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VIEWPOINT

A Practical Guide for Clinical Approach to Patients With Huntington's Disease in Korea

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PREFACE: OVERVIEW OF HUNTINGTON'S DISEASE IN SOUTH KOREA

Huntington's chorea was initially described in 1872 by Dr. George Huntington (1850–1916).[1] Roughly a century later, in 1988, the first clinically diagnosed cases of Huntington's disease (HD) in South Korea were reported.[2] Following the identification of the genetic cause of HD,[3] the first genetic analysis of Huntington's chorea in South Korea was published in 1996.[4]

In South Korea, the genetic test for HD has been covered by the National Health Insurance System (NHIS) since August 2005. Advancements in genetic testing and a greater understanding of the disease have made HD diagnosis easier than in the past. A recent study examining the 10-year prevalence of HD in South Korea, based on data registered between 2010 and 2019 in the NHIS database, reported an annual incidence of 0.29/100,000 and a 10-year prevalence of approximately 2.2 per 100,000.[5]

Despite advancements in understanding this disease, the clinical management and medical infrastructure for HD remain notably limited in South Korea. Approximately one-third of individuals diagnosed with HD discontinue medical follow-up, and among those who continue to seek medical care, there is a tendency to incur substantial medical expenses.[5] The annual medical costs for an individual with HD are estimated to be approximately 6 million KRW or more, which is sustained over a period of 9 years following diagnosis.[5] These statistics underscore the urgent need for significant improvements in various aspects of our medical system to provide effective support for patients with HD and their families in South Korea. A recent analysis on caregiver burdens of HD patients in Korea revealed that the caregiving burdens for HD patients are notably high and comparable to those expected in patients with more common dementias.[6]

In an effort to enhance clinical practice and bolster the medical support system for HD in South Korea, the Korean Huntington's Disease Society (KHDS) was established in July 2022. This development occurred approximately two years after the initiation of the first Korean Huntington's Disease Cohort (KHDC) study.[6] A total of 13 centers were involved in constructing the initial cohort. However, following the establishment of the KHDS, the KHDC expanded to include 30 sites and continues to actively

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recruit additional sites for participation (Figure 1).

This study serves as preliminary groundwork for the development of clinical guidelines for HD in South Korea. Subsequently, the taskforce of the KHDS on the Clinical Management of HD compiled fundamental and updated knowledge concerning the diagnosis and treatment of patients with HD. The initial draft provided by the taskforce underwent meticulous review by a panel of esteemed experts from the Korean Movement Disorders Society. Our aim is for this comprehensive effort to assist clinical practitioners in South Korea in making informed and efficient decisions based on the current resources available in the country. Moreover, we welcome any suggestions and proposals to further refine and advance the clinical guidelines for HD in South Korea in the future.

EPIDEMIOLOGY

Prevalence and incidence of HD

Over the years, numerous studies have endeavored to estimate the prevalence and incidence of HD across various countries and regions. A meta-analysis encompassing publications from 1985 to 2010 reported a pooled incidence of HD of 0.38 per 100,000 person-years, with a global overall prevalence of 2.71 per 100,000 person-years.[7] In a more recent meta-analysis including studies from 2011 to 2022, there was a slight increase in both indices, with an annual HD incidence of 0.48 per 100,000 person-years and a global overall prevalence of 4.88 per 100,000 person-years.[8] Although these ratios demonstrated a marginal increase compared to previous meta-analyses, the difference was not statistically significant.[8] An improved rate of diagnosis, due to the wider availability of genetic testing, as well as aging populations and increased patient survival rates, might contribute to the observed increase in prevalence and incidence.

Significant variations in the prevalence and incidence of HD are observed between countries and regions, suggesting ethnic disparities. Europe and North America exhibit notably higher HD incidence rates than Asia. In addition, Europe, North America, and Oceania had higher prevalence rates than Asia and Africa (Figure 2). These discrepancies suggest that HD occurs less frequently within the Asian population than in Western populations. However, a notable divergence in HD occurrence exists between the Middle East and East Asia; the prevalence and incidence rates in the Middle East closely resemble those in Europe, North America, and Oceania, while rates in East Asia are notably lower (Figure 2).[7,8] These disparities in HD prevalence across distinct ancestral populations are believed to stem from genetic variations at the *HTT* locus.[9] Generally, populations with a higher HD prevalence tend to exhibit a greater average length of CAG repeats in the huntingtin (*HTT*) gene. As illustrated in Figure 3, European populations typically exhibit a range of 18.0–18.7 repeats, whereas most studied Asian popula-

