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Review Article

Huntington's Disease: An Up-to-Date

Rafaela Magalhaes Britto Pacheco de Moraes[1]*, Karina Silveira Massruhá[2] and Maria Sheila Guimarães Rocha[1]

[1]*Department of Neurology, Hospital Santa Marcelina, São Paulo, Brazil*

[2]*Faculdade Santa Marcelina Medical Student, São Paulo, Brazil*

***Corresponding Author**: Rafaela Magalhaes Britto Pacheco de Moraes, Department of Neurology, Hospital Santa Marcelina, São Paulo, Brazil.

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Abstract

Introduction: Huntington's Disease (HD) is a rare genetic neurodegenerative disorder with an autosomal dominant inheritance.

Epidemiology: Prevalence of HD has increased probably due to wider availability of the genetic test, aging populations and longer patient survival [3]. The worldwide service-based prevalence of HD is 2.71 per 100,000.

Etiology and Genetics: HD is caused by trinucleotide (cytosine-adenine-guanine [CAG]) expansion in the first exon of the huntingtin (HTT) gene. HD is defined when the number of CAG repeats is 40 or more, and the mutation is highly penetrant (repeat length). The onset of HD is between the third and fifth decade of life with an average age of 40 years old.

Pathophysiology: HD is primarily characterized by neuronal loss in the striatum and cortex. There are several other brain areas that have been included in being affected, such as the thalamus, substantia nigra, and cerebellum.

Clinical Features and Diagnosis: Motor impairment, behavioral changes and cognitive loss are the three main components affected in HD. The diagnosis consists of motor symptoms in the presence of a positive genetic test (CAG-expanded allele of the HD gene) or family history of HD.

Differential Diagnosis: For patients negative for CAG repeat expansion in HTT, the differential diagnosis consists of hereditary and acquired causes. Hereditary conditions include autosomal dominant and recessive genetic conditions, X-linked and Maternal inheritance and acquired causes are autoimmune or inflammatory, metabolic, neoplasia and cerebrovascular diseases, drugs, toxic and infections.

Biomarkers and Disease-Modifying Therapy: HD is being considered a potential good model for the development of biomarkers of direct relevance to pathogenesis.

Treatment: There is no currently available treatment that can forestall, cure, or delay disease progression. Therapy is focused on symptom management, supportive care, and the provision of reassurance to maximize function and optimize the quality of life.

Multidisciplinary management and Prognosis: HD addresses all aspects of patient care, not only from a pharmacological perspective. The three main features of HD (motor, behavioral and cognitive) are responsible for leading to disability and death, usually from an intercurrent illness about 15 - 20 years after the age of onset.

Keywords: *Huntington's Disease (HD); Cytosine-Adenine-Guanine (CAG); HD Gene*

Introduction

Huntington's Disease (HD) is a rare genetic neurodegenerative disorder with an autosomal dominant inheritance. Classically, it has an insidious onset in mid-life with a triad of signs and symptoms such as movement disorder, cognitive impairment and psychiatric features. There is a rare juvenile form, which symptoms can manifest in childhood and adolescence, presenting more severely and rapidly. Huntington's disease is a fatal condition, remains incurable and it is devastating to patients and their families.

Epidemiology

The HD mutation is found in all human populations, but the prevalence of HD differs significantly between populations of different ancestry, with the highest prevalence in populations of European descent and it was originally described in North America in families of British descent [1]. Because the majority of worldwide HD cases occur in Caucasians, European migration around the world appears to have determined overall prevalence more than any other historic factor [2].

Over the last few decades, the prevalence of HD has increased probably due to wider availability of the genetic test, aging populations and longer patient survival [3]. The worldwide service-based prevalence of HD is 2.71 per 100,000 [4]. Prevalence of 5.70 per 100,000 people in North America, Europe, and Australia, as well as 0.40 per 100,000 people in Asia [4]. Estimates of the prevalence of HD in the United States range from 4.1 - 8.4 per 100000 people. The prevalence in most European countries ranges from 1.63 - 9.95 per 100000 people, while its prevalence is less than 1 per 100000 in Finland and Japan [4]. The prevalence of HD remains understudied in many populations outside of the developed world and it is possible that other ethnic groups have comparable rates to Western Caucasians, but unrecognized owing to low ascertainment and limited research.

