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Psychiatric symptoms in a woman with chorea-acanthocytosis

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Chorea-acanthocytosis is an uncommon neurodegenerative disorder, usually with a low rate of progression. It is characterized by Huntington disease-like involuntary movements, cognitive decline, behavioral changes, seizures and polyneuropathy.

Chorea-acanthocytosis belongs to the group of neuroacanthocytosis syndromes, a group of genetically defined diseases associated with progressive degeneration of the basal ganglia and peripheral red blood cell acanthocytes.

The onset of the disease is variable in its manifestations and psychiatric symptoms may dominate the clinical picture.

Case report: A 48-year-old woman with a history of seizures since age 35 developed behavioral and affective changes that led to her referral to our mental health unit. She had an unsteady gait, motor clumsiness, emotional instability and impulsivity. Personality changes related with medical illness were diagnosed despite a normal neurological survey.

Subsequent development of choreic involuntary movements, evidence of striatal atrophy on MRI and detection of acanthocytes in a peripheral blood smear allowed diagnosis.

The role of the basal ganglia in psychiatric manifestations and the pathophysiology of chorea-acanthocytosis are discussed.

Key words: Chorea-acanthocytosis, Neuroacanthocytosis, Psychiatric symptoms, Chorein, Basal ganglia

Actas Esp Psiquiatr 2013;41(2):133-6

Síntomas psiquiátricos en una enferma de corea-acantocitosis

La corea-acantocitosis es un raro trastorno neurodegenerativo de curso lentamente progresivo, caracterizado por movimientos involuntarios semejantes a la corea de Hungtinton, deterioro cognitivo, cambios en la conducta, crisis convulsivas y polineuropatía.

Pertenece al grupo de las neuroacantocitosis, enfermedades genéticamente definidas, en las que se asocia la degeneración progresiva de los ganglios de la base y la presencia de acantocitos en sangre periférica.

La forma de inicio es heterogénea pudiendo ser los síntomas psiquiátricos su primera manifestación.

Caso clínico: mujer de 48 años que comenzó con crisis convulsivas a los 35 años y aparición posterior de cambios de conducta y afectivos que motivaron la consulta en salud mental. Presentaba alteración en la marcha, torpeza motora, inestabilidad emocional e impulsividad y fue diagnosticada de cambio de personalidad debido a enfermedad médica, aunque los primeros estudios neurológicos resultaron negativos.

La evolución posterior con aparición de movimientos coreicos, atrofia del núcleo estriado en RMN y detección de acantocitos en sangre periférica posibilitaron el diagnóstico.

Se discute el papel de los ganglios basales en las manifestaciones psiquiátricas y la fisiopatología de la enfermedad.

Palabras clave: Corea-acantocitosis, Neuroacantocitosis, Síntomas psiquiátricos, Coreína, Ganglios basales

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INTRODUCTION

Chorea-acanthocytosis is a hereditary autosomal recessive disease[1] in which the mean age of onset is 35 years and life expectancy is shortened.[2]

It is caused by mutations in the *VPS13A* gene that encodes chorein, a protein involved in membrane structure, the intracellular transport system[3,4] and, possibly, dopamine release from neuronal vesicles.[5]

Chorea-acanthocytosis belongs to the neuroacanthocytosis syndromes, exceptionally rare syndromes with a prevalence of 1 to 5 cases/1,000,000 inhabitants for each disorder.[4] The neuroacanthocytosis syndromes include four different conditions: chorea-acanthocytosis (CHAC) and McLeod syndrome , which have clinical similarities: Huntington disease-like choreic movements,[1] cognitive decline, psychiatric manifestations, and neuropathic and myopathic involvement, and two other disorders, Huntington disease-like 2 and panthotenate kinase-associated neurodegeneration (PKAN), in which neuromuscular involvement or seizures are absent.

