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Juvenile Huntington's disease: a case report and literature review

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Huntington's disease is the most frequent neurodegenerative disease with a prevalence of fewer than 10 cases per 10,000 inhabitants; the juvenile form is responsible for less than 10% of all cases. Huntington's disease belongs to the group known as "triad syndromes," which evolve with cognitive, motor and neuropsychiatric manifestations. Around 30% of patients debut with behavioral symptoms, which are a major challenge for management by patients, families, and caregivers.

Huntington's disease (HD) is reviewed and a case of juvenile onset is reported in this article. The characteristics of juvenile-onset Huntington's disease (HD) differ from those of adult-onset HD, as chorea does not occur, although bradykinesia, dystonia, and signs of cerebellar disorder, such as rigidity, are present, frequently in association with convulsive episodes and psychotic manifestations.

Keywords:
Huntington's disease, juvenile variant, abnormal behavior

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Enfermedad de Huntington juvenil: presentación de un caso y revisión bibliográfica

La Enfermedad de Huntington es la patología neurodegenerativa más frecuente, con una prevalencia menor de 10 casos por cada 100000 habitantes, representando la variante juvenil menos del 10%. Pertenecce al grupo de los llamados "síndromes triada", que cursan con manifestaciones psiquiátricas, motrices y cognitivas. Alrededor del 30% de los pacientes debutan con alteraciones conductuales, representado su manejo una de las mayores dificultades tanto para el paciente como para su familia o cuidadores.

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En este artículo realizamos una revisión de la enfermedad y exponemos un caso de inicio juvenil, cuyas características difirieren de la presentación habitual en la edad adulta, ya que no aparece corea pero sí bradicinesia, distonía y signos de alteración cerebelosa como la rigidez, con mayor asociación con crisis convulsivas y clínica psicótica.

Palabras clave:
Enfermedad Huntington, variante juvenil, alteraciones de conducta.

INTRODUCTION

Huntington's disease (HD) was described in 1872 by the American physician George Huntington, based on observations of patients attended by his father and grandfather in East Hampton, Long Island. The condition was designated "hereditary chorea."

There are references to an epidemic dance as early as 1374 ("Saint Vitus' dance"). In 1500, Paracelsus suggested that chorea originated in the central nervous system. In 1832, John Elliotson identified hereditary forms of chorea and Charles Waters, in 1841, mentioned HD in a letter to a friend, describing it as a "singular convulsive disorder, clearly of hereditary origin and more common among the lower classes."

In 1932, P.R. Vessie found, during an investigation of a family with HD, that the disease arose from three men who emigrated in the 17th century from England to the town of Salem, in the New World. Many of their female descendents had been burned at the stake during the famous Salem trials¹ because they were considered witches. He also found that the families affected generally had many children, some of whom exhibited criminal behavior, hypersexuality, depression, and suicide attempts.

We report the case of a female patient with juvenile-onset Huntington's disease who was admitted to acute care of the Psychiatry Department due to attempted suicide, severe behavioral disorders, and hard-to-control seizures.

CLINICAL CASE

The patient was an 18-year-old woman who was admitted to the intensive care unit (ICU) after an attempted suicide by drug overdose.

Her medical and surgical history included no known drug allergy, asthma diagnosed in childhood that had not required treatment since then, seizures since the age of 16 that were being treated with oxcarbazepine, and cesarean section at the age of 16, during which tubal ligation was performed without the knowledge of the patient. She had used cannabis since the age of 11 years, formerly used cocaine and intravenous heroin, and occasionally drank alcohol.

The patient's family history included the death of her mother in a psychiatric hospital at the age of 37, with epilepsy and diagnosed of Huntington's chorea. Her maternal grandfather had been diagnosed clinically of Huntington's chorea. Her maternal aunts were receiving psychiatric treatment and presented tremor of the limbs; one was confined to a wheelchair. Her father was a heavy drinker and had numerous encounters with the law as a result of aggression and attempted homicide using a knife.