The onset of HD is between the third and fifth decade of life with an average age of 40 years old and a survival time of 15 up to 20 years after the onset of the clinical picture [5]. Although the range is large and varies from two years to older than 80 years, it rarely presents in patients younger than ten years or older than 70 years. The Venezuelan kindreds manifest an earlier mean age of onset (34.35) when compared with Americans (37.47) and Canadians (40.36). Environmental factors and modifying genes are thought to influence the age of onset in these populations [6].

Etiology and genetics

In 1983, the HD gene was mapped to chromosome 4. Ten years later, the gene was isolated and localized at position 4p16.3 [7]. HD is caused by trinucleotide (cytosine-adenine-guanine [CAG]) expansion in the first exon of the huntingtin (HTT) gene [7]. This mutant huntingtin protein exhibits toxic properties that cause synaptic dysfunction and neuronal death, particularly inthe striatum, deeply causing implications for information processing in corticostriatal circuits [3,8]. The length of the triplet repeat in HTT is responsible for determining whether an individual will develop the disease, and it is the most important factor in determining the age of onset of HD (inversely correlated with the length of the expansion) [6,9]. HD is defined when the number of CAG repeats is 40 or more, and the mutation is highly penetrant (repeat length) [10]. For 36 - 39 CAG repeats, it is considered an incomplete penetrance, and the individuals are categorized as carriers of HD alleles [11].

Thus, if they develop symptoms, which usually tend to associate with a late-onset clinical manifestation, the diagnosis of HD is made [3]. Those with 27 to 35 repeats are not associated with HD, but the CAG repeats are unstable, and the individual carries a risk of expansion during intergenerational transmission (repeat length) [10].

Large increases of repeat-length usually involve paternal transmission, implying predisposition to CAG repeat instability particularly during spermatogenesis [11]. This is well-known in juvenile-onset cases (HD in patients younger than 20 years), called the phenomenon

of genetic anticipation, in which the age of onset of HD tends to decrease in successive generations. The Juvenile HD represents about 5 - 10% of all affected patients and usually has a larger length of expansions. However, the CAG repeats length accounts for approximately 70% of the variance in age of onset, the remainder is influenced by substantial variability such as genetic and environmental modifying factors [12].

The typical age of onset is between 21 and 50 years. Allele lengths among this group range from 40 to 58 CAG repeats [6]. The most commonly found repeat sizes are between 40 and 50 CAG repeats, which can manifest symptoms at any age (as children, adults, or elderly) [6]. On the other hand, those with late onset become symptomatic at 51 years and have repeat lengths that extend from 40 to 45 CAGs [6].

Pathophysiology

From a neuropathological point of view, HD is primarily characterized by neuronal loss in the striatum and cortex) [13]. There are several other brain areas that have been included in being affected, such as the thalamus, substantia nigra and cerebellum. HD also seems to course with atrophy of the Hypothalamic Lateral Tuberal Nucleus [14]. However, they are all far less pronounced than those in the Caudate nucleus and the Putamen.

The basal ganglia comprise the largest subcortical system in the brain extending from the telencephalon through the midbrain. Among the many unique features of the basal ganglia is the fact that it is composed almost entirely of GABAergic neurons. The neostriatum, the largest single nucleus in the basal ganglia, not surprisingly comprises almost entirely GABAergic neurons [15]. In the striatum, GABAergic Medium-Sized Spiny neurons (MSNs) are most affected, and degeneration of these neurons occurs progressively [13].

Indirect pathway MSNs are believed to be affected earlier than direct pathway MSNs. If these neurons degenerate, a loss of input to the external Globus Pallidus (GPe) will induce an imbalance in the basal ganglia circuitry, leading to inhibition of the subthalamic nucleus, which in turn would release inhibition to the thalamus, inducing overflow of glutamate activity in the cortex and hyperkinetic movements [16].

Increased firing rates in GPe and decreased firing rates in internal Globus Pallidus (GPi) were found in an HD patient [17] which could explain why deep brain stimulation of the GPi can improve abnormal movements in some HD patients [18,19].

