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REVIEW PAPER

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What is the unique nature of the Huntington's Disease?

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ABSTRACT

Introduction. Huntington's disease is a rare neurodegenerative disease, inherited in an autosomal dominant manner. Every child in the family whose parent is a carrier of the mutant gene has a 50% risk of inheriting the disease. Genetic tests unambiguously confirm whether a person at risk is ill or not. Symptoms include movement, neuropsychiatric and cognitive disorders. Currently, the disease is incurable and there are no effective methods for its treatment.

Aim. The aim is to present information about Huntington's disease, its inheritance, symptoms and pathologies, as well as to draw attention to its unique impact on patients and their families.

Material and methods. A literature review of the following databases has been conducted: PubMed, Science Direct, EBSCO, Springer Link.

Results. Huntington's disease, due to the autosomal dominant inheritance, disturbs the whole family system. Over several generations, a family can struggle with the problems of taking care of several patients at the same time, providing children with information about the risk of falling ill, making decisions about genetic testing, and starting a family or having children.

Conclusion. Huntington's disease is a challenge for healthcare professionals who are not always prepared to solve unique, multi-generational problems in families with Huntington's disease.

Keywords. CAG repeat, chorea, family system, genetic disease, HD gene

Introduction

Huntington disease (HD) is a rare, progressive neurodegenerative disease that belongs to a unique group of autosomal-dominant disorders. This disorder belong to trinucleotide repeat disorders and is caused by CAG trinucleotide repeats in the 5´ coding region of the IT15 (Interesting Transcript15) gene located on locus 4p16.3.[1,2]

The Huntington's gene has a unique feature of repeating a trinucleotide DNA (triplet) with a repeat length of 6 to 35 in the normal population.[3] The number of repetitions in the range of 27–35 does not cause the symptoms of the disease to develop, but due to the phenomenon of anticipation, it is associated with an increased risk of mutation in the next generations. The phenomenon of anticipation lies in the fact that the higher the number of repetitions, the earlier the age of illness and its more severe course.[4,5] It mainly concerns inheritance from father, which is the result of high in-

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stability of CAG sequences in spermatogenesis. Genetic anticipation is the reason for the emergence of a juvenile form of HD in families. Every child in a family whose parent suffer from HD has a 50% risk of inheriting the gene. A range of 36-39 repetitions of a CAG triplet can cause the disease, but the gene penetration is incomplete.

For people with 40 and more repetitions, the penetration is 100%, which means that every such person will fall ill if he lives to a certain age.[6] After full-blown HD develops, patients live about 15-20 years, slightly longer than in other neurodegenerative diseases. In the family, it often occurs in several people at the same time, for example in the case of a spouse, children, grandchildren, and several generations even up to 30 years.

Aim

The aim of this paper is to present information about Huntington's disease, its inheritance, symptoms and pathologies, as well as to draw attention to its unique impact on patients and their families.

Description of HD from 1872

The name of the disease comes from the name of the doctor George Huntington, who in 1872 published an article named "On Chorea" in the Medical and Surgical Reporter. He gave a detailed description of the progressive and hereditary chorea, inexorably progressive, and always fatal: "When either or both the parents have shown manifestations of the disease, and more especially when these manifestations have been of a serious nature, one or more of the offspring almost invariably suffer from the disease, if they live to adult age. But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from the disease. This you will perceive differs from the general laws of so-called hereditary diseases, as for instance in phthisis, or syphilis, when one generation may enjoy entire immunity from their dread ravages, and yet in another you find them cropping out in all their hideousness. Unstable and whimsical as the disease may be in other respects, in this it is firm, it never skips a generation to again manifest itself in another; once having yielded its claims, it never regains them. In all the families, or nearly all in which the choreic taint exists, the nervous temperament greatly preponderates, and in my grandfather's and father's experience, which conjointly cover a period of 78 years, nervous excitement in a marked degree almost invariably attends upon every disease these people may suffer from, although they may not when in health be over nervous".[8] In several decades, the chorea described by Huntington was widely recognized as a unique disorder. The name was changed to Huntington's disease because it became obvious that the disease is not only associated with the occurrence of movement disorders.