The absence of Kell antigens in the red blood cell membrane and the presence of cardiomyopathy differentiate McLeod syndrome from CHAC.[6,7]

CASE REPORT

The patient was a 48-year-old woman who had secondarily generalized partial seizures since age 35 and was referred to our mental health unit at age 45 for emotional instability and behavioral disorders.

The patient was unaware of her illness and complained of forgetfulness and clumsiness.

She exhibited mild disinhibition, loss of stopping distance in the course of thought or verbosity, difficulties to focus attention, occasionally disconnected speech, motor hyperactivity and a tendency to handle objects within her reach, emotional volatility with expressions of sadness, including verbalizing thoughts about death: "I would not mind dying," and moments of inappropriate laughter. She neglected her personal hygiene and made errors of judgment.

Her movements were coarse and sometimes uncontrolled, her gait was bizarre and she reported frequent falls.

We interpreted her emotional and behavioral problems as a change of personality due to her underlying medical condition, in this case epilepsy, and added low doses of quetiapine and clonazepam to the usual treatment with valproic acid. The patient had no tolerance problems and her emotional instability and restlessness improved. However, her attention difficulties, errors of judgment and motor disorders persisted.

We requested an MRI, which disclosed no significant findings, and a neurological assessment in which the patient's symptoms were categorized as "functional."

The patient continued follow-up in our clinic for four years with a clinical situation. During that time, her clinical conditions remained similar with no changes in therapy. However, she required more supervision due to difficulties with her self-management: group home, family home and psychiatric rehabilitation unit. Given the increase in her falls and motor disorders, a new neurological assessment was requested. At this time, chorea, ballism and tics (especially facial tics and some phonatory tics), occasional ataxic gait, dysarthria, and swallowing difficulties were observed.

A new brain MRI showed symmetrical bilateral atrophy of the striatum.

By correlating the clinical data and the absence of a family history, Huntington disease was ruled out; copper determination eliminated Wilson disease.

The neurophysiological study found a mixed acute myopathic-chronic neurogenic pattern.

Noteworthy biochemistry findings were CPK above 1400 U/L in several different determinations and a slight elevation of AST, ALT and LDH.

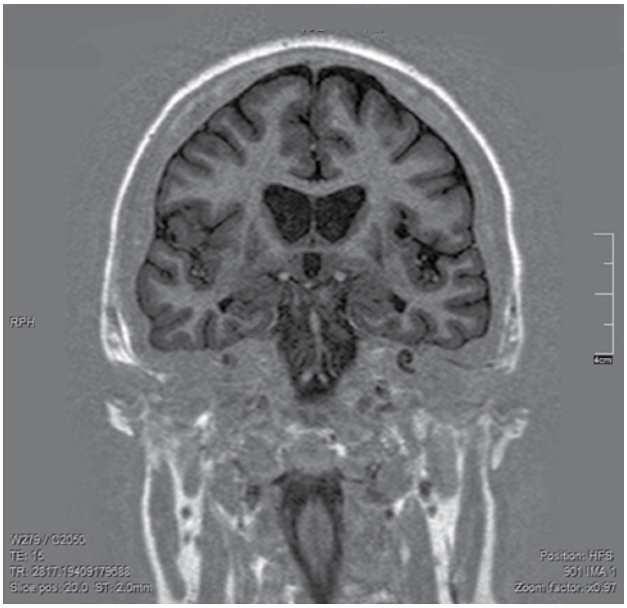

Figura 1 | *Atrophy of the striatum, MRI image (P del Valle)*

The presence of acanthocytes in peripheral blood was the definitive finding for the diagnosis of neuroacanthocytosis.

Among the neuroacanthocytosis syndromes, only chorea-acanthocytosis and McLeod syndrome course with epilepsy and myopathy, in addition to choreiform clinical manifestations. The diagnosis of exclusion between the two was made by determining Kell antigens on the red blood cell membrane; the presence of these antigens ruled out McLeod syndrome.