Clinical features

Subtle abnormalities of HD begin many years before diagnosable motor onset, and it is called the prodromal period. Patients are expected to perform poorly on neurocognitive tests nine to 15 years from diagnosis compared to a control population [20]. Deficits in this period include mild cognitive impairment (around 40%) [21] visuomotor performance, working memory [22], apathy, and irritability [23]. Abnormalities regarding oculomotor function include anti-saccade and memory-guided saccade impairment, especially in vertical saccades [24]. In addition, it is also demonstrated impaired tongue protrusion forces [25] and finger tapping tasks [26].

Table 1 summarizes the symptoms of HD. Motor and cognitive features of HD are presumably linked to cortical-basal ganglia circuits [8,9].

Motor Symptoms	Cognitive Loss	Behavioral Symptoms
Chorea: Predominantly affecting the distal extremities and facial muscles in early disease stage	Decrease of attention	Depression
Recurrent falls	Decreased initiation	Anxiety
Deficits in postural control	Decreased emotional recognition	Lack of affect

Poor dynamic balance, mobility and motor performance	Decreased mental flexibility	Irritability
Dystonia: As the disease progresses, it becomes more prominent	Decreased planning capacity	Apathy
Akinetic-Rigidity: As the disease progresses, there is more rigidity accompanied by minimal chorea; Juvenile Huntington also courses with early rigidity;	Decreased visuospatial function	Psychosis and aggression
Dysarthria: As the disease progresses	Decreased learning and retrieval of new information	Suicidal ideations and attempts
Dysphagia: At advanced stage disease	Impulsivity and disinhibition	Anosognosia: Lack of awareness

Table 1: *Main clinical features.*

Motor disorder

Involuntary movement disorder

In adult patients with HD, chorea is the most common and usually one of the first symptoms, which gives HD its characteristic clinical appearance [3]. Chorea is characterized by abrupt, brief, and non-stereotyped movements, predominantly affecting distal extremities and facial muscles [27]. In early disease, hypotonia with hyperreflexia is notable as well. During disease progression, chorea generally becomes more florid and widespread, affecting diaphragm, pharynx and larynx, producing dysarthria, dysphagia, involuntary vocalizations, and interfering with movement [28]. In the end-stage of the disease, chorea decreases, and a parkinsonian akinetic-rigid state and dystonia predominate with contractures and immobility [29]. Dystonia, an involuntary movement disorder, is characterized by prolonged, sustained and abnormal postures.

Impairment of voluntary movements

Akinetic-rigid parkinsonism and incoordination are the second component of HD's motor disorder and the most prominent in juvenile patients [3,9]. As said before, this impairment happens in adults in end-stage disease. This major component progresses more steadily, and it is more correlated to functional disability than chorea [30].

In addition, other motor manifestations include ideomotor apraxia, difficulties with motor persistence (inability to sustain simple voluntary acts such as sustained tongue protrusion), and gait disorders such as slower stepping response times, poorer dynamic balance and recurrent falls [29,31]. Abnormal eye movements include delay in the initiation of volitional saccades and reduced saccade velocity at the beginning of the disease, which is characterized by the absence of saccadic movement with preservation of smooth pursuit. In more advanced stages, voluntary saccades, and refixation are impaired [32].

The Unified Huntington's Disease Rating Scale (UHDRS) is currently the scale widely used for the motor features of HD. This clinical and research tool includes motor, cognitive, behavioral, emotional, and functional components such as eye movements, speech, chorea, dystonia, rapid alternating movements, bradykinesia, and gait.

Cognitive loss

The features of cognitive disability in Huntington disease are similar to vascular dementia and Parkinson's disease due to striatal-subcortical brain pathology, which differs from Alzheimer's disease [32]. Differently from Alzheimer's disease, the anamnestic subtype is more common than the amnestic subtype in HD [29].

Cognitive impairments appear to emerge years before the diagnosis of HD and it has a progressive progression. Cognitive characteristics in HD include cognitive slowing, a decrease of attention, initiation, emotion recognition, mental flexibility, planning, visuospatial functions, learning and retrieval of new information, lack of awareness of deficits, impulsivity, and disinhibition [3,20,33,34]. Speech can be disrupted in HD can be disrupted, but the language is relatively preserved [35].

