Symbol Digit Modality Test, the Stroop Color Word Test, and the Verbal Fluency Subtest of the Multilingual Aphasia Examination [102]. In asymptomatic HD gene carriers, subtle cognitive deficits may be present many years before the onset of motor symptoms [103]. Asymptomatic gene carriers test lower than non-carriers in all portions of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and there is an inverse correlation between the scores and the number of CAG repeats in the HD gene carriers [104].

Executive functioning and efficiency in HD are affected by changes in the speed of cognitive processing, attention, initiation, planning, and organization, as well as by perseveration, impulsivity and decline of other regulatory processes [105–107]. In HD, patients have difficulty learning new information and retrieving

previously learned information, possibly due to impaired speed of processing and organizing information [108]. A change in the speed of cognitive processing is one of the earliest and most sensitive indicators of early HD, as completion of previously ordinary mental tasks becomes more time consuming [105, 108]. The slowing of cognitive processing may result from recruitment of alternate cerebral pathways for cognitive tasks, as an attempt to compensate for deficits in implicit memory [109, 110].

Perceptual problems further compound the cognitive issues from early on, sometimes more than a decade before the onset of more obvious symptoms of HD [103]. More specific perceptual deficits include the inability to recognize the emotions of others communicated by facial expression, perception and estimation of time, spatial perception, and smell identification [111–114]. Lack of awareness of one's own symptoms, actions and feelings may be impaired in as many as one-third of individuals with HD. This is thought to result from interruptions in the pathways between the frontal lobes and the basal ganglia and is felt to be a type of agnosia [115]. Central visual and auditory processing deficits additionally contribute to general perceptual and cognitive impairment [116].

Although typical aphasia or impairment in semantic memory is rarely seen in HD, language and communication are still remarkably affected, primarily by deficits in articulation, initiation, and cognitive processing. Individuals with HD may have difficulties with the integration of thought sequencing, information processing, muscle control, and breathing. Despite impairment in language output, comprehension may be relatively preserved, even in advanced stages of HD [100, 117].

Psychiatric Symptoms

Depression is the most common psychiatric presentation in HD, affecting up to 40% of patients in the course of the illness [118, 119]. The symptoms may start in the pre-motor manifest stage, evidenced by subtle impairment of working memory [97, 120]. Depression in HD has all the symptoms and signs of major depression syndrome, such as sustained low mood, tearfulness, sadness, low self-esteem, loss of appetite, sleep disturbances, feelings of guilt, shame, hopelessness, and helplessness [121]. In severe cases, depression may progress and individuals may develop psychotic symptoms such as delusions and hallucinations or even more profound psychomotor retardation and catatonia. Sometimes it may be difficult to distinguish depression from other symptoms seen with HD, such as apathy, circadian sleep dysregulation, weight loss, impaired attention, and concentration span. Apathy, in particular, is one of the most common symptoms of the disease and is gradually progressive, in synchrony with other symptoms of neurodegeneration, such as motor and cognitive decline [119, 122]. The course of depressive symptoms does not follow the pattern of progression one would expect if the process was directly linked to the pathophysiology of neurodegeneration [88]. On the contrary, depression is most common at early points in the illness, during the period

around the initial diagnosis and in the early stage when the impairments begin affecting daily functioning [123]. Subsequently, depressive symptoms seem to decline in prevalence [123]. Nonetheless, the use of strict diagnostic criteria for major depression usually helps to establish an accurate diagnosis.

Symptoms suggestive of bipolar disorder such as elated affect, mania, and agitation, as well as alterations between depressive and manic episodes may develop in approximately 10% of patients [119, 124]. Irritability in HD may be severe, presenting with outbursts of anger and aggression, affecting up to two-thirds of patients in the course of the illness [125]. One should be cautious not to mistakenly diagnose HD-associated dysexecutive syndrome as bipolar disorder, given that some symptoms of the former, such as irritability, impulsivity, disinhibition, and hypersexuality may imitate symptoms of the latter disorder [106].

