GENETIC TESTING IN DIAGNOSIS ELUCIDATION

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Abstract: *The genetic test confirms or invalidates a genetic disease, playing a crucial role in the diagnosis and care of the patient. We present the case of a 38-year-old patient who has experienced attention, concentration, memory deficiencies and increased irritability 5 years ago. Their evolution is associated with involuntary movements of the upper and lower limbs. Because the onset of the symptomatology coincided with the passing of the patient through a very stressful period, it was decided to admit her to the Psychiatric department on numerous occasions. Extensive etiopathogenic evidence led to the confirmation of Huntington's disease diagnosis following the genetic test (48 CAG repeats at the level of one allele).*

INTRODUCTION

Through the mechanism of the genetic code, there are transmitted features and predispositions, pulses and tendencies with a role in the rhythm and the trajectory of content of one individual's psychological development. The individualization of the individual's language and personality is conditioned by learning and motivation exercises, depending on environmental factors.(1)

The nervous system is more frequently affected by a genetic abnormality than any other system of organs, probably due to the large number of genes involved in its development (approximately one-third of the human genome). One third of all hereditary diseases also have a neurological component. Neurogenetic diseases can be divided into inherited metabolic diseases of the nervous system, development diseases of the nervous system (most of them recognizing the acquired chromosomal aberrations with non-Mendelian transmission as production mechanism), and finally, hereditary-degenerative diseases in the emergence of which the influence of genetic factors is recognized.(2)

Huntington's disease is a neurodegenerative, chronic, progressive disease and is the most common cause of primary chorea. Since the onset of the disease, the mean survival rate is 15 years. It is a genetic disease that is transmitted autosomally dominant with complete penetration. The responsible gene is found at the end of the short arm of chromosome 4(4p16.3) and is called IT15. The genetic defect consists in the abnormal repeat of the CAG nucleotide triplet (cytosine-adenine-guanine) encoding glutamine. The coded IT15 protein is called huntingtin and its normal function is not yet known. The critical threshold for disease emergence is the minimum 35 repeats of the CAG triplet, which results in a long polyglutamine sequence in huntingtin molecules. The longer this chain is, the sooner the onset of the disease. It is known that this amplification of the CAG repeat occurs from one generation to another, and the more and more early onset of the phenomenon is called anticipation. Since the modified huntingtin can no longer be removed by the ubiquitin-proteasome system, it is initially accumulated intracytoplasmatically. Subsequently, after a selective proteolysis process, it is transported at the nuclear level, where it forms aggregates that ultimately lead to neuronal death. Neural loss is predominantly located in certain regions of the central nervous system, the caudal nucleus and the putamen being the most affected, which is also macroscopically revealed in the neuropathological examination. From a neurochemical point of view, the disease is characterized by a marked decrease in the amount of Gamma-Aminobutyric Acid (GABA) and glutamate decarboxylase (the enzyme that synthesizes GABA from glutamate) in the basal ganglia. The levels of acetylcholine, encephalin and P substance are also reduced.(3)

Huntington's disease is a neurological disorder with a symptomatic triad composed of dyskinesia (behavior disturbance), behavioral disorders and dementia.(4)

It is the most common choreiform neurodegenerative disorder.(5)

CLINICAL CASE

We present the case of a 38-year-old patient who has experienced attention, concentration, memory deficiencies and increased irritability 5 years ago. Their evolution is associated with involuntary movements of the upper and lower limbs. Because the onset of the symptomatology coincides with the passing of the patient through a very stressful period, it is decided to admit her to the Psychiatric department on numerous occasions. Following the psychotherapy and the treatment with Tiapridal and Rivotril, a slight improvement in symptoms is observed.

Personal pathological antecedents are insignificant, and the heredo-collateral antecedents are declarative: mother with hypertension. The patient denies exposure to toxic factors.

Systemic objective examination: Blood Pressure (TA) 130/80 mmHg, ventricular rate (AV)-84/minute regular, electrocardiogram (ECG)-sinus rhythm.

Neurological examination: conscious and cooperative patient, walks without support, disordered movements of all limbs (choreic), perioral and ocular dyskinesia, axial and limb muscular hypotonia, without motor deficits, without dysmetricity at the index-nose or heel-knee test, globally live

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symmetrical deep tendon reflexes (ROT), plantar reflex in flexion, without surface or deep mio-arthro-kinetic sensitivity disorders, apraxia, executes simple and inconstantly complex orders, dysarthria without sphincter disorders.

