

Current knowledge and future directions in Huntington's disease

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Abstract

Huntington's disease (HD) is an inherited neurodegenerative disorder due to abnormal CAG triplet repeats in the IT-15 gene. It is characterized by a triad of progressive motor, psychiatric and cognitive symptoms resulting from striatal neuronal loss. HD is most prevalent in Western countries, and a particularly high prevalence in Latin America has been reported. In this article, we present a state-of-the-art review of HD, including the identification of different polymorphic markers in the genes coding for UCHL1, HIP1, PGC1 α , GRIK2, TBP, BDNF, and ZDHHC17, which could be associated with the age at onset of motor signs in the presence of abnormal CAG repeats.

Despite significant advances in our understanding of the disease, there are still gaps in the comprehension of its pathophysiology, and there is no effective therapeutic target to prevent the clinical onset of the disease or delay its progression. Current pharmacological management is palliative, and the evidence to generalize surgical approaches such as pallidotomy is insufficient. Recently, different therapies that target neurodegeneration and the synthesis of mutant Huntingtin (mHtt) have shown promise, as well as fetal neural cell transplantation into the striatum, which is offered as a surgical option providing hope for the development of a true disease-modifying treatment that allows the recovery of motor and cognitive functions through anatomical and functional integration of grafted neurons.

This narrative review aims to provide an approach to HD's most relevant aspects, from its pathogenesis and associated genetic polymorphisms to current treatment options.

Keywords: Age at onset; Huntington disease; Htt protein; Polymorphism.

Introduction

Huntington's disease (HD) is an autosomal dominant disorder due to an abnormal repetition of the CAG triplet, which triggers the mutation of the protein called Huntingtin (Htt).¹ Htt predominates in the cytoplasm, although some N-terminal fragments are located within the nucleus. Nuclear localization of the mutant huntingtin (mHtt) is even higher, therefore, alterations in the transcription of genes could be associated with toxicity.² Htt gene (IT-15), located in the short arm of chromosome 4 (4p16.3), presents an expansion of CAG near the 5' end in exon 1, which codes for glutamine (Gln or Q).

In HD, the presence of a long tail of polyglutamine (poly Q) was reported from residue 17.³ Migliore et al. reported that the normal length of the CAG repeats is below 35 triplets; more than 36 triplets are associated with the appearance of HD. However, the presence of an intermediate length allele (36-39) would be sufficient to cause HD only in older ages.⁴

The abnormal CAG repetition in the IT-15 gene is the triggering factor of neurodegeneration and cerebral dysfunction in HD,⁵ and is the most significant risk factor for its progression,



especially in the deterioration of the motor and cognitive symptoms. Further to this point, Chao et al.⁶ identified two other risk factors in HD: the instability of the triplet and genetic modifiers. Several studies show that the age of onset (AO) in HD is different among families and individuals that have identical CAG tails length. Reported CAG repetitions vary from 40 to 100 units, and AO is usually between 20 and 50 years.² The coexistence of genetic and environmental modifiers would contribute to these differences in the population.⁴

Global health impact of HD

Despite the great advances in the understanding of the disease, from its discovery to the present-day (Table 1), a lot of questions remain regarding its pathophysiology; there is no curative treatment and current symptomatic management continues to be a challenge. HD is more prevalent in Western countries: a prevalence of 10-15/100,000 inhabitants was reported both in Caucasians and people of European descent, with 12/100,000

and 6.4/100,000 for England and Ireland, respectively.⁷ In 2015, approximately 30,000 people in the United States and Canada were diagnosed with HD, and 150,000 were at risk of developing the disease. Contrarily, Japan presents the lowest prevalence, followed by South Africa and Finland.⁸

Scarce publications in Latin America exhibit a remarkable high prevalence; the most cases of HD were reported in 2015 in Maracaibo, Venezuela (700 cases/100,000 inhabitants)⁸ and Mexico City (4/100,000).⁹ By 1975, the population with the second-highest HD prevalence in the world was Cañete, Peru, with 40/100,000,¹⁰ and, despite there being few scientific publications in Colombia supporting statistical data regarding the real prevalence of HD, in 2011 some reports estimated it at 250/100,000, with a total of approximately 4,566 affected,¹¹ which could mean that Juan de Acosta, Colombia, is one of the populations with the highest density of cases of HD on a global scale.¹²

Table 1. Timeline of main contributions to HD research from discovery to the present day