Her psychiatric history included being adopted at age 3. The patient was seen by a psychologist at the age of 5 years because her adoptive mother found her to be very restless. She was discharged after a few sessions with the recommendation that limits be set. No follow-ups or controls were carried out until she was 12 years old, when she was admitted to a pediatric hospital for 3 months for behavioral disorders and heteroaggressive behavior towards her mother. She had several episodes of self-aggressive behavior at the age of 15, with a suicide attempt in which she cut her veins and jumped out of a moving vehicle, which required hospital admission. She had two hospital admissions after drug overdose (oxcarbazepine) suicide attempts, both cases requiring admission to the ICU. On discharge she was diagnosed of "acute psychotic disorder" and "harmful cannabis use" and was sent to a foster care center until she was transferred to a psychiatric clinic. She remained confined in the hospital until she reached adulthood. She received the diagnoses of "Other Non-Organic Psychotic Disorders," "Mixed and Other Personality Disorders," "Mental and Behavioral Disorders Due to Poly Drug Use" and "Dissociative (and Conversion) Disorder." At discharge she was prescribed haloperidol drops 30-30-30, clorpromazine 25 mg 1-1-1, levomepromazine 25mg 0-0-1, diazepam 10mg 1-1-1, flunitrazepam 1mg 0-0-1, and oxcarbazepine 300mg 1-1-1. While she was institutionalized, she tried to escape from the center twice, attempted suicide once by oxcarbazepine overdose, and assaulted another patient with a knife without causing serious injuries. Six days after discharge from the hospital when she reached adult age, she was again admitted to the ICU for a new drug overdose.

Previous personality: She had always been a restless child with a tendency to irritability. Since the age of 12 years, her irascibility had become exacerbated and she was excitable, very impulsive, and had very low frustration tolerance. At the age of 16 years, she started to exhibit explosive behaviors, with attacks of violence and numerous suicide threats. A chronological relation existed with the onset of seizures. She was highly promiscuous and often ran away from home. However, her mother described her as sociable and extroverted, very affectionate and docile when calm, complacent, but with little social awareness. She was presumptuous and had a tendency to fabulation.

Personal history: The patient was a native of Brazil, born of an unwanted pregnancy due to her family's precarious economic situation. During pregnancy, her mother had obstetric complications due to malnutrition. The delivery was vaginal and uncomplicated. She was nursed by her mother. One year after delivery, her mother started to exhibit behavioral disorders and was frequently tied up by the patient's father until the mother was finally admitted to a psychiatric hospital when the patient was 3 years old. At this time the patient was adopted by a single woman who was an acquaintance of the family when her father refused to take responsibility for her.

Her psychomotor development was normal. She suffered repeated respiratory infections up to the age of 5 years and showed multiple tics during childhood.

She has resided in Spain since the age of 7. When she attended school, she was expelled several times for behavior disorders.

At the age of 10, the patient returned to Brazil where she lived in a situation of poverty and social exclusion; at this age she began to consume drugs. She became pregnant at the age of 15 and began to suffer seizures and important behavioral disorders after delivery. She was hospitalized after a suicide attempt.

At discharge, she returned to Spain with her daughter. Months later, she was admitted to the hospital for oxcarbazepine overdose that required admission to the ICU. Two days after discharge, she again tried to commit suicide and was readmitted to the ICU and then to psychiatry. She was transferred from the psychiatry department to a psychiatric clinic where she received schooling to the 10th grade level.

At present, the patient is living with her adoptive mother. She is the mother of a two-year-old girl who is cared for by her adoptive aunt and uncle. The patient was a charge of the autonomous community until she reached the age of 18 due to inadequate family support. She is now completing the process of regularizing her legal situation in Spain.

Current disease: This 18-year-old female patient was admitted to the emergency room in the early morning after being picked up by emergency services in a subway station, where she was found with diminished consciousness (Glasgow 10 points) secondary to an oxcarbazepine overdose and alcohol intoxication.