HD gene

The identification of the HD gene was based mainly on the analysis of a large Venezuelan HD kindred with an extremely high frequency of the disease, due to the high frequency of inbreeding. The HD gene was mapped to the tip of the short arm of chromosome 4 in 1983 using standard linkage analysis. However, scientists needed another 10 years to isolate it and to identify the underlying mutation that causes HD. But it was not until 1993 when the HD gene was finally identified by The Huntington's Disease Collaborative Research Group, including 58 scientists from six independent research groups and introduced for diagnostic and preclinical tests.[9] Using the haplotype analysis of coupling disequilibrium in HD families of different ethnic groups, they identified a small segment of 4p16.3 as the probable location of the mutation. The new gene, IT-15, isolated using cloned trapped exons from the target area, was shown to contain a polymorphic trinucleotide CAG repeat within the coding region of the gene that was expanded and unstable on one of the chromosomes of all 75 HD families examined. The gene locus was found to span 180 kb, consisting of 67 exons, and encoding a protein (huntingtin) of ~350 kDa.[10] One year later the international clinical and genetic community has created the guidelines for the appropriate molecular genetic testing of HD.[11] HD is unique due to its single gene autosomal dominant nature and can be accurately identified in patients prior to the onset of any symptoms, while still considered 'premanifest'.[12]

Genetic tests and its consequences

People at risk, over the age of 18, may undergo a presymptomatic study to find out if they actually carry a mutated gene. This is a choice that selects few people at risk (5% to 10%) and requires a multi-day consultation with genetic counselors, neurologists, and often a psychiatrist or psychologist.[3]

Due to the long-term and difficult course of the disease, confirmation of clinical diagnosis of HD has unique consequences for the patient and other family members. A patient's reaction to the disease may be unpredictable.[13] A negative diagnosis sometimes helps to explain worrying symptoms and therefore is a relief for the patient and his family. However, HD diagnosis can cause or worsen an existing depression - the risk of suicide increases just before and after the beginning of the disease. Predictive testing is very important for people with a family history of HD before significant life-changing events such as marriage or pregnancy occurs.[14] If the diagnosis is confirmed, other people in the family (patient's partner, children, grandchildren,

siblings) will need information and emotional support, especially if there is no previously known family history of HD.[15]

Symptoms and forms of HD

Pathological findings in HD include mostly progressive degeneration of basal ganglia but also of other brain regions, such as the substantia nigra, cerebral cortex, hippocampus, lateral tuberal nuclei of the hypothalamus and parts of the thalamus.[16]

Clinical diagnosis of the disease is based on the observation of involuntary movements and insidious beginning of mood disturbance in individuals with family history of the disease. The symptoms include motor, neuropsychiatric and cognitive abnormalities that aggravate progressively.[17]

There are 3 HD forms differing in the onset, clinical picture and course of the disease. Classic form consists approximately 80% of patients and Juvenile (The Westphal variant of HD) affect people before 20 years of age. Late onset HD (10% of patients) begin after 60 years of age and the diagnosis of the disease is often never made. In the family history there is no information about the disease, which due to the variability of the clinical picture has not been diagnosed as HD, but as Alzheimer's, Parkinson's or other neurological disease, especially if it is the first situation in the family.[18] The de novo mutation accounts about 10% of cases.[19]