Behavioural

The neuropsychiatric symptoms are a common manifestation of HD and can be present at early onset. The symptoms are gradually progressive and cause substantial disability in later stages. In early-stage disease, the patient usually presents with executive dysfunction, and the most common symptoms are depression, anxiety, lack of affect, irritability and apathy [23,36]. The progression of the disease may include some severe psychiatric problems, the European Huntington's Disease Network suggested that around 20% of the cases present delusional depression, psychosis, aggression, suicidal ideation and attempts [3,37].

HD can course with anosognosia, a hard feature for the family members and the professionals to deal with. It was first described by Joseph Babinski in 1914, referring to the unconsciousness of hemiplegia. It is characterized when the patient's perception of an obvious disease manifestation differs from that of other objective observers as an example, the patient is constantly presenting choreic movements in his left arm, but he doesn't recognize it, so he keeps using it to hold things as he would normally do.

HD patients normally are unaware of their motor symptoms, cognitive deficits, and behavioral disorders [38]. This implicates riskier acts that lead to negative consequences for the patient and family. Considering the fact that HD has its pathophysiology resumed in the compromise of the cortical afferents to the basal ganglia and related frontal-striatal loops, it is possible that part of the knowledge in HD patients are not psychologically motivated, but organic and directly neurological [39].

Loss of awareness is related to disease severity in terms of CAG repeats, motor and cognitive impairment, and functional decline (awareness). Unfortunately, it's still underdiagnosed despite its importance directly reflecting on the adherence to rehabilitation and to seek clinical care.

Furthermore, we list non classical features that can also be seen in HD:

- Circadian rhythm disturbances
- Weight loss
- Vomiting
- Constipation
- Epilepsy (rare)

Diagnosis

The diagnosis consists of the development of unequivocal signs of motor symptoms in the presence of a positive genetic test (CAG-expanded allele of the HD gene) or family history of HD [9,41] (Table 2).

Diagnosis	
Huntington's disease	Typical clinical features + Positive genetic test Or Family history

Table 2: *Diagnosis of HD.*

The extrapyramidal movement disorder is measured by the UHDRS scale. A total score of roughly 15 is strongly supportive of the diagnosis [3].

Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) can support the diagnosis if there is a characteristic image and in the absence of other substantial changes of a patient with positive family history/genetic test [3]. Besides that, those exams are important to rule out other conditions.

The typical image of HD is asymmetrical atrophy predominating in the caudate-putamen, and often, to a lesser extent, cerebral cortex and other subcortical white matter [25,42]. Those alterations can be demonstrated using advanced imaging techniques in pre-symptomatic patients [23,43]. In advanced HD cases, brain weight may be reduced by 25 - 30% [42].

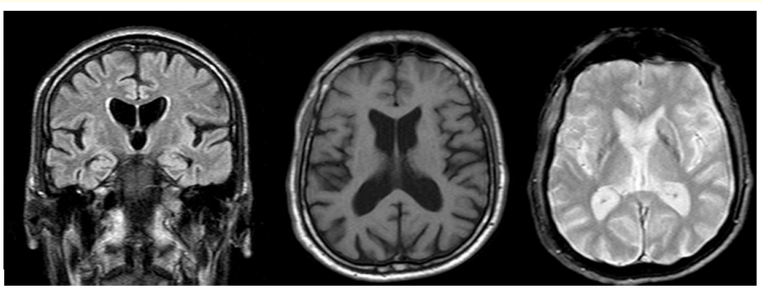

Figure: A- *Hippocampal and global atrophy; B- T1 Caudate atrophy; C- FFE iron accumulation in the Pallidus.*

Differential diagnosis

For patients negative for CAG repeat expansion in HTT, the differential diagnosis consists of hereditary and acquired causes. Hereditary conditions include autosomal dominant and recessive genetic conditions, X-linked and Maternal inheritance, and acquired causes are autoimmune or inflammatory, metabolic, neoplasia and cerebrovascular diseases, drugs, toxic and infections (Table 3) [44].

Neuroimaging such as brain MRI plays an important role to identify other aetiologies.