The risk of suicide was recognized even by Huntington in his publication in 1872 and has remained a significant concern to present. Identified risk factors include depression, single marital status, childlessness, living alone, and family history of suicide [126]. Additional factors that modify the risk include the level of insight, the severity of affective symptoms, and social support [127–129]. Up to 25% of HD patients may attempt suicide in the course of the disease, with a mortality rate of 5–13% [130, 131]. The rate of suicide is higher in pre-symptomatic individuals at risk for HD [18, 130, 132]. Individuals that are undergoing predictive testing for HD may also be at an increased risk for suicide [127, 129]. The risk of suicide should be discussed with patients, their families, and caregivers. As suicide is a preventable outcome of disease, suicidal ideation should be screened for during each clinical visit.

Psychotic features in HD may include a multitude of symptoms, auditory or visual hallucinations, delusions, particularly of the paranoid type, as well as social withdrawal [118, 122, 131]. The lifetime prevalence of psychosis in HD is between 1 and 15%. However, additional familial modifiers may affect the incidence [119, 122, 133]. In cases when psychiatric symptoms occur before motor symptoms, patients may be mistakenly diagnosed with schizophrenia [134]. In such cases, the subsequent emergence of chorea may be further mistakenly interpreted as neuroleptics related tardive dyskinesia. Therefore, in a psychiatric setting, a high index of suspicion for HD is advised in cases of progressive chorea, in association with an uncertain or unreliable family history. In most such cases, clarifying the family history and monitoring for other signs of HD is sufficient to confirm the diagnosis. However, in certain instances, the issue can only be settled by genetic testing.

Although recent theories have implicated the basal ganglia and frontal lobes in the development of obsessive-compulsive disorder (OCD), HD patients rarely develop the full syndrome. Nonetheless, some HD patients may develop a preoccupation with misophobia, contamination, or may engage in excessive checking and rechecking routines. Some individuals may become fixated on a perceived need or a prior unresolved issue [135]. If the symptoms become so severe as to interfere with the quality of life, a treatment usually applied for OCD may be indicated.

Sleep disturbances are common in HD, and they contribute to progression and overall deterioration. Polysomnographic sleep patterns in HD have been studied sporadically in small groups of patients, providing variable results. However, more recent studies have confirmed delayed nocturnal sleep onset latency as one of the earliest sleep-related findings, with a virtual absence of nocturnal respiratory disturbances in early HD [136]. Polysomnographic studies correlated delayed sleep onset, awakenings, and reduction of slow-wave sleep with the severity of motor symptoms, duration of illness, and degree of caudate atrophy on computed tomography (CT) [137].

Personality changes are hard to categorize but are clearly evident very early in HD. There are various terms used to define them, such as organic personality disorder, dysexecutive syndrome or frontal lobe syndrome, as there is no specific diagnosis to encompass them. The earliest personality changes are often manifested by anxiety, irritability or apathy [138]. Overall, personality changes seem to be widespread in HD, perhaps more common than depression, and sometimes may precede the onset of cognitive and motor symptoms by many years [12, 139, 118].

Diagnosis

HD should be considered in the differential diagnosis of any disorder presenting with a combination of symptoms that includes chorea, dementia, and psychiatric disturbances. The diagnosis is relatively easy to establish in individuals with typical clinical features and a positive family history of HD. Non-inherited disorders that can present with chorea such as thyrotoxicosis, cerebral lupus, cerebrovascular disease, polycythemia or tardive dyskinesia usually can be excluded by routine laboratory tests and by their clinical course. The recommended basic laboratory workup would include a blood count, with a smear for acanthocytes, sedimentation rate, metabolic panel, thyroid parameters, vitamin B12 level, and autoantibodies including lupus anticoagulant, antinuclear, anticardiolipin, antistreptolysin, and anti-DNase-B antibodies [140]. As there are viable treatment options for it, Wilson's disease should always be included in the differential diagnosis of movement disorders and screened for by serum ceruloplasmin levels [141].