Year	Reference	Contribution
1872	(73)	HD is a disease of the nervous system, characterized by involuntary movements of the muscles, affecting the upper and lower limbs.
1995	(32)	Alleles of different bp were identified in the CCG trinucleotide sequence; 176bp allele is the most prevalent in HD.
2000	(74)	The abnormal expression of polyQ in the N-terminal of the Htt is shown to be associated with neuropathological and behavioral deficits and the progression of HD.
2001	(75)	Huntingtin has 35 fragments of Glutamine at its N-terminal, when it mutates can present more than 38 fragments in aggregates that carry neuronal death by apoptosis.
2002	(76)	A heterogeneous decrease in the cortical tape is located in patients with HD. This decrease was present in patients in different clinical stages, and they seem to come from cortical regions posterior to previous ones.
2003	(77)	The main characteristics of HD are motor, psychiatric and cognitive alterations. As the disease progresses, a variety of visual, attention, concentration, language, and memory disorders occur.
2004	(78)	The use of the drug olanzapine in HD is proposed for the reduction of motor and psychiatric symptoms.
2005	(79)	The number of CAG repeats in people with HD and their relatives is shown by a molecular diagnosis through the use of polymerase reaction (PCR) and electrophoresis on agarose gels and polyacrylamide to provide genetic counseling on one chain.
2006	(30)	It was identified that in addition to the CAG repeat in HD, there is a polymorphic CCG repeat that can interfere with PCR-based diagnostics.
2007	(80)	Psychiatric manifestations such as depression, mania, psychotic disorders, insomnia, and sexual disorders are part of HD because of the problems that arise from cortical neuropathological changes.
2008	(47)	Some patients with HD are associated with OCD. It is suggested the association with a disability at the level of the caudal ventromedial nucleus and related neural circuits. Additional tests are needed to determine the neurobiological mechanisms of these disorders. Although some medications have been associated with specific symptoms, no specific treatment strategy has been developed.
2009	(81)	A glycolytic decrease in the striatum was identified through a PET-FDG in patients with HD who present motor symptoms and advanced cognitive deterioration related to dementia.
2010	(13)	The pathophysiology of HD is characterized by a degeneration of the caudate nucleus and cell loss in the globus pallidus, subthalamic nucleus, nucleus accumbens, cerebellum, and part of the cortex, where pyramidal neurons of layers III, V, and VI degenerate.
2012	(82)	It is shown that the transient infusion of ASO (antisense oligonucleotides) in the cerebrospinal fluid delays the progression of the disease in mice with HD.
2013	(83)	It explores the synaptic evidence, axonal dysfunction, and neuritic dystrophy that come from neuronal death in patients with HD.
2014	(84)	It is suggested the use of medications (tetrabenazine, olanzapine, and aripiprazole) for reducing the production of dopamine.
2015	(85)	It proposes new therapies to treat HD, such as neural transplantation of fetal tissue, RNAi (RNA interference), and Tgasei (transglutaminase inhibitors).
2016	(86)	It was found that vascular diseases are indirectly related to HD due to factors that influence the sympathetic hyperfunction of ANS.
2017	(87)	It was demonstrated that delayed condition and reduction of somatosensory evoked potentials are not related to delayed conscious perception of sensory stimulus.
	(6)	It was identified that maternal and paternal transmission may lead to expansions or contractions of CAG repeats, but there is a higher prevalence on the paternal side due to larger expansions.
	(69)	It describes the methods of obtaining neural stem cells (NSC) for the treatment of HD through transplantation and the differentiation of medium GABAergic spiny neurons.
2018	(88)	It was identified that the effect of HD is greater on the left hemisphere due to striatal atrophy.
	(65).	It was identified that ASO IONIS-HTRx was able to decrease levels of abnormal Htt protein and also was associated with good dose tolerance without relevant adverse effects.
2019	(30).	
		It was identified that the FOXP2 gene mutation is associated with morphological and functional abnormalities in both cerebral hemispheres, involving the core nuclei.
2020	(60)	It was identified in a 26-week phase II clinical trial that PBT2 improves cognition in HD patients.

The lack of scientific research on Latin American populations is possibly related to social neglect and misinformation among the inhabitants due to the limited availability of HD studies. Government intervention in the treatment of HD patients in these populations would help to develop new studies aimed at better understanding the underlying mechanisms of the disease, the expression of local polymorphisms, and the identification of potential therapeutic targets.

HD pathogenesis

HD is characterized by a degeneration of the caudate nucleus, with cellular loss involving the globus pallidus, subthalamic nucleus (STN), nucleus accumbens, cerebellum, and pyramidal neurons in layers III, V, and VI of the cerebral cortex.¹³ As illustrated in **Figure 1**, medium spiny neurons (MSNs), which make up 95% of total striatal neurons, are more likely to neurodegeneration¹⁴ and they exert a GABAergic inhibitory function on the nuclei of the thalamus, inhibiting movement

as a consequence of the inability to excite the motor cortex.¹⁵ Once the striatum receives glutamatergic, dopaminergic, and serotonergic afferent, it sends efferent through two control paths, a direct inhibitory (striatonigral) and the direct excitatory (striatopallidal). The alteration in the activation of both circuits would lead to the appearance of bradykinesia or hyperkinesia.¹⁶

Alterations at the STN lead to a decrease in the activity of the internal globus pallidus/substantia nigra pars reticulata complex (GPi/SNpr). The striatal degenerative process begins in the subpopulation of GABA-enkephalinergic neurons, leading to the dysfunction of the indirect circuit and subsequent inhibition of the STN by the external globus pallidus (GPe). By decreasing the excitatory effect of the STN on the GPi/SNpr complex, its inhibitory effect on the thalamus decreases, which raises the Thalamo-cortical activity, and produces the appearance of the involuntary movements that are characteristic of HD¹⁷ (**Figure 1**).