She was admitted to the intensive care unit. At 3:00 AM she presented two episodes of generalized tonic seizures that remitted with the administration of 13 mg of intramuscular diazepam. She later had a partial left-body episode and was given a loading dose of phenytoin (5 ampoules), followed by an infusion of valproic acid. A cranial CT scan was normal and EEG revealed a focal lesion in the left fronto-temporal zone.

The next morning she was evaluated in a psychiatry inter-consultation visit. The patient explained that the day before, after arguing with an unknown man with whom she had just had sexual intercourse, she drank a large amount of alcohol (about 10 bottles of beer) and began to have imperative auditory hallucinations in which she was ordered to commit suicide. She obeyed and took oxcarbazepine tablets in the kitchen of her home, where her aunt and uncle were. She then went to the subway, where she was attended by emergency services. She expressed possibly overvalued ideas of harm which she focused on her aunt and uncle, accusing them of trying to take her daughter away, this being the cause of her present suicidal, although vaguely structured, ideation. She was admitted to the acute ward of the psychiatry department. That same night she had an episode with loss of consciousness and generalized convulsions with tonic-clonic movements, rolling of her eyes, and no loss of sphincter control, which remitted with the intramuscular injection of an ampoule of diazepam.

In an interview with the mother, the mother stated that since the patient had been discharged from the psychiatric clinic six days earlier she had been very active, continuously going in and out of the house, wearing a lot of makeup, provocative clothing and exhibiting sexual disinhibition. She indicated that for the last 2 years, beginning shortly after the birth of her daughter, she had been very irritable, with innumerable episodes of self-destructiveness and physical and verbal aggressiveness toward others. She denied talking to herself or unmotivated laughing or perplexity, but she noted that she had sometimes heard voices; when asked, the patient responded that her grandmother was speaking to her.

An inter-consultation with neurology was ordered for management of her seizures and with cytogenetics to rule out Huntington's disease as the origin of her condition.

From the start, the patient had a regressive, infantile attitude and exhibited significant sexual disinhibition. She

was unpredictable and had numerous episodes of self- and heteroaggressiveness. The patient has had many incidents of psychomotor agitation requiring mechanical restraint and sedation, some being so violent that intervention was required by security personnel and the attention of emergency room staff.

She self-induced vomiting after eating, claiming that she wanted to lose weight. She explained that she had been doing this for years, adding that eating increasingly disagreed with her. On the other hand, she craved food, with compulsive and very rapid eating, having choked on her food several times, some of which required performance of the Heimlich maneuver to prevent asphyxiation.

During her admission she had more than 120 seizures episodes and up to 54 epileptic episodes were counted. These episodes were described as a sudden loss of consciousness and abrupt fall to the floor with some mild head injury. In some cases, the episode was preceded by a feeling of dizziness and lasted 1 to 2 minutes with violent generalized tonic-clonic movements. However, in some cases she only had tonic convulsions with a clenched jaw, rolling of the eyes, opisthotonos, sphincter relaxation, reduced oxygen saturation and sialorrhea in some cases. Almost all of the episodes described above were controlled with 1 or 2 ampoules of diazepam 10 mg injected intravenously. In the post-critical period she was perplexed and less responsive to external stimuli. One time she had sinus arrhythmia of 84 to 116 beats per minute.

She had convulsive episodes of another nature, most preceded by the patient feeling cross, but apparently without any aura, with disconnection from her surroundings; these episodes were of longer duration (2 to 4 minutes) and had less intense tonic-clonic movements, no sphincter relaxation, stable vital signs, and a very short or nonexistent post-critical period. Most episodes remitted without medication.

After recovery from the post-critical period, the patient tended to be very restless, with auto- and heteroaggressive attacks.

She has presented episodes of perplexity that lasted hours, during which she made no visual contact and was mute, giving the impression of hallucinatory-delusional activity. When the episode ended, the patient was extremely anxious, claiming that she could see and hear her daughter. According to the patient, this is not the first time that this has occurred and it occurs when she feels intense anxiety.

She attempted suicide many times while institutionalized, including trying to hang herself, cutting the veins in her throat, and taking a drug overdose. Many of these attempts required admission to the ICU. The patient states that the precipitating factor was that she understood that she could

not fulfill her duties as a mother because of her illness. She has also had uncountable self-harm attempts, such as eating plastic and glass.