There are several familial disorders with clinical features that may overlap with HD, such as X-linked McLeod neuroacanthocytosis syndrome, as well as autosomal recessive disorders, including Chorea-acanthocytosis, Spinocerebellar ataxia type 17, and Dentatorubral-pallidoluysian atrophy [142–145]. Even a very detailed family history may not be able to distinguish the latter disorders from HD. There are also at least two disorders with an autosomal dominant inheritance pattern and clinical features very similar to HD, that should be taken into consideration: Huntington disease-like1, a slowly progressive prion disease [146, 147], and Huntington disease-like 2, that is clinically indistinguishable from HD, but is much more prevalent in individuals of African descent [148]. Negative family history does not necessarily exclude a diagnosis of HD. There are several instances in

which HD may be present in the context of negative family history, such as parental or ancestral death before the age of HD expression, an intermediate number of paternal CAG repeats resulting in meiotic instability and expansion in the subsequent generation into HD range, lack of information about family and de novo mutation.

Although clinical evaluation and family history analysis still play a very important role, genetic testing is now considered the gold standard in the diagnosis of HD. When completed in clinically plausible cases, genetic testing has a sensitivity as high as 98.8% and specificity of 100% [149]. Genetic testing can be used for confirmation of the diagnosis in asymptomatic patient, or as predictive testing in an asymptomatic individual at risk for HD. However, the availability of genetic testing in a non-curable disease has raised a myriad of ethical and practical questions [150–152]. Nonetheless, there is a wide consensus that genetic testing should not be a single encounter, but rather a process that involves confidentiality, informed consent, and multidisciplinary supportive counseling, before, during, and after testing and disclosure [153, 154]. The role of psychological and psychiatric counseling is crucial during this process, as the risk of suicide in HD tends to peak around the time of diagnosis [129]. Predictive testing is discouraged in minors, and it is usually pursued only in exceptional circumstances [155]. Despite the availability of the test, only a small proportion, less than 10%, of asymptomatic at-risk individuals decide to undergo predictive testing [154]. Although psychological attributes are similar among individuals who do and do not pursue testing [156], baseline behavioral status has been more strongly associated with the decision to undergo predictive testing than motor symptoms [157]. Following genetic testing, about half of individuals who tested negative for the HD gene had less depression when compared prior to testing, but depression remained the same or worsened in two-thirds of individuals with a positive HD genetic test [157]. In addition, individuals undergoing predictive genetic testing are often concerned about potentially losing their medical insurance as a result of possible subsequent discrimination [156]. Therefore, a structured process of genetic testing for HD that involves psychological and social support, as well as genetic counseling, is justified.

There are several diagnostic options available in the process of family planning for couples affected or at risk for HD. During the initial stages of pregnancy planning, a couple may choose pre-implantation genetic testing in the context of an in vitro fertilization procedure in a specialized center. In this procedure, maternal oocytes are fertilized by the partner's sperm in vitro, and resulting embryos undergo genetic testing prior to implantation. Only embryos without the HD mutation are implanted, assuring that the child born after this procedure will be free of HD [158].

Diagnostic options during pregnancy at risk for HD, include chorionic villus sampling, which can be performed at 8–10 weeks after conception. Amniocentesis may be performed at 14–16 weeks after conception. After the tissue is tested, termination of the pregnancy may be considered by the parents if an HD mutation is found [158]. Non-invasive prenatal diagnosis techniques are also being developed using circulating fetal DNA in the maternal blood to perform testing for the HD mutation during the first trimester of pregnancy [158–160].

Treatment

Currently, there is no disease-modifying therapies or a cure for HD. Therefore, treatment is based largely on lifestyle interventions, supportive management, and symptomatic treatment.

Healthy lifestyle habits may be important not only to symptomatic HD patients but also to asymptomatic carriers. Avoidance of alcohol, drugs, and tobacco is not only good advice for the general population but may also have significant implications in the pre-manifest HD population. A recently completed study on a large cohort of HD patients suggests that the frequent use of tobacco, alcohol, and illicit drugs (including cannabis) may significantly accelerate the onset of motor symptoms in HD, by 2.3, 1.0, and 3.3 years, respectively, with the effects being significantly more prominent in women [161]. Moderate physical activity, such as walking, biking or swimming, is known to have a clear benefit for general health, but particularly in HD, which may help to optimize motor function and hence stabilize motor deficits [162]. In HD, a moderate adherence to the Mediterranean diet has been reported to correlate with a better quality of life, lower comorbidity and less motor impairment [163]. The use of vitamins and dietary supplements is a relatively common practice in the HD community, although such use has not shown any specific benefit to HD patients in clinical trials [164]. Medical practitioners should be vigilant and monitor for signs of overuse of vitamins that may result in toxicity, such as vitamins D, E, K, and A [165].