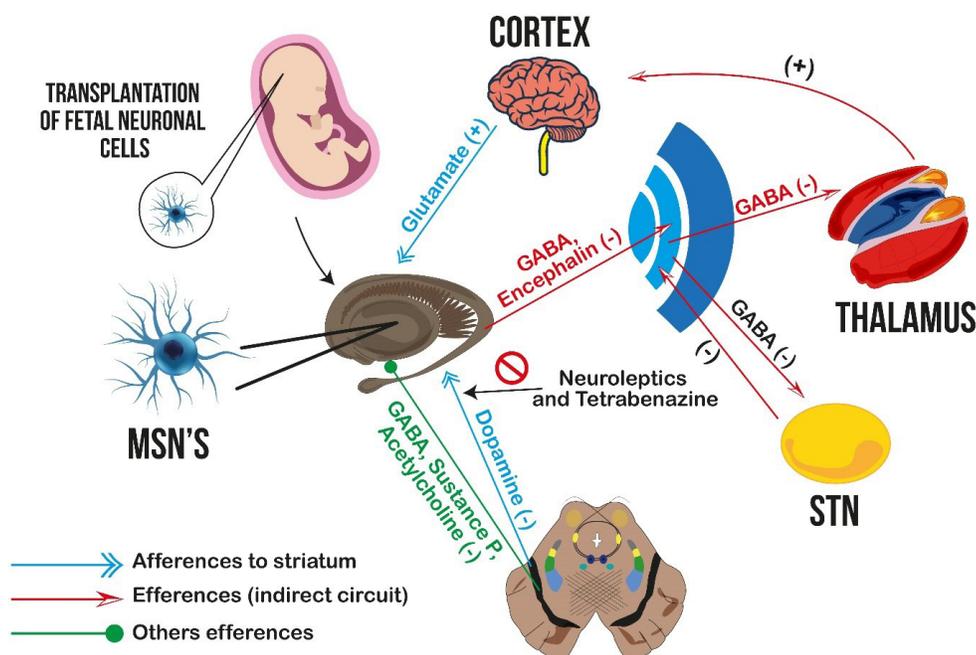


Figure 1. Pathophysiological changes and possible future therapeutic targets in HD. In HD, there is an alteration of the indirect basal ganglia circuit, with degeneration of the medium spiny neurons (MSN) of the striatum, which normally sends GABAergic and enkephalinergic inhibitory signals to the external globus pallidus (GPe). The slightly inhibited GPe increases its inhibitory signals towards the subthalamic nucleus (STN), which then enhances its inhibitory signals towards the internal globus pallidus (GPi). As a consequence, the GPi reduces its inhibition signals towards the thalamus, which in turn results in the increase of excitatory signals to the cortex. This mechanism explains hyperkinesia and the choreic movements present in HD. The current therapeutic targets in the management of HD include the blockade of the dopamine receptors through the neuroleptics, and the inhibition of the transport of vesicular monoamines 2 (VMAT2) through tetrabenazine, in order to decrease the production of dopamine, serotonin, and noradrenaline. The transplantation of fetal neuronal cells will constitute an option for surgical treatment in the future.

Polymorphic association in HD

Multiple research has been focused on another association: the inverse relationship between the number of repetitions of the CAG triplet and the AO.¹⁸ It is expected that the greater the number of repetitions of this sequence in the patient, the motor symptoms appear will appear at a younger age. The length of the CAG repeat varies among individuals because of its transmission instability; in men, the instability of the triplet prevails, so there is an increase in the length of the repetition when the mutation is transmitted by the father, which causes individuals to present HD at an earlier age.¹⁹

In addition to the CAG repeats, it has been suggested that environmental factors would determine an important role in the AO of HD. Tanaka et al. identified that after oral supplementation with 2% trehalose, a disaccharide found in different foods, a protective effect was observed in murine models, reducing brain atrophy and ventricular dilation ($p=0.008$).²⁰

Similarly, a delayed onset of motor symptoms was reported when transgenic R6/1 HD mice were exposed to an enriched

environment, involving exposure to novel objects of different shapes, sizes, textures, and compositions.²¹ In humans, although these remain largely unidentified, there is emerging preclinical and clinical evidence for physical and cognitive activity, stress, and diet could act as potential modulators of HD onset and progression. In this regard, an association has been found between a passive lifestyle and an earlier onset of 4.6 years.²²

On the other hand, short-term improvements have been observed with combined physical, cognitive, and occupational rehabilitation, including a variety of activities such as exercise programs and playing coordination-based video games. There is not enough evidence to associate clinical evolution to head traumas, hospitalizations, adherence to the Mediterranean diet, Coenzyme Q10 supplementation, and alcohol intake, nevertheless, some dietary factors such as milk intake and coffee (2 cups/day) have been associated with earlier onset.²² Regarding main risk factors, different polymorphisms have been identified in exonic and non-coding regions (**Table 2**), which, associated with mHtt expression, generate a deleterious effect on the disease (**Figure 2**).