Hereditary causes of chorea	Acquired causes of chorea
Autosomal dominant: • Huntington's disease • Huntington's disease like type 1 and 2 • Benign hereditary chorea • Fahr's disease • Neuroferritinopathy • Spinocerebellar ataxia types 1, 2, 3 and 17 • Paroxysmal nonkinesigenic dyskinesia • Paroxysmal kinesigenic choreoathetosis	**Autoimmune or inflammatory:** • Antiphospholipid syndrome • Behçet disease • Celiac disease • Hashimoto encephalopathy • Polyarteritis nodosa • Primary angiitis of central nervous system • Sarcoidosis • Sjogren syndrome • Sydenham chorea • Systemic lupus erythematosus
Autosomal recessive: • Ataxia-telangiectasia • Choreo-acanthocytosis • Friedreich ataxia • Huntington disease like 3 • Neuronal ceroid lipofuscinosis • Porphyria • Wilson's disease	**Metabolic or endocrine:** • Hepatic failure • Hyperthyroidism • Hypoparathyroidism • Eletrolic disturbies (calcium, sodium magnesium) • Polycythemia vera • Pregnancy-induced (chorea gravidarum) • Pseudohypoparathyroidism • Renal failure • Vitamin deficiency (B1, B12, niacin)
X-linked: • McLeod syndrome • Lesch-Nyhan disease	**Cerebrovascular:** • Arteriovenous malformation • Intracerebral hemorrhage and Subarachnoid hemorrhage • Ischemic stroke • Moyamoya disease • Postpump chorea

Maternal inheritance:	Infection:
• Mitochondrial disorders	• AIDS-related • Creutzfeldt-Jakob disease • Diphtheria • Encephalitis • Lyme disease • Malaria • Meningitis • Neurocysticercosis • Neurosyphilis • Progressive multifocal leukoencephalopathy • Tuberculous meningitis

Table 3: *Differential diagnosis of HD.*

Also, there are other possible causes of acquired chorea, including neoplasias involving the basal ganglia and paraneoplastic syndromes and toxic causes that can lead to chorea, like alcohol intoxication or withdrawal or other elements intoxications (manganese, mercury, thallium, and toluene) [44].

As a very important differential to be considered, there is a large list of drugs that can cause chorea for several mechanisms, as you can see in table 4.

• Dopaminergic drugs (COMT inhibitors with levodopa, dopamine agonists, levodopa)
• Dopamine blocking agents (amantadine, anticholinergics, atypical neuroleptics, typical neuroleptics)
• Dopamine depleting agents (tetrabenazine, reserpine)
• Anticonvulsants (carbamazepine, gabapentin, lamotrigine, valproic acid)
• Calcium channel blockers (verapamil, flunarizine)
• Central nervous system stimulants (Amphetamines, cocaine)
• Others: baclofen, benzodiazepines, digoxin, cyclosporin, lithium, opioids, isoniazid, levofloxacin, sympathomimetics, tricyclic antidepressants

Table 4: *Drug induced chorea.*

Biomarkers and disease-modifying therapy

Considering HD is caused by a single gene mutation and has increasingly well-studied pathogenesis, it is potentially a good model for the development of biomarkers of direct relevance to pathogenesis [9].

Currently, the Unified Huntington's Disease Rating Scale is a worldwide used instrument for the HD patient follow up, as it scores every singular component of the clinical features providing a better understanding of the disease progression. However, it may not be sensitive enough to present with relevant changes in the early stages of the disease, compromising the identification of the correct time to intervene. Quantitative clinical biomarker assessments such as tongue force variability, metronome-guided tapping, grip force, and oculomotor assessments, and cognitive tests, are being developed. As an increasingly important topic in HD, it's necessary to identify these biomarkers which are capable of detecting subtle changes of disease progression in order to accurately assess the effectiveness of disease-modifying therapies [29].

There are several rational targets for therapeutic development being studied based on the pathobiology of HD, as it is being unraveled, offering targets for treatments. Novel agents are part of clinical trials supported by an array of biomarkers which target positive outcomes involving gene silencing and huntingtin lowering agents aimed at diminishing the production of the mutant protein [3]. HD is emerging as a model for strategies to develop therapeutic interventions, not only to slow progression of manifest disease but also to delay, or ideally prevent, its onset. However, up to now, there is no drug proven efficacy regarding disease- modifying treatment.

