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Effect of Tetrