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REVIEW ARTICLE

Updated Review on Huntington's Disease (HD)

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ABSTRACT

Huntington's disease is a devastating inherited neurodegenerative disease characterized by progressive motor, cognitive, and psychiatric symptoms. Patients may present with any of these symptoms, and familiarity with the phenotype is therefore important. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes before this. It results from genetic mutations involving trinucleotide repeats of the huntingtin gene, which encodes the huntingtin protein. HD is presently the most widely studied genetic neurodegenerative disease that has diagnostic and predictive genetic testing, with the possibility of gene-targeted therapy in the near future. Neuroimagingcanplayan important diagnostic and prognosticrolein HD by evaluating affected regions of the brain by using techniques such as MR imaging, FDG-PET, MR spectroscopy, and diffusion tensor imaging.

Keywords: Huntington's disease, Psychiatric, Neurogenerative, Huntingtin protein, Genetic mutations

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CONTENTS

1. Introduction

Huntington's disease is a devastating inherited neurodegenerative disease characterized by progressive motor, cognitive, and psychiatric symptoms. Patients may present with any of these symptoms, and familiarity with the phenotype is therefore important. Chorea and loss of balance are early symptoms that patients notice, although families often notice cognitive or personality changes before this. The disease occurs in all racial groups but is most common in people of northern European origin. Its prevalence in the Western hemisphere is 7-10/100 000.w1 The mean age of onset of symptoms is 40 years, but juvenile onset (<20 years) and older onset (>70 years) forms are well recognized[1]. The Huntington's Disease Association (HDA) has records of 6161 adults with

symptomatic Huntington's disease and 541 children with juvenile Huntington's disease (in England and Wales) at the time of writing. This is a conservative estimate of prevalence because it includes only those people in contact with the HDA, and it suggests that the true prevalence of the disease is higher than previously thought.1 Although relatively uncommon, Huntington's disease can be devastating for patients and their families. People who are at risk of developing the disease because of a family history face difficult decisions about genetic testing. We review the features of Huntington's disease, recent advances in management, and advances in the practice and ethics of genetic testing that may be relevant to a wide spectrum of health professionals[1,2].

Epidemiology:

Huntington's disease is a rare neuropsychiatric disorder with a prevalence of 5-10 per 100,000 in the Caucasian population. In Japan, a much lower prevalence of about one-tenth of prevalence of the Caucasion population is described. Recently, several phenocopies have been described, all of which have an even lower prevalence[5].

2. Pathophysiology

The most neuropathology in HD shows within the neostriatum, in which gross atrophy of the caudate nucleus and putamen is accompanied by selective neuronal loss and astrogliosis. Marked neuronal loss also is seen in deep layers of the cerebral cortex. Other regions, including the globuspallidus, thalamus, sub thalamic nucleus, substantianigra, and cerebellum, show varying degrees of atrophy depending on the pathologic grade. Huntington's disease affects both cognitive and motor abilities. Patients experience chorea-over-the-top jerky movements which are uncontrolled. Due to these erotic movements, many see increased muscle tone, also called dystonia. Often, the uncontrolled muscles begin with those farthest along the limbs from the trunk, i.e. fingers and toes, and those muscles in the face and tongue. Memory, especially working memory, becomes severely limited. A loss of this type of memory is due to damage of the caudate nucleus and other subcritical areas. Nonetheless, damage to basal ganglia is reflected in the inability to follow procedural memory. Implicit memories are also lost, culminating in difficulty chewing and swallowing[6]. However, long term memory is still available, and episodic memories, with prompting, can still be accessed. Cognitive speed, inability to concentrate, trouble processing problems to come to a solution, and spatial functioning are all impaired. It is harder for Huntington's disease patients to initiate behaviours, yet once started, they become fixated on these behaviours, losing sight of other activities. Additionally, between 13 and 71% of those with Huntington's disease also suffer from anxiety. One study showed that about 34% of Huntington's disease patients experience changes in their anxiety[7]. No relationships seem to appear between anxiety and age or in gender. A positive relationship is seen between anxiety and agitation, because of struggling relationships or because of both begins to manifest as a result of the onset of disease and the many upcoming and ongoing changes.