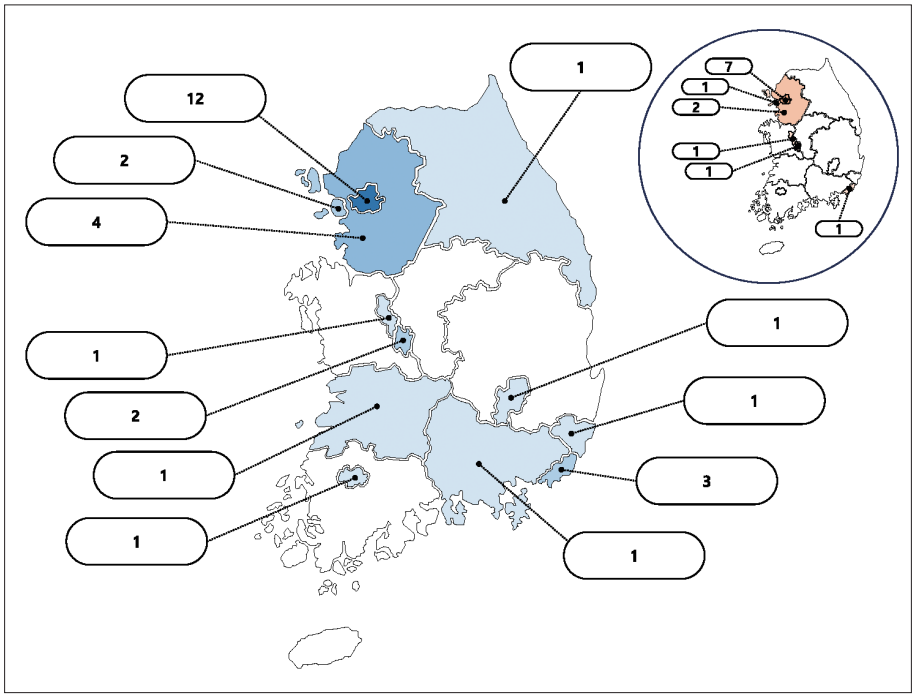

Figure 1. Number of participating sites within the South Korean HD cohort study. The first cohort study involved 13 sites (small circles), whereas the expanded KHD cohort currently encompasses 30 sites. HD, Huntington's disease; KHD, South Korean Huntington's Disease.

tions exhibit a repeat size of lower than 18.[10-21] In addition to differences in CAG repeat length, differences in the frequencies of haplotypes and CCG polymorphisms in the *HTT* gene may also be attributed to geographic and ethnic variations in HD epidemiology.[22]

A recent survey in South Korea estimated the prevalence of HD to be approximately 2.22 per 100,000 people, with an annual incidence of 0.29 per 100,000 person-years.[5] These figures

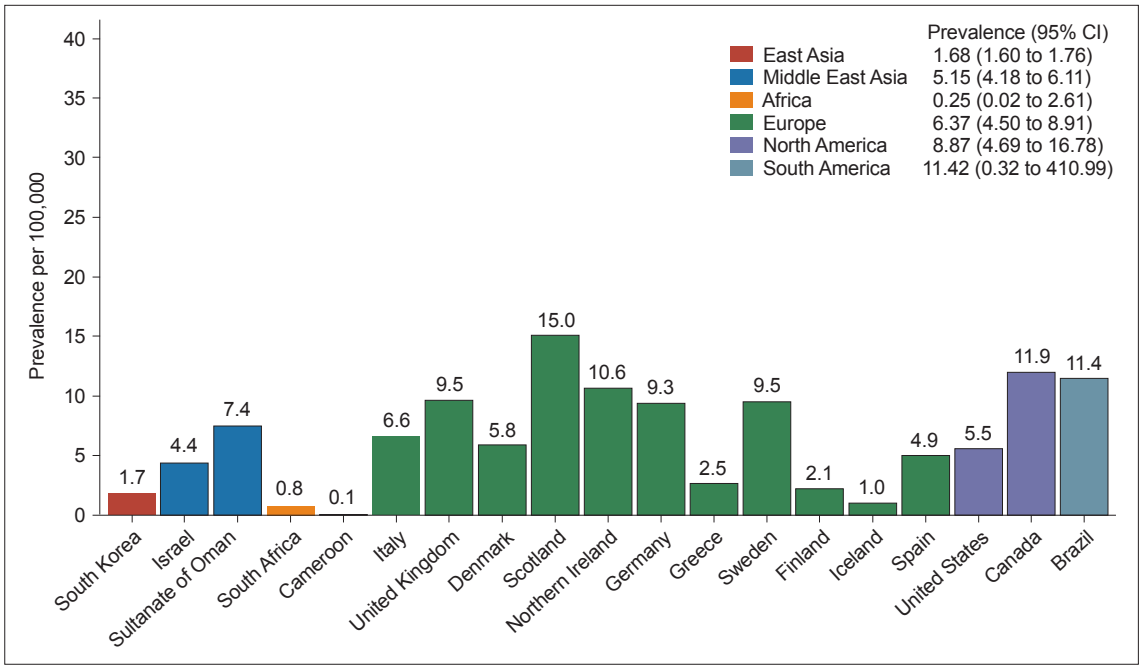

Figure 2. Prevalence of HD in various countries based on a systematic review and meta-analysis of studies published from 2011 to 2023. Modified from Medina et al. Mov Disord 2022;37:2327-2335.[8], under the terms of the Creative Commons Attribution License (CC BY). CI, confidence interval; HD, Huntington's disease.

