Clinical Symptomatology of Huntington's Disease

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10.1 Definition

Huntington's disease (HD) is a dominantly inherited autosomal neuropsychiatric degenerative disease with a fatal prognosis. The main clinical features are motor impairment (especially choreatic dyskinesias and the impairment of voluntary movements) and behavioral changes (especially cognitive deterioration and personality changes). The mutation is the expansion of the C-A-G (cytosine-adenine-guanine) triplet repeats 40 and more repetitions on the short arm of fourth chromosome. The prevalence of HD is approx. 1:10–15,000 [1]. The typical onset of HD is in the fourth decade, though there also occur relatively rare cases of juvenile or late onset HD forms.

10.2 Introduction

In 1872, a 22-year-old doctor, James Huntington, published a description of a disease that occurred in the region of East Hampton, Long Island, where he was born and where he lived [2]. In his publication, he summarized all the basic features of the disease: its hereditary character, fatal prognosis, adult onset and, of course, its characteristic symptoms: movement disorder, behavioral changes, and dementia. His patients came from the immigrant families of East Anglia, presumably from the town of Bures in Suffolk, who had settled in New England. These families were probably the original source for spreading the disease in the USA.

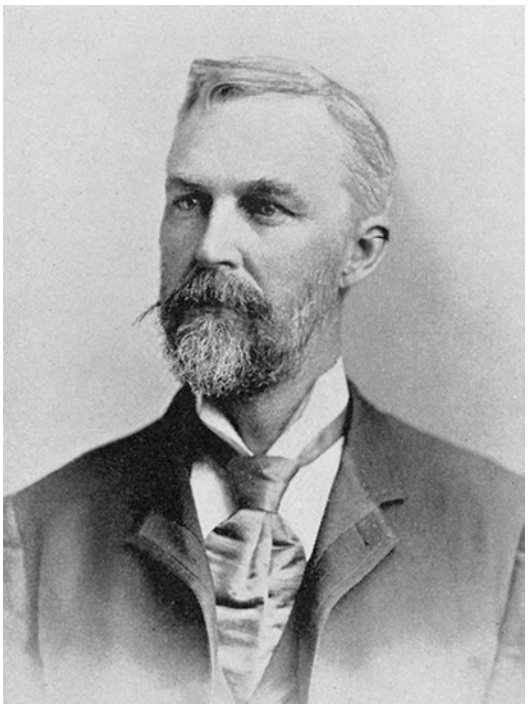

Photo 10.1 George Huntington

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Of great importance for HD research was a discovery by a Venezuelan physician named Americo Negrette, who in the 1950s detected the source of HD. It was found within an isolated community by Lake Maracaibo with about 10,000 inhabitants of whom more than 100 suffered from the disease [3]. Blood samples of the affected individuals of this region enabled the identification in 1983 of a genetic marker on the short arm of the fourth chromosome, and also the mutation itself: an unstable C-A-G (cytosine-adenine-guanine) triplet on the short arm of fourth chromosome [4].

The "healthy" gene produces huntingtin protein. Not all the functions of this protein have been examined in detail, but it is known for its essential role in embryonic brain development and for hematopoiesis [5].

Mutation produces huntingtin with abnormally expanded polyglutamine chains. Pathological huntingtin differs from the physiological one structurally and functionally. Physiological and mutated huntingtin both intervene in a number of cellular processes: apoptosis, axonal transport, structural and functional changes of the cell membrane, production of neurotrophic factors, etc. [6, 7]. Most significant is that the organism is unable to remove the mutated protein from the nerve cell. The expanded polyglutamine chain prevents the protein from entering the ubiquitin proteasome system, degrading intracellular proteins and likely causing a great number of pathological processes through the accumulation of protein in aggregates [8].

Recent estimates of HD prevalence in Europe and the Americas have been approximately 5.70 per 100,000 [1]. HD is relatively more frequent in host countries of historical European migration (USA, Canada, or Australia).

The typical age of onset of the first HD symptoms is between 35 and 50 years. Both sexes are affected to the same extent. The average survival time ranges from 15 to 20 years. The disease manifests itself considerably more rarely (about 5% out of all cases) in the premature age (juvenile HD) or by the age of 20 (HD with an early onset). This form of the disease usually has other clinical signs than the so-called classical form of HD. Late onset of HD with the first signs after the age of 60 is also very rare (about 5%, see below).