The pronounced alterations that occur with the disease stage in the corticostriatal circuit of HD mouse models suggest that therapeutic strategies in human HD must be targeted to different molecular mechanisms in prodromal, early, and late HD [45].

Treatment

Up to this moment, there is no currently available treatment that can forestall, cure, or delay disease progression. Thus, therapy is focused on symptom management, supportive care, and the provision of reassurance to maximize function and optimize the quality of life. Most of the symptomatic treatment is derived from anecdotal clinical experience [46]. The movement disorder is treated if the patient presents disability secondary to it, for example, for chorea, treatment is indicated only if it is prominent and interferes with function, causes pain, injury, falls, poor sleep, and weight loss [47].

The unique medication licensed by the US Food and Drug Administration (FDS) for treat HD is tetrabenazine, which also helps to treat dystonia [29,49]. Some experts prefer antipsychotic drugs to treat chorea, and others occasionally try other agents as amantadine, benzodiazepines, and baclofen, which have a questionable efficacy (HD review 2012/Oxford). The antipsychotic drug widely used is olanzapine, which can be even more helpful because of its side effects such as sedation to calm down the mood swings and improve sleep quality and increase of appetite to provide weight gain.

The psychiatric and cognitive features of HD generally are treated with standard therapies; however, the last group of clinical features does not show many benefits with the drugs. Depression can be treated with antidepressants; however, the preference is citalopram due to its anxiolytic properties [49].

In table 5, the treatment is summarized according to clinical features.

Symptom	Drug	Dose	Main side effects
Chorea	Tetrabenazine	12.5 - 200 mg/day	Sedation, depression
	Olanzapine	2.5 - 20 mg	Sedation, tardive dyskinesia, parkinsonism, neuroleptic malignant syndrome, raised triglycerides, weight gain
	Amantadine	100 - 300 mg	Sedation, drowsiness, gastrointestinal disturbances, hallucination, swollen ankles, confusion, livedo reticularis, nightmares
Dystonia	Clonazepam	0.5 - 5 mg	Daytime sedation, increased risk of falls, cognitive impairment, drowsiness, confusion
	Tetrabenazine	12,5 - 200 mg/day	As in "Chorea" above
	Baclofen	10 - 30 mg	Sedation, drowsiness, gastrointestinal disturbances, confusion, hypotension
Akinetic-rigid parkinsonism	Levodopa	100 - 1200 mg	Dyskinesias, gastrointestinal disturbance, postural hypotension, insomnia, agitation, increased chorea, psychiatric symptoms
Spasticity	Baclofen Tizanidine	10 - 30 mg 2 - 24 mg	Sedation, drowsiness, gastrointestinal disturbances, confusion, hypotension
Bruxism, dystonia	Botulinum toxin	6 - 12 mg/day	Muscle weakness

Table 5: *Symptomatic drug treatment for motor symptoms.*

Symptom	Drug	Dose	Side effects
Psychosis, irritability	Olanzapine	2.5 - 20 mg	For all atypical neuroleptic: • Sedation, drowsiness • Tardive dyskinesia • Parkinsonism • Neuroleptic malignant syndrome • Raised triglycerides • Weight gain. • Gastrointestinal disturbance As typical neuroleptic, can cause more sedation, more parkinsonism, dystonia, akathisia, hypotension, constipation, dry mouth, weight gain, tardive dyskinesia, higher risk of neuroleptic malignant syndrome than atypical neuroleptics
	Quetiapine	25 - 100 mg/day	
	Tiapride	50 - 1000 mg/day (used for hyperkinesia and gait disturbance as well	
	Risperidone	1 mg - 6 mg /day (can decrease chorea as well)	
	Haloperidol	5 - 20 mg/day (can decrease chorea as well)	
Treatment-resistant psychosis	Clozapine	12.5 - 300 mg/day	As for other atypical neuroleptic, plus agranulocytosis, myocarditis, and cardiomyopathy
Psychosis with prominent negative symptoms	Aripiprazole		As for other atypical neuroleptic, plus akathisia, blurred vision
Depression/anxiety	Citalopram	20 - 40 mg/day	As a selective serotonin reuptake inhibitor (SSRI): - Gastrointestinal disturbance - Drowsiness, fatigue - Reduce libido and ability to obtain or keep an erection - Weight gain - Syndrome of inappropriate antidiuresis - Postural hypotension - Risk of suicide As SSRI, plus sleep disturbances As for SSRI, plus raised cholesterol as for SSRI Weight gain, edema, sedation, headache, dizziness, tremor. Useful for sedation when insomnia is a problem gastrointestinal disturbance, weight gain, drowsiness, insomnia, hypertension, agitation, syndrome of inappropriate antidiuresis, palpitations
	Fluoxetine	20 - 40 mg/day	
	Paroxetine	12,5 - 37,5 mg/day	
	Sertraline	50 - 150 mg/day	
	Mirtazapine	15 to 45 mg/day	
	Venlafaxine	37,5 - 150 mg/day	
Mood instability	Lithium (especially for mania or hypomania)	300 - 1200 mg/day (narrow therapeutic window)	Renal insufficiency, delirium, hypothyroidism, tremor gastrointestinal disturbance, tremor, fatigue, sedation, confusion, dizziness, weight gain, blood dyscrasia, hyperammonemia, liver dysfunction, hair loss
	Sodium Valproate	500 - 1000 mg/day 200 - 1600 mg/day	Gastrointestinal disturbance, hypersensitivity reactions, drowsiness, ataxia, blood dyscrasia, liver dysfunction, hyponatremia, dizziness
	Carbamazepine		