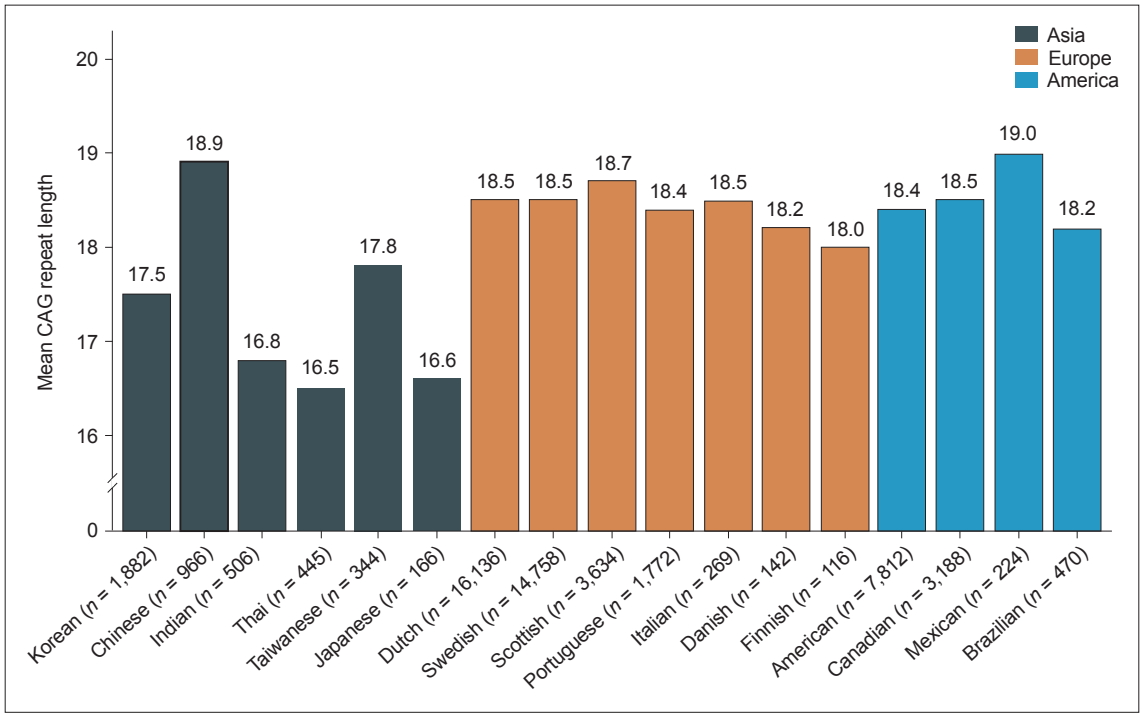

Figure 3. Ethnic diversity in mean CAG repeat length in the general population. The number next to the ethnicity represents the allele count.

indicate lower rates compared to those reported in Western populations but higher rates than previously expected based on earlier reports.

Frequency of reduced penetrance and intermediate alleles in general populations

HD patients typically exhibit 36 or more CAG repeats within the *HTT* gene. However, 36–39 CAG repeats are associated with reduced penetrance, resulting in a later age at onset and slower disease progression than those observed in patients with full penetrance (≥ 40 CAG repeats).[9] In addition, alleles with between 27 and 35 CAG repeats are classified as intermediate alleles, which are prone to genetic instability and might expand into the disease-causing range within one generation.[9] A comprehensive analysis across three population-based cohorts from British Columbia, the United States, and Scotland revealed that among 7,315 asymptomatic individuals, 0.25% (with an allele frequency of 0.12%) exhibited reduced penetrance, while 6.20% (with an allele frequency of 3.13%) harbored intermediate alleles.[11] This prevalence pattern was corroborated by another study involving five large European population-based cohorts,[14] which had similar frequencies of reduced penetrance and intermediate alleles.

In the South Korean population, among 941 asymptomatic individuals, reduced penetrance and intermediate allele frequencies were notably lower, at 0.11% (with an allele frequency of 0.05%) and 1.38% (with an allele frequency of 0.69%), respectively.[10] This finding mirrors the lower prevalence of HD in South Korea than in Western countries.

In other Asian populations, intermediate alleles were found in 2.6% of 966 alleles among Chinese individuals[11] and in 0.5% of 430 alleles among Thai individuals.[13] Interestingly, a recent study indicated that East Asian individuals had the lowest prevalence of intermediate alleles (0%, 0/258) among diverse global populations.[18] However, the inclusion of only a limited number of East Asian individuals in these studies suggests the need for a larger sample study to accurately determine the true prevalence in this population.

PATHOPHYSIOLOGY

Molecular pathogenesis

Extensive data support the pivotal role of mutant HTT (mHTT) fragmentation in the pathogenic mechanism of HD.[23] mHTT fragments originate either from an abnormal splicing event leading to the formation of the *HTT* exon 1 protein or