As mentioned above, the substance of the mutation which gives rise to HD is an expansion of C-A-G triplet repetition. 40 and more triplets means the full penetrance and the individual is sure to develop the disease [9, 10]. In cases of individuals with 35–39 triplets, the prognosis is uncertain (so-called "grey diagnostic zone" or "incomplete penetrance") [11]. A number of triplets between 27 and 34 will not cause HD to manifest, but it is considered "unstable" as in up to 10% of all cases the number of triplets may increase through intergenerational transfer above the critical level necessary for HD occurrence [12, 13]. However, intergenerational contractions (reductions of the number) of triplets have also been rarely recorded. The higher the number of triplets, the more unstable the condition and the more likely to affect onset of HD—see Fig. 10.1 [14, 15].

The inverse relationship correlation between the number of CAG repeats and the age at onset

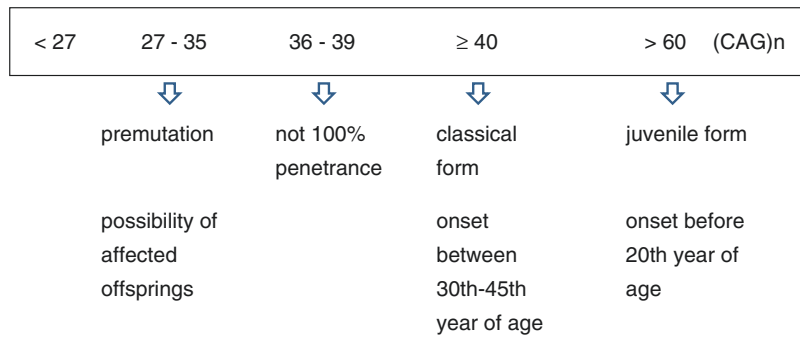

Fig. 10.1 The relation between the number of CAG triplets (CAG)n, clinical form of Huntington's disease and age at the onset

of the clinical signs of HD (the more CAG triplets present, the sooner the disease develops) has been demonstrated in many studies (e.g., [16, 17]). However, this relationship is obvious only in individuals with big (over 60) and marginal (36–39) numbers of triplets. The number of CAG triplets is a crucial but not sufficient factor that determines the age of onset of clinical HD, it determines it only partially [18, 19]. We can presume the existence of a range of other influencing factors, so-called gene modifiers, that are currently objects of further investigation and research [20]. It is interesting here that homozygous composition does not appear to influence the age of onset of HD, but does predict more serious clinical process [21].

Paternal transmission is a significant factor in the number of CAG triplets as the expansion of CAG triplets takes place most frequently during spermatogenesis [12, 22] or through some as yet unknown mechanism depending on the sex of the ancestor and the embryo of descendant [13, 23, 24].

10.3 Clinical Manifestation

10.3.1 Preclinical Findings in the Mutation Carriers and Phenoconversion

The onset of "soft" signs preceding the full HD manifestation (or in other words the transition from health to the disease phenotype) is called "phenoconversion". Phenoconversion in HD is traditionally defined as the onset of chorea. However, it is inadequate to use just one motor sign to characterize the disease onset. Many nonspecific symptoms (motor, cognitive, psychiatric, functional) could precede the definite clinical manifestation, sometimes by as long as 10 years [25–30].

MRI neuroimaging can also capture significant changes, such as atrophy of the caput nuclei caudate [31], cortex, or white matter, many years before the full clinical manifestation itself [32–34]. In studies with functional magnetic resonance of individuals at risk of HD, some changes were spotted before the clinical manifestation of HD [35].

There are also interesting findings regarding a decline in ability to decode facial expressions not only in cases of HD sufferers but also in carriers of the HD mutation [36–38].

A few large sample observational studies have focused on capturing the complex nature of abnormalities in the "preclinical" period: Cohort, Pharos, Predict-HD, or Track-HD.

10.3.2 Clinical Forms

10.3.2.1 Classical HD Form

The classical HD form is most frequent (app. 90% out of all cases), with the first signs appearing between the ages of 35 and 50, though the character and combination of symptoms may vary significantly (see Tables 10.1 and 10.2).

Movement Impairments

Choreatic dyskinesias are abrupt, involuntary, irregular, and non-stereotypical movements in random distribution of both proximal and acral muscle groups.

Dyskinesia is accentuated by physical and mental effort. It could be partially inhibited by psychic relaxation and disappears during sleep.

At low intensity, chorea may be overlooked or mistaken for signs of psychomotor restlessness.