She has been caught on several occasions hiding knives and making heteroaggressive threats towards other patients.

In the psychopathologic examination, the patient is alert, aware, and oriented in time and space and auto- and allopsychically. She is attentive, approachable and partially cooperative. She looks well-groomed. Her attitude is regressive and occasionally complacent. She exhibits mild psychomotor inhibition with slight rigidity and bradykinesia. She shows reduced eye contact. Referred and frank anxiety is present and the patient demands medication to suppress her autoaggressive ideas. Her language is spontaneous and slow, with an increased response time; her discourse is coherent but poor. Low mood with emotional lability, although with conserved affective resonance. She tends to be irritable. Apathy, asthenia, anergy, abulia and anhedonia are absent. She does not have pathologic ideas of guilt, ruin, or hypochondriac thoughts. The patient has a chronic death wish, with vague suicide planning, related to her awareness of her deterioration. She has conserved chrono-biological rhythms, bradypsychia. Possibly overvalued ideas of harm focused on her adoptive family and some of the hospital ward staff. No influence phenomena were present. Complex visual and auditory hallucinations were present, almost always in the form of her daughter crying, which made the patient feel intense anxiety. She showed marked self-aggressiveness and uncontrollable heteroaggressiveness. No derealization or depersonalization phenomena were present.

In an attempt to control her behavioral disorders, a variety of medications have been prescribed (olanzapine, aripiprazole, haloperidol, quetiapine, oral and depot risperidone, and lithium salts) with scant therapeutic response. The only medication that calmed her to some extent was intramuscular pipothiazine 100mg every two weeks, in addition to anticonvulsant agents (valproic acid 1500 mg a day, lamotrigine 125 mg a day). Treatment with ciproterone acetate was started at a dose of 200 mg.

Complementary Tests

Blood tests, including the basic blood cell count, differential count, proteins, electrolytes, ESR, PCR, biochemistry, lipid profile, liver profile, thyroid profile; amylase-lipase; kidney function and copper levels. All parameters were normal except for CK 209 and leukocytes 55.1%. Urinalysis and urine sediment: no abnormal findings. Urine culture: negative. Valproic acid levels (with 1500mg daily): 91 ug/mL. HBV, HCV, HIV and syphilis serology: negative. Normal ECG. EEG: focal lesional activity in the left frontotemporal zone. Cerebral CT scan without contrast: no

pathologic findings. Cerebral MR: no alterations in signal intensity were observed in the white or grey matter. The basal ganglia showed no significant abnormalities. No alterations of the midline structures were observed. SPECT: irregular cortical uptake was visible in transverse, sagittal and coronal projections. The right putamen and head of the left caudate were hypoperfused. Magnetoencephalography: signs of affection of central temporal structures of the left hemisphere. The background rhythm was normal.

Neuropsychological Evaluation: the neuropsychological examination was conducted according to an evaluation protocol consisting of the following tests: Edinburgh Inventory (laterality), Buschke Test (memory), Symbol-Digit Test (attention and processing speed), Pien fist-palm-hand Subtest (limb kinetic apraxis), COWAT (categorical evocation), Stroop Test and Luria Go-No Go Tests (control of inhibition), London Tower (planning and sequencing), PASAT and Brown-Peterson tasks (working memory), Trail-making Test (cognitive flexibility), WAIS similarities and proverbs subtests (abstraction), and the Pien Problem-solving Subtest (mathematical reasoning). The patient was left-handed, cooperative, and disoriented in time. Conclusions: The patient presents a picture of focal cognitive deficits characterized by disturbances in the processes of short-term memory fixation. She has difficulty in sustained attention, working memory, planning, impulse control, problem-solving, abstraction, limb praxis and reduced categorical evocation. This array of neuropsychological alterations corresponds to moderate-grade delayed maturation of cortico-subcortical focal dorsolateral prefrontal zones and cortical affection of temporal zones. At the same time, she has a series of behavioral disorders characterized by: irritability, poor impulse control, disinhibition, and emotional instability, which correspond to moderate-to-severe grade affection of subcortical zones of the orbitofrontal zone and anterior cingulate area that is affecting the patient's social and personal life. Clinical judgment: Moderate-to-severe deficitary syndrome of the cortico-subcortical type in the dorsolateral prefrontal, orbital, and anterior cingulate zones, as well as cortical affection of the temporal zones.