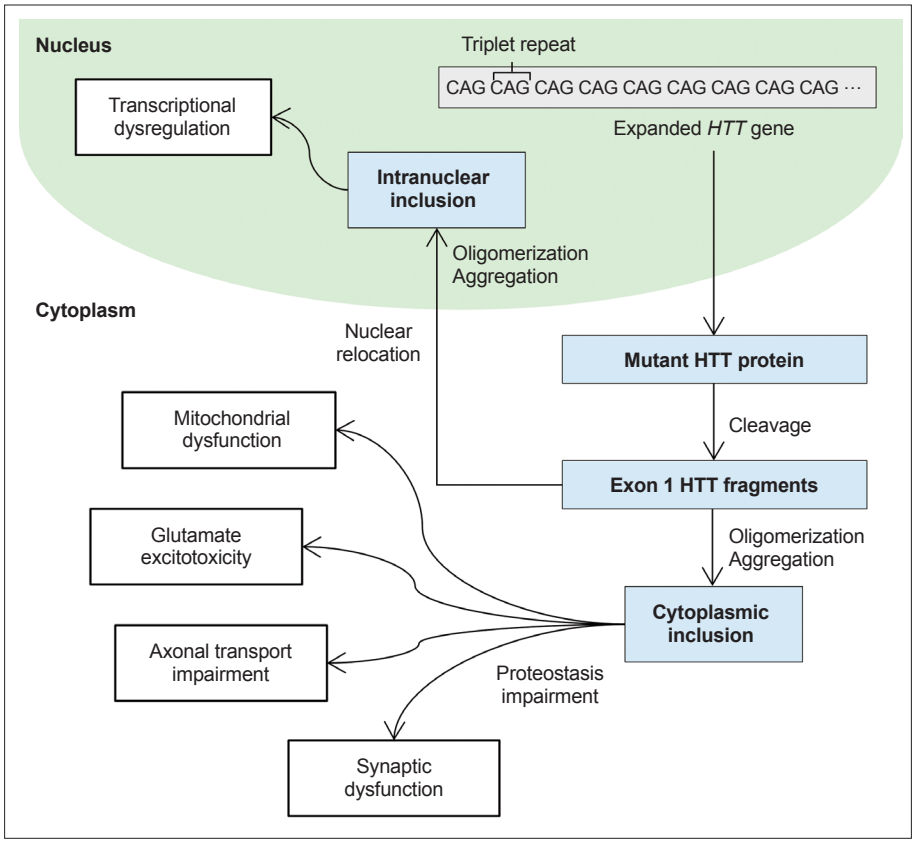

Figure 4. Molecular basis of pathogenesis of Huntington's disease. HTT, huntingtin.

through the cleavage of full-length *HTT* by enzymes such as caspases, calpains, and other proteases (Figure 4).[24] These mHTT fragments instigate neuronal dysfunction and cell death through various pathways, mainly through direct effects from the exon 1 mHTT fragment, the tendency of mHTT to cause abnormal aggregation, and the negative impact of mHTT on cellular proteostasis, axonal transport, transcription and translation, and mitochondrial and synaptic function.[25] Other potential pathogenic mechanisms have been proposed, including reduced levels of brain-derived neurotrophic factor, glutamate excitotoxicity from cortico-striatal projections, and the deleterious effects of repeat-associated non-ATG translation proteins.[26,27]

The differential expression levels of *HTT* across various cell types contribute to variations in the concentrations of mHTT fragments. Neurons typically exhibit greater *HTT* expression than glial cells, a factor likely contributing to the predominant neuronal pathology observed in HD.[28] Among the neuronal cells, medium spiny neurons (MSNs) located in the striatum are particularly susceptible to the harmful effects of mHTT.[29] Striatal pathology in HD progresses through two phases: an early phase characterized by the loss of MSNs from the indirect pathway, leading to a hyperkinetic phenotype, and a late phase involving the loss of MSNs from the direct pathway, resulting in a hypokinetic phenotype.[30] The precise mechanism underlying the selective vulnerability of MSNs from the indirect pathway in the early phase is incompletely understood. However, dopamine D2 receptors, which are selectively expressed in indirect MSNs, may substantially contribute to the onset and development of HD.[31]

Macroscopic and microscopic pathology

Postmortem investigations have revealed a diffuse pattern of atrophy primarily affecting the caudate and putamen in HD patients. This degeneration manifests along gradients on the caudo-rostral, dorso-ventral, and medio-lateral axes. While the globus pallidus and nucleus accumbens are also impacted, the effects are comparatively less pronounced.[32] A classification system has been proposed for the pathologic stages of HD, consisting of the following five grades (0–4):[33]

- Grade 0: Clinical signs of HD are present, yet no observable microscopic or macroscopic abnormalities related to the disease are evident.
- Grade 1: Microscopic observation reveals moderate fibrillary astrocytosis without macroscopic abnormalities in the caudate or putamen.
- Grade 2: Macroscopic changes become evident in the caudate and putamen but not in the globus pallidus.
- Grade 3: Fibrillary astrocytosis is observed in the lateral segment of the globus pallidus without involvement of the medial segment.
- Grade 4: Macroscopic changes include a shrunken and yellow-brown caudate, an expanded anterior horn of the lateral ventricle, and a reduced nucleus accumbens. Additional changes may occur in other brain regions, such as the thalamus, subthalamic nucleus, white matter, and cerebellum, particularly in Grades 3 and 4.