Table 10.1 Neurological symptoms of Huntington's disease

Common symptoms	Less common symptoms (except juvenile form)
Chorea	Epileptic paroxysms
Dystonia	Cerebellar symptoms
Rigidity	Lesions of pyramidal tract
Bradykinesis, hypokinesis, akinesis	Myoclonus
Motor impairment	
Eye movements impairment	
Dysarthria	
Dysphagia, hyperphagia	
Cachexia	
Incontinence	
Sleeping disorders	

Table 10.2 Psychiatric symptoms of Huntington's disease

Personality changes; behavioral disorders – Alcohol abuse, changes in sexual behavior, lack of sexual restraint, aggression, criminality, apathy
Depression
Irritability
Anxiety
Psychomotor restlessness
Hallucinations and delusions
Isolated cognitive deficits
Dementia

While chorea is the classic symptom of HD, and often indicative of the diagnosis, considering its relatively late presentation in the course of the disease, its diagnostic function may be overestimated. As chorea typically manifests only after years of subtle psychopathological symptoms, it is difficult to accurately determine the actual onset of the disease.

Despite its crippling effects, chorea may be overestimated from the therapeutic point of view as well as the impairment of voluntary movement and dystonia usually are more significant. Sometimes it really accomplishes an invaliding impact though.

During incipient stages of the choreatic syndrome, involuntary movements are present especially in the perioral area of the face and may be mistaken for voluntary grimacing or expressions associated with excitement, stress, and anxiety. Also, mild choreatic movements of the upper limbs could be misinterpreted as simply expressive gesticulations.

Random movements of the limbs may be described as aimless or purposeless, even though some patients are very good at camouflaging them by shifting the involuntary movement into one that seems "purposeful," e.g., scratching one's cheek, playing with small objects, crossing one's legs, etc. (so-called "parakinesia" phenomenon).

During the progression, these movements become more pervasive and striking (though with variable intensity) in various muscle groups, with facial expressions ranging from surprise to anger, amazement, fear, etc. Grimacing, tongue protrusions, and moving lips become more frequent, as well as chaotic, random eye movements with diminished ability to focus. Rapid and brief eyelid contraction similar to blepharospasm accompanied with elevation of the eyebrows is also characteristic. Sound phenomena could be present, such as phonation of sighing or grunting as a consequence of involuntary movements of the respiratory muscles and vocal cords.

The neck muscles execute irregular swinging movements of the head, subtle elevations of the limbs at the shoulder and elbow joints, and abduction—adduction or flexion—extension of individual fingers.

Besides proximal and acral movements (e.g., typical shifting of feet on the floor—shuffling with the sole when sitting) of the lower limbs, choreatic dyskinesia may be manifested by hyperextension of the big toe ("PseudoBabinski" syndrome, "PseudoSiccard"), similarly to dystonia, in which case hyperextension of the big toe is fixed for longer period.

Some symptoms are very characteristic of chorea. They result from so-called global motor impersistence, i.e., the inability to maintain the sustained position.

Tongue Protrusion Test

The patient is not able to keep the protruded tongue still—involuntarily keeps putting it back into the mouth. Also, lateral movements of the tongue are not smooth and coordinated.

Grasp Sign

When pressing hands of the examiner, the patient involuntarily loosens and clutches hands as if he or she was "rubbing" the doctor's fingers.

Dance-Like Gait

Those afflicted by HD very often perform a "dance-like gait," they waddle from side to side. The gait can sometimes resemble a "gluteal, myopathic type" of gait, but in this case there are also dyskinesias of the limbs present. Waddling gait in hips which gives impression of a dancing act gave name to this choreatic phenomena (in Latin "chorea" and in Greek "choros" means "a dance").

Due to dyskinesias, the affected persons may not be capable of performing appropriate daily activities; their movements are inadequate; their aim, intention, and coordination get stuck. During such intensive involuntary movements, the affected may be at risk of injury. Later in the disease progression, speech abilities degrade considerably, with characteristic explosive—sometimes even saccadic—dysarthria and altered phonation. Dyskinesia also interferes with swallowing. Intensive choreatic dyskinesias may restrict one's capacity for self-care, worsen stability and lead to falls. More often, however, chorea is rather a source of social difficulties.

In the progression of the disease, chorea worsens significantly, but after some time the intensity spontaneously diminishes and transforms into dystonia and then finally akinesia.