Cytogenetics Inter-consultation: The patient has a normal allele (15) and an expanded allele (52) of the IT15 gene, which is associated with Huntington's disease, thus confirming the diagnosis.

EPIDEMIOLOGY

Huntington's disease (HD) is characterized by motor, cognitive, and psychiatric disorders.

It is the most common neurodegenerative disease, with a prevalence in the Caucasian population of 5 to 7 per 100,000 inhabitants, greater than in other races, and is due

to a higher number of CAG triplets.^{2,3} It is also common in central Asia and exceptional in Finland and Japan; its prevalence in blacks may be underestimated.⁴

The typical age of onset is between 35 and 40 years, although it may debut at any age. In 10% of patients, HD occurs before the second decade of life; of these patients, 5% have an onset before the age of 14 and 1% before the age of 10. In the juvenile subtype, transmission is paternal in 70-80% of cases⁵ and the disease is characterized by bradykinesia, rigidity, and important cognitive disorders, with epilepsy occurring in 50%. When the onset of HD comes after the age of 65, the predominant clinical manifestations are choreic and cognitive function is relatively well conserved.⁶

The mean duration of the disease is 17 years, with variants in evolution from 2 to 40 years.

Spermiogenesis is more unstable than oogenesis, so the affected patients with the largest number of triplets are male and there is an association with early-onset disease and with genetic anticipation phenomena.⁷

No family history is found in 8% of patients,⁸ although most cases are transmitted paternally.

The possibility of a lower incidence of cancer in patients with HD has been reported, possibly in relation to positive regulation of TP53.⁹

ETIOPATHOGENESIS

HD is a hereditary disorder with a dominant pattern and genetic anticipation phenomena. The origin of HD on the IT15 gene of chromosome 4p16.3 was identified in 1983.¹⁰ Mutation of this gene expands the repetition of polyglutamine, (CAG)_n, which is situated on exon 1. In the general population, triplet repeats range from 6 to 35, whereas in patients with HD 40 to 121 repeats are found.¹¹ A risk of hereditary transmission exists with 27 to 35 repeats and penetrance is incomplete with 35 to 39 repeats.

The huntingtin protein that is encoded, of unknown function, accumulates in neuronal cytoplasm and nucleus,¹² which leads to cell apoptosis.¹³ It is a ubiquitous protein¹⁴ since neuronal loss is observed in the striate (particularly the caudate and putamen), cerebral cortex (the frontal and temporal lobes above all), hippocampus and subthalamic nucleus, resulting in the loss of up to 25% of cerebral volume.¹⁵ In the case of juvenile-onset disease, cerebellar degeneration has been observed,¹⁶ as well as alterations in the energy metabolism of peripheral tissues¹⁷ that are not observed in adults.

Disturbances in neurotransmission systems have been observed, with a reduction in dopamine receptor density,¹⁸

which is closely related to cognitive deterioration,¹⁹ especially of executive and memory functions.

It has been hypothesized that pathogenic mechanisms may differ in accordance with the age of onset of the disease, suggesting that the debut of juvenile-onset HD is much more dependent on the number of CAG triplet repeats than the adult variant. However, when the number of repeats is very high (more than 80), the correlation between triplet number and age of onset is lost, which shows that other epigenetic mechanisms²⁰⁻²² contribute to phenotype variability.⁵

CLINICAL MANIFESTATIONS

Psychiatric manifestations²³ present the most difficult problems for patients and caregivers,²⁴ being the first manifestation of HD in 31% of cases.²⁵ The progression of symptoms, particularly in the early stages, is uncertain.²⁶