Mitochondria enzymes:

In biochemical studies defects in respiratory chain is found in HD individuals. The activity of complex II/III are greatly decreased in comparison of complex IV in HD patients but pre symptomatic patients has shown no changes in the activity of complex II, III and IV. Minor changes were observed in respiratory chain enzymes of cerebral cortex but no changes were observed in blood cells. The other enzymes of oxidative metabolism were also reported with reduced activity in the striatum. The levels of aconitaseand pyruvate dehydrogenase complex were also significantly decreased in HD individuals. These decreased enzymes levels were observed in symptomatic patients having atrophy of striatum[8].

Molecular understandings:

The huntingtin gene is present on the short arm of chromosome four. The huntingtin gene is believed to have a role in cell signaling as well as adenosine monophosphate as a binding protein and to help the body prevention of cell toxicity and cell death. The wild type of gene is generally seen in the nervous system. The protein has presence in the cytoplasm and vesicles of neuronal cells in the brain. This specific gene codes for three cytosineadenine-guanine (CAG) cycles that are repeated up to 27 times in a normal, wild type genome. If an individual has between 36-40 repetitions, he/she has a chance of developing Huntington's disease. The mutation that occurs in Huntington's disease involves this trinucleotide cycle continuing to repeat unchecked 40 or more times which forms the mutant huntingtin protein found in axon one of the gene[9].

3. Clinical features of HD

The disease was originally named Huntington's chorea after George Huntington, who wrote the first detailed description in 1872. More recently, however, the name has changed to Huntington's disease to reflect the fact that chorea is not the only important manifestation of the disease. Many non-motor symptoms may be more disabling and distressing than the motor symptoms.2-4 One study assessed the effect of cognitive and motor symptoms on the ability of 67 people with early Huntington's disease to carry out activities of daily living, and found that cognitive impairment was associated with reduced functional ability independent of motor impairment[10]. Imaging and postmortem studies have shown that the disease is characterized by cerebral atrophy. Atrophic changes are initially seen most prominently in the striatum (part of the basal ganglia) and later become more widespread. Huntington's disease progresses over 15-20 years. The onset of disease is currently defined as the point at which characteristic motor signs develop this is when a patient moves from being a "premanifest gene carrier" to having "manifest" disease. This distinction is somewhat arbitrary because most patients develop cognitive or psychiatric symptoms (or both) during the prodromal ("premanifest") period, often many years before any motor signs are seen.

Motor symptoms:

The motor symptoms of Huntington's disease can be divided into two categories: added involuntary movements such as chorea, and impaired voluntary movements, which

cause limb incoordination and impaired hand function. These symptoms are worsened by loss of postural reflexes. The pattern of symptoms tends to change over time, with chorea declining and dystonia, rigidity, and bradykinesia becoming more marked[11].

Cognitive symptoms:

Cognitive impairment includes slowing of thought processing and deterioration of executive functions (high level cognitive processes that control other aspects of cognitive function). Typically, patients report difficulty with multitasking, concentration, and short term memory. Thinking style becomes more concrete and less efficient, and the planning, initiation, and organization of time, thoughts, and activities become harder. People with Huntington's disease are often impulsive and develop psychomotor perseveration. Visuospatial perception can also deteriorate[12].

Psychiatric symptoms:

Depression is one of the most common psychiatric symptoms and occurs as part of the disease, rather than merely as a response to diagnosis. A recent survey of 2835 patients with the disease found that 40% had symptoms of depression, and 50% reported having sought treatment for depression in the past. Other reported psychiatric symptoms include obsessive-compulsive symptoms and psychosis.w3-w5 It is important to recognize psychiatric symptoms in Huntington's disease so that symptomatic treatment can be offered. This may be difficult later in the disease because diagnoses may be obscured by other features of the disease; depression, for example, may be difficult to detect in a patient who has altered facial expressions and tone of voice. Conversely, metabolic symptoms such as weight loss and sleep disturbance may be wrongly attributed to depression.