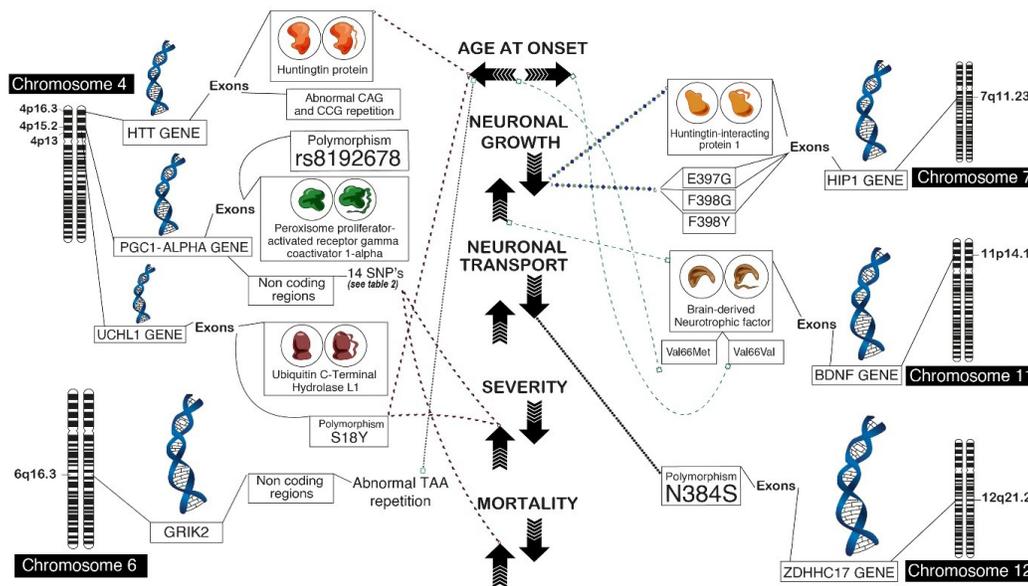


Figure 2. Association between polymorphisms identified to date and the main clinical features in the progression of HD. 4p 16.3 (HTT): CAG (exon 1) and CCG (codon 2642) repetitions, associated with delay in AO. 4p 15.2 (PGC1-ALPHA): rs2970865, rs2970866, rs4383605, rs2946386, rs2970869, rs17576121, rs2970870, rs7695542, rs2970873, rs2946385, rs12374310, rs7665116, rs2970855, rs2970848 and rs8192678, in coding and non-coding regions, associated with increased severity of symptoms and mortality. 4p13 (UCHL1): rs5030732 (S18Y), in exon 3, which has been associated with delay in AO and greater severity of symptoms. 6q 16.3 (GRIK2): TAA repetitions, associated with delay in the AO. 7q 11.23 (HIP1): Polymorphisms associated with neuronal death. 11p 14.1 (BDNF): rs6265 (exon 2), with two phenotypic variants associated with delay (Val66Met) and increase (Val66Val) of AO. 12q 21.2 (ZDHHC17): N384S in exon 11, which is associated with decreased neuronal transport.

Table 2. Genes and polymorphic variants associated with HD

	Identified Polymorphisms	Type	Chromosome	Gene / Region	Effect
(23) (25)	rs5030732	SNP	4	UCHL1 / Exon 3	— Phenotype with a serine replacement by tyrosine in position 18 of the protein (ser18Tyr) — Reduces the age at onset
(23)	E397G F398G F398Y	SNP	7	HIP1 / Exonic	— Neuronal death
	N384S		12	ZDHC17 / Exon 11	— Alteration of neuronal transport
	V66M rs6265		11	BDNF / Position 196 of exon 2	— Alteration of neuronal transport and BDNF protein production
(26)	rs2970865	SNP	4	PGC1-alpha / Promoter region	
	rs2970866				
	rs4383605				
	rs2946386				
	rs2970869				
	rs17576121				
	rs2970870				
	rs7695542				
	rs2970873	SNP	4	PGC1-alpha / Intron 1	
	rs2946385	SNP	4	PGC1-alpha / Intron 2	
	rs12374310	SNP	4		
	rs7665116*	SNP	4		
	rs2970855	SNP	4	PGC1-alpha / Intron 5	
	rs2970848	SNP	4	PGC1-alpha / Intron 7	
rs8192678	SNP	4	PGC1-alpha / Exon 8		
(31)	Polymorphic CAG Sequence	Polymorphism repetition of trinucleotides	4	HTT / Exon 1	— Modifies the Htt sequence — Reduces the age at onset
(19)	Polymorphic CCG Sequence			HTT / Exonic Codon 2642	
(89)	Polymorphic TAA sequence		6	GRIK2 (GLuR6) / Region 3' non-coding. A 155 bp allele	— Reduces the age at onset
(27)	rs1232027	SNP	5	Intronic (Locus 5q14.1)	— Age at onset — Huntington's disease progression
	rs557874766			Exonic (Locus 5q14.1)	
	rs10611148		15	Intronic (Locus 15q13.3)	

