Reporte de caso

Obsessive-Compulsive Disorder Symptoms in Huntington's Disease: A Case Report

Juan Carlos Molano-Eslava[1]
Ángela Iragorri-Cucalón[2]
Gonzalo Ucrós-Rodríguez[3]
Carolina Bonilla-Jácome[4]
Santiago Tovar-Perdomo[5]
David V. Herin[6]
Luis Orozco-Cabal[7]

Abstract

Introduction: Few cases of obsessive-compulsive disorder (OCD) symptoms preceding the clinical onset of Huntington Disease (HD) or during later stages of the disease have been reported in the literature, but the nature of this association and its neurobiological mechanisms have not been well-investigated. *Objectives*: To review the scientific literature regarding OCD symptoms in patients with HD and describe a case study from our clinic. *Methods*: Extensive literature searches were performed to identify reports of patients with concurrent HD and OCD symptoms. Results: Recent studies and the current case report suggest that OCD symptoms may predate or coincide with motor, affective or behavioral symptoms in patients with HD. The development of OCD and HD symptoms may involve structural and functional changes affecting the orbital and medial prefrontal cortex, ventromedial caudate nucleus, and pallidal sites. *Conclusions*: Some patients with HD develop symptoms associated with OCD. Progressive and differential neuropathological changes in the ventromedial caudate nucleus and related neural circuits may underlie this association. No specific treatment strategy has been developed to treat these patients; however some medications attenuate associated symptoms. Further testing is needed to determine the neurobiological mechanisms of these disorders.

Key words: Obsessive-compulsive disorder, Huntington disease.

1 Médico psiquiatra. Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia. Facultad de Medicina, Universidad de los Andes, Bogotá, Colombia.
2 Médica neuróloga. Clínica de Memoria, Clínica La Inmaculada, Bogotá, Colombia.
3 Médico del Hospital Universitario Fundación Santa Fe de Bogotá, Colombia. Facultad de Medicina, Universidad de los Andes, Bogotá, Colombia.
4 Médica. Western Psychiatric Institute and Clinic. Pittsburg, PA, Estados Unidos.
5 Médico graduado de la Facultad de Medicina, Universidad de los Andes. Bogotá, Colombia.
6 PhD, Department of Psychiatry, University of Texas Health Science Center at Houston, Texas, Estados Unidos.
7 Médico. PhD en Neurociencias. Facultad de Medicina, Universidad de los Andes, Bogotá, Colombia.

Título: Síntomas del trastorno obsesivo-compulsivo en la enfermedad de Huntington: reporte de caso

Resumen

Introducción: Algunos reportes de caso indican que pacientes con enfermedad de Huntington (EH) pueden presentar síntomas obsesivo-compulsivos (TOC) antes del desarrollo de la enfermedad y durante ésta, pero no se ha estudiado la naturaleza de esta asociación y sus mecanismos neurobiológicos. *Objetivos*: Revisar la literatura científica acerca de la asociación entre EH y síntomas TOC y reportar el caso de un paciente con estas condiciones. *Método*: Búsqueda selectiva de literatura relevante. *Resultados*: Estudios recientes y el caso aquí reportado sugieren que los síntomas TOC pueden presentarse antes de la EH y durante ésta. El desarrollo concurrente de estas patologías puede estar mediado por cambios estructurales y funcionales de la corteza prefrontal orbital y medial, región ventromedial del núcleo caudado y regiones palidales. *Conclusiones*: Algunos pacientes con EH desarrollan síntomas de TOC. Cambios neuropatológicos progresivos y diferenciales en el caudado ventromedial y circuitos dependientes pueden mediar esta asociación. No se ha desarrollado una estrategia terapéutica para el tratamiento de estos pacientes; sin embargo, algunos medicamentos parecen ofrecer mejoría sintomática parcial a los sujetos afectados. Se requieren mayores estudios acerca de los mecanismos neuropatológicos involucrados en esta asociación.

Palabras clave: trastorno obsesivo-convulsivo, enfermedad de Huntington.

