Successful Neuropharmacologic Therapy of Huntington’s Disease: A Case Report

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ABSTRACT
The authors report the successful neuropharmacological treatment of a patient affected by Huntington’s disease. This treatment was guided by the assessment of circulating neurotransmitters before and after two types of stress challenges: orthostasis + exercise and oral glucose tolerance test. Both procedures demonstrated the predominance of neural sympathetic over adrenal sympathetic plus parasympathetic hypoactivity. Taking into account that neural sympathetic activity is positively correlated with the functioning of the noradrenergic neurons located at the (A5) nucleus, which antagonize (C1) adrenaline medullary activity, we designed the therapy to normalize that imbalance. The results allow us to postulate that the Huntington’s disease is a central nervous system disorder characterized by overactivity of the (A5)-noradrenergic (NA) plus median raphe serotonergic [(MR)-5HT] circuitry plus the underactivity of the (A6)-NA and dorsal raphe (DR)-5HT nuclei.

INTRODUCTION
Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder with midlife onset characterized by motor, psychiatric, and cognitive symptoms. Progressive loss of medium-spiny neurons that produce gamma-aminobutyric acid (GABA) in the striatum and other central nervous system (CNS) structures has been considered an important phenomenon that underlies this disease. Changes involving the cerebral cortex lead to further dysfunction in cortico-striatal-pallidal circuitry.1 In addition, HD is associated with a cytosine-adenine-guanine (CAG) triplet repeat expansion in the IT15 gene. The genetic mutation underlying this disorder has been localized to the short arm of chromosome 4 and was found to consist of an expansion and instability of a polymorphic trinucleotide repeat (CAG) in gene IT15.

The decrease in cholinergic (ACh) activity probably explains the deficit in memory retrieval observed in HD. Loss of inhibitory GABAergic function and increased dopamine (DA) turnover has been proposed as an explanation for the emergence of psychotic symptoms in HD. In addition, Huntington’s disease manifests clinically as a triad of choreic movements, cognitive decline, and psy-
Taking into account that both motility and psychiatric disorders have been associated with neurochemical abnormalities that include hypernoradrenergic and hypo-GABAergic and hyposerotonergic activities, we attempted to treat HD patients through neuropharmacologic manipulations addressed to normalize the above physiological disturbances. Therapy was based on the assessment of circulating neurotransmitters during both the supine-resting, and 1-minute orthostasis/5-minute exercise test and throughout the oral glucose challenge. This issue has been widely discussed in two recently published review articles. These procedures have guided us in the design of successful neuropharmacologic therapy in more than 25,000 patients affected by both psychiatric and non psychiatric diseases.

**CASE REPORT**

A 32-year-old woman with a diagnosis of HD was referred to our institute for neurochemical and neuroautonomic investigation in October 2005. She had a 6-year history of slowly progressive ataxic gait, falling, abnormal posturing of her left arm, and slurred speech. On examination she had also mild chorea of the left fingers and mild difficulties on routine cognitive testing. Eye movements showed a saccadic pursuit movement. There were not pyramidal signs. Neuropsychometry showed a verbal IQ of 79 and performance IQ of 75, with an estimated IQ of 90. Verbal subsets showed average results; nonverbal reasoning and memory functioning was defective. Genetic testing was positive for HD. The patient’s rating on the Unified Huntingdon’s Disease Rating Scale (UHDRS) was 36 points (range, 6 to 47) with blocks of more than 14 CAG triplets.

Levels of plasma catecholamines [noradrenaline (NA), adrenaline (Ad), and dopamine (DA)] and plasma indolamines [platelet serotonin (p-5HT), plasma serotonin (f-5HT), and plasma tryptophane (trp)] were analyzed according to previously described procedures. The analytical method was high pressure liquid chromatography with electrochemical detection. The equipment was a Waters 525 pump and electrochemical detector M460, with a Millenium software for data analysis (Waters Corporation, Milford, MA). Platelet aggregation was also assessed in this patient in order to rule out the possibility of an imbalance of the f-5HT/p-5HT ratio.

Neuropharmacologic agents administered to the patient included the following:

- doxepin, a NA-uptake inhibitor plus 5-HT-uptake inhibitor (in a ratio of 40%/60%, respectively); mirtazapine, an alpha-2 and 5-HT-2 antagonist that triggers the release of both NA and 5HT from axons;
- yohimbine, an alpha-2 antagonist that enhances the release of NA from axons and triggers excitation of the dorsal raphe (DR)-5HT neurons, which are crowded by alpha-2 inhibitory autoreceptors;
- pindolol, a 5-HT-1A antagonist that enhances the firing activity of the DR-5-HT neurons;
- prostigmine, an inhibitor of acetyl cholinesterase that crosses the blood-brain-barrier and excites NA neurons of the locus coeruleus (LC)-NA neurons (A6 nucleus).