*Higher statistical significance among reported SNPs, $p = 0,012$

Since Htt is present in regions that allow its interaction with other proteins, such as protein 1 or protein 2 (HIP-1, HIP-2), glyceraldehyde-3-phosphate dehydrogenase, calmodulin, and Htt associated with protein 1 (HAP-1), 16 polymorphisms corresponding to the genes of these proteins are also associated with prognosis and other aspects of HD. There is evidence that some polymorphisms in the intronic regions of HIP1 correlate with an increase in neuronal death.²³

In a study performed on 946 Caucasian subjects with HD, Metzger et al. confirmed that the allelic variation in S18Y is responsible for 1.1% of the variations concerning the AO, while the Y allele is associated to younger age cases. This association had been previously reported by Naze et al., who identified a protective effect of the S18Y polymorphism in the Ubiquitin carboxy-terminal hydrolase L1 gene (UCHL1), delaying the AO, as well as in the Y allele, although to a lesser extent.²⁴ Despite evidence shows that the protective effect of these polymorphisms is weak, this represents an important basis for the development of a potential therapeutic target.²⁵

The study carried out by Taherzadeh-Fard et al. identified in a cohort of 400 patients in Bochum, Germany, polymorphisms in the Peroxisome proliferator-activated receptor gamma coactivator 1-alpha gene (PGC-1 α), indicating the inhibition of the function of PGC-1 α by the mHtt. In this cases, the loss of transcriptional control and mitochondrial dysfunction would be linked to the pathogenesis of HD.²⁶ A total of 15 single nucleotide polymorphisms (SNPs) were identified in the PGC-1 α gene (PPAEGC1A), 8 in the promoter region (rs2970865, rs2970866, rs4383605, rs2946386, rs2970869, rs17576121, rs2970870, rs7695542), 1 in the intron 1 (rs2970873), 3 in intron 2 (rs2946385, rs12374310, rs7665116), 1 in intron 5 (rs2970855), 1 in intron 7 (rs2970848) and 1 in exon 8 (rs8192678)²⁶ (Table 2).

Hensman et al. conducted a meta-analysis that correlated motor, cognitive, and imaging deterioration in two cohorts: TRACK-HD and REGISTRY ($r=0.674$). The GWAS analysis was significant ($p=1.12 \times 10^{-10}$) for three genes located on chromosome 5: MSH3, DHFR, and MTRNR2L2, which were associated with the progression of the disease. The rs557874766 SNP was reported with a highly significant association, after adjusting the AO ($p=1.58 \times 10^{-8}$). This SNP represents the Pro67Ala variant in the MSH3 protein and is associated with a reduction in the rate of change on the Unified Huntington's Disease Classification Scale (UHDRS). Among the included polymorphisms, rs1232027 presented the greatest statistical significance in its association ($p=1.12 \times 10^{-10}$).

The list of SNPs reported in this meta-analysis is extensive, and they all were associated with the progression of the disease, such as, rs10611148, rs73786719, rs3889139, rs114688092, and rs79029191, among others.²⁷

Other polymorphic markers studied include GRIK2, TBP, BDNF, and ZDHHC17, not all of which show an influence on AO.²³ TAA repeats in the GRIK2 gene (also called GLuR6) and does not show a modifying effect on AD in HD patients.²⁸ Metzger et al. found that the protein encoded by the TBP gene forms insoluble aggregates to neuronal cells in subjects with the disease, but it is not associated with AO nor acts as a genetic modifier. Likewise, N384S polymorphism identified in the ZDHHC17 gene produces alterations in neuronal transport due to its interaction with mHtt.²³

Another polymorphism (V66M) identified in the brain-derived neurotrophic factor gene (BDNF), which encodes a growth factor for the neural cells of the striatum, leads to the substitution of valine by methionine at position 66 of the BDNF protein (Val66Met). The transcription of the BDNF protein is regulated by Htt, thereby mHtt not only decreases the production of BDNF but also its transport.²³ Although the mechanism by which the V66M polymorphism exerts an effect on the disease by interacting with the Htt is still unknown, it is considered that patients with Val66Met phenotypes would present a delayed AO, especially when there are 42-49 CAG repeats, whereas those with Val66Val phenotypes would present an earlier AO. However, the available evidence doesn't show statistically significant differences among BDNF genotypes or their allele frequency between patients with HD and controls.²⁹

Also, it has been identified that mutations in the FOXP2 gene, which encodes a transcriptional repressor necessary for the organization of cortical-thalamic-striatal circuits, generate structural and morphological abnormalities in both cerebral hemispheres, including the basal ganglia. This has been directly associated with receptive and expressive difficulties in patients as a result of the accumulation of protein isoforms in the cell cytoplasm that generate phenotypic alterations associated with the correct development of language, such as alterations in the lexicon and its comprehension, as well as a lower capacity for information retrieval.³⁰

Research carried out in the population of Juan de Acosta, Colombia³¹ that there could be more than one origin of HD. In this study, not only CAG repetitions were found at the 5' end of the gene, but also a polymorphic sequence was identified in the triplet CCG with more than eight repetitions.