Introduction

Huntington's disease (HD) is an autosomal, dominantly inherited, neurodegenerative disorder which manifests during middle adult life (40´s). This disorder affects 4-8 individuals per 100000 people in European populations, whereas in Japan, less than 1 per 100000 individuals have this disorder (1). The diagnostic hallmark of HD includes cognitive deficits, mood alterations and motor disturbances (2) such as chorea and other motor disorders (dystonia, dysathria, gait disturbances). However, behavioral problems and neuropsychiatric conditions are also often present (3,4), and accumulating evidence suggests that obsessive compulsive disorder (OCD) symptoms may precede the clinical onset of HD or emerge during the later stages of the disease. Unfortunately the mechanisms underlying these comorbid disorders and treatments for the dual condition have not been well-investigated (3).

Thus, the goal of this article is to review the scientific literature on OCD symptoms in patients with HD and describe a case study from a patient presenting to our clinic. Additionally, we will explore the potential neurobiological mechanisms underlying this association and discuss the medications used to treat these comorbid conditions.

HD Pathophysiology

HD is caused by expanded CAG repeats in the 5´ region of the huntingtin gene located on chromosome 4p16.3 (5-7). Wild-type chromosomes contain between 6-34 CAG repeats, while HD chromosomes

contain 36-121 repeats (8). Significant positive associations have been described between the repeat length and various clinical features of HD, such as age of onset, disease severity and age of death (9).

Huntingtin is a 3136 amino acid protein that is extensively expressed in the mammalian brain, particularly in neuronal cell bodies and dendrites of large neurons (10,11). Numerous proteins have been shown to associate with the N-terminal polyglutamine fragment and C-terminal HEAT repeats of huntingtin, suggesting that it may act as a scaffolding protein in multiple signaling pathways (12,13) including those involved in neurogenesis and cellular processes necessary to maintain cellular viability (14-17). Some researchers hypothesize that increased polyglutamine fragments in mutant huntingtin may alter protein-protein interactions, leading to selective neuronal dysfunction and neurodegeneration (11,18). The mechanisms underlying neural degeneration are unknown (19), however polyglutamine fragment-induced toxicity, huntingtin aggregation, transcription factor alterations, abnormal axonal transport, mitochondrial dysfunction, and activation of apoptosis may be involved (20,21).

This neurodegeneration has been localized to fronto-striatal systems (22). For example, there is marked and selective neuronal death with astrogliosis in the caudate nucleus, putamen and deep layers (III, IV, and VI) of the cortex (23). Of striatal neurons, medium spiny efferent neurons (GABA-ergic) are primarily affected in HD (24,25).

Neuropsychiatric and behavioral Changes in Patients with HD

Recent reports suggest that behavioral problems and neuropsychiatric conditions are often present in patients with HD (4). For example, Craufurd et al. (26) demonstrated that loss of energy and initiative, poor perseverance and quality of work, impaired judgment, poor self-care and emotional blunting are often present in HD patients. In addition, depression, apathy and irritability are some major affective symptoms found in those with HD. In fact, major depression and intermittent explosive disorder occur in >30% of these patients (27). Furthermore, HD patients exhibit executive dysfunction and progressive cognitive decline, resulting in increased functional impairment after controlling for motor disturbances, (28). These cognitive and behavioral symptoms usually emerge following changes in cortical architecture (29), but may also predate the onset of motor symptoms. The mechanisms causing early or late non-motor symptoms remain unknown.

OCD Symptoms in Patients with HD

In contrast, the relationship between OCD and HD has been

little-investigated, despite the fact that both diseases are associated with striatal dysfunction (30) and that the number of case reports of obsessive-compulsive symptoms either preceding the clinical onset of HD or during later stages of the disease is increasing (31). For example, Dewhurst et al. (32) reported "obsessional features" in 7 of 102 patients at onset of HD. Twenty years later, Tonkonogy and Barrera (33) described a patient with obsessive and compulsive symptoms, namely ideas of contamination and compulsive hand washing, associated with affective disturbances and cognitive decline characteristic of HD. Additionally, Cummings and Cunningham (34) described two unrelated HD patients with late onset OCD symptoms (i.e., compulsions of cleaning). De Marchi et al. (35) described a pedigree in which three cases of OCD and two cases of pathological gambling were identified prior to clinical onset of HD, and Scicutella (36) reported a 72-year-old patient who developed HD and OCD. More recently, Patzold and Brune (37) described a 42-year-old woman successfully treated with sertraline for obsessive thoughts which emerged 10 years after the onset of HD. Furthermore, Beglinger et al. (38) demonstrated that the probability of obsessive-compulsive symptoms increased with severity of HD, such that obsessions and compulsions were three times greater in patients with motor symptoms than in patients at risk with no motor abnormalities.