In order to evaluate cognitive function, which is often impaired in chorea-acanthocytosis, the neuropsychological examination included the Wechsler Adult Intelligence Scale (WAIS-III), revised Barcelona Test (RBT), Benton Visual Retention Test, Wisconsin Card Sorting Test (WCST), Stroop task and frontal system behavior scale .

The results showed great variability in the test results and different functions, with average performance on some and frank deterioration on others. Still, the results were better than expected given the patient's functional difficulties. The most significant findings were:

Two WAIS-III evaluations made in five years showed stable intellectual capacity (total IQ 82). We did not have a premorbid IQ, but low scores on tests believed to be less sensitive to cognitive impairment suggested possible borderline intelligence.

The RBT revealed an overall decline in cognitive performance: score 80 (cutoff 85), Z score: -1.06 and T score: 39.33, which was suggestive of progressive cognitive impairment. The most significant defects were in attention, verbal memory, praxis and executive functions.

CONCLUSIONS

The onset of CHAC is heterogeneous and psychiatric symptoms are often present, as in other neurodegenerative disorders: disinhibition, impulsivity, depressive disorders, obsessive disorders, psychotic symptoms or cognitive impairment of varying intensity.[8]

The presence of atypical psychiatric symptoms should lead us to search for an underlying organic cause, especially when these symptoms are the form of onset of the disorder.

The role of the basal ganglia in the pathogenesis of psychiatric symptoms derives from the fronto-subcortical circuits.[10] Alexander proposed five main circuits, two related to motor function and the rest connected to nonmotor areas of the frontal lobe involved in aspects of planning, working memory, attention and emotional regulation.[11] The basal ganglia are involved in the control of cognition, decision making and complex behavioral planning.[12-14]

Affectation of a circuit by alterations that impact its integrity or function produces symptoms similar to those that would be caused by direct injury to the specific cortical region to which it is connected. Cortico-striatal dysfunction is associated with impulsivity, apathy and impaired executive functions.

In our patient, neuropsychological tests showed slowed psychomotor rate, difficulty in abstraction and concept formation, loss of mental flexibility, tendency to perseveration, memory impairment and problems in planning tests.

In relation to the rest of the clinical manifestations, the neuropathy and myopathy were moderate.[5] One-half of patients have seizures; as in this case, some can precede the onset of movement disorders by almost a decade,[2] as can CPK elevation.

Characteristics include protrusion of the tongue, orofacial dyskinesia, involuntary vocalization, and tongue and lip biting to the level of self-mutilation.[9,15,16]

The absence or reduction of chorein in red blood cells is determined by Western blotting,[5,6] The meaning of the change in this protein and other proteins in the McLeod or Huntington syndromes leads us to reflect on the role that each of these proteins-chorein, protein XK and huntingtin, respectively-has in this final common pathway to basal ganglia degeneration.[6]

The multisystemic nature of this disease suggests that the protein defect leads to structural instability in different cell types. There has also been speculation about the role in this disease of anomalies in membrane protein band 3, an erythrocyte anion transporter for the exchange of HCO_3-/Cl-.[2,15]

The course is slowly progressive and autonomic nervous system dysfunction can lead to death.[2,5]

Treatment is symptomatic and consists of anticonvulsants (valproic acid, phenytoin and clobazam); lamotrigine and carbamazepine can aggravate involuntary movements[17]; dopaminergic antagonists or dopamine depleters (tiapride, clozapine, tetrabenazine) and deep brain stimulation (DBS) to alleviate the motor disturbances; antidepressants when mood disorders exist that worsen quality of life, which respond better than other symptoms to treatment; injections of botulinum toxin into the genioglossus muscle for the tongue protrusion; and speech, physical and occupational therapy to maintain the patient's mobility and independence.

Genetic counseling should be given to the patient and family members, although the study is difficult due to the large size of the gene and heterogeneity of its mutations.[6,15]

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