This is another variation that alters the sequence of the Htt, suggesting the existence of two CAG-CCG haplotypes as the source of mutations in HD. The CCG triplet, adjacent to the CAG region, is a polymorphic region with repetitions in the 3' end ranging between 6 and 10.³¹ There are 5 allele variations reported in the CCG region including 170, 176, 179, 182 and 185 base pairs (bp); 176 bp is the most frequent allele in HD patients, which could interfere with a PCR based diagnosis.³²

Clinical evolution and diagnosis of HD

HD includes a triad of motor, cognitive and psychiatric symptoms. Other prevalent signs are weight loss, alterations of circadian rhythm, and dysfunction of the autonomic nervous system.³²

Although HD progression variate, it can be divided into 3 stages: initial stage, which includes subtle changes in coordination, altered processing speed, irritable mood, and even depression; intermediate stage, when movement disorders become major problems, as well as changes in thinking and reasoning,³³ in addition to dysarthria and dysphagia with risk of bronchoaspiration,³⁴ and late stage, when the patient is completely dependent on others for their care due to inability to carry out daily activities such as walking and speaking, at this stage, the patient presents language impairment, lack of initiative and poor family and friends recognition.³³

Neuropsychiatric symptoms

Main changes in HD comprise psychomotor and executive skills, social cognition/emotion processing, and memory. Altered psychomotor speed has a considerable impact on daily life, and is most commonly demonstrated in timed tasks such as substituting symbols or digits and drawing trails. This symptom is the earliest one, and is the best predictor of HD's progression.³⁵

Associated with altered cognitive speed, executive skills are affected, including problems with attention, planning, and multitasking. Furthermore, memory impairment is highly reported in HD, compromising not only declarative but procedural memory. Alterations in social cognition and emotion processing are shown, beside difficulty in the recognition and processing of vocal and facial expressions.³⁵ Similarly, the deficit in the recognition of negative emotions, such as anger and disgust, fear, and sadness, constitutes an important prodromal sign detected in patients with greater motor symptoms.³⁶

Psychiatric disorders are frequent manifestations of HD and include schizophreniform symptoms, personality changes, affective disorders, illusions, hallucinations, paranoia, decreased libido, sleep disorders, and neglect of personal hygiene.³⁷

Apathy, anxiety, and depression are also common neuropsychiatric features found in HD, as well as in other movement disorders, such as Parkinson's disease.³⁸

Motor symptoms

Motor symptoms are a central feature of HD, including chorea, dystonia, bradykinesia, rigidity, myoclonus, tics, tremor, and loss of voluntary movements.³⁸

Chorea prevails as the cardinal symptom of this pathology, establishing the differential diagnosis,³⁹ and it is defined as excessive, involuntary, and short duration movements, which are semi-intentional.⁴⁰ Chorea is a component of a set of signs collectively known as the hypokinetic syndrome, which is also characterized by bradykinesia, muscular stiffness, and not rarely epilepsy.⁴¹

To be highlighted, HD has two phases, a hyperkinetic phase with prominent chorea in the early stages, which tends to stabilize, and a second phase characterized by the aforementioned hypokinetic syndrome, associated with disease duration and CAG length, contrary to chorea.⁴² The type of movement affected is also related to the stage in which appears; involuntary movement alterations occur in adults, especially in the early-moderate stage, while dysfunction of voluntary movement occurs in further stages. Other motor features include abnormal postures due to inappropriate sustained muscle contractions (i.e., dystonia).⁴⁰

Motor phenotypes in HD are classified into three main categories, according to the 31 motor items of the UHDRS, based on calculating a mean chorea score and a mean parkinsonism score ranging from 0 to 4 points, and further calculation of the parkinsonism/chorea index (P/C index):⁴³ chorea-dominant phenotype (C-HD), parkinsonism-dominant phenotype (P-HD), and mixed-motor phenotype (M-HD). These phenotypes are associated with differing neuropsychiatric disturbances and cognitive impairments in such a way that P-HD patients exhibit an increment in the frequency and severity of neuropsychiatric symptoms as well as greater cognitive impairment than C-HD, while C-HD phenotype shows lower apathy and depression scores than M-HD phenotypes and better performance in all cognitive functions when compared with M-HD and P-HD.⁴³