Our group was recently consulted in a case of a 45-year-old woman who met diagnostic criteria for HD and OCD (39). The patient sought medical attention for conciliation insomnia, hyporexia, 4kg weight loss, emotional liability, anxiety and obsessive-compulsive symptoms. Specifically, she reported being constantly worried about contamination, washing her hands and teeth repeatedly throughout the day (20-30 times a day) and spending great part of her day cleaning her body, during the past 18 months. She also reported trying not to touch light switches, money or any surface that could be touched by someone else. In addition, the patient reported having difficulty concentrating, remembering recent events and performing mathematical operations to the point she had to quit her job a year ago. She also reported mild involuntary choreoathetoid movements of the upper extremities and difficulty walking during the past 6 months. Her deceased mother was diagnosed with HD at age 42. Similarly, her sister, now 58, was diagnosed with HD during her early forties.

The neurological examination on admission was remarkable for choreoathetoid movements of the right upper limb, head tilting to the left side, and a wide-based, unsteady gait. On the mental state examination, the patient was alert, oriented in time, place and person; although hypoprosexic. There was no evidence of hallucinations or

delusions. She exhibited short-term memory deficits; long-term memory without alterations. Her intelligence was above average but she had discalculia. She spoke slowly and with a low tone. Her thought process was slow too and had recurrent ideas of cleanliness or fear of becoming infected or contaminated. Her mood was dysphoric, with depressive affect and severe anxiety. She felt sad when she thought about the possibility of having HD. The patient was evaluated by a dermatologist who diagnosed irritative dermatitis probably due to her compulsive hand-washing.

CBC count with differential, glycemia, hepatic and renal function tests, TSH levels, VDRL and urinalysis were normal. Magnetic Resonance was performed which revealed increased subarachnoid space surrounding cortical sulci and gyri, suggesting cortical atrophy. PET scan with [18F] Fluorodeoxyglucose (FDG) revealed a marked, symmetrical and bilateral, reduction of FDG uptake in the caudate. Neuropsychological testing (Barcelona diagnostic tests, WAIS III, Rey figure y Wisconsin Card Sorting Test) revealed abnormal attention, short-term memory deficits, discalculia, and deficits in task planning and execution, all of which suggest cognitive deficits of subcortical origin compatible with HD. The patient was diagnosed with OCD, possible HD and mayor depression. HD was confirmed by genetic testing which revealed 44 CAG repeats compared with 25 repeats of the healthy allele. The patient was started on olanzapine 2,5mg PO BID and paroxetine 40 mg PO per day. After 4 weeks of treatment, obsessional thoughts decreased significantly and the affect improved. Motor symptoms remain the same.

Neurobiological Mechanisms Underlying the Relationship between OCD Symptoms and HD

Functional and structural imaging studies have consistently demonstrated that HD patients exhibit frontal and striatal hypometabolism along with thalamic hypermetabolism (40,41). Together the studies suggest HD is not exclusively confined to the striatum, but also affects striatum-elated structures, such as the frontal cortex. Alexander et al. (42) proposed five segregated circuits between the basal ganglia and selected frontal cortical areas. Specifically, neuropsychiatric symptoms (cognitive, affective and behavioral) in HD patients have been attributed to orbitofrontal-, anterior cingulate- and lateral prefrontal-striatal circuit dysfunction (22), possibly caused by basal ganglia and cortical neurodegeneration or developmental alterations, which lead to reduced basal ganglia output to the frontal cortex and further frontal dysfunction (43-45).

In addition, alterations in neurotransmitter systems may contribute to functional and structural

changes within these circuits. For example, numerous post-mortem studies and in vivo studies using PET scan have demonstrated decreased binding for D1 and D2 receptor-ligands in the striatum and frontal cortex of patients with clinical HD (46-50). Decreased binding for opiate receptors (44) and the benzodiazepine site on GABAA receptors (51) have also been documented in the striatum and medial prefrontal cortex and caudate nucleus, respectively.