The most common age of onset (classic form) is the fourth and fifth decade, when life stabilization is achieved, when HD patients have already made the majority of professional, financial and family decisions related to, among others, the number of children. This HD form is characterized by the presence of a triad of symptoms: involuntary movements, behavioral and mood disorders, and cognitive impairment. These symptoms occur in patients of varying intensity and various compilations. The spectrum of motor symptoms in HD is broad and includes predominantly chorea involuntary movements, saccadic eye movement disorders, postural and balance disorders, dystonic and myoclonus movements, dysarthria, dysphagia, and Parkinson syndrome in the late stage of the disease.[20,21] These changes result from damage to the movement loop responsible for the regulation of muscle tone and the function of skeletal muscles and reflexes. Uncontrolled body movements cause HD patients to be perceived as people under the influence of alcohol and because of motor disorders; they may push or hit other person accidentally. Other, less known, but common and frequently occurring symptoms of HD are: uncontrolled weight loss, sleep disorders, circadian rhythm dysfunction, and dysfunction of the autonomic nervous system.[22] Movement disorders make it impossible to perform daily activities such as washing, dressing, using the toilet, cooking and eating meals. Dysarthria and dysphagia intensify during the course of the disease, which can lead to choking and aspiration pneumonia. All patients develop hypokinesia and muscle stiffness that lead to bradykinesia and severe akinesia.[23] The most common causes of death are pneumonia, injuries resulting from falls or suicides, which occur much more often than in the general population.[24]

Neuropsychiatric disorders are dominated by depression (about 40% of patients), dysphoria, psychomotor agitation, irritability, apathy, anxiety, suppression of behavior and euphoria.[25] Depression syndrome in people at the early stage of the disease may be the first symptom of the pathological process, but it can also react to stress resulting from awareness of the genetic burden of the disease. In HD patients, there was also a family predisposition for the occurrence of psychotic symptoms. In families where at least one person has the disease manifested by psychotic symptoms, the risk of developing psychosis in other members burdened with its disease is about four times higher than in families burdened with HD without symptoms of psychosis.[26] The presence of psychotic disorders may suggest schizophrenia. In 40-50% of patients, over a dozen years before the onset of the first symptoms of HD, personality changes are observed.[27] Irritability associated with HD, which is signaled by members of the immediate family, can be severe and result in outbursts of anger and aggression.[28] Over half of the patients develop obsessive-compulsive disorder during the disease course, and perseveration behavior (75% of patients). [29,30]

Symptomatology of cognitive dysfunction includes executive-related disorders associated with apathy, attention deficit memory, difficulties in memorizing new information, difficulty in extracting information from autobiographical memory without a time gradient, (which is in turn characteristic of Alzheimer's disease) dysfunctional memory and spatial disorders. However, language functions and semantic memory are relatively better preserved.[31] An important feature of HD is a lack of awareness or lack of insight into the nature or severity of symptoms that the patient experiences, despite its visible symptoms. This may include a lack of awareness of any disease characteristic, including all three domains of motor, cognitive or behavioral symptoms.[32]

This feature makes it important to consider family members as helpful (sometimes key) sources of information that provide objective assessments of patient symptoms, function levels, and should be involved in assessing the patient's health and decision making. Neuropsychiatric symptoms in HD may precede the onset of motor disorders even up to 15 years before full-blown disease, which contributes to delaying the proper diagnosis of the disease, especially in the absence of a positive history of HD or treatment of a completely different disease (e.g. depression or schizophrenia).

Of particular interest is the juvenile form of the disease (JHD), with a large number of CAG repeats. The first symptoms occur before the age of 20.[33] This form affects 5-10% of carriers of the mutant gene, and only 1% of symptoms occur before the age of 10. JHD is characterized by a difference, but above all a variety of clinical symptoms, especially in the initial stage of the disease. In the case of a negative family history, it makes it difficult and definitely delay the time of making the correct diagnosis. The parkinsonian syndrome (stiffness and bradykinesis) dominates among movement disorders, not chorea. In the Westphal variant, dystonia, ataxia, dysarthria and pyramidal symptoms are observed more often than in the classical form. Mood and behavior disorders are the first symptom of the juvenile form of Huntington's disease in almost 1/3 of patients. The spectrum of disorders is very wide: from irritability, impulsiveness, depressed mood through addiction to alcohol and drugs. It may lead to psychotic states with aggressive behaviors and depressions with thoughts and suicidal attempts, which often require hospitalization in psychiatric wards.[34] Depression and suicide are a significant problem in this population, especially if they have witnessed a family member's illness.[35] Death occurs on average after 8-10 years from the first symptoms.