Previous studies employing magnetic resonance imaging have provided supportive evidence for this pathological classification system of HD.[34]

CLINICAL SPECTRUM OF HD

Motor features

Chorea

Chorea is the prototypical and most common motor manifestation of HD, occurring in 90% of affected patients.[35] Chorea is more common in adult patients than in juvenile patients, and it typically initiates in the early stages, plateaus, and regresses during the late stages of the disease. In the early stages of HD, chorea is subtle in the extremities, and it is either unnoticed (i.e., anosognosia) independent of cognitive dysfunction, or its presence is denied by the patient, who may camouflage it by semi-purposeful movements (i.e., parakinesia). Forehead chorea manifests as enlarged palpebral fissures with eyebrow elevation and frontalis contractions. Motor impersistence is one of the cardinal features of HD and is associated with insuppressible overactivity in HD patients.[36] It leads to an inability to maintain voluntary muscle contraction at a steady level when the patient is asked to maintain tongue protrusion ("flycatcher's tongue") or handshake ("milkmaid's grip").[36] Symptoms of chorea in HD patients vary in severity, affecting other motor and nonmotor symptoms (NMSs), daily activities, hospitalization, and quality of life.[36,37] As chorea progresses, patients experience recurrent fall injuries due to postural instability and gait disturbance.[38] Moderate to severe chorea might lead to numerous NMSs, including pain, sleep disturbance, nutritional deficits, and weight loss, as well as social embarrassment and difficulties in communication.[35]

Dystonia

The prevalence of dystonia is reported to be 91%–95% in adult patients, and the most affected body region is the upper limbs, with internal rotation of the shoulder and sustained fist clenching.[39,40] Dystonia worsens as the disease progresses, and its severity is correlated with disease duration and the use of antidopaminergic agents.[39]

Myoclonus

Myoclonus is commonly observed in patients with juvenile-onset HD[35] and is rarely reported as a predominant and disabling motor feature in patients with adult-onset HD.[41] Myoclonus in HD can be generalized, multifocal, or action-induced cortical myoclonus.[42]

Tourette syndrome

Tics in HD are reported in both juvenile-onset and adult HD patients.[43] However, the pathophysiology of the relationship between HD and Tourette syndrome (TS) needs further investigation to determine whether TS and HD are comorbid or whether TS is an atypical manifestation of HD.

Parkinsonism

As the disease progresses, chorea often spontaneously subsides in HD patients. However, parkinsonism can develop and progress to akinesia, severe rigidity, and mutism in the final stages.[35] Since symptomatic treatment for chorea involves reducing dopaminergic transmission by either blocking dopamine receptors or depleting presynaptic dopamine, it may impair motor functions, leading to drug-induced parkinsonism in HD patients.[44] Therefore, hyperkinetic and hypokinetic motor symptoms in HD patients require balanced treatment based on the functional consequences of these movement disorders in individual patients. Late-onset HD patients could be misdiagnosed as having atypical parkinsonism due to their variable motor features, such as dystonia, ataxia, and abnormal oculomotor findings, as well as numerous NMSs, including depression, dementia, and dysautonomia.[45]

Impaired voluntary motor control

In HD, the progressive deterioration of voluntary motor control is prevalent in gait, balance, coordination, oculomotor function, swallowing, and speech. This deterioration is correlated with an acceleration of functional decline.[35]

Cognitive features

Cognitive dysfunction in HD patients can precede clinical diagnosis by 15 years, and gradual deterioration of cognitive function is highly predictive of typical motor symptom development.[46] According to the REGISTRY study, approximately 8% of patients reported cognitive impairment as the first symptom, while 13% reported a mixed onset of motor, cognitive, and psychiatric symptoms.[47] Cognitive features of HD begin with nonamnestic mild cognitive impairment and progress into a broad range of cognitive deficits in the executive, learning and memory, attention, perception, and language domains.[48] In South Korea, the prevalence of dementia in HD patients is approximately 40% and gradually increases to 80% in patients over 80 years of age.[5] Cognitive performance is poorer in the parkinsonism-dominant group than in the chorea-dominant and mixed-motor phenotype groups, independent of disease duration and severity.[49] Interestingly, patients are often unaware of their cognitive problems. Therefore, physicians should take a history from caregivers, be alert to cognitive behavioral changes and share adaptive strategies with caregivers to maintain patients' functional capabilities.[35]

Executive function

Executive dysfunctions encompass slow cognitive processing speed, attentional deficits, and deterioration in decision-making, planning, organization, and sequencing.[50]

Learning and memory

Difficulties in the retrieval of knowledge and the acquisition of procedural information are characteristic features.[35] Compared to people with Alzheimer's dementia (AD), individuals with HD showed better performance on yes/no recognition testing but not on free delayed recall.[51] HD patients exhibit predominant retrieval deficits, whereas AD patients exhibit memory deficits primarily in encoding and storage.[50,51] HD patients can exhibit deficits in implicit memory, which is a collection of coordinated movements and skills, e.g., riding a bicycle, driving a car, chewing, and swallowing.[35] Manifest HD patients have shown impairments in verbal, episodic, visuospatial, prospective, and echoic memory.[52]

Perception

Both premanifest and very early manifest HD patients can exhibit an inability to perceive information.[35] This may include recognition of facial emotional expressions and odors, an understanding of time, visuospatial perception, and overall awareness.[53]