In contrast, numerous functional imaging studies showing increased activity in the orbitofrontal cortex, anterior cingulate, caudate nucleus and thalamus in patients with OCD (reviewed by Baxter et al.) (52). Furthermore, structural changes of corticolimbic regions of the frontal lobes (orbitofrontal and medial prefrontal cortex), ventromedial caudate nucleus and pallidal sites have been associated with the development of obsessive and compulsive symptoms in humans (34). These findings suggest that dysfunction of fronto-subcortical circuits plays a significant role in OCD, similar to HD. For example, Baxter et al. (52) suggested that overactivity of the orbitofrontal cortex and ventromedial caudate along with hypoactivity of lateral prefrontal cortex would tend to disinhibit the thalamus via its predominant direct pathway tone, leading to compulsive behaviors. Accordingly, recovery from OCD after treatment with selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants is associated with lateralized or bilateral reductions in orbitofrontal cortex, anterior cingulate and caudate nucleus activity (53,54).

In addition to striatal degeneration, dysfunction of neuropeptide systems may be involved in co-occurrence of HD and OCD. For example, HD and OCD patients exhibit increased somatostatin levels and immunoreactivity in selective CNS regions (55,56). Furthermore, chronic administration of serotonin reuptake inhibitors that effectively treats OCD symptoms decreases somatostatin contents in selective brain regions (57). Thus, multiple mechanisms are likely involved in the presentation of OCD symptoms in HD patients.

However, as stated by Patzold and Brüne (37): "whereas the link of OCD and HD is intuitively obvious, the clinical and pathophysiologic association between the two disorders is still obscure to some extent." Specifically, the neural mechanisms underlying the development of OCD in patients with HD remain unclear. It is possible that differential neurodegeneration in the caudate nucleus, frontal cortex or other structures within fronto-subcortical circuits may explain differential neuropsychiatric symptoms in these patients. For example, executive dysfunction in early stages of Huntington's disease is specifically associated with striatal and insular atrophy (58). Similarly, progression in neuropsychiatric symptoms of

HD is correlated with differential dopaminergic dysfunction in HD patients (59). Based on the above it is possible to hypothesize that differential and progressive neuropathologic changes, likely involving the ventromedial caudate or associated prefrontal subregions and modulatory neurotransmitter systems, are responsible for the development of OCD symptoms in patients with HD. In fact, progression of HD severity has been linked to the development of OCD symptoms in these patients. In a recent study, Beglinger et al. (38) demonstrated that the probability of HD patients having obsessions and compulsions increased with both greater diagnostic certainty and greater functional impairment. A future post-mortem study characterizing the progression of neuropathological changes within fronto-subcortical circuits would allow us to test this hypothesis.

Similarly, we lack evidence about the right treatment for patients with OCD symptoms and HD. Previous reports suggest that patients with HD and behavioral or affective symptoms benefit from SSRI treatment. Ranen et al. (60) successfully treated two consecutive cases of genetically confirmed Huntington's disease in which severe irritability and aggressiveness required inpatient admission. Patel et al. (61) administered fluoxetine, an SSRI, and L-deprenyl in a 19-year-old female with Huntington's disease with significant improvement of affective, behavioral, and motor function. Interestingly, there is only one published report of a patient with HD and OCD symptoms treated with sertraline (37). Olanzapine, an atypical antipsychotic, has been used to control motor and behavioral disturbances in patients with single-diagnosis HD (62). In addition, olanzapine has been used successfully in patients with severe OCD alone (63) or with schizophrenia (64), despite reports of atypical antipsychotics evoking OCD-like symptoms (65,66). Undoubtedly, clinical studies are needed to determine the effectiveness in the treatment of these co-morbid conditions.

Conclusions

OCD symptoms may precede or coincide with motor, affective or behavioral symptoms in patients with HD. Both diseases are invariably associated with dysfunction of striatal neural circuits such as prefrontal-striatal circuits. Multiple mechanisms have been proposed to account for striatal degeneration in HD and related circuit dysfunction. Specifically, structural and functional changes affecting orbital and medial prefrontal cortex, ventromedial caudate nucleus and pallidal sites have been suggested to play a role in the development OCD symptoms in HD. Anecdotal evidence suggest that SSRIs alone or in combination with atypical antipsychotics like olanzapine may be useful for these patients. Howe-

ver, these hypotheses need further testing.

