Letter

DOI: 10.5582/irdr.2021.01148

Posterior reversible encephalopathy syndrome due to arterial hypertension may mark the onset of the symptomatic phase in Huntington's disease

Maurizio Giorelli*

Operative Unit of Neurology, "Dimiccoli" General Hospital, Barletta, Italy.

SUMMARY Autonomic dysregulation of cardiovascular functions marks early Huntington's disease (HD). Blood-brain barrier (BBB) is dysfunctional in HD. A 37-year-old female carrying 41 CAG triplets in the huntingtin gene acutely presented with a multifaceted syndrome attributable to posterior reversible encephalopathy syndrome (PRES). Syndrome was associated with arterial hypertension (AHT). The syndrome fully recovered both by imaging and clinical signs after normalization of arterial pressure during hospitalization. Immediately after hospital discharge, the patient developed a complex psychiatric syndrome and choreic movements that represented conversion to the symptomatic phase of HD. A one-year later follow up clearly showed the patient had developed the symptomatic stage of HD by presenting both psychiatric symptoms and choreic movements. Onset of AHT may represent an early premonitory signal of HD becoming manifested. Induction of PRES might be associated with BBB impairment in HD.

Keywords Huntington's disease, arterial hypertension, autonomic dysfunction, posterior reversible encephalopathy syndrome, blood-brain barrier

1. Introduction

Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by the abnormal expansion of a trinucleotide (CAG) repeat in the *huntingtin* gene of chromosome 4 (*1*). A triad of symptoms consisting of either an extrapiramidal movement disorder as well as cognitive and behavioral impairment characterizes HD (*2*).

People with the same number of triplet repeat expansion may indeed start to develop symptoms at different ages, clearly showing that both genetic and epigenetic factors are involved in disease onset and symptoms appearance (*2*). Arterial hypertension (AHT) has been found to delay development of motor symptoms in a large cohort of HD patients harboring a range of 40-50 CAG triplets and collected from the Registry project of the European Huntington's Disease Network (*3*).

A 37-year-old female presented to the ED reporting episodes of visual blurring and ideative slowing, severe headache not responsive to common anti-inflammatory drugs, and disturbance of speech. At first evaluation she presented with mixed aphasia, hesitations, difficulty on starting speech, and phonemic parafasias. Motor deficits and extrapyramidal signs (including chorea) were both absent. Her arterial blood pressure (BP) was 190/100 mmHg and required aggressive intravenous anti-hypertensive therapy (urapidil) to reach full normalization. The patient reported to have both the father and the paternal uncle affected by HD and to have herself uncovered to have 41 CAG triplets on one of the two huntingtin (HTT) alleles while performing genetic testing two years earlier. She had not suffered from any symptom nor had her neurological examination been found abnormal in regular checkups performed by a movement disorder specialist up to the date of evaluation. She had only suffered from rare episodes of "empty head" and her BP was frequently found elevated in the few months earlier (180/100 as average).

At acceptance, a cranial tomography (CT) was performed with the help of contrast medium. The exam showed the presence of several focal areas of hypodensity at the subcortical level of both parieto-occipital regions. A diagnosis of posterior reversible encephalopathy syndrome (PRES) was made on the basis of clinical-radiological findings. Two days after admittance to hospital, magnetic resonance imaging (MRI) of the brain revealed areas of altered signal consistent with cerebral edema on both sides of parieto-occipital regions as well in the left frontal lobe in both FLAIR and DWI sequences (Figure 1). Constant

measurement of BP revealed persistently normal values (130/80 mm Hg as average) after administering Ramipril 5 mg/qd and amlodipine 5 mg/qd per os. Normalization of pressure parameters lead to disappearance of all symptoms including headache and disturbance of speech. A second MRI conducted 10 days later revealed great volumetric reduction of the already reported areas of altered signal (Figure 2). Pathological conditions known to be triggers to PRES were excluded by deep investigation during hospitalization. The patient was finally dismissed with advice to continue the prescribed anti-hypertensive therapy.

At a first follow up, two months later, the patient complained of episodes of confusion and misperceptions consisting of vision of animals. In addition, subtle and inconstant choreic movements had appeared in the distal segments of her limbs. A clinical evaluation performed one year later showed the patient had entered the full symptomatic phase of HD, characterized by both psychiatric and motor (choreic) phenomena. A written informed consent was obtained from the patient for publication of this case report.

Effect of AHT on risk, time of symptoms onset and speed of progression is still debated when discussing pathogenesis of any neurodegenerative disease. AHT has been associated with delayed onset of HD in one study, especially when anti-hypertensive medications were used *(3)*.

At variance with the latter study, the case in the present study developed onset of all HD-related symptoms after presenting with PRES due to AHT. Several reports have recently demonstrated the presence of early autonomic dysfunction in both premanifest HD mutation carriers as well as in early symptomatic HD patients (*4-6*) and might be the trigger of AHT in the patient described herein. The pathogenesis of PRES is not fully understood but evidence suggests that systemic mean arterial pressure (MAP) exceeding the brain's autoregulatory capability may lead to focal dilation in cerebral blood vessels, resulting in vasodilation and vasoconstriction (*7*). This can result in the extravasation of fluid and in vasogenic edema.

Brain vessels characterized for impairment of continence and increase in blood-brain barrier permeability due to abnormalities in tight junctions and increase in endothelial transcytosis in HD (*8,9*). Rapid surges in BP as is seen in untreated AHT at the onset, and endothelial dysfunction of cerebral vessels due to HTT deposition may, at least in part, explain PRES pathogenesis in the case reported herein.

Aggressive and continuous measurement of blood pressure is a key medical behavior as its detection and treatment induction may delay turning to symptomatic phase in HD carriers. Suggesting a protective role of anti-hypertensive drugs is intriguing and should be strongly and deeply verified further with prospective studies.