The diagnosis of extrapyramidal syndrome of bilateral hypotonic-hyperkinetic type is formulated (Huntington's chorea under observation).

Neurological-cognitive assessment: MMSE = 28/30 points (- 1 point in information reproduction, -1 point in language - copying the drawing), MoCA = 19/30 points (- 1 point of visual-spatial integration, - 2 points of attention, -1 point of language, - 1 point of abstraction, -5 points of reminder).

Native MRI cerebral exam.

Results:

Several non-specific, homogeneous, diffusely delimited areas of glyosis, hyperintense T2 and FLAIR, isointense T1, located deeply in the semioval centers and bilaterally radiated corona.

Slight flair hypersignal at the level of the bilateral putamen, relatively symmetrical, in the anterior third.

Enlarged perivascular spaces in the basal nuclei.

Atrophy of the corpus callosum.

Brainstem and cerebellum with RM morphology within normal limits.

There are no substitutional masses for the spaces at the level of the cerebellopontine angle or in the peripontine tank.

Expansion of silvian valleys and of the cortical pericerebellar and pericerebellum sulcuses.

Ventricular system located on the midline, symmetrically enlarged, without signs of intracranial hypertension.

Paranasal and mastoid sinuses with normal development and pneumatics.

Conclusions:

Diffuse, symmetrical cerebral atrophy.

Ventriculomegaly.

Genetic testing - molecular screening for the identification of CAG trinucleotide expansion in the HTT gene (Huntington's disease).

Method: After the extraction of genomic DNA, the repetitive region (CAG)n in the HTT gene was amplified. The resulting fragments were analyzed to estimate the number of (CAG) repeats.

Result:

The allele 1: 49 ± 2 CAG repeats.

The allele 2: 17 ± 1 CAG repeats.

The expansion of CAG trinucleotides in the HTT gene with clinical significance has been identified.

The diagnosis of Huntington's disease was confirmed.

Individuals who are not affected show expansions of up to 26 repeats. Between 26 and 37 repeats represent a pre-mutation (with increased risk for descendants). Patients with Huntington's disease have more than 39 repeats on an allele.

The genetic test has been repeated and confirmed both in the country and abroad.

DISCUSSIONS

What is Huntington's disease (HD)?

HD is clinically characterized by the presence of a triad composed of chorea, cognitive decline, and a positive family history. Chorea consists of involuntary, continuous, abrupt, rapid, brief, unsustained irregular movements that flow randomly from one body part to another. Patients can suppress chorea partially and temporarily and frequently incorporate movements into semipurposeful activities(parakinesia). Affected patients have a peculiar, irregular gait. Besides chorea, other motor symptoms include dysarthria, dysphagia, postural instability, ataxia, myoclonus, and dystonia. Motor impersistence is the inability to maintain constant voluntary muscle contraction such as in the characteristic milkmaid's grip during a handshake. The tone is decreased, and the deep reflexes are often hung up and pendular.(6)

The signs and symptoms grow insidiously, starting between the ages of 35 and 50. Dementia or psychiatric disturbances (e.g. depression, apathy, irritability, anhedonia, antisocial behavior, bipolar or schizophreniform disorders) occur before or simultaneously with the movement disorders. The disease evolves, walking becomes impossible, swallowing becomes difficult and dementia is severe. Because most patients require institutionalization, discussions about the terminal care period should take place early.(7)

Virtually all patients have a family history of a similar condition transmitted in an autosomal dominant manner. Caudate and putamen atrophy on neuroimaging studies is another feature supportive of the diagnosis of HD.(6)

Once the disease has been observed in its full form, its recognition does not require any particular clinical perspicacity. The main difficulty occurs in patients whose family history is lacking, but who express progressive chorea, emotional disturbances and dementia. This problem has largely been overcome with the identification of the mutation. It is now possible to analyze the DNA from a blood sample in order to confirm or exclude the diagnosis. The presence of more than 39 CAG repeats in the Huntington site essentially confirms the disease and provides some information about the presumed onset age; a smaller number of repeats leave room for interpretation, and sequences between 39 and 42 repeats may not manifest if the patient does not live enough for the disease to develop.(8)

What is the Westphal variant?

In 10% of cases of HD, the onset is before age 20(juvenile or Westphal variant). The disease is then characterized by the combination of progressive parkinsonism, dementia, ataxia, and seizures.(6)

What are other common causes of chorea?