These neurons send excitatory axons to the dopaminergic A10 mesocortical neurons, which release DA at the frontal cortex. This effect is mediated by α1 postsynaptic receptors. In addition, those frontal cortex postsynaptic neurons (GABA plus glutamatergic) send inhibitory axons to striatal and mesolimbic structures responsible for involuntary movements, and thought disorders, respectively.
Absolute disappearance of the motility disorder was registered at the 12th week. Sleep was essentially normalized by this neuropharmacologic intervention. Delta sleep stage absent before the trial was present during the improvement period. The supine-resting and orthostasis/exercise test and the OGTT were normal. The UHDRS scale decreased to 12 points 6 months after starting the neuropharmacologic treatment and has been maintained to the present (April 2007).

**DISCUSSION**

The results we report are consistent with the hypothesis that this HD patient had neural sympathetic activity that overwhelmed adrenal sympathetic activity. We have exhaustively demonstrated that the peripheral autonomic nervous system (ANS) profile depends on the hyperactivity of the NA neurons located at the (A5) pontomedullary nucleus. This nucleus sends inhibitory axons to the Ad neurons located at the rostral ventrolateral medullary regions (C1) nuclei, which are responsible for the adrenal glands’ secretion (80% of Ad). In addition, the (A5)-NA neurons interchange axons with the (LC)-NA or A6 neurons. Both nuclei modulate each other because they are crowded with alpha-2 inhibitory receptors. Thus, the raised levels of plasma NA seen in this patient strongly suggest that the (A6)-NA neurons are diminished by the (A5)-NA axons. Considering that both the DR-5HT and the (A10)-DA neurons are excited by the (A6)-NA axons, it is possible to infer that a deficit of these neurotransmitters exist at the cortical level. This postulated deficit fits well with both the movements and psychiatric disorders associated with HD. The dramatic improvement triggered by our neuropharmacologic therapy supports our hypothesis.

Other authors have postulated that HD patients present with peripheral

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**RESULTS**

Supine-resting plus orthostasis plus exercise test showed raised values of NA that increased after both types of challenges: 465 pg/mL, 538 pg/mL, and 987 pg/mL, respectively. Values of plasma Ad were lower than normal and did not show significant changes during the test: 23 pg/mL, 21 pg/mL, and 18 pg/mL, respectively. DA values were raised in the three periods: 36 pg/mL; 42 pg/mL; 51 pg/mL. Diastolic blood pressure showed greater-than-normal values in the three periods, whereas systolic blood pressure readings were normal. Normal heart rate values did not change throughout the testing.

Greater-than-normal NA and DA values were recorded during the oral glucose tolerance test (OGTT) throughout both pre- and post-glucose periods. Ad values were normal in all periods.

Raised levels of p-5HT and lowered values of trp were registered before and after the two types of challenges, orthostasis and exercise, and OGTT.

Clinical improvement was registered beginning in the third week after starting the neuropharmacologic therapy.

Drug doses were as follows: doxepin, 25 mg before supper; mirtazapine, 15 mg before bed; yohimbine, 2 mg before breakfast and dinner; pindolol, 5 mg before breakfast and dinner; prostigmine (Neostigmine), 7.5 mg before breakfast and dinner; 5-hydroxytryptophan, 25 mg before supper and bed. The reasoning behind instituting this therapy was to enhance the activity of the locus coeruleus (A6)-NA neurons and DR-5HT neurons and (A10)-DA neurons. These three monoaminergic nuclei innervate the frontal cortex responsible for the voluntary motility and consciousness, which is the opposite profile to that occurring in HD patients.

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- 5-Hydroxy-tryptophan, a serotonin precursor.

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sympathetic predominance, however, they used rudimentary procedures to assess the ANS. They were not able to differentiate neural from adrenal sympathetic activity because they do not assess circulating catecholamines and indolamines, before and after adequate challenges. Thus, they are not able to conclude which CNS circuitry is responsible for the peripheral hypersympathetic activity they postulate.

The raised p-5HT values found in our HD patient fit well with the fact that other psychiatric disorders (psychosis and depression) also present with this abnormality. With respect to this, it has been exhaustively demonstrated that MR-5HT activity is positively correlated with p-5HT values. The above postulations are reinforced by our findings showing that neuropharmacologic therapy addressed to enhance both (A6)-NA and DR-5HT activities improved our HD patient. However, these results were obtained in a single patient and warrant additional trials in other patients.

Other authors including Christofides et al have reported raised p-5HT levels in HD patients were raised (approximately 500 ± 50 ng/mL). Although they reported these values as normal, our results obtained from routine assessment of circulating neurotransmitters in more than 20,000 normal subjects demonstrates that normal values of p-5HT are 322.4 ± 39 ng/mL.

REFERENCES