Suicide risk:

Patients with Huntington's disease are more likely than members of the general population to commit suicide according to a meta-analysis of studies that reported mortality associated with mental disorders (standardized mortality ratio of 290).W6 A survey of 4171 carriers of the Huntington's gene with premanifest and manifest disease found that 17.5% had suicidal thoughts at or around the time of assessment and 10% of those surveyed had made at least one suicide attempt in the past. Suicidal ideation was highest in gene carriers who were nearing the threshold of being diagnosed with manifest disease (those with soft motor signs of Huntington's disease), and in those who were beginning to lose their functional ability and independence (those with stage 2 disease)[13]. Risk factors for suicide in Huntington's disease include depression and impulsivity. Some people with the disease also have suicidal thoughts in the absence of depressionw7: for some, thoughts of suicide seem to be a rational response to their imminent loss of independence.

Metabolic symptoms:

Huntington's disease causes metabolic symptoms, which include catabolic weight loss, endocrine dysfunction, and sleep disturbance.

Advanced disease:

By the time patients have endstage disease they are profoundly disabled. Communication may be severely limited and muteness is common, which can result in agitation and frustration. Huntington's disease does not cause global dementia, however, and the ability to recognize and interact with people is often preserved. Huntington's disease is a catabolic condition, and this, combined with marked dysphagia, means that it can be difficult to provide sufficient nutrition to maintain a patient's weight[14].

Eye movements:

Pathological findings of eye movements can be the first symptoms in early stages of HD and also have been described in premanifest HD gene carriers. Therefore, special attention should be paid to the examination of eye movements during the neurological investigation in premanifest and young people in particular. The clinical examination can be complemented by vestibule oculography, which can objectify subtle findings and depict subclinical alterations. One of the first findings in early stages of HD can be an incomplete suppression of the optokinetic nystagmus. Slowing of saccade velocity and a delay in initiating volitional saccades is found additionally. In contrast, smooth pursuit is not altered in early stages. With disease progression, all mentioned functions are altered including refixation.

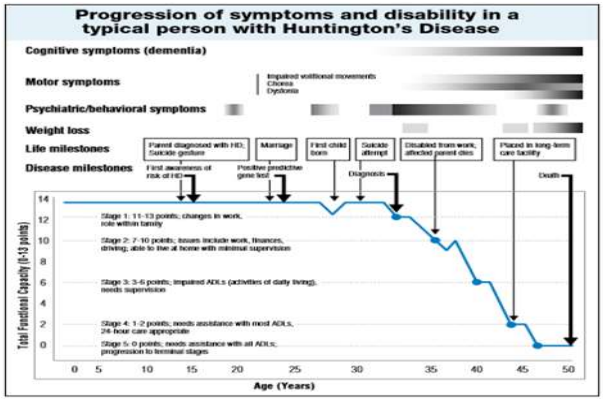

Fig 1: Symptoms and stages of HD

4. Diagnosis

The diagnosis is based on the clinical symptoms and signs in a person with a parent with proven HD. First, it is obligatory to take a precise history from the person with symptoms followed by a detailed family history. When all information has been obtained the diagnosis is not very difficult, although non-specific clinical pictures can be misleading. Also when the parent is not known or has died due to another cause at a young age, the clinical picture can be difficult to recognize[15]. It is often necessary to request old information in the form of medical records and autopsy reports. The current gold standard is DNA determination, showing a CAG-repeat of at least 36 on the huntingtin gene on chromosome 4. Before 1993, a family history with clinical and morphological verification in at least one of the parents or grandparents was obligatory. The clinical criteria currently necessary are still motor changes with or without psychiatric or cognitive changes. However, in most cases a combination of the three main signs is present. The combination with the family history is sufficient for

diagnosis. No imaging, general blood tests or other diagnostic tools are helpful. For all diagnostic tests, it is necessary to obtain informed consent from the patient. This is important because if that person is given a diagnosis of Huntington's disease, then probably many more individuals around the patient will be confronted with an increased risk of Huntington's disease. Extensive studies are underway to detect biomarkers (clinical, blood, MRI) and hence the transition determining parameters. Several studies are now focusing on changes in function and changes in brain imaging (MRI) before clinical overt manifestation is present[16]. It seems that brain volume and brain connections show changes several years before any clinical manifestation is present.