Acknowledgements

Supported by SEMILLA grant from Los Andes University (LO-C) and U.S. National Institute on Drug Abuse DA023548 (DVH).

References

1. Harper PS. The epidemiology of Huntington's disease. Hum Genet, 1992;89(5):365-76.
2. Vonsattel JP, DiFiglia M. Huntington's disease. J Neuropathol Exp Neurol. 1998;57(5):369-84.
3. Cummings JL. Behavioral and psychiatric symptoms associated with Huntington's disease. Adv Neurol. 1995;65:179-86.
4. Paulsen JS, Ready RE, Hamilton JM, Mega S, Cummings JL. Neuropsychiatric aspects of Huntington's disease. J Neurol Neurosurg Psychiatry. 2001;71(3):310-4.
5. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, et al. A polymorphic DNA marker genetically linked to Huntington's disease. Nature. 1983;306(5940):234-8.
6. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993;72(6):971-83.
7. MacDonald ME, Novelletto A, Lin C, Tagle D, Barnes G, Bates G, et al. The Huntington's disease candidate region exhibits many different haplotypes. Nat Genet. 1992;1(2):99-103.
8. Read AP. Huntington's disease: testing the test. Nat Genet. 1993;4:329-30.
9. Andrew SE, Goldberg YP, Kremer B, Telenius H, Theilmann J, Adam S, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet. 1993;4(4):398-403.
10. Strong TV, Tagle DA, Valdés JM, Elmer LW, Boehm K, Swaroop M, et al. Widespread expression of the human and rat Huntington's disease gene in brain and nonneural tissues. Nat Genet. 1993;5(3):259-65.
11. Trottier Y, Devys D, Imbert G, Saudou F, An I, Lutz Y, et al. Cellular localization of the Huntington's disease protein and discrimination of the normal and mutated form. Nat Genet. 1995;10(1):104-10.
12. Andrade MA, Bork,P. HEAT repeats in the Huntington's disease protein. Nat Genet. 1995;11(2):115-6.
13. Kazantsev A, Preisinger E, Dranovsky A, Goldgaber D, Housman D. Insoluble detergent-resistant aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells. Proc Natl Acad Sci USA. 1999;96(20):11404-9.
14. Hoogeveen AT, Willemsen R, Meyer N, de Rooij KE, Roos RA, van Ommen GJ, et al. Characterization and localization of the Huntington disease gene product. Hum Mol Genet. 1993;2(12):2069-73.
15. Gutekunst CA, Levey AI, Heilman CJ, Whaley WL, Yi H, Nash NR, et al. Identification and localization of Huntington in brain and human lymphoblastoid cell lines with anti-fusion protein antibodies. Proc Natl Acad Sci USA. 1995;92(19):8710-4.
16. Duyao MP, Auerbach AB, Ryan A, Persichetti F, Barnes GT, McNeil SM, et al. Inactivation of the mouse Huntington's disease gene homolog Hdh. Science. 1995;269(5222):407-10.
17. Dragatsis I, Levine MS, Zeitlin S. Inactivation of Hdh in the brain and testis results in progressive neurodegeneration and sterility in mice. Nat Genet. 2000;26(3):300-6.
18. Orr HT, Zoghbi HY. Trinucleotide repeat disorders. Ann Rev Neurosci. 2007;30:575-621.
19. Greenamyre JT. Huntington's disease: getting closer. Am J Psychiatry. 2007;164(9):1318.
20. Walling HW, Baldassare, JJ, Westfall TC. Molecular aspects of Huntington's disease. J Neurosci Res. 1998;54(3):301-8.

