

Huntington's disease like phenotype

New data from Brazil and what we know between heaven and earth.

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, characterized by involuntary movements, predominantly chorea, associated to behavioral and cognitive impairment^{1,2}. HD is caused by expansion of a CAG repeat in the coding region of the IT15 gene located on chromosome 4p16.3, that encodes a protein called huntingtin. The expanded polyglutamine tract encoded by the CAG repeat expansion is toxic and critical in HD pathogenesis². The most prominent neuropathological finding is atrophy of the striatum^{1,2}.

The prevalence of HD in the Caucasian population ranges from 0.5-1 in 10,000. Mean age at onset is between 35 and 50 years, and the disease progresses inexorably and has a mean duration of 17-20 years, and no effective treatment is currently available².

In general about 1% of all cases of clinically or pathologically defined HD do not have the HD mutation and these cases are known as Huntington's disease-like phenotype (HDL) or HD phenocopies³.

To date, there are 4 phenocopies known as HDL1, 2, 3, and 4. HDL1 is caused by a octapeptide repeat insertion in gene encoding prion protein, HDL2 is associated to triplet repeat expansion in gene encoding junctophilin-3, HDL3 is a autosomal recessive disease, which a causative mutation is unknown, and HDL4 or spinocerebellar ataxia type 17 (SCA17) is caused by

triplet repeat expansion in gene encoding TATA-box binding protein (TBP)³⁻⁹. Additionally, dentatorubral-pallidolusian atrophy (DRPLA), caused by a triplet repeat expansion in gene encoding atrophin-1, is associated to HD phenocopies. Others diseases that may have a HD phenocopies are neuroacanthocytosis (mutation in gene encoding chorein), neurodegeneration with brain iron accumulation (NBIA) or pantothenate kinase-associated neurodegeneration (PKAN), caused by mutations in the PANK2 gene, neuroferritinopathy (mutations in gene encoding ferritin light-chain), and spinocerebellar ataxias (SCAs) types 1 and 3³⁻⁹.

Margolis et al. in 2004 studied HDL2 in a series of patients with HD or HDL of North America and Japan, and demonstrated that HDL2 is very rare, with a frequency of 0 to 15% among patients, exclusively found in patients with African ancestry¹⁰. Other studies performed in other countries, including Portugal, Japan, and Poland, did not detected any case of HDL2¹⁰⁻¹².

In Latin America, particularly in Brazil, Teive et al. described in 2007 the first case of HDL2 in a patient without African ethnic origin¹³. However, on further questioning the patient's grandmother was reported to be "dark-skinned", presumably indicating an African ethnic background¹⁴. In 2008, Santos et al. also described a Brazilian patient with HDL2 with apparent Eu-

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FENÓTIPO DOENÇA DE HUNTINGTON-SÍMILE: NOVOS DADOS DO BRASIL E O QUE NÓS CONHECEMOS ENTRE O CÉU E A TERRA

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ropean ancestry¹⁵. Nevertheless, additional genetic studies confirm that the origin of the HDL2 mutation in that patient has most probably originated from an African ancestor¹⁶⁻¹⁸.

In this issue of *Arquivos de Neuro-Psiquiatria* Rodrigues et al. from Ribeirão Preto School of Medicine, University of São Paulo, in a collaborative study with the Neurology Department of School of Medical Sciences, University of Campinas, São Paulo, Mount Sinai School of Medicine, New York, USA, Ludwig-Maximilians-Universität, Munchen, Germany, and Hopital Pitié-Salpêtrière, Paris, France, present a very interesting study analyzing clinically and genetically 29 Brazilian patients with HDL phenotype¹⁹. In this group of HDL patients the authors studied the occurrence of HDL2, SCAs types 1, 2, 3, and 17, DRPLA, and chorea-acanthocytosis (ChAc). They found 3 patients with HDL2 and 2 patients with ChAc. The etiology of HDL was not found in 79,3% of the patients¹⁹.

These findings suggest that HDL disorders are clinically and genetically very heterogeneous, and additional studies are needed to solve this intriguing problem^{3,10-12}.