Dystonia (sustained muscle contractions that result in twisting and repetitive movements or abnormal postures of the affected parts of the body) usually occurs during the middle stages of the classical form of HD, for example, trunk dystonia often becomes a source of significant gait disorder.

Besides chorea and dystonia, some patients also show signs of myoclonus (an involuntary, brief, and short twitching of muscles), or rarely as tics.

Severe, generalized **parkinsonian syndrome** does not manifest itself until the late stages of HD (so-called secondary Westphal variant—i.e., immobility without dyskinesias). The affected persons are then completely immobile and subject to secondary complications, such as decubiti and/or infections. Rigidity is often present in middle stages of HD, though this may be a consequence of antipsychotic therapy or other causes.

In contrast to the symptoms outlined above, **the impairment of voluntary movement** is underestimated in clinical practice. However it contributes significantly to the patient's invalidity as it is responsible for motor failures at many basic daily activities. Clumsiness, slowness of movements, and a lack of coordination both concerning the upper limbs during a focused, aimed activity and the whole body during coordination of the gait stereotype are not just the consequence of dyskinesias but an independent symptom.

Unlike dyskinesia, impairment of voluntary movement correlates to the progression and length of the disease and also with cognitive deterioration [39].

Another strange and characteristic sign of HD is a specific facial expression of emotional blunting with a hint of slight annoyance to disgust (facies Huntingtonica).

Gait disorders, usually developing during the middle stages of the disease significantly contribute to worsening quality of life. There occurs a distinctive "dancelike" gait interrupted by sudden involuntary movements, though falls are relatively rare. In later stages with worsening dystonia, bradykinesia, rigidity and postural instability, falls occur more frequently.

Dysarthria is a very frequent symptom of HD. Speech disorder develops in the middle to late stages of the disease, but may also appear in earlier years. In the course of the disease, speech degrades and eventually becomes totally inarticulate. An explosive or saccadic speech pattern—called hyperkinetic dysarthria—is characteristic. Sometimes speech may also be interrupted by involuntary sounds of grumbling and sighing.

Dysphagia is a serious symptom of HD and may even have fatal consequences especially in patients at later stages. It is necessary to monitor carefully problems with swallowing liquid or solid food. For the aspiration of food is typical coughing; wet or gargling vocalization immediately after eating; vomiting within several minutes of a meal; recurrent respiratory tract infections. Physicians/caregivers should be aware of so-called quiet aspiration which may even remain clinically mute for long periods and have to be examined specifically, e.g., by videofluoroscopy. There may also be rare instances of so-called hyperphagia, i.e., swallowing large unchewed bites, probably under the influence of an uncontrollable feeling of hunger, when the patient may be at risk of suffocating.

Gradual **cachectization** in most patients is a typical feature of the late stages of the disease. It need not be related to a striking loss of appetite or problems with standard food intake. The weight

loss cannot be satisfyingly explained and does not correspond with the impact of dyskinesias. Degeneration in the lateral nuclei of the hypothalamus is presumed to affect the process [40–42]. Early cachexia indicates a worse prognosis.

With individual variation, after 10–15 years of development of the abovementioned symptoms, patients with the classical form of HD become fully dependent on caregivers, and die after 15–20 years of the HD development in a marantic state, usually from complications, such as infection, decubiti, etc.

Neuropsychiatric Disorders

The first symptoms of HD are usually subtle **changes in behavior and personality** [43–45]. There are two typical scenarios of development.

In the first model, the patient manifests and develops a gradual loss of interest in one's surroundings, children and their needs, one's partner, appearance. An early development of feelings of **apathy**, distinct from the potential presence of depression, and emotional numbness are characteristic [46–50].

The affected individuals suffer a decline in work performance as a consequence of the development of executive dysfunction. This scenario may result in the chronic loss of employment, poverty, and a decline in social and economic status.

This situation may come about years before the onset of even minor choreatic dyskinesias which is typically the trigger for the clinical diagnosing and genetic testing.

The second clinical scenario also begins with the development of behavioral and personality disorders, but of a different, productive type. Instead of apathy, patients manifest increased **irritability** and states of **anxiety** [46, 47, 51–54]. Due to this anxiety, patients are very often incapable of handling formerly trivial tasks. Family members may notice dramatic and anxious reactions of the sufferer to casual and inconsequential events, such as the late arrival of a family member; deciding what clothes to wear; and whether to accept an invitation. In many cases of HD patients, the anxiety is often and vehemently manifested through somatoform symptoms, such as headaches, backaches, and digestive problems, which the patients describe as dominant problems.