Due to the complexities of HD, supportive management should not only be aimed at patients but also caregivers and families. Supportive services are most effectively delivered through a comprehensive, multidisciplinary, yet dynamic, program that adjusts to the progressive nature of the disease [166].

In the early stages of the disease, patients and their families can derive a significant benefit from psychological counseling which can help alleviate the stress of genetic testing, manage expectations during the progression of the disease, facilitate effective communication among family members, manage behavioral problems, and monitor for signs of suicide risk. At such time as disease progression affects working capacity, a social worker can assist patients with applications for disability and medical benefits. As the disability progresses, patients and their caregivers benefit from home health service visits for help with daily activities, which in turn may also help prevent caregiver burn-out. With the progression of motor symptoms, physical therapy services may help enhance strength, flexibility, and coordination, help prevent contractures, and also aid in gait reconditioning and fall prevention [167]. Occupational therapy is helpful with training in the use of assistive devices and adapted utensils. Furthermore, periodic speech therapy evaluations are recommended for evaluation and management of swallowing, for prevention of aspiration pneumonia, to improve speech clarity and to provide assistive communication devices when applicable. Multiple observational studies (without control groups) of multidisciplinary rehabilitation in HD demonstrated not only improvements in motor function but also reduction in depression and

anxiety [168, 169]. Positive effects on the gray matter have also been shown on neuroimaging, as well as improvement in cognitive function [170]. A living will, advanced medical directives and surrogate decision maker designation should be addressed by a physician or social worker before the patient becomes cognitively unaccountable [171]. In the later stages of the disease, placement in an assisted living or nursing care facility becomes necessary. In terminal stages, enrollment in hospice for comfort care is an appropriate option to consider [172]. Over the years, multidisciplinary clinics have emerged as a destination where patients, caregivers, and affected families can address a multitude of problems and needs at one location. Further initiatives are being pursued with the intent of moving multidisciplinary care from the clinic and outreach to patient's homes as they become immobile with the progression of the illness [173].

Pharmacological therapy in HD is primarily utilized for the treatment of symptoms and does not have any beneficial effect on the progression of the disease. Therefore, initiation and choice of pharmacological therapy for any symptom should be based on the patient's needs and preferences, in corroboration with the caregiver. Often, impairment in patient's perception of their own symptoms may initially result in a delay in treatment [115]. Additionally, the superposition of psychiatric symptoms and cognitive decline affect compliance and increase the risk of complications related to possible incorrect dose intake and interactions. The risks and benefits of medications should be discussed not only with patients but also with caregivers, as well as the possible need, for early supervision with the dispensing of the medications.

Currently, there are no evidence-based treatment recommendations for cognitive decline in HD, as prior clinical trials have not identified any viable pharmacological options. Cholinesterase inhibitors have been proven to be ineffective in designated clinical trials, while preliminary reports from the MITIGATE-HD memantine trial presented at the 2010 Huntington Study Group symposium, suggested worse outcomes for some motor symptoms and only partial improvement of some cognitive measures [174–176]. Apart from general supportive measures, it is important that the physician closely monitor for and correct any toxic metabolic encephalopathies which may result from medications utilized for psychiatric and motor symptoms, as well as other associated conditions in each individual case [177].

The choice and use of pharmacotherapy for psychiatric symptoms are largely based on general psychiatric indications for each medication in the context of the set of psychiatric symptoms in consideration, as there is practically no evidence-based support for its use in HD [176]. As per common practice and expert opinion, selective serotonin reuptake inhibitors (SSRI), as well as serotonin-norepinephrine reuptake inhibitors (SNRI) are the mainstay of pharmacotherapy for depression in HD, primarily due to their favorable side effect profile, safety, and tolerability [178]. Popular SSRIs include fluoxetine, paroxetine, sertraline, citalopram, and escitalopram. Commonly used SRNIs include venlafaxine, duloxetine, and desvenlafaxine. Additional choices may include an atypical antidepressant, such as mirtazapine or bupropion. Tricyclic antidepressants are generally out of

favor due to their anticholinergic profile and may worsen hyperkinesia and cognition. Monoamine oxidase inhibitors are largely avoided, due to intolerability. Antidepressants may sometimes exert an initially stimulating effect, resulting in impulsive, disruptive, and self-destructive behaviors. In the United States, all antidepressants carry a black box warning emphasizing that antidepressants may worsen suicidal impulses and behaviors.