5. Pharmacological Approaches

The time point at which symptomatic medication is started has no direct influence on the neurodegenerative process, and thus should be considered very critically based on the patients' needs. The aim should be to guarantee the best quality of life. Intended benefit and side effects have to be assessed individually and questioned regularly. In particular, in early stages, drug therapy should be initiated according to the patient's own wishes and should not be driven by the demand of relatives, who, for example, might feel embarrassed by the involuntary movements or cannot stand doing nothing while the patient is suffering according to their perception[17].

A few substances have been shown in clinical trials to have beneficial effects on HD-related motor symptoms and chorea in particular. Based on these trials, first evidence-based treatment guidelines are available, for example published by the American Academy of Neurology. These guidelines, however, are discussed controversially by experts who have collected decades of experience in treating HD patients[18]. Many agents have been tested to reduce choreatic movements including, for example, neuroleptics, monoamine depleting agents, benzodiazepines, antiepileptic's, acetyl cholinesterase inhibitors, and glutamate antagonists. Nevertheless, there is not enough evidence to propose long term guidelines for the symptomatic treatment of HD-related motor symptoms, and double-blinded controlled treatment trials are needed urgently.

Tetrabenazine:

The monoamine depletor tetrabenazine (TBZ) has been shown to effectively reduce chorea in HD and is therefore recommended by American and European guidelines. In contrast to typical or atypical neuroleptics, TBZ carries a less severe risk of developing tardive dyskinesia. In general, TBZ is well tolerated and serves as a good candidate to start medical treatment of choreatic movements even in early stages. Possible side effects include depression, parkinsonism, insomnia, akathisia, and sedation[19]. Starting with 12.5 mg per day, the dosage of TBZ can be increased weekly in 12.5-mg steps distributed three times per day. The maximum dose is discussed controversially, but usually limited to 100 mg per day. If comedication includes strong cytochrome P450 2D6 (CYP2D6) inhibitors eg, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, or other antidepressants such as, eg, bupropion, or the subject turns out to be a CYP2D6 slow metabolizer by genotyping, the maximum dose should be restricted to half, although no distinguishing features have been found in patients exhibiting various CYP2D6 activities. Notably, despite undoubtable beneficial effects on chorea, certain cognitive functions can worsen under medication with TBZ.

Neuroleptics:

If both chorea and psychiatric symptoms like agitation and psychosis are predominant features, neuroleptics, which act by blocking the dopamine transmission, could be chosen preferentially. Although atypical neuroleptics should be favored with respect to their better profile of adverse effects, typical neuroleptics such as haloperidol, fluphenazine, or chlorpromazine will have to be used if chorea is very severe or psychosis is accompanied by aggressiveness. Particular attention has to be paid if HD patients show parkinsonian-like symptoms[20]. Medication with most neuroleptics can worsen Parkinsonism. Several atypical neuroleptics have been chosen to treat chorea in HD patients. Olanzapine, risperidone, and aripiprazole have been reported to improve chorea in some small open-label studies or case series. Weight gain is a common side effect of neuroleptics but can even be of advantage for HD patients since unintended weight loss is in many cases a progressing burden in HD. Another relevant side effect is sedation. Aripiprazole is well tolerated and may also improve psychiatric symptoms. In European countries, tiapride (starting 2×50 mg, recommended maximum dose: 1000 mg/day) is widely used as a first-line medication.34 Much hope was placed in the dopamine-stabilizing agent pridopidine. Although no improvements in the modified motor-ranking scale after 6 months could be objectified, the UHDRS total motor score seemed to improve at a dose of 90 mg/day. At the moment, pridopidine is not recommended as a first-line treatment in HD-related chorea[21].

Benzodiazepines

Chorea is known to worsen in psychologically demanding situations or under stress. Therefore, low dosages of benzodiazepines can be added to the medication transitionally to cushion these emotional effects. The risk of drug abuse and dependency, however, has to be respected.