In pre-diagnostic phases, changes in personality, irritability, disinhibition, anxiety and difficulties associated with multitasking are common. Alterations in saccadic ocular movements are seen.²⁷

Frequent symptoms (20-50%) are depression, disinhibition, euphoria,²⁸ and aggressiveness; 5 to 12% of patients suffer obsessions and compulsions,²⁸ delusional ideas, hallucinations and sexual disorders being rare (less than 5%).^{8, 28} Sexual disorders include reduced libido and inhibition of orgasm as well as hypersexuality; the development of paraphilias not being uncommon.²⁹ Most psychotic clinical manifestations coincide with cognitive deterioration or dementia.^{6, 28} Apathy and lack of initiative, dysphoria, irritability, impulsive behavior, agitation, anxiety, careless personal care³⁰ and impaired judgment are typical.

Depression occurs in 50% of patients and suicidal thoughts are common, with more than 25% of patients attempting suicide repeatedly. Suicide is consummated 5 to 10 times more often than in the general population³¹ (about 5 - 10% of patients).

Cognitive dysfunction³² usually is manifested in the long-term memory, as well as in executive functions like organization, planning, checking, flexibility, and acquisition of new motor skills.

The wide variety of symptoms, many of them reflecting frontal dysfunction, is consistent with asynchronic degeneration of the fronto-subcortical circuit,³³ e.g., dorsolateral syndrome, which is expressed as a depressive mood and loss of flexibility, and orbitofrontal syndrome expressed as impulsivity, euphoria, and changes in personality.³⁴

Patients usually conserve appetite, but weight loss is typical.³⁵ Weight loss has been related to a large number of CAG repeats,³⁶ possibly as a consequence of hypermetabolic state.

As the motor and cognitive clinical manifestations worsen, patients die from complications of falls, inanition, dysphagia, or aspiration;⁸ delirium is common.^{28, 37}

Atypical presentations exist, which are more frequent in juvenile-onset HD, in which chorea is absent but bradykinesia, dystonia and signs of cerebellar alterations such as rigidity do appear, with a more frequent association with seizures and progressive myoclonic epilepsy^{38,39} and psychotic clinical manifestations. When the condition appears in childhood, manifestations of autism, major behavior disorders, learning difficulties⁴⁰ and spasticity⁴¹ are frequent.

A form with an important component of rigidity (Westphal variant) has been described, with major cerebellar atrophy, which is associated with a rapidly progressive course in young patients with large triplet expansion.

DIFFERENTIAL DIAGNOSIS

When typical clinical manifestations and a positive family history are present, the diagnosis is not difficult. However, there are diseases that have a phenotype that is indistinguishable from HD,⁸ such as Huntington-like disease 2 (which is frequent in African-Americans and South Africans), dentato-rubro-pallido-luysian atrophy and other familial conditions. Other diseases course with CAG triplet expansion¹² (such as dentato-rubro-pallido-luysian atrophy, spinobulbar muscular atrophy, and spinocerebellar ataxia types 1, 2, 3, 6 and 7) and share the same characteristics of neurodegeneration, autosomal dominant transmission, and genetic anticipation phenomena. It is important to remember the high incidence of psychiatric and cognitive disorders in patients with degenerative cerebellar diseases, which suggests the participation of the cerebellum in the modulation of emotions and cognition.⁴² The differential diagnosis must be made with neuroacanthocytosis, dyskinesia tarda, chorea gravidarum, hyperthyroidism-induced chorea, vascular hemichorea, Sydenham chorea and chorea associated with antiphospholipid antibodies.

In the juvenile form, hepatolenticular degeneration and subacute sclerosing panencephalitis must be ruled out.

"Triad syndromes" (dyskinesia, dementia, and depression)²⁸ have been discussed with reference to basal ganglia degenerative diseases such as HD, Parkinson disease, and Wilson disease, which are characterized by motor, cognitive, and psychiatric manifestations.

DIAGNOSIS

The diagnosis of certainty is reached by genetic study of the mutation.

There are numerous publications on imaging techniques in HD in the literature.