For the management of psychotic symptoms with or without depression, the usual choices include new generation neuroleptics such as olanzapine, quetiapine, ziprasidone, aripiprazole, and risperidone [179, 180]. Classic neuroleptics are used less frequently due to a more pronounced side effect profile which may include worsening of cognition, tardive dyskinesia, and dystonia. For the treatment of periodic agitation, irritability or aggressive behaviors, mood stabilizers such as valproic acid, carbamazepine or other anticonvulsant medications are widely utilized, as well as olanzapine, a new generation neuroleptics [179]. Lithium is rarely prescribed due to its potential to worsen involuntary movement, as well as cardiac, endocrine, and metabolic issues. Short-acting benzodiazepines such as lorazepam and alprazolam are preferred choices for acute agitation or anxiety attack treatment. For chronic anxiety, the usual first choices are SSRI's, non-benzodiazepine anxiolytic bupropion or long-acting benzodiazepine clonazepam [178]. Obsessive-compulsive symptoms may respond to SSRI's or a new generation neuroleptic in refractory cases [178]. Although some experts have suggested that stimulants may be beneficial for the treatment of apathy, they should be used with great caution due to their potential to worsen irritability and abuse potential. For sleep disorders, some experts suggest mirtazapine, the benzodiazepine receptor inducer zoldipem, the atypical sedating antidepressant trazodone or new generation neuroleptic quetiapine [176, 178].

There are multiple treatments available for the options of chorea and other motor symptoms in HD. As opposed to the treatment of cognitive and psychiatric symptoms, there are well-defined evidence-based treatments that can be recommended for chorea in HD. The vesicular monoamine transporter-2 (VMAT-2) inhibitors tetrabenazine and deutetrabenazine have demonstrated effectiveness in reducing chorea in HD in well-designed multicenter trials [181, 182]. Both medications received the United States of America Federal Drug Administration (USFDA) approval for treatment of chorea in HD, tetrabenazine in 2008 and deutetrabenazine in 2017. Although both medications demonstrated statistically significant reductions in chorea scores, they have no effect on the natural progression of the illness. Compared to tetrabenazine, the newer medication deutetrabenazine, contains deuterium in its molecule, a naturally occurring non-toxic form of hydrogen. This extends the active metabolites half-lives and minimizes through-to-peak drug concentration fluctuations and peak concentration-related toxicity. In a meta-analysis comparison, deutetrabezine may have less adverse effects than tetrabenazine, particularly a lower rate of psychiatric adverse effects such as irritability, agitated depression, and suicidal ideation [183]. In addition, deutetrabenazine has demonstrated a tendency towards reduction of dystonia [182]. However, head to head comparison studies would be needed to substantiate and clarify such

claims. Nonetheless, both medications have a similar side effect profile and carry a USFDA black box warning for potential worsening of suicidal ideation in the context of untreated or inadequately treated depression. Additional contraindications include concomitant MAOI or reserpine treatment and hepatic impairment. Both medications have the same precautions, which include renal impairment, QTc interval prolongation, pregnancy (category C), lactation, and concomitant use of CYP 2D6 inhibitors, such as fluoxetine and paroxetine, which are often used for depression in HD [181, 182].