Amantadine:

The usefulness of amantadine (recommended dose: 300–400 mg/day) in the treatment of chorea is discussed controversially, since results of the present trials are not concordant. Accordingly, this N-methyl-D-aspartate (NMDA) receptor antagonist could be an option in individual patients to improve chorea[22]. In our experience, it is not recommended as a first-line medication in early symptomatic patients although its use is recommended right after tetrabenazine by the American Academy of Neurology guidelines.

Riluzole:

The initially high expectations in using riluzole for the treatment of chorea in HD have diminished since results of randomized controlled trials did not show the expected improvements. Besides, notable side effects were reported,

but restricted to high doses of 200 mg/day. In conclusion,a time- and dose-dependent positive effect of riluzole in the treatment of chorea is discussed, but no generalized recommendation can be given for the use of this drug.18 Thus, in our experience riluzole does not serve as first-line medication in the treatment of chorea in early symptomatic HD patients, although it is recommended in third position for treating chorea in HD by the American Academy of Neurology guidelines[23].

Non pharmacotherapy

Any nonpharmacological approach in treating motor symptoms in early HD faces a two-fold difficulty. Firstly, although we know that subtle motor deficits do occur, it is not known whether these deficits confer a relevant impairment in activities of daily living and, thus, should be treated. Even moderate chorea does not necessarily impair everyday functioning. Instability of gait and falls are much more predictive of relevant disability46 but whether these are actually motor-mediated (eg, chorea) or due to reduced cognition and more impulsive and aggressive behavior leading to reckless walking is not always clear. The second problem stems from the fact that, from a pathophysiological point of view, it could be expected that procedural motor learning, on which standard physiotherapy (PT) and occupational therapy (OT) typically are based, is selectively impaired in this disorder. However, from a more pragmatic point of view, there is evidence that even in basal ganglia disorders nonpharmacological treatment approaches can be a promising option, as has been shown repeatedly, eg, Tai-Chi Chuan in Parkinson's disease[24].

In HD, the most recent study focuses on gait and stability in mid-stage HD and shows small benefits by an intervention of comparatively low intensity (PT twice weekly). A randomized, controlled trial involving both group sessions and instructed home exercises over the course of 9 months showed medium to large effect sizes on chorea and gait while also improving some cognitive measures (see section, Cognitive dysfunction - nonpharmacological approaches).

Overall, it can be shown that, even in early stages of HD, nonpharmacological interventions of varying degrees of intensity can lead to substantial gains in motor function, particularly gait and balance, which need to be maintained by repeated application, however. Safety and tolerability usually are excellent and exceed that of pharmacotherapy. For a practical approach, the Huntington's Disease Physiotherapy Working Group (PWG) has put together a multilayered, treatment-based classification proposing different interventions for the different stages of HD.

Future therapeutic approaches

HD is a physically, psychologically and socially devastating neurological disorder knowing about the disease and care for patients has increased now a days. Huntington's disease is a lifelong disease for both the individual and the family. From the moment the gene was localized in 1983, and particularly after 1993, attention has focused on the pathophysiological pathway with the aim of developing a therapy. It was the first autosomal dominant disease where diagnosis became possible and it was the first trinucleotide disease to be described about CAG. Consequently, since from 1993 many researchers has shown interest on this disorder. The number of publications has increased enormously. The basic studies mainly focus on the pathophysiology and the search for biomarkers. A better understanding of the pathophysiology will surely lead to drug development to interfere in the pathological process. The second issue is the search for reliable, early to detect and clinically relevant markers for onset of the end course of the disease[25]. In parallel with the rational pathway to find solutions to treat this disorder, attention is being paid to find the best care for all the patients and at high risk persons at this point in time.

6. Conclusion

HD is a progressive age-dependent neuropathological disorder in which the immune activation is seen to be predominant in both the CNS and the periphery.Although major advances have been made in the clinical, genetic, and neuropathological understanding after the discovery of the mutation that causes HD, therapeutic options are still limited to symptomatic medication and supportive approaches. Symptoms of HD are multifaceted, including physical alterations as well as cognitive and behavioral problems, and in addition do concern the entire family and the social environment.These multiple clinical investigations are promising to identify therapies that may improve the quality of life for HD patients in future.

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