In conclusion, among patients with HDL phenocopies, HDL2 and HDL4 are the most common mutations identified in different series. Most cases of HDL remain without an identifiable cause. In summary, quoting Shakespeare: "There are more things in heaven and earth, Horatio, / Than are dreamt of in your philosophy" (Hamlet)²⁰.

REFERENCES

- Cardoso F. Huntington's disease and other choreas. *Neurol Clin* 2009;27:719-736.
- Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol* 2011;10:83-98.
- Wild EJ, Mudanohwo EE, Sweeney MG, et al. Huntington's disease phenocopies are clinically and genetically heterogeneous. *Mov Disord* 2008;23:716-720.
- Holmes SE, O'Hearn E, Rosenblatt A, et al. A repeat expansion in the gene encoding junctophilin-3 is associated with Huntington disease-like 2. *Nat Genet* 2001;4:377-378.
- Margolis RL, O'Hearn E, Rosenblatt A, et al. A disorder similar to Huntington's disease is associated with a novel CAG repeat expansion. *Ann Neurol* 2001;50:373-380.
- Rosenblatt A, Ranen NG, Rubinsztein DC, et al. Patients with features similar to Huntington's disease without CAG expansion in huntingtin. *Neurology* 1998;51:215-220.
- Vuillaume I, Meynieu P, Schraen-Maschke S, Destée A, Sablonnière B. Absence of unidentified CAG repeat expansion in patients with Huntington's disease-like phenotype. *J Neurol Neurosurg Psychiatry* 2000;68:672-675.
- Margolis RL, Rudnicki DD, Holmes SE. Huntington's Disease Like-2: review and update. *Acta Neurol Taiwan* 2005;14:1-8.
- Quinn N, Bathia K, Brown P, et al. Movement disorders. In: Clarke C, Howard R, Rossor M, Shorvon S. *Neurology. A queen square textbook*. Wiley-Blackwell, Oxford, UK, 2009:155-187.
- Margolis RL, Holmes SE, Rosenblatt A, et al. Huntington's disease-like 2 (HDL2) in North America and Japan. *Ann Neurol* 2004;56:670-674.
- Costa MC, Teixeira-Castro A, Constante M, et al. Exclusion of mutations in the PRNP, JPH3, TBP, ATN1, CREBBP, POU3F2, and FTL genes as a cause of disease in Portuguese patients with a Huntington-like phenotype. *J Hum Genet* 2006;51:645-651.
- Sulek-Piatkowska A, Krysa W, Zdzienicka E, et al. Searching for mutation in the JPH3, ATN1, and TBP genes in Polish patients suspected of Huntington's disease and without mutation in the IT15 gene. *Neurol Neurochir Pol* 2008;42:203-209.
- Teive HAG, Becker N, Munhoz RP, et al. Huntington's disease like 2: the first case report in Latin America in a patient without African ethnic origin. *Mov Disord* 2007;22(Suppl 16):S27.
- Rodrigues GGR, Walker RH, Brice A, et al. Huntington's disease-like 2 in Brazil: report of 4 patients. *Mov Disord* 2008;23:2244-2247.
- Santos C, Wanderley H, Vedolin L, Pena SD, Jardim L, Sequeiros J. Huntington's disease-like 2: the first patient with apparent European ancestry. *Clin Genet* 2008;73:480-485.
- Rodrigues GGR, Teive HAG, Tumas V. Huntington's disease-like 2 and apparent ancestry. *Clin Genet* 2009;75:207.
- Sequeiros J, Santos C, Jardim LB. Response to Tumas et al. *Clin Genet* 2009;75:208.
- Parra FC, Amado RC, Lambertucci JR, Rocha J, Antunes CM, Pena SDJ. Color and genomic ancestry in Brazilians. *PNAS* 2003;100:177-182.
- Rodrigues GR, Walker R, Bader B, et al. Clinical and genetic analysis of 29 patients with Huntington's disease-like phenotype. *Arq Neuropsiquiatr* 2011;69:419-423.
- Shakespeare W. *Hamlet*. Dover Thrift Editors. Dover Publications. New York, USA, 1992.