21. Sawa A, Tomoda T, Bae BI. Mechanisms of neuronal cell death in Huntington's disease. Cytogenet Genome Res. 2003;100(1-4):287-95.
22. Lichter DG. Movement disorders. In: Lichter DG, Cummings JL, editors. Frontal-subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press; 2001. p. 260-313.
23. Vonsattel JP, Myers RH, Stevens, TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. 1985;44(6):559-77.
24. Ferrante RJ, Kowall NW, Beal MF, Richardson EP Jr, Bird ED, Martin JB. Selective sparing of a class of striatal neurons in Huntington's disease. Science. 1985;230(4725):561-3.
25. Albin RL, Reiner A, Anderson KD, Dure ES 4th, Handelin B, Balfour R, et al. Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Ann Neurol. 1992;31(4):425-30.
26. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol. 2001;14(4):219-26.
27. Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofatter JA, Conneally PM. Onset symptoms in 510 patients with Huntington's disease. J Med Genet. 1993;30(4):289-92.
28. Rothlind JC, Bylsma FW, Peyser C, Folstein SE, Brandt J. Cognitive and motor correlates of everyday functioning in early Huntington's disease. J Nerv Ment Dis. 1993;181(3):194-9.
29. Nopoulos P, Magnotta VA, Mikos A, Paulson H, Andreasen NC, Paulsen JS. Morphology of the cerebral cortex in preclinical Huntington's disease. Am J Psychiatry. 2007;164(9):1428-34.
30. Modell JG, Mountz JM, Curtis GC, Greden JF. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci. 1989;1(1):27-36.
31. Anderson KE, Louis ED, Stern Y, Marder KS. Cognitive correlates of obsessive and compulsive symptoms in Huntington's disease. Am J Psychiatry. 2001;158(5):799-801.
32. Dewhurst K, Oliver J, Trick KL, McKnight AL. Neuro-psychiatric aspects of Huntington's disease. Confin Neurol. 1969;31(4):258-68.
33. Tonkonogy J, Barreira P. Obsessive-compulsive disorder and caudate-frontal lesion. Neuropsychiatry Neuropsychol Behav Neurol. 1989;2(3):203-9.
34. Cummings JL, Cunningham K. Obsessive-compulsive disorder in Huntington's disease. Biol Psychiatry, 1992;31(3):263-70.
35. De Marchi N, Morris M, Mennella R, La Pia S, Nestadt G. Association of obsessive-compulsive disorder and pathological gambling with Huntington's disease in an Italian pedigree: possible association with Huntington's disease mutation. Acta Psychiatr Scand. 1998;97(1):62-5.
36. Scicutella A. Late-life obsessive-compulsive disorder and Huntington's disease. J Neuropsychiatry Clin Neurosci. 2000;12(2):288-9.
37. Patzold T, Brune M. Obsessive compulsive disorder in Huntington disease: a case of isolated obsessions successfully treated with sertraline. Neuropsychiatry Neuropsychol Behav Neurol. 2002;15(3):216-9.
38. Beglinger LJ, Langbehn DR, Duff K, Stierman L, Black DW, Nehl C, et al. Probability of obsessive and compulsive symptoms in Huntington's disease. Biol Psychiatry. 2007;61(3):415-8.
39. Martin JB, Gusella JF. Huntington's disease: pathogenesis and management. N Engl J Med. 1986;315(20):1267-76.
40. Young AB, Penney JB, Starosta-Rubinstein S, Markel DS, Berent S, Giordani B, et al. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. Ann Neurol. 1986;20:296-303.
41. Berent S, Giordani B, Lehtinen S, Markel D, Penney JB, Buchtel HA, et al. Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. Ann Neurol. 1988;23(6):541-6.

42. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357-81.
43. Andrews TC, Brooks DJ. Advances in the understanding of early Huntington's disease using the functional imaging techniques of PET and SPET. Mol Med Today. 1998;4(12):532-9.
44. Weeks RA, Ceballos-Baumann A, Piccini P, Boecker H, Harding AE, Brooks DJ. Cortical control of movement in Huntington's disease: a PET activation study. Brain. 1997;120(Pt 9):1569-78.
45. Bartenstein P, Weindl A, Spiegel S, Boecker H, Wenzel R, Ceballos-Baumann A, et al. Central motor processing in Huntington's disease. A PET study. Brain, 1997; 120(Pt 9):1553-67.
46. Reisine TD, Fields JZ, Stern LZ, Johnson PC, Bird ED, Yamamura HI. Alterations in dopaminergic receptors in Huntington's disease. Life Sci. 1977;21:1123-8.
47. Cross A, Rossor M. Dopamine D-1 and D-2 receptors in Huntington's disease. Eur J Pharmacol. 1983;88(2-3):223-9.
48. Sedvall G, Karlsson P, Lundin A, Anvret M, Suhara T, Halldin C, et al. Dopamine D1 receptor number-a sensitive PET marker for early brain degeneration in Huntington's disease. Eur Arch Psychiatry Clin Neurosci. 1994;243(5):249-55.
49. Antonini A, Leenders KL, Spiegel R, Meier D, Vontobel P, Weigell-Weber M, et al. Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease. Brain. 1996;119(Pt 6):2085-95.
50. Ginovart N, Lundin A, Farde L, Halldin C, Bäckman L, Swahn CG, et al. PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease. Brain. 1997;120(Pt 3):503-14.
51. Holthoff VA, Koeppe RA, Frey KA, Penney JB, Markel DS, Kuhl De, et al. Positron emission tomography measures of benzodiazepine receptors in Huntington's disease. Ann Neurol. 1993;34(1):76-81.
52. Baxter LR Jr. Functional imaging of brain systems mediating obsessive-compulsive disorder. In: Charney DS, Nestler ES, Bunney BS, editors. Neurobiology of mental iIness. New York: Oxford University Press; 1999. p. 534-45.
53. Baxter LR Jr, Mazziotta JC, Pahl JJ, Grafton ST, St George-Hyslop P, Haines JL, et al. Psychiatric, genetic, and positron emission tomographic evaluation of persons at risk for Huntington's disease. Arch Gen Psychiatry. 1992;49(2):148-54.
54. Schwartz JM, Stoessel PW, Baxter LR Jr, Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. Arch Gen Psychiatry. 1996;53(2):109-13.
55. Altemus M, Pigott T, L'Heureux F, Davis CL, Rubinow DR, Murphy DL, et al. CSF somatostatin in obsessive-compulsive disorder. Am J Psychiatry. 1993;150(3):460-4.
56. Mazurek MF, Garside S, Beal MF. Cortical peptide changes in Huntington's disease may be independent of striatal degeneration. Ann Neurol. 1997;41(4):540-7.
57. Kakigi T, Maeda K, Kaneda H, Chihara K. Repeated administration of antidepressant drugs reduces regional somatostatin concentrations in rat brain. J Affect Disord. 1992; 25(4):215-20.
58. Peinemann A, Schuller S, Pohl C, Jahn T, Weindl A, Kassubek J. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci. 2005;239(1):11-9.
59. Pavese N, Andrews TC, Brooks DJ, Ho AK, Rosser AE, Barker RA, et al. Progressive striatal and cortical dopamine receptor dysfunction in Huntington's disease: a PET study. Brain. 2003;126(Pt 5):1127-35.
60. Ranen NG, Lipsey JR, Treisman G, Ross CA. Sertraline in the treatment of severe aggressiveness in Huntington's

disease. J Neuropsychiatry Clin Neurosci. 1996;8(3):338-40.
61. Patel SV, Tariot PN, Asnis J. L-Deprenyl augmentation of fluoxetine in a patient with Huntington's disease. Ann Clin Psychiatry. 1996;8(1):23-6.
62. Laks J, Rocha M, Capitao C, Domingues RC, Ladeia G, Lima M, et al. Functional and motor response to low dose olanzapine in huntington disease: case report. Arq Neuropsiquiatr. 2004;62(4):1092-94.
63. Marazziti D, Pallanti S. Effectiveness of olanzapine treatment for severe obsessive-compulsive disorder. Am J Psychiatry. 1999;156(11):1834-5.
64. Poyurovsky M, Kriss V, Weisman G, Faragian S, Kurs R, Schneidman M, et al. Comparison of clinical characteristics and comorbidity in schizophrenia patients with and without obsessive-compulsive disorder: schizophrenic and OC symptoms in schizophrenia. J Clin Psychiatry. 2003;64(11):1300-7.
65. Patel B, Tandon R. Development of obsessive-compulsive symptoms during clozapine treatment. Am J Psychiatry. 1993;150(5):836.
66. Morrison D, Clark D, Goldfarb E, McCoy L. Worsening of obsessive-compulsive symptoms following treatment with olanzapine. Am J Psychiatry. 1998;155(6):855.

Interest conflicts: None of the authors reported interest conflicts in this article.

Received for assessment: October 14, 2008
Accepted for publication: November 20, 2008

Correspondence
Luis Felipe Orozco-Cabal
Neurociencias-Facultad de Medicina
Universidad de los Andes
Carrera 1ª Nº 18A-10
Bogotá, Colombia
luiorozc@uniandes.edu.co