Depression develops in 40% of all cases [43, 46, 47] and bipolar affective disorder could be present. Suicidal tendencies are a serious problem for this group of patients, with suicide rates of 4–6 times higher than the general population [46, 47]. Some data suggest a prevalence of suicide attempts as high as 13% within this population. It is necessary to emphasize that suicidal behavior is a threat at any stage of HD, even prior to the diagnosis [55, 56].

While **psychotic manifestations** are relatively rare in the initial phases of the disease [53, 54], common neuropsychiatric features of HD include paranoid tendencies together with irritability and aggressive behavior. Early symptoms may include feelings or acts of jealousy, and suspicion. Hallucinations are relatively rare.

Obsessive thoughts, compulsive behavior, and perseverance are also common [57, 58].

Interestingly, many HD patients are unaware of their symptoms [59] with almost half the cases of HD diagnosed patients [60] reporting no symptoms. Such a **lack of self-awareness** (anosognosia or denial) can cause problems, especially when the sufferer wants to pursue activities he is not capable of managing (e.g., driving, dealing with finances).

While problems associated with hypersexuality—sexual aggressivity, promiscuity, and sexually provocative behavior—are sometimes observed in early phases of HD, impotence is a more frequent phenomena [61]. Verbal and brachial aggression [25, 43, 46, 47] very often directed only at their closest family members is noted particularly in cases of patients who have had these tendencies throughout their entire life. Anxiety, depressive and psychotic symptoms, obsessive-compulsive disorder, and delirium may predispose sufferers of HD to aggressive behavior. Very often the triggering factor is psychosocial stress brought about by a change of environment, being assigned multiple tasks within a short period, feelings of inadequacy resulting from imperfect speech comprehension, troubles with routine tasks, or conflicts with authorities.

Manifestations of minor criminality (e.g., petty thefts) or problems with alcohol [62–64], while often perceived as simply "unprincipled" demonstrations of asocial behavior may be early indications of pathological changes characteristic of HD. Pathological changes in affects and behavior may also result in divorce, the loss of custody of children, and alienation. Not until years later, when other clinical manifestations of HD surface, the aforementioned signs can be attributed to this diagnosis.

Cognitive Disorders

Minor cognitive changes very often precede the typical clinical picture with dyskinesias [50, 65–67], though the decline of cognitive function in HD is neither universal nor progresses evenly, as the rate of development of dementia varies among individuals.

In early stages of HD, isolated cognitive deficits dominate, especially disorders of executive functions, attention, learning, memory, and changes in psychomotor speed [68]. Sometimes a long-term stationary character can be observed. The extent of cognitive deterioration need not correspond proportionately with other behavioral or neurological symptoms.

As far as memory is concerned, working and short-term memories are affected most, while long-term memory is relatively stable and well preserved. For basal ganglia affection generally (thus including HD) disorders of procedural memory are typical (motor skills—driving, walking, etc.). Memory storage appears to be unaffected by HD. Impairments in retrieval may be remediated through recognition, cues, or associations.

Memory disorders are also impacted by the executive dysfunction: the inability to conceptualize action, or plan for the future; a lack or disruption of control over certain performance procedure and time structures; and at the same time a diminished capacity to accommodate disruptions or unexpected shifts in the activity.

Executive dysfunction also inevitably impacts the capacity for selection, storage, and voluntary recollection of substantive information from memory. Such executive function disorders, typical of the early stages of HD, are mainly responsible for HD sufferers' incapacity first for professional work/activity and later for normal everyday activities [69].

The progression of the disease ultimately leads to full-blown dementia, with a global loss of cognitive function incommensurate with age which interferes with daily activities.

Dementia of the so-called subcortical type is typical for HD, with executive dysfunction typified by changes in psychomotor pacing, behavior disorders (irritability, apathy, obsessive-compulsive manifestations, etc.), mood, and anxiety. Unlike dementia of cortical type (e.g., Alzheimer's disease), the fatic, practic, and gnostic functions are relatively preserved in case of HD, though with further cognitive deterioration, cortical functions also become substantially affected.

10.3.2.2 Juvenile Form of HD (JHD)

JHD starts before the age of 20 and occurs in approximately 5% of all HD cases [70]. In about 1–2% of all cases, symptoms manifest before the age of 10 and very rarely even in the preschool age.

The manifestation of HD in the affected children or adolescents usually differs significantly from the classical form of HD. A child and parent both suffering from HD would present very different symptoms, such that one would hardly identify the same disease in progress.