Language

HD patients may exhibit delays in initiating speech, decreased syllable rates, reduced numbers of words produced, diminished levels of syntactic complexities, and increased paraphrasing errors with word-finding difficulties.[54] Metabolic imaging revealed that impaired linguistic processing in HD patients was associated with the left striatum and specific portions of the striatum.[55]

Psychiatric features

Psychiatric features are highly prevalent in both premanifest and manifest HD.[35,56] In adult-onset HD patients, the initial manifestation is more likely to be motor than psychiatric, while juvenile-onset HD patients are equally likely to present with motor, cognitive, or psychiatric features.[56] Psychiatric disturbances

in HD patients are often underdiagnosed, leading to inadequate treatment[57] despite their debilitating impacts on patients and their families, potentially causing financial exploitation and hospital admissions.[37,58] Unlike continuously worsening motor and cognitive functions, affective and behavioral disorders show an irregular pattern of deterioration as the disease progresses.[56] Among various psychiatric symptoms, depression, apathy, and irritability are prevalent across all stages of HD, while hallucinations and delusions occur more often in advanced stages of the disease.[58]

Other nonmotor features

NMSs and signs of HD include a range of metabolic alterations (weight loss), disrupted circadian rhythm (sleep disturbance), and dysautonomia (cardiovascular, gastrointestinal, and genitourinary disorders). Patients with HD experience weight loss, bowel problems, and vivid dreams even more frequently than those with Parkinson's disease.[59] NMSs in HD can occur before the onset of motor symptoms and correlate with disease duration, total functional capacity, and disease stage. NMSs in HD affect patients' quality of life with a variable level of importance.

CLINICAL ASSESSMENT OF HD

Clinical diagnosis of HD

Diagnosis is based on family history, personal history, neurological and psychiatric examinations, and genetic and any other appropriate testing. The diagnostic schemes for presymptomatic, prodromal and manifest HD are summarized in Table 1. Genetic confirmation of HD is based on a CAG expansion of 36 or more repeats in the *HTT* gene. Full penetrance of HD in mutation carriers is exemplified by > 39 CAG repeats, reduced penetrance is observed between 36–39 repeats, while 35 or fewer repeats are considered normal.[26]

Evaluation of motor dysfunction and severity

Motor dysfunction and severity are evaluated with the Unified Huntington's Disease Rating Scale (UHDRS), including total functional capacity, functional assessment, and independence subscales. The UHDRS-Total Motor Score (TMS) assesses eye movements, speech, alternating hand movements, dystonia, chorea and gait. The UHDRS-TMS is sensitive to changes in motor function over time. The details of these scales are explained below.[60] Of note, motor abnormalities in HD patients are rated on a "diagnostic confidence" scale (0–4) according to the probability of manifestation and not according to TMS scores.

Evaluation of cognitive impairment

A screening test such as the Mini-Mental State Examination or Montreal Cognitive Assessment (MoCA) may demonstrate only minor changes. The MoCA is perhaps the simplest and most widely used screening test. The Symbol Digit Modalities Test and Stroop Word Reading Test are the best tools for evaluating cognitive function in HD patients. Moreover, the verbal fluency test (category), Stroop color naming test, Stroop interference test, trail making test (Parts A and B), and verbal fluency test (letters) can be used to evaluate cognition in HD patients.

To diagnose 3 categories of HD (Table 1), the presence of "major cognitive disorder" in individuals needs to be determined based on the DSM-5 criteria as follows. First, modest cognitive decline from a previous level of performance is documented in one or more cognitive domains. Second, cognitive impairment interferes with independence in everyday activities. Comparatively, "minor cognitive disorder" in individuals with HD is defined as cognitive decline that does not interfere with independence but requires greater effort, compensatory strategies, or accommodation. Secondary cognitive impairment due to depression has to be ruled out.[61-63]

Evaluation of neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI) assesses the frequency (4-point rating scale) and severity (3-point scale) of 10 neuropsychiatric disturbances (delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior). The NPI offers advantages over previous psychiatric research in HD. Behavior symptoms can be assessed with the problem behavior assessment (short), hos-

Table 1. Criteria for diagnoses in individuals with an expanded CAG-repeats in huntingtin

Diagnosis	Presymptomatic HD	Prodromal HD	Manifest HD
Motor (diagnostic confidence level)	0 or 1	2	3 or 4 2 (with significant progression in cognitive decline)
Cognition	No cognitive signs or symptoms	AND/OR minor cognitive disorder	AND/OR minor/major cognitive disorder

It is expected that the ability to define signs and symptoms would be enhanced by longitudinal follow-up and assessments (modified from Ross et al. Mov Disord Clin Pract 2019;6:541-546.[61], under the terms of the Creative Commons Attribution Non-Commercial License [CC BY NC]). Following the diagnostic confidence level of the Unified Huntington's Disease Rating Scale: 0, normal (no motor abnormalities); 1, nonspecific motor abnormalities; 2, motor abnormalities that may be signs of HD (50%–89% confidence); 3, motor abnormalities that are likely signs of HD (90%–98% confidence); 4, motor abnormalities that are unequivocal signs of HD (> 99% confidence).
HD, Huntington's disease.