The structural changes are relatively specific in the early phases of the disease, with early affectation of the caudate and putamen. The deterioration of psychomotor and executive functions, as well as the visuo-spatial and memory process, appears to be derived from basal ganglia pathology that interrupts normal cognitive processes by altering the cortico-striato-thalamo-cortical circuits.^{15, 43}

In voxel-based morphometric analysis (VBM) studies, described as the most sensitive test for quantifying atrophy,⁴⁴ a large decrease in striatal grey matter density is observed in the caudate, putamen, and globus pallidus. A gradient of neuronal loss with a caudo-rostral and dorso-ventral pattern has been suggested because stages with less evident motor and cognitive clinical manifestations are associated with less changes in the grey matter.^{45, 46} The alterations are more pronounced with greater CAG expansion,⁴⁵ although this claim is disputed.⁴⁴

Recent studies have found significant atrophy in the substantia nigra, hypothalamus, thalamus,⁴⁷ amygdala, insular cortex,^{43, 44} premotor and pre- and post-central gyri, in contrast with older studies in which the extra-striatal changes in grey matter density in the hypothalamus and cerebral cortex are not prominent.⁴⁵

In postmortem studies^{48,49} of patients with Huntington's disease, important findings include cortical thinning of the dorsolateral prefrontal cortex and occipital lobe; loss of volume of the globus pallidus and amygdala are observed only in very advanced stages.⁵⁰

Hypothalamic atrophy has been related with the reduction of dopaminergic neurons,⁵¹ disturbances in nyctemeral rhythm and sexual function with weight loss,³⁵ amygdalar atrophy with emotional disturbances, changes in personality, and deficit in the facial recognition of disagreeable emotions (such as fear and anxiety). Atrophy of the left insula appears to be related with a deficit in recognizing displeasure,⁵² particularly facial. Atrophy of the Broca area has been seen in patients with HD with impaired language, and atrophy of the ocular frontal field and pars reticulata of the substantia nigra seems to be related to the oculomotor abnormalities observed in these patients.⁵³

It has been hypothesized that neurons in HD may be at "risk" before apoptosis and that clinical manifestations appear in this phase, meaning that functional techniques

may be more sensitive than structural techniques to early changes.¹⁵

The possible existence of biomarkers in subclinical phases has been remarked.⁵⁴ Structural MR findings include changes in the volume of the striate and other cerebral regions,⁵⁴ such as the thalamus, hippocampus, amygdala, hypothalamus, cerebellum, and frontal and insular cortex, detecting atrophy of the caudate about 11 years earlier and of the putamen 9 years before clinical onset. It has even been affirmed that caudate volume may be diagnostic of HD 2 years before the debut of the disease with a certainty of 100%.⁵⁵ In functional MR we observed abnormalities in cerebral activation in response to specific cognitive and motor tasks, encountering⁵⁴ a reduction in the activation of the striate (particularly the caudate), occipital, parietal, frontal, somatomotor, and insular cortex, medial frontal gyrus and thalamus, as well as an increase in activation of the supplementary premotor cortex, superior frontal gyrus, inferior parietal lobe, and anterior cingulate.⁵⁶ The same increase in activation has been found in the hippocampus, possibly in compensation for the caudate.^{15,57} DTI reveals microstructural abnormalities^{54,58,59} with increased diffusion, particularly in the putamen, but also in the caudate, periventricular white matter, and globus pallidus, as well as in the corpus callosum, anterior and posterior margins of the internal capsule, and subcortical frontal white matter. These findings suggest that these changes contribute to the disruption of pyramidal and extrapyramidal circuits, as well as the implication of the compromised cortical circuit in subclinical cognitive and motor alterations in pre-symptomatic phases.⁶⁰ In PET and SPECT,^{58,61} we observed changes in the brain metabolism and reduction of the perfusion of basal ganglia and extra-striatal regions, especially in the prefrontal cortex and frontoparietal and temporoccipital regions, reinforcing the theory about the causal association between basal ganglia pathology, abnormal cerebral cortex perfusion, and cognitive dysfunction.^{15,62,63} A reduction in glucose metabolism and blood flow in the lentiform nucleus has been related with the severity of the motor clinical manifestations, as well as the cognitive deficit (episodic memory, attention, and motor skills), with hypermetabolism of the frontoparietal and temporoccipital cortex. Recently, microglial activation has been observed by PET in subclinical or initial phases of the disease, suggesting the possible contribution to neuronal dysfunction and death, and possibly propagating and favoring disease progression.⁶⁴ In some studies, the neurologic decline has been correlated with subcortical atrophy measured by the bicaudate radius, but suggests that the neuropsychological state correlates better with the percentage of cerebrospinal fluid, a measure of overall atrophy.^{65,66} In a study with spectroscopic MR,¹⁵ diminished signals of metabolic markers of "neuronal health" and metabolic energy (such as creatinine) in the striate were found in patients with HD, the reduction in creatinine levels