Both classic and new generation neuroleptics have been used in clinical practice for chorea in HD and have the additional benefit of lessening concomitant psychiatric symptoms. However, neuroleptics also have the potential disadvantage of exacerbating dystonia, tardive dyskinesia, and parkinsonism, with a higher propensity to cause neuroleptic malignant syndrome compared to VMAT-2 medications. Most experts agree that initially, the new generation neuroleptics, should be used due to their better side effect profile, but advanced cases with severe chorea in association with psychosis may require classic neuroleptics. Frequently considered new generation neuroleptics include olanzapine, risperidone, and aripiprazole, while commonly used classic neuroleptics include haloperidol, fluphenazine, and chlorpromazine [184]. The benefits of neuroleptics have been documented mainly in relatively small, open-labeled studies [176]. Additional medications used for the treatment of chorea include amantadine, for which there has been limited concordance in prior studies, and clonazepam, which may also be beneficial for myoclonus, but shares a potential risk of dependency and abuse with other benzodiazepines [178]. In any case, the use of all these medications should be tailored individually to the patient's needs and tolerability.

Pharmacologic treatment of dystonia is often needed in advanced stages of HD, both in the juvenile and adult form and may include benzodiazepines, baclofen, and occasionally dopaminergic anti-parkinsonian medications. Botulinum toxin injections may also be used for focal dystonia [184]. Anticholinergic medications such as benztropine and trihexyphenidyl are best avoided due to potential cognitive side effects, as well as the potential to precipitate delirium.

Experimental Therapeutics and Prospects

Over the last decade and a half, ninety-nine clinical trials have been completed in HD, evaluating 41 compounds and 11 non-pharmacological interventions, including cell therapies, for possible therapeutic effects, with an overall very low success rate at 3.5% [185]. The most significant outcomes were the two USFDA approvals for tetrabenazine and deutetrabenazine for the treatment of chorea.

As the HD gene mutation can be identified decades before disease onset, the ultimate aim of therapy would be to delay the onset of the disease or possibly completely prevent it from emerging. Current HD research is, therefore, focused on finding the most accurate markers of progression in the pre-manifest phase, to

enable evaluation of efficacy for potential therapeutic agents prior to the emergence of HD symptoms. Large neuroimaging observational studies have demonstrated that quantitative measurements of the striatum and adjacent brain regions, as well as some cognitive and motor scales, are reliable biomarkers of degenerative progression in pre-manifest HD [186]. Additional markers are being verified including neurofilament light protein in the blood, total tau concentration, and mutant huntingtin protein quantification in the cerebrospinal fluid [187–189].

Correlation between the age at onset of HD and CAG repeat length within the Huntingtin gene, accounts only for approximately 50% of the variance in age at onset, due to the effects of additional genetic modifiers [23, 28]. Hence, there is a remarkable research interest in identifying genetic modifiers that accelerate or delay HD expression as a potential disease-modifying treatment targets [190]. Recently, this has been facilitated by the development of the Genetic Modifiers of Motor Onset Age (GeM MOA) website, where researchers can use single nucleotide polymorphisms as genetic markers within a genome-wide association studies database, in search of genetic HD modifiers [191].

To date, the most promising advances in HD research have been accomplished in the field of gene therapy. In an autosomal dominant disorder such as HD, silencing the mutant gene may potentially have a disease-modifying or even curative effect. The main principles in gene silencing include repression of transcription of DNA information into messenger RNA by using zinc finger proteins, repression of translation of mutant huntingtin by antisense oligonucleotides, and blocking protein translation by RNA interference techniques [160]. Gene silencing techniques have demonstrated a consistent and significant reduction in mutant huntingtin expression in animal HD models [192]. In 2017, a phase 1b–2a clinical trial evaluating the safety of antisense oligonucleotide (ASO) therapy in HD in humans, has been completed. The study utilized ASO designed to inhibit huntingtin messenger RNA and thereby reduce concentrations of mutant huntingtin. It entailed intrathecal bolus application of ASO every four weeks for 4 doses, in patients with early HD. The final report cited a favorable safety profile of this treatment, without the encounter of serious adverse events, with an observed dose-dependent reduction in concentrations of mutant huntingtin in CSF [193]. Open-label extension of this study has continued beyond the completion of 1b–2a phase. In 2018, the pivotal phase 3 trial has been initiated to evaluate the efficacy and safety of this intrathecally administrated ASO drug. There are two additional ongoing phase 1b–2a clinical trials evaluating safety and pharmacokinetics of intrathecal application of two distinct allele-specific ASO drugs, designed to lower only mutant huntingtin. All these studies are expected to be completed by late 2020 or early 2021 and HD community is eagerly awaiting the outcomes.

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