The onset of JHD varies considerably, due largely to the fact that the disease is manifesting in a developing brain. For this reason the diagnosis is often very difficult, especially in the absence of a positive family history.

The transition from subclinical manifestations detected only by specific methods (e.g., neuropsychological testing) to the stage of the obvious clinical manifestation detectable by objective examination, observation, and interview (phenoconversion—see above) is very vague, making it difficult to assess the chronology of the disease.

The first manifestations may be either motor, cognitive, or behavioral. Siesling [71] found behavioral disorders in JHD as the initial manifestation in 70% of all cases, compared to motor in 48% and cognitive in 27%. Similar results have also been detected by the Ribaï study [72].

So far there have been very few clinical studies dealing with JHD symptoms and its dynamics and there is a lack of systematic data. The life expectancy in JHD is shorter than in the classical form, approximately 10 years from the first manifestations [70, 72, 73], though some studies do not indicate a distinctively shortened life span in comparison with the classical form of the disease [74].

Psychopathology of JHD

The first indications of a JHD disorder are that of intellect. A typical initial manifestation is failure to cope with school demands particularly due to a combination of some aspect of cognitive disorder (at a very early age there occurs mental retardation, in older children already indications of some cognitive deterioration) with a slowing of motor function, lack of coordination of movement, and voluntary movement disorder.

Manifestations as temper tantrums, aggressivity, antisocial behavior, and obsessive-compulsive features are frequent. Depression is also a very frequent symptom. Psychotic manifestations in JHD occur more often than in the adult form.

Motor Symptoms of JHD

The character of motor symptoms is what distinguishes the clinical image of JHD from its adult form. The most characteristic symptoms of JHD are hypokinesia, rigidity, and dystonia, accompanied by rapidly progressive stability and gait disorders. In the middle stages, there is a distinctive shaking of the head and the upper part of the trunk, kinetic tremor of upper limbs with occasional trunk myoclonus. In JHD, there may also occur compulsive spasmodic movements. Neurological examination often reveals pyramidal tracts lesions as increased reflexes and the presence of plantar response, etc. Severe involvement does not occur.

There is a relatively early onset of dysarthria, which in later stages may progress to mutism and dysphagia sometimes accompanied with hypersalivation. Dysphagia can cause choking, coughing, postprandial vomiting, and aspiration pneumonia.

The most common manifestation of JHD is a rapidly progressive and invalidizing atypical parkinsonian syndrome in combination with diverse psychopathologies. This form is sometimes referred to as primary Westphal variant of HD, unlike secondary Westphal variant which is the late stage of the adult form of HD (when akinesia replaces dyskinesia), and the diseased is not able to carry out voluntary motor activities.

Supranuclear gaze palsy is another commonly associated symptom, though it does not usually appear until the middle stages of JHD. In such cases, both vertical and horizontal movements get stuck, and in very serious cases the eyes are fixed forward and the whole head moves when trying to look aside.

Rarely, typical choreatic dyskinesias may also occur, but normally it is either absent or not evident to clinical observation. If present, they tend to occur in cases of individuals whose JHD onset started in adolescence. With cases at the onset by 10 years of age, it is totally rare.

Other manifestations are epileptic seizures—which occur in as many as 40% of all cases of JHD [70, 71]. They can be both generalized (very often of tonic-clonic character) and focal and there are cases of the clinical image of progressive myoclonic epilepsy.

From the middle stages of the disease, cachectization appears constantly. Cachexia is a very serious sign. It need not be linked with a lack of appetite or with problems of ordinary food intake. Weight loss cannot be explained satisfactorily and does not correspond with the impact of dyskinesia.

Patients require hypercaloric intake; approximately 4000–6000 calories daily is recommended. Weight loss (or the "onset of weight loss") is always considered an alarming sign which is necessary to try to address.

The advanced stages of JHD are characterized by repeated falls with injuries, which, together with a gradual loss of active mobility and dystonic postures, ultimately leads to total immobilization and mutism. Serious cachexia with dysphagia may require a percutaneous endoscopic gastrostomy (PEG). Infectious complications increase (pneumonia, decubiti) and patients died in a marantic state.

10.3.2.3 Late Onset Huntington Disease

This form of the disease manifests in persons over 60. It comprises approximately 5% of all cases of HD. Onset after the age above 70 is exceptional. It may be presumed that minor symptoms had been present but undetected a long time beforehand.