Table 6: *Symptomatic drug treatment for behavioral symptoms*

Symptom	Drug	Dose	Side effects
Cognitive impairment	Donepezil	5 - 10 mg/day	Bradycardia, insomnia, fatigue, headache, myalgia, diarrhea, anorexia, nausea, abdominal pain
	Rivastigmine	6 - 12 mg/day	Gastrointestinal disturbances, hyperhidrosis, fatigue, weight loss, confusion, somnolence, nightmares, tremors
	Memantine	5 - 20 mg/day	Gastrointestinal disturbances, somnolence, hypertension, drowsiness, headache

Table 7: *Symptomatic drug treatment for cognitive symptoms.*

Symptom	Drug	Dose	Side effects
Circadian rhythm disturbances (Insomnia)	Zopiclone	3.75 - 7.5 mg/day	Drowsiness, confusion, memory disturbance, gastrointestinal disturbance
	Zolpidem	5 - 10 mg/day	
Constipation	Standard laxatives		Gastrointestinal disturbance, dehydration
Bladder instability	Oxybutynin	2,5 - 10 mg/day	Gastrointestinal disturbances

Table 8: *Symptomatic drug treatment for other symptoms of HD.*

Multidisciplinary management

As HD is a neurodegenerative disease with a dominant genetic component that leads to death, after all, specific topics are inevitably questioned by the family. Questions about what could be done in advance and if their heirs will also suffer from the disease trigger parents, siblings, partners, and children. At this point, patient education rises as an increasingly important issue allied to multidisciplinary management. The question of whether patients and/or family members should be made aware of the genetic risks and at which point of their lives, they should be taking the genetic tests. The ideal point is being counseled by a geneticist at the time there is comprehensive enough of the consequences of the hereditary component. Not only the patient with HD should be managed in a multidisciplinary clinic, but also the whole family needs to be supported.

The multidisciplinary management addresses all aspects of patient care, not only from a pharmacological perspective. Besides Neurologist, Neuropsychologist, Neuropsychiatrist, Psychologist and Clinical geneticist/Genetics counselor for diagnosis and management, a multidisciplinary team of health professionals and supportive caregivers address the broad physical and psychological needs of patients and families and manages issues through long- term follow-up [49,50] (Figure 1).