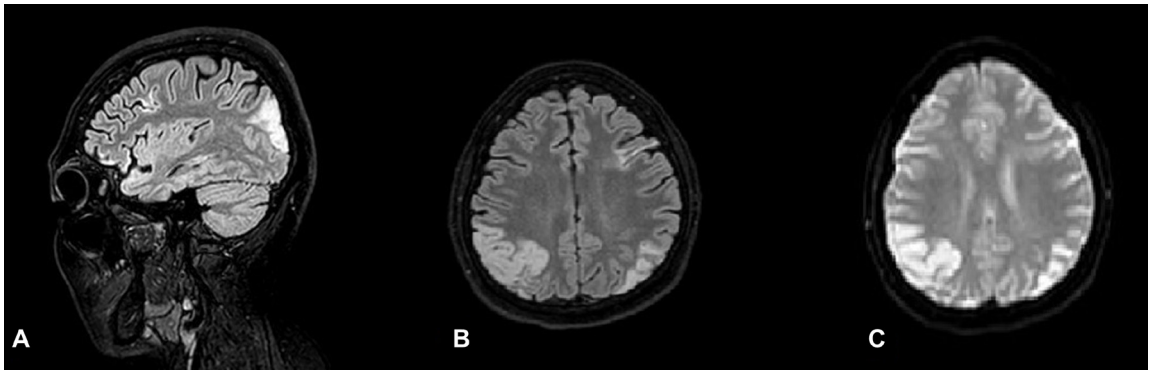

Figure 1. Magnetic Resonance Imaging of subject's brain showing bilateral parieto-occipital hyperintensities in FLAIR (A, B) as well in DWI (C) sequences compatible with oedema due to PRES.

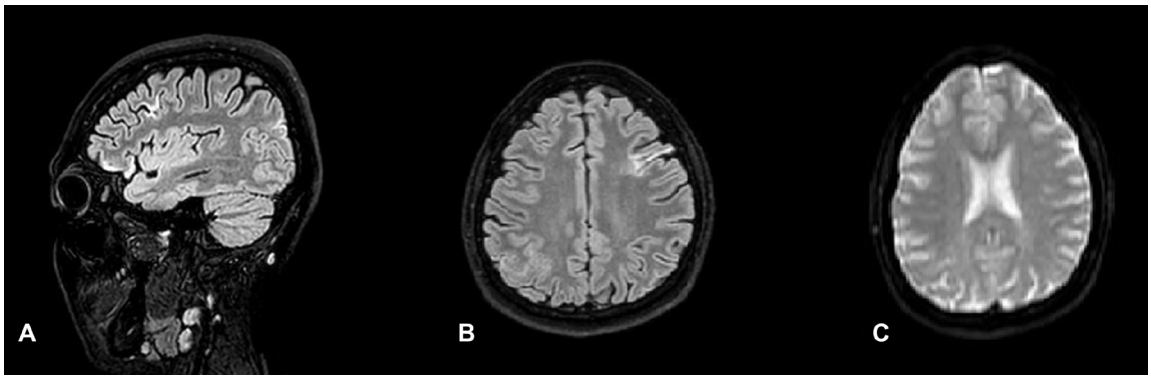

Figure 2. Magnetic Resonance Imaging showed almost complete resolution of brain hyperintensities 10 days later as shown both by FLAIR (A, B) and DWI (C) sequences.

Funding: None.

Conflict of Interest: The author has no conflict of interest to disclose.

References

1. Wexler NS, Lorimer J, Porter J, *et al*. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proc Natl Acad Sci U S A. 2004; 101:3498-3503.
2. Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. Cell. 2015; 162:516-526.
3. Valcárcel-Ocete L, Fullaondo A, Alkorta-Aranburu G, García-Barcina M, Roos RAC, Hjermind LE, Saft C, Frontali M, Reilmann R, Rickards H; REGISTRY investigators of the European Huntington's Disease Network (EHDN), Zubiaga AM, Aguirre A. Does arterial hypertension influence the onset of Huntington's disease? PLoS One. 2018; 13:e0197975.
4. Bellosta Diago E, Pérez Pérez J, Santos Lasaosa S, Viloria Alebesque A, Martínez Horta S, Kulisevsky J, López Del Val J. Circadian rhythm and autonomic dysfunction in presymptomatic and early Huntington's disease. Parkinsonism Relat Disord. 2017; 44:95-100.
5. Kobal J, Meglic B, Mesec A, Peterlin B. Early sympathetic hyperactivity in Huntington's disease. Eur J Neurol. 2004; 11:842-848.
6. Kobal J, Melik Z, Cankar K, Bajrovic FF, Meglic B, Peterlin B, Zaletel M. Autonomic dysfunction in presymptomatic and early symptomatic Huntington's disease. Acta Neurol Scand. 2010; 121:392-399.
7. Fittro K, Dizon R. Understanding posterior reversible encephalopathy syndrome. JAAPA. 2018; 31:31-34.
8. Drouin-Ouellet J, Sawiak SJ, Cisbani G, *et al*. Cerebrovascular and blood-brain barrier impairments in Huntington's disease: Potential implications for its pathophysiology. Ann Neurol. 2015; 78:160-177.
9. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018; 14:133-150.

Received November 28, 2021; Revised January 23, 2022; Accepted February 2, 2022.

**Address correspondence to:*
Maurizio Giorelli, Operative Unit of Neurology, "Dimiccoli" General Hospital, Viale Ippocrate 11, Barletta 76121, Italy.
E-mail: Maurizio.giorelli@aslbat.it

Released online in J-STAGE as advance publication February 10, 2022.