HD treatment

Currently, Huntington's disease is incurable, there are no effective treatments - it leads to disability and total dependence on care.

Current treatment of HD is often symptomatic and focuses in decreasing dysarthria, dystonia, swallowing complication, incontinence as well as psychological problems and irritability. Therapy for the disease and co-morbid psychiatric symptoms (psychosis or bipolar disorder, episodic aggression and agitation not managed by behavioral interventions) could be treated better by neuroleptic medications. Some patients need raising doses of anti-chorea medications over time, hence re-evaluation of therapy is advised. Some other patients may develop increased dystonia and rigidity in parallel with HD progression, thus reducing the anti-chorea medicines may be crucial. In 2008, tetrabenazine became the first drug for HD, approved in the US, due to its important reduction of chorea determined by the double-blind placebo controlled TETRA-HD study. However patients should be aware of some side effects that may occur, before treatment begins.[36] HD often leaves patients without good treatment options. The lack of treatment options combined with the inevitably deadly nature of the disease contributes to a suicide rate of 5 to 10 times higher in HD patients than in the general population.[37]

Typical course of HD

A typical person with HD gets to know about the condition when a parent is diagnosed with the disease. It happens at the average age of 15, then the person often discusses or attempts suicide. At the age of 16, he or she knows that there is a 50% risk of inheriting the neurodegenerative disease. At the age of 25 (usually already married), predictive DNA testing begins and he or she learns about the inherited mutant HD gene. Two years later, after a prenatal test result is negative for the disease, a woman may have her first child born. At the average age of 34 years, he or she may be diagnosed with beginning of cognitive and motor signs of the disease. In the next 5 years, he or she may be dysfunctional at work and can experience the death of her affected parent. At the average age of 46, a person may be placed in a long-term care facility for 24-hour assistance. The typical person with HD dies in her early 50s. The mutant genes display the same phenotype as heterozygotes, and the phenomenon of "anticipation".[38]

The unique nature of Huntington's disease

The unique nature of HD results from its inheritance. The disease in the family extends over several generations. Every child who has an HD parent has a 50:50 chance of inheriting the faulty gene. Diagnostic and preclinical tests that have been performed since 1993, confirm unambiguously whether a person is ill or not. In every person who has the result of additions, will definitely develop HD, hence such fears in potential patients before performing the genetic test.[39] However, a small number of potentially endangered people are deciding to implement them. The disease disrupts the entire family system. It appears at the moment of the greatest life stabilization, when the most important decisions related to even having children are taken, when the next generations - grandchildren - exist. This situation cannot be reversed. HD does not disappear with the death of the patient, as is the case in other diseases. All children may get sick and each of them may have a different form and other clinical symptoms.

There is always a change in relationships within a family. A marriage may break up because of the blame on the spouse for transferring the gene.

In HD, there is also a unique impact of the disease on family caregivers, who often take care of several generations of patients (parent, spouse, siblings, children). They are afraid about getting sick or that HD may develop in other family members. An additional burden is the tension due to the decision to pass this information to children and other family members.[40] The disease is hidden in the family, it is not discussed on a daily basis, but it is always present in it. It is hidden for fear of social stigmatization or discrimination.[41]

The carrier "silently observes" subsequent family members in terms of possible symptoms and effects of HD, and this is very difficult due to the variety of disease symptoms.

Conclusion

The unique nature of the disease and the complex problems of patients and their families are a challenge for healthcare professionals. HD is a rare disease and employees of both medical and social assistance do not have experience working with people and families affected by HD. They are not always prepared to solve problems resulting from the complex dynamics of change in families with Huntington's disease, from multigenerational disease. You should also pay attention to family carriers, they bear the main burden of caring for the sick in the family.

In our country since 2002, there is the Polish Huntington's Disease Association, which associates people with HD, their carriers and relatives as well as doctors and medical staff (http://www.huntington.pl).

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