Diagnosis and imaging

The final diagnosis is mainly on neuroimaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), using radioactive markers that identify altered brain areas in HD.⁴⁴

Some studies reveal a decrease in the metabolic activity of the basal ganglia, including the lenticular and caudate nucleus, through PET.⁴⁵ The presence of these findings in the caudate nucleus correlates with a deterioration of the overall functional capacity of the patient while, when present in the putamen, it correlates with greater severity of motor symptoms.⁴⁶

Functional and structural imaging studies have determined that HD patients have frontal and striatal hypometabolism along with thalamic hypermetabolism.⁴⁷ The use of PET SCAN may confirm the decrease of neurotransmitter markers in the early onset of HD in the striatum.⁴⁸ Numerous postmortem and in vivo studies using PET have confirmed a decrease in the binding of D1 and D2 receptor ligands in the striatum and frontal cortex of HD patients, as well as a decrease in the binding of opiates and benzodiazepines to GABA receptors, which have been documented in the striatum, the medial prefrontal cortex and the caudate nucleus.⁴⁷

MRI allows the identification of atrophy into the striatum, as well as degeneration at the hypothalamic level. These changes have been reported in patients with the asymptomatic mutation, suggesting that degenerative events begin before signs can be observed.³⁹

DNA analysis can be performed in peripheral blood or other tissues, in search of CAG repeats on chromosome 4.⁴⁹ In addition, it is possible to perform prenatal diagnosis through DNA analysis of any nucleated embryonic cell obtained by amniocentesis between weeks 15 and 17 of gestation, or a sample obtained from the chorionic villi between weeks 10 and 12. In some countries, another alternative that allows preimplantation diagnosis for in vitro fertilization is available, which consists in obtaining an embryo cell during the eight-cell phase and analyzing its DNA with the objective to implant in the maternal uterus an embryo that does not contain the Pathological elongation of CAG.⁵⁰

Therapeutic approach to HD

The management of motor disorders includes pharmacological, surgical, and physical therapy. The most used drugs are dopamine receptor blockers (neuroleptics) such as tiapride, pimozide, risperidone, and fluphenazine. These treatments are beneficial in treating chorea due to their movement suppressing effect. Prolonged use of these drugs may increase the risk of adverse events and worsen other signs of the disease, such as dystonia and muscle stiffness. Moreover, tetrabenazine, approved by the FDA in 2008 and which is currently considered the first treatment

option, is more effective in the management of chorea.⁵¹ This drug produces the presynaptic depletion of dopamine, serotonin, and norepinephrine in the brain, altering the efferent signals that control movement by the reversible inhibition of the vesicular monoamine transporter 2 (VMAT2).⁵²

Deutetrabenazine, a new VMAT2 inhibitor, was approved by the FDA in 2017 and is the second drug used to treat chorea.⁵³ Through results reported by the First-HD study, it was concluded that this medication significantly improves the chorea and has better tolerability for patients.⁵⁴

Deutetrabenazine differs from tetrabenazine by being a molecule with 6 deuterium atoms instead of 6 hydrogen atoms at specific positions.⁵³ These characteristics confer certain advantages to the use of this drug: deuterium (a hydrogen isotope), attenuates the metabolism of drugs and in turn prolongs the half-life, even with a lower dose than the one administered with tetrabenazine.⁵⁵ These differences in the pharmacokinetic properties of deutetrabenazine improve the risk-benefit factor for the patient, providing a significant decrease in the possibility of developing adverse effects such as agitation, akathisia, anxiety, depression, drowsiness, fatigue, insomnia, and parkinsonism.⁵⁴ Clonazepam, levetiracetam, and amantadine are other useful drugs in the treatment of chorea. However, they are of limited use because of their adverse reactions.^{56,57}

The pharmacological scheme to treat psychiatric disorders will vary according to the clinical picture. Possible treatments include antidepressants, antipsychotics, and mood stabilizers. Antidepressants such as sertraline, citalopram, and fluoxetine may also contribute to the control of obsessive-compulsive disorder.⁵⁸

On the other hand, the most commonly used antipsychotic drugs include risperidone, quetiapine, and olanzapine. The goal of antipsychotic treatment is to inhibit agitation and violent outbursts, among other symptoms resulting from mood disorders or psychosis.⁵⁹ These drugs should be used with caution because they can trigger different movement disorders. Likewise, the use of mood stabilizers such as carbamazepine, valproate, and lamotrigine are useful for the management of emotional variations associated with bipolar disorder.⁶⁰

One of the experimental drugs under examination is a chaperone molecule that interrupts the interaction between biological metals (mainly copper) and abnormal proteins expressed in the brain, thus preventing brain neurodegeneration.