being associated with deterioration of attention, verbal fluidity, and visuo-motor skills.

Recent studies with event-related potentials (ERP)^{51,67} and low-resolution brain electromagnetic tomography (LORETA) have related HD with hypoactivation of the prefrontal cortex, particularly the anterior cingulate cortex, which may be related with a dopaminergic deficit.^{18,68}

Little has been published on EEG in HD, although a recent study reported epileptoid abnormalities in up to 74% of a sample,⁶⁹ indicating a higher frequency of these abnormalities in juvenile forms so HD should be considered in the differential diagnosis of young people with seizures.⁵ It has been observed recently that stimulating the memory reveals changes in brain function even before the onset of signs of disease.⁷⁰

We found no reports on magnetoencephalography findings in HD.

TREATMENT

At present there is no effective treatment for HD, although there are various lines of investigation.^{71,72}

The disease is managed symptomatically using medication, occupational therapy, physical therapy, and the support of social services.

It has been reported that the typical antipsychotics (haloperidol and pimocide in most studies) can improve chorea at the expense of deteriorating voluntary movements.⁷³ NMDA receptor antagonists⁷⁴ such as riluzole and amantidine⁷⁵ have been used experimentally for the treatment of motor disorders.

It also has been seen that the combination of haloperidol and lithium carbonate may control irritability and impulsivity better than monotherapy.⁷⁶ In some studies, beta-blockers (propranolol)⁷⁷ have been reported as effective.

Among the atypical antipsychotics, risperidone has been shown to improve abnormal involuntary movements and psychotic clinical manifestations.^{78,79} Olanzapine appears to be a good alternative, particularly for the control of psychiatric manifestations, with moderate results with regard to motor symptoms, possibly because of its tremor-producing effect.⁸⁰

In animal models, findings suggest that treatment with high-dose sertraline produces good control of behavioral disorders, detention of cerebral atrophy, improvement of motor symptoms, stimulation of neurogenesis, and increased life expectancy.⁸¹

The problem is that effectiveness was evaluated in a small sample of patients who were heterogeneous for disease stage and clinical manifestations.

Noteworthy experimental therapies include the search for drugs that prevent the aggregation of huntingtin protein (such as *Drosophila*⁸²), gene therapy (intracellular antibodies⁸³ and RNAi⁸⁴), neurotrophic⁷⁴ and neuroprotective factors such as coenzyme Q10^{85, 86} and transplantation of striate fetal cells with the aim of delaying or reversing HD. The results suggest certain improvement of some cognitive symptoms,^{87, 88} although questions remain regarding safety.⁸⁹

CONCLUSIONS

Huntington's disease debuts with psychiatric manifestations in approximately 30% of cases, the most frequent symptoms being changes in personality, depression, and severe behavioral disorders like disinhibition and aggressiveness.

Given the fact that numerous diseases, both neurologic and systematic, course with psychiatric manifestations, obtaining a good medical history, always including the family history and the necessary complementary tests, reduces the probability of diagnostic errors such as occurred in the case reported in this article, which delays both the adoption of adequate therapeutic measures and the search for the hospital and/or extra-hospital resources of psychological, social, and economic support that these patients require.

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