pital anxiety and depression scale, Snaith irritable scale and Columbia suicide severity rating scale.[63]

Unified Huntington's Disease Rating Scale

The UHDRS was developed by the Huntington Study Group to assess the clinical features of HD patients.[64] The UHDRS is composed of 6 sections (motor, cognitive, behavioral, functional assessment, independence scale, and total functional capacity). A Korean version of the UHDRS is available.[6,65]

The UHDRS-TMS is composed of 15 items and has a maximum score of 124. The items of the UHDRS-TMS include chorea, dystonia, parkinsonism, motor performance, oculomotor function, and balance. The original version was published in 1996 and was updated and expanded in 1999 with the intention of increasing its applicability. Different item combinations of the UHDRS-TMS have been used: 4 shortened versions were published 1 year later (TMS1–4), including a modified motor score as well as reported subitem scores focused on gait, chorea, and dystonia or items related to bradykinesia. The internal consistency of the UHDRS-TMS has been reported to be very good in patients with manifest HD (Cronbach's alpha 0.95–0.97).[64,66] The test–retest reliability (0.96 and 0.97) also seems to be very good in patients with manifest HD, although studies have reported correlation coefficients.[66] Interrater reliability in patients with manifest HD is very good, with an intraclass correlation coefficient of 0.94, albeit in a small sample study (n = 24).[64] In the same study, the interclass correlation coefficient was lower for the chorea (0.82) and dystonia (0.62) subscores.[64] As expected, the UHDRS-TMS score was negatively correlated with the UHDRS-Total Functional Capacity Scale score and disease stage,[65] as well as with other UHDRS functional and cognitive scales.

NATURAL COURSE

Natural course and progression of HD

After clinical manifestation, HD patients exhibit steady neurological deterioration. Many studies have attempted to measure the progression of HD.[67-70] The annual progression rates derived from the results of these studies are summarized in Table 2. Notably, although most neurological symptoms steadily deteriorate after onset, chorea progresses quickly in the early stages and reaches a plateau before worsening as the disease progresses.[70]

Due to heterogeneity in the progression of diverse clinical symptoms in HD patients, simple functional staging is useful for clinical practice. The Shoulson and Fahn Staging Scale (SF scale) classifies the progression of HD into 5 stages based on the total functional capacity score of the UHDRS (Table 3).[71,72] However, the SF 5-step classification is not based on meaningful biological deterioration or clinical impact, such as in cancer staging; there is an argument that it is better to use simple 3-step clinical stages (Table 4) than SF staging.[73] Recently, the HD Integrated

Table 2. Annual progression rate in selected motor, cognition, behavior, and function outcomes[64,67-70,85-90]

Outcome	Annual progression rate
Motor outcome	
Total motor score	2.9–6.4
Chorea score	0.3–1
Cognition outcome	
MMSE score	-0.7
Verbal fluency score	-2.1–0.2
SDMT score	-1.5–-0.2
Stroop score	
Color naming	-4.8–-1.8
Word reading	-4.1–0.4
Interference	-1.4–-0.2
Behavior outcome	
Frequency	-1.5–0.1
Frequency × severity	0.6–1.2
Function outcome	
Total functional capacity score	-1.4–-0.4
Functional checklist score	-1.8–-1.0

MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modalities Test.

Table 3. SF rating scale for assessment of progression of HD

SF stage	TFC total score	Approximate years since motor diagnosis	Description
I	11–13	0–8	Only marginal decline in employment engagement and otherwise independence in basic functions, such as financial management, domestic responsibilities, and ADLs (eating, dressing, and bathing).
II	7–10	3–13	Work ability is typically lost and slight assistance in basic functions is required.
III	3–6	5–16	There is inability to engage in employment and major assistance in most basic functions is required.
IV	1–2	9–21	Major assistance in financial affairs, domestic responsibilities, and most activities of daily living is required. Care may still be provided at home but an extended care facility may better meet assistance needs.
V	0	11–26	Fulltime skilled nursing care is required.

SF, Shoulson and Fahn; HD, Huntington's disease; TFC, total functional capacity; ADLs, activities of daily living.

Staging System, which comprises a biological research definition and evidence-based staging centered on biological, clinical, and functional assessments, was introduced (Figure 5).[74]

The most valid factors associated with the natural course of HD are age at onset and CAG repeat length. One study reported that younger age at onset is related to faster rates of motor, cognitive, and functional progression.[75] Another study revealed that patients with late-onset HD had a much faster progression rate than patients with usual HD, reaching the severe stage an average of 2.8 years earlier.[76] The effect of CAG repeat length is more complex than that of onset age and has shown controversial results. For example, one study reported that the CAG repeat length was correlated with rapid progression,[77] while another study reported the opposite results.[78] In 2019, a longitudinal study in which 443 HD patients were followed up for up to 6 years reported that motor-cognitive function and volumes of the caudate and putamen and the white matter ventricle were associated with CAG repeat length and patient age.[79] Based on the evidence to date, the CAG repeat length is likely to be the most reliable predictor of progression rate in HD patients.