Some studies suggest that Httm aggregation could be due to interaction with metals (such as copper and iron). PBT2 is an 8-hydroxyquinoline drug that chelates metals, thereby lowering metals to non-pathogenic levels.⁵² There is evidence that PBT2 improves cognition in HD patients; this was observed in a 26-week phase II clinical trial in 106 patients, and has also been studied in animals, specifically in HD mice where motor control improvements were shown.⁶¹

Monoclonal antibodies are another treatment option under study for HD. VX15/2503, a humanized IgG4 monoclonal antibody against the 4D semaphorin protein (SEMA4D), was developed by the Vaccinex company to reduce speed and prevent neurodegeneration in HD patients.⁶² SEMA4D is a signaling molecule that regulates most of the central processes for neuroinflammation and neurodegeneration, including glial cell activation, neuronal growth cone collapse, and apoptosis of neural precursors. By blocking the activity of SEMA4D, VX15/2503 prevents the activation of microglia and astrocytes, cells that, in a chronic activation, contribute to neurodegenerative processes. Furthermore, VX15/2503 allows the differentiation and formation of oligodendrocytes, cells with a high potential for remyelination of damaged nerve cells.⁶³

In addition, antisense oligonucleotides (ASOs) are synthetic single-stranded DNA molecules, which when entering a cell, through parenteral administration, join the pre-mRNA in the nucleus and lead to degradation by the action of ribonuclease H (RNase H). In HD, ASO binds to Htt mRNA, silencing or blocking the production of toxic proteins.⁶⁴

IONIS-HTTRx, a 20-nucleotide synthetic sequence, is an ASO treatment for HD developed by Ionis Pharmaceuticals,⁶⁴ which made a phase 1/2 clinical trial (NCT02519036) in late 2017. The study involved 46 patients at nine centers in Great Britain, Germany, and Canada, who were randomized to receive IONIS-HTTRx in increasing doses or placebo through their spinal canal. The study examined the pharmacokinetics and pharmacodynamics of IONIS-HTTRx. The results showed that IONIS-HTTRx was able to decrease the levels of abnormal Htt protein in early-stage patients, with good dose tolerance, and without rapid adverse effects. A key finding was that by increasing the dose of IONIS-HTTRx, the levels of Httm protein decreased in the CSF.⁶⁵

As options for surgical treatment, pallidotomy and deep brain stimulation have been studied without obtaining conclusive results.³⁷ Currently, a strategy under active research is the

transplantation of fetal neurons in the striatum. Several recent clinical trials, although still in the framework of pilot studies, are the first attempts at a modifying treatment in HD. The basis of this strategy lies in the concept of neuroplasticity, according to which neurons modify their structures and connections throughout their lives to address physiological needs. In general, data indicates that the processes of implanted human striatal progenitors expand into the injured striatum and project to striatal target regions.⁶⁶

The above implies that it is possible to remediate cell loss in a neuronal circuit by providing neurons phenotypically similar to those lost. Intra-striatal transplantation of fetal neuroblasts provokes the reconstruction of neuronal circuits in mice with HD, reporting clinical improvement in post-injector chorea and bradykinesia, which may be an effective therapeutic strategy for treating HD patients in the future.⁶⁷ This effect is also related to the release of BDNF stimulated by the graft, which generates cell growth and differentiation. At least 5 clinical trials, implemented the same follow-up protocol (CAPIT-HD), showed variable results, obtaining in some cases sustained clinical improvement for up to six years post-transplant, compared to non-transplant patients, while in other cases trials no significant differences were seen when compared with controls.⁶⁸

The use of pluripotent stem cells (hPSC) as a substitute cellular source, might constitute an alternative to the use of fetal tissue cells, due to their ability to differentiate into the 3 primary germ layers, and to divide indefinitely without transforming, which offers an unlimited supply of starting material. The cells for this purpose can be obtained from HD patients themselves, therefore, they will contain the CAG elongation in the Htt gene, as well as the previous genetic correction required to generate cells with a normal number of CAG repeats from them. Clustered regularly interspaced short palindromic repeats (CRISPR) is a recent technique that allows performing these corrections.⁶⁹

Non-pharmacological strategies are currently used as complementary therapy for the integral care of the HD patient. Among them, physiotherapy is applied to maintain mobility for as long as possible and to minimize the risk of falls.⁷⁰ Psychotherapy aims to address behavioral problems, contributes to the development of coping strategies, and helps to establish effective communication between family members.⁷¹ Speech therapy is also performed to manage speech alterations and eating/swallowing difficulties and to instruct patients in the use of communication devices.^{60,72}

Conclusions

Although numerous publications have contributed to the understanding of HD and the identification of polymorphisms associated with disease features, a lack remains regarding the effect of genetic variations on other relevant aspects of clinical evolution, including the severity of symptoms. Furthermore, a better understanding of the above would lead to the identification of potential therapeutic targets, since currently there is no cure for the disease, and therapeutic approaches are aimed at the control of both motor and psychiatric symptoms. Currently, new therapeutic options in HD target the use of surgical options such as fetal neural transplants into the striatum. However, ASOs as a targeted therapy to block mHtt synthesis, as well as monoclonal antibodies, were shown to reduce and prevent neurodegeneration, and constitute options that have shown promise in the disease development.

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