The clinical features of late onset HD resemble the symptoms of the classical form, but the progression is slower and less functionally debilitating. The hallmarks are mild to moderate chorea and cognitive impairment, gait disorder, and dysarthria. Behavioral symptoms such as apathy or irritability, depression or even psychosis may be present, though only infrequently.

Due to its relatively "benign character" (though not in all cases!), the patients are often able to maintain an active lifestyle for many years, only occasionally requiring nursing support.

Late onset HD is generally underdiagnosed, with major consequences for descendants, who remain unaware of this potentially serious hereditary disease [75–77] (Table 10.3).

Table 10.3 Typical features of late onset Huntington disease [77]

• Dominant motor symptoms (chorea, gait disorders)
• Slow progression of cognitive deficits to dementia
• Slow progression of functional disability
• Frequent negative family history
• Borderline or low pathologic expansion of CAG triplets

10.4 Diagnosis

It is relatively easy to diagnose HD particularly in situations when we are aware of any family history of severe neuropsychiatric disease (e.g., an affected ancestor died in a psychiatric hospital) and when the patient exhibits symptoms of dyskinesia together with a behavioral disorder and cognitive deficit (Table 10.4).

Accurate diagnosis may not be so simple in situations, where family history is missing (unknown paternity or no information about one side of the family in the case of parents' divorce, new mutation, etc.) or the patient and family are in denial about the condition and refuse to share relevant information. The clinical picture may also vary from one patient to another, depending on the stage of the disease and the prevalence of

Table 10.4 The manifestation of main symptoms in particular forms of Huntington's disease

Symptom	Juvenile form (onset by the age of 20)	Classical form (onset between 35 and 50)	Late form (onset over the age of 60)
Chorea	Usually not present	From the early stage	From the early stage
Dystonia	Present from the early stages	From the middle stage	Not present
Parkinson's syndrome	Present from the early stages	From the late stage	Not present
Epileptic paroxysms	Present	Atypical symptom	Not present
Lesions of pyramid pathway	Present	From middle stage	Not present
Cerebellar symptom	May be present	Atypical symptom	Not present
Affective disorders	Present from the early stage, later it disappears	Present from the early stage, later it disappears	Not present
Dementia	Present, fast progression	From the early or middle stage	Not present
Psychotic states	Present from the early stage	Any stage	Atypical symptom
Disease progression	Very fast (death within 10 years of the first signs)	Medium (death within 15–20 years from the first signs)	Slow
Heredity	Usually paternal	Both paternal and maternal	Both paternal and maternal, however often not present

symptoms (dominant psychiatric or neurologic symptoms may dominate in some families).

Nonetheless, the possibility of HD should be considered whenever the adult slowly develops behavioral changes or cognitive deficits in combination with motor handicaps of a choreatic or dystonic character, even in the absence of similar problems in the family medical history. If the family history is indicative, even minor behavioral changes, personality disorders, or just discrete memory disorders should be taken into consideration.

Genetic test confirms only the presence of the mutation! A positive test for the HD mutation in a person who does not otherwise show any HD symptoms does not confirm a diagnosis of the disease but just a genetic predisposition.

Genetic testing can be theoretically carried out in a few model situations:

Diagnostic testing is carried out in the case of a reasonable clinical suspicion for HD. The testing either confirms or disproves the clinical diagnosis with 100% certainty. The patient must always be informed that his or her blood is being taken for genetic testing which will either confirm or disprove the HD diagnosis. The patient has to agree to the testing procedure and confirm compliance in writing. Exceptions to this written protocol can only be made in cases where the patient so severely affected that he or she is physically incapable of giving consent.

Predictive (presymptomatic and prenatal) testing may be carried out in heretofore healthy individuals at risk of HD. A presymptomatic test may be carried out on descendants of an affected person who wish to know whether or not they have inherited the HD mutation.

The prenatal test is carried out through the analysis of amniotic fluid (amniocentesis, biopsy choria) in the course of pregnancy of a diseased or positively tested woman, or the wife of a diseased or positively tested partner, who wishes to know the genetic status of her unborn child.

Presymptomatic testing of HD has serious ethical considerations [78–81]. The disease is fatal, incurable, and causes progressive devastation of the motor and mental faculties. Known carriers are burdened with high stress not only regarding their own future quality of life but their posterity, as a positive result entails 50% hereditary risk for the next generation. Last but not least, a positive test for the HD also has multiple negative impacts on "healthy" family members and loved ones.