It is probable that levodopa-induced chorea in parkinsonism in the most common cause of chorea. Usually this diagnosis is not difficult once the history is available. The combination of chorea and psychiatric symptoms can be found in Wilson's disease. However, the diagnosis is easily made by finding a Kayser-Fleischer ring, low-plasma ceruloplasmin, and evidence of hepatic dysfunction. Sydenham's chorea is a form of autoimmune chorea, preceded by a group A streptococcal infection. Rarely encountered in the United States, this condition is one of the most common causes of chorea in underdeveloped areas. Systemic lupus erythematosus and primary antiphospholipid antibody syndrome are other causes of autoimmune chorea. Senile chorea is a condition in which chorea is the only feature; no family history of HD is present.(6)

How is genetic diagnosis of HD confirmed?

The HD gene (designated IT15) has been identified near the tip of the short arm of chromosome 4(4p16.3).(6) An unstable expansion of the CAG repeat sequence is present at the 5' end of this large (210 kb) gene.(6) The HD gene encodes a 348-kDa protein called huntingtin.(6) Aggregation of mutant huntingtin may be part of the pathogenesis of HD.(6) With 40 or more repeats, a person develops HD with 100% certainty, but with repeats of 36 to 39, there is incomplete penetrance. The intermediate range, from 27 to 35 repeats, does not cause HD, with a few reported exceptions. All alleles of 27 repeats and higher are unstable and prone to expand in future generations,

particularly when transmitted by a male parent.(6)

There is a general relationship between the number of CAG repeats and the age at the onset of symptoms. It was found that the longer sequence on any of the two alleles is the one that determines the onset age, the magnitude of the expansion on the normal allele having no influence.(8)

HD families also display "anticipation" or progressively earlier onset of disease in successive generations, typically with increasing CAG repeat size.(6) Such findings allow genetic testing of at-risk individuals before the onset of symptoms.(6) However, until effective treatment is available for HD, many ethical and legal dilemmas associated with genetic testing remain to be solved. (6)

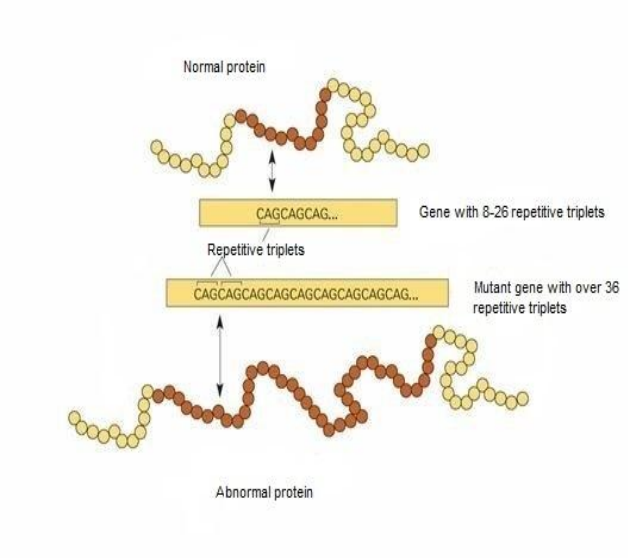
What are the neuropathologic findings in HD?

The most important pathologic findings in HD are neuronal loss and gliosis in the cortex and striatum, particularly the caudate nucleus. Chorea seems to be primarily related to loss of medium spiny striatal neurons projecting to the lateral pallidum. This results in functional hypoactivity of the STN with consequent hyperactivity of the thalamic tier. Cortical thinning in various parts such as sensorimotor, parietal, occipital, and inferior temporal lobes is now being recognized in HD and has been associated with earlier cognitive symptoms.(6)

What is the treatment for HD?

Unfortunately, to date no therapeutic intervention has been capable of halting the relentless progression of HD. In the adult form, death occurs after a mean duration of 15 years, whereas in the juvenile variant the mean survival is 9 years. In both observational and randomized controlled trials tetrabenazine has been shown to reduce HD chorea significantly. Tetrabenazine is now considered the treatment of choice for chorea associated with HD as well as other choreas. Other treatments include neuroleptics, which temporarily relieve both chorea and psychosis by interfering with dopaminergic transmission. However, these drugs cause several side effects, including TD. Selective serotonin reuptake inhibitors are the first-choice class of drugs for the treatment of depression in HD also have been reported to be effective in the treatment of irritability and obsessive-compulsive behaviors.(6)

Figure no. 1. The normal and the mutant HTT gene together with the associated proteins



(Adaptation after *publications.nigms.nih.govfindingssept08imageshunt_gene_big.jpg*)

CONCLUSIONS

Genetic testing is especially important if family history is lacking, but the clinical picture suggests Huntington's disease.

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