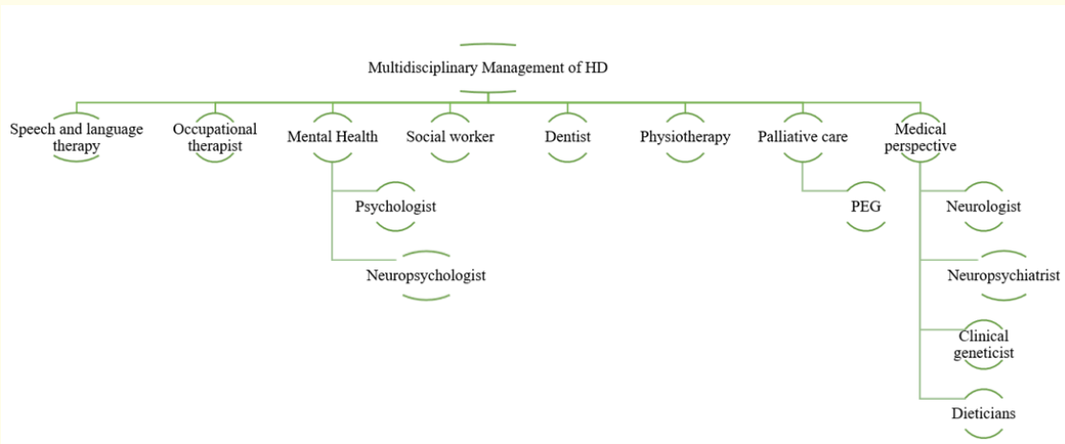

Figure: 1: *Multidisciplinary management of HD.*

Speech and language therapy should be provided in advance to guarantee a better quality of life and avoid choking and aspiration (dysphagia assessment and counseling). In addition, dieticians enabling adequate nutrition from a calorific perspective to prevent malnutrition and its harmful effects, furthermore, to avoid. Physiotherapy for being able to keep with daily activities as long as it is possible and to provide some rehabilitation, exercise program, assistive equipment, and especially for gait problems, which is potentialized if allied to occupational therapy. Occupational therapist for home safety and adaptive equipment. Social workers should maximize the patient's independence and safety, disability counseling, besides guiding the family through the social factors that may arise, financial and life planning counseling. Dentist to ensure appropriate dental care. Advanced directives focus on relieving suffering and supporting the best possible quality of life for patients and their families. The principles of palliative care are appropriate throughout the disease progression and it is an ongoing process in which patient's goals, values, and beliefs are discussed between them, their family and health care providers. Percutaneous endoscopic gastrostomy (PEG) feeding should be discussed in advance so the patient and the family calmly understand what could be done in long term conditions to optimize the quality of life and prevent weight loss, recurrent chest infections, or inadequate caloric input.

Prognosis and quality of life

HD is a rare neurodegenerative disorder characterized by motor, behavioral, and cognitive manifestations. These three main features are responsible for leading to disability and death, usually from an intercurrent illness about 15 - 20 years after the age of onset [6]. Unfortunately, there is currently no treatment to slow the progression of the disease.

The nonmotor aspects of HD (cognitive and emotional features) can be more highly associate with a functional disability than motor impairment, especially if the patient is unaware of his deficits, which increases the risk of institutionalization [51]. Regarding motor impairment, it predicts functional disability better than chorea does [30].

HD has a huge impact on the individual's quality of life due to the lifelong influence of the disease, unawareness, dementia, and physical disability. The impact starts with the beginning of the symptoms and lasts because of the awareness of the genetic risk of the family and certain future disability. HD symptoms are responsible for social disengagement, low conversational participation, and slowed mentation [52].

Anosognosia is another adverse point that implicates in prognosis and quality of life. Once the patient presents with anosognosia, it can compromise the management treatment because the patient doesn't realize the actual need for it as he doesn't recognize the deficit he has. It is one more obstacle to guide the correct treatment or to provide quality of life.

HD seriously affects the patient's daily and economic activities, social interaction, communication, family dynamic, career, autonomy, functional competence, dignity, nutrition, safety, comfort, marriage and reproductive decisions.

Although the CAG repeat number contributes the most to determine the age at onset, it is not recommended to make prognostic statements based on it [12].

Conclusion

HD is a rare genetic neurodegenerative disorder with an autosomal dominant inheritance that unfortunately, has no treatment until now to slow down, delay or stop the disease, leading to death in 15 to 20 years after onset. However, it is being considered potentially a good model for the development of biomarkers of direct relevance to pathogenesis, expecting positive findings in the next few decades. The symptomatic treatment is considered efficacious in helping to provide best quality of life to the patient and caregivers, mainly when allied to the multidisciplinary management. To sum up, it is extremally important for the neurologists not to forget about the genetic counseling in order to diminish the consequences of the hereditary inheritance to the patient and family.

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