An international protocol-based presymptomatic testing procedure has been designed with the aim of minimizing negative, catastrophic consequences [82]. This includes several consultations: genetic, neurological, psychological, and psychiatric. Individual sessions are aimed at providing a detailed overview of the disease and the testing procedure to the applicant; verifying the patient's insight on the issue; clarifying his/her motivation and the benefit of the test; and last but not least, at determining the applicant's adaptive capacity to handle burdensome situations.

The entire process of the predictive protocol reduces—though does not eliminate—the risk of suicide considerably [79]. Short- and long-term consequences of predictive testing have been examined in many studies [78, 81, 83, 84].

According to the protocol, physicians may not refuse to do the predictive test but they may recommend postponing it. Aside from clear contraindications such as suicidality and depression, a number of other situations may arise whose importance is subjectively determined depending on the personal judgement of the given psychiatrist (for example, their willingness to accept risk and individualize treatment versus an entirely formal approach with no personal engagement of the examiner). As a rule, the recommendation to continue or postpone the test stems usually from the clinical experience of the psychiatrist. The most important variable in this respect is probably played by the presence or lack of motivation and self-advocacy in the patient; furthermore by their personality structure, maturity, adaptation mechanisms, duration and depth of HD awareness and knowledge of the quality of their background and other factors.

Many years of experience with the predictive protocol at many centers worldwide show that the implementation rate of the genetic test is relatively low, ranging between 5 and 25% in various countries [85].

With current preimplantation genetic diagnosis technique it is possible that a person at risk of

HD can give birth to a child who is not a carrier of the HD mutation, without the necessity of confronting the people at risk with their genetic status [86, 87].

10.4.1 Huntington's Disease Phenocopies

Approximately 1% of patients with typical classic HD-like manifestations lack the causative mutation [88]. Such cases are considered "Huntington's disease-like syndromes" or "Huntington's disease phenocopies" (HDP). HDP are clinically and genetically heterogeneous. The etiological diagnosis of the respective HDP is usually difficult to establish (see Table 10.5).

10.4.2 The Problems of Caregivers

Due to its complexity, HD is a typical example of a disease that affects not only its carriers but also the whole family and extended care group. Physicians and scientists have been focused mainly on the biological principles of the disease and on a search for possible therapy. A great deal of attention is given to patients and carriers; however, the problems and needs of caregivers (who bear the burden of psychological stress) nursing the patients are not in the center of the attention [89, 90].

The partner of the HD patient, for example has to face a lot of problems, such as a lower economic status, the loss of free time, and the loss of independence.

Other serious problems include the risk of HD transmission on the descendants (feelings of guilt for passing on the mutation, the inability to convey to the children the nature and level of the risk) and the character of the disease itself which often severely disrupts the partner's psyche.

The afflicted sometimes alter their behavior and personality, even committing violence on their partners or children through pathological jealousy, sexually motivated aggression, phychotic symptoms, or rage.

Children in families with HD often have difficulty comprehending situation with all its ramifications (why the parent is aggressive, understanding the change in behavior, etc.) It is impossible to generalize the consequences of such long-term problems for the development of the children, but they definitely have a considerable negative impact on the whole family.

Under the stress of the manifestation of HD symptoms, not to mention the broader social, economic, and emotional costs, in most cases partners in long-term relationships with HD-affected persons develop severe depression, anxiety and panic disorders, negative behavior and/or aggressive outbursts towards the diseased. Even talking about HD often becomes a family taboo and is not allowed to be discussed in public or even within the wider family circle. The partners, as well as the persons at risk, describe their state as one of "permanent sadness," often requiring medical intervention.

Table 10.5 Huntington's disease phenocopies (HDP) of adulthood

Clinical entities with a typical picture of HDP
Dentato-rubro-pallido-luysian atrophy (DRPLA)
Spinocerebellar ataxia type 17 (SCA 17) or Huntington disease-like 4 (HDL4)
Choreoacanthocytosis
McLeod syndrome
Neuroferritinopathy
Huntington disease-like 1[a]
Huntington disease-like 2[a]
Huntington disease-like 3[a] (onset at preschool age)
Disorders only rarely fulfilling the clinical picture of HDP
Spinocerebellar ataxia type 2, type 3
Friedreich ataxia
Pantothenate kinase-associated neurodegeneration (onset in childhood and adolescence)
Wilson disease

[a]Extremely rare in Europe

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