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FUNCTIONAL AND MOTOR RESPONSE TO LOW DOSE OLANZAPINE IN HUNTINGTON'S DISEASE

Case report

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ABSTRACT - Previous reports on the use of olanzapine in Huntington's disease (HD) used doses ranging from 10-30 mg. We report a case of HD with marked delusions and behavioral impairment assessed by the Unified Huntington's Disease Rating Scale at baseline and four months later treated with a low dose of olanzapine. The patient improved in motor, psychiatric and activity of daily living symptoms after four months of treatment. The response to a low dose of olanzapine in HD may be an indicator of efficacy in similar cases. Further randomized controlled trials can properly assess these findings.

KEY WORDS: Huntington's disease, olanzapine, behavioral abnormalities, functional capacity.

Resposta funcional e motora a doses baixas de olanzapina na doença de Huntington: relato de caso

RESUMO - Relatos de casos sobre o uso de olanzapina na doença de Huntington (DH) usaram doses variando de 10-30 mg. Este é um relato de caso de DH avaliado pela Unified Huntington Rating Scale no início e quatro meses depois com uma dose baixa de olanzapina. A paciente melhorou dos sintomas motores, psiquiátricos e nas atividades de vida diária após os quatro meses de tratamento. A resposta a baixas doses de olanzapina na DH pode ser um indicador de eficácia em casos similares. Mais estudos controlados randomizados podem avaliar apropriadamente esses achados.

PALAVRAS-CHAVE: doença de huntington, olanzapina, transtornos de comportamento, capacidade funcional.

Huntington's disease (HD) is a heredodegenerative disorder of the central nervous system, transmitted as dominant autosomic inheritance with a 100% penetrance. It is caused by a three nucleotide basis (CAG) repetition at the IT15 gene, which resides in the short arm of chromosome 4[1-2]. HD is characterized by insidious onset of neurological manifestations including choreic movements, dysarthria, dysphagia, ideomotor and eyelid apraxia, postural instability, dystonia, dysfunction of eye movements and rarely myoclonus. Incontinence of urinary and anal sphincters (common in the terminal stage of HD), autonomic dysfunction including hyperhydrosis, and pressure lability are other signs and symptoms of the disease. Seizures may occur in 3% of adult HD patients. Neuropsychiatric signs and symptoms may occur before, during or after neurological manifestations. They are present in 35 to 73%, and a wide range of disturbances are reported: affective, behavioral, personality changes which include depression, bipolar disorder, manic episodes, agitation, impulsiveness, aggressiveness. Cognitive symptoms are present in all HD patients at some stage of the disease, characterized by a subcortical dementia profile[3]. The neuroimage shows atrophy of caudate nuclei as the typical feature. The genetic testing is able to confirm the presence of the disease and polymerase chain reaction (PCR) shows an expanded trinucleotide (CAG) repeat sequence.

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Neuroleptic drugs are the mainstay therapy in HD for controlling motor and psychiatric disturbances. Olanzapine is a dopaminergic–serotonergic antagonist, and has been suggested as an alternative therapy for HD[4-8].

We report a case of HD treated with low dose olanzapine regarding its motor and functional response as assessed by the Unified Huntington´s Disease Rating Scale (UHDRS)[9]. The UHDRS is a protocol by which patients are evaluated on a series of criteria, each of them receiving a score from 0 (normal) to 4 (incapacitated). Motor signs and symptoms on UHDRS include chorea and rigidity, balance, eye movement, and ability to walk; the behavioral section of the scale includes frequency and severity of depression, irritability, and disruptive/ inappropriate behavior; whereas functional UHDRS includes the ability to perform activities of daily living such as preparing a meal, walking around familiar places, or moving from one chair to another.

The family and the patient signed an informed consent to permit this case report.

CASE

A forty-nine year-old Caucasian female started to have obsessive worries about dirt and compulsive cleaning in her house two years ago. Hypersexuality and persecutory delusions (strange people in her house) developed six months later. At this time, the family noticed the emergence of involuntary movements affecting the face and the extremities that quickly became generalized, with interference in the activities of the daily living. The patient´s father and three brothers presented choreic movements as the first clinical feature, with better preservation of cognition.

Neurologic examination, laboratory testing and magnetic resonance imaging of the brain (MRI) were performed initially. The UHDRS was performed at baseline and repeated four months later. The neurologic examination showed face and limb choreiform movements more apparent when walking, motor impersistence signs, slow and dysmetric saccades and choreiform gait.

The laboratory testing (complete blood count with blood smear, electrolytes, liver and thyroid function profile, lipid profile, sedimentation rate, glucose, syphilis serology) was normal. MRI showed bilateral caudate atrophy and widening of cortical sulci.

Olanzapine 2.5 mg/day was prescribed and maintained for 4 consecutive months. The UHDRS scores before and 4 months after prescription of olanzapine are shown in Table 1.

The patient developed slight (+/4+) bilateral ankle edema at the second month that remained stable until the fourth month. No other side effects were observed.

DISCUSSION

There are eight reports[4-11] describing the use of olanzapine in HD, and only three reports using the UHDRS for assessment[5-7,10]. Also, the studies and case reports published so far have dealt with either the motor, functional or behavioral symptoms[4,5,7,8,11].

They have all shown improvement in motor and behavioral UHDRS subscales with high doses of olanzapine and good long term tolerability[5,6, 8].

There are two reports using olanzapine in combination with a second drug. Dipple[4] used olanzapine (5 mg/d) and lofepramide (140 mg/d) during six months, with improvement documented on Quantified Neurological Exam[12]. Grove et al.[11] used olanzapine (5 mg/day) and valproic acid (1500 mg/day) in two HD patients, with improvement of the psychiatric manifestations.

In Brazil, Etchebehere et al.[13] described one HD patient whose brain SPECT imaging was performed before and after five days of olanzapine (10 mg/d).

Table 1. UHDRS score before and after olanzapine.

	Baseline		After 4 Months		Comments
	Raw	%	Raw	%	
I Motor	60/124	48.38	56/124	45.16	Improvement (1)
III Behavioral	32/84	38.09	21/84	25	Improvement (2)
IV Functional	4/25	28	13/25	52	Improvement (3)
V Functional	50/100	50	60/100	60	Improvement (3)
VI Functional	3/13	23.07	4/13	30.76	Improvement (3)

Comments: (1) improvement in the motor scale for tongue protrusion, finger taps, Luria's sequence, and gait; (2) marked improvement, with the control of obsessions, compulsions, and delusions; (3) the activities of daily living were resumed; she started to take the medication on her own, dress, bathe, and use the toilet without help. Wilcoxon Matched-Pairs Signed-Ranks Test: W+=7; W-=8; n=5; p<=1

No assessment of clinical response was described. We treated our patient with 2.5 mg/d of olanzapine, while in other studies the dose ranged from 5 mg/d to 30 mg/d.

We evaluated three clusters of the disease as assessed by the UHDRS.This report shows the improvement of motor, functional and behavioral symptoms to a low dose of olanzapine.

Our patient was treated for 4 consecutive months whereas the other reports describe a range from two weeks to 36 months of medication. She improved in the motor scale for tongue protrusion, finger taps, Luria's sequence, and gait. The activities of daily living were resumed. She started to take the medication on her own, dress, bathe, and use the toilet without help. The behavioral subscale showed a marked improvement, with the control of obsessions, compulsions, and delusions. Bilateral ankle edema was observed at the fourth month, as the only adverse effect.

Three studies/case reports that used the UHDRS had higher severity scores on motor and behavioral scales at baseline when compared to our patient[5,6,10]. Another report[7] showed less severity scores than ours on motor and behavioral scales but also used olanzapine in higher dose (10 mg). On the other hand, only one case report[6] used all the subscales of the UHDRS as in our case, although their patient had no psychiatric symptoms. The other studies verified only motor subscale[10] or motor and behavioral subscales[5, 7].

Although we have observed clinically relevant improvements in this case report, these differences from baseline to endpoint assessments (after 4 months) did not reach conventional level of statistical significance. However, the response shown to a low dose olanzapine treatment in HD may be considered an indicator of possible efficacy of olanzapine in HD; further studies (randomized controlled trials) can properly assess these findings.

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