There are few studies on HD patients in advanced stages. Patients with advanced HD present severe motor and cognitive impairments requiring nursing home placement in most cases. Therefore, neurologists cannot evaluate patients properly at this stage. Caregivers are often unwilling to participate in research because they are exhausted from long-term care for this disastrous disease or become patients of manifest HD. Therefore, further studies on the advanced and terminal stages of patients with HD are needed.

Survival of HD patients

The approximate life expectancy of HD patients is known to be approximately 15–20 years. In South Korea, one study analyzed the survival of 47 patients with genetically confirmed HD

Table 4. Brief clinical stages for assessment of progression of HD

Clinical stage	Description	SF stage
Early	Patients are generally still active in most areas of functioning, and are often still working or driving.	I
		II
Moderate	Patients become unable to perform complex functions such as work, driving or shopping independently, but still take care of ADLs and simple household tasks.	III
Advanced	Patients can no longer take care of ADLs without help.	IV
		V

SF, Shoulson and Fahn; HD, Huntington's disease; ADLs, activities of daily living.

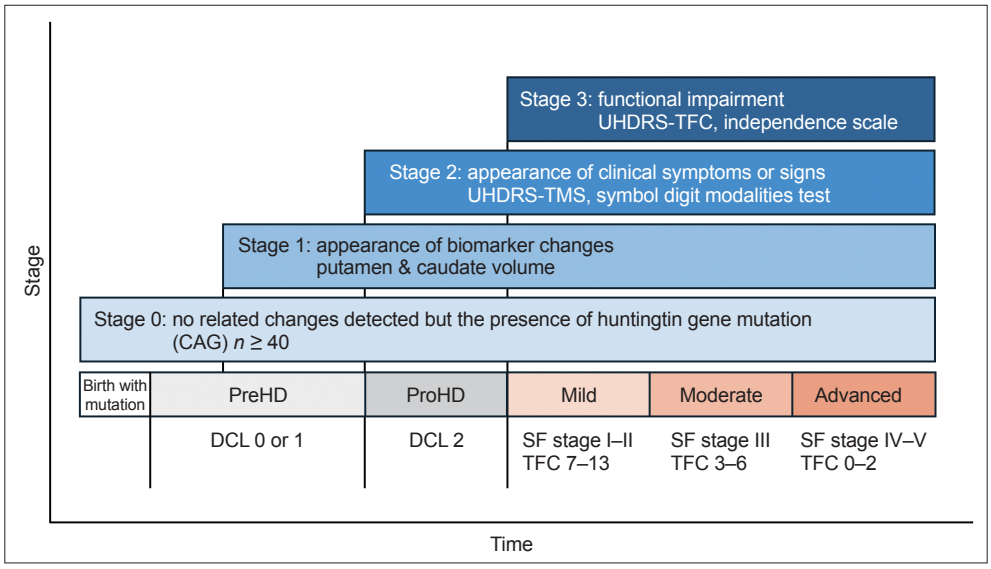

Figure 5. Overview of progression in patients with HD from birth.[61,71-74] The individuals with a mutated HD gene can be categorized according to diagnostic criteria such as preclinical HD, prodromal HD, and manifest HD (Table 1). Progression of symptoms and functional decline in patients with manifest HD can be assigned to three stages from mild to advanced manifest HD (Table 4). Recently, the new biological classification named HD-ISS was proposed which characterizes individuals of HD for research purposes. Stage 0: individuals with HD gene mutations without any pathological changes starting at birth. Stage 1: Only relevant biomarker changes are present. Stage 2: The appearance of clinical symptoms or signs is measurable with the UHDRS-TMS or symbol digit modalities test. Stage 3: Functional impairment starts in patients with manifest HD. HD-ISS, Huntington's Disease Integrated Staging System; HD, Huntington's disease; PreHD, presymptomatic HD; ProHD, prodromal HD; DCL, motor diagnostic certainty level; UHDRS, Unified Huntington's Disease Rating Scale; TMS, total motor score; TFC, total functional capacity; SF, Shoulson–Fahn.

in 2016.[80] The mean age at onset was 46.1 ± 14.0 years, and the mean age at death was 57.8 ± 13.7 years. The median survival was 14.5 years. The median survival of HD patients without genetic confirmation has been reported to be 15–18 years in Western populations, and a European HD network cohort study revealed a median survival of 35 years from symptom onset.[81] The shorter survival in South Korea may be explained by the greater mean age at onset, differences in the *HTT* haplotypes and CCG polymorphisms, influence of other sociocultural factors, and population-specific comorbidities.[80]

In addition to disease progression, age at onset is known to be a predictor of survival in HD patients. Patients with juvenile-onset (younger than 20 years) and late-onset (older than 50 years) disease were reported to have shorter disease durations than HD patients with common onset (20–50 years).[82] CAG repeat length was found to predict shorter survival in a study reported in 2022.[83] This study also reported that older age and male sex predicted shorter survival. A recent study in South Korean patients reported that survival after disease onset was shorter in patients with late-onset HD (age at onset ≥ 60 years) than in those with common-onset HD, and longer CAG repeats and greater age at onset were associated with shorter survival in South Korean HD patients.[84]

Conflicts of Interest

The authors have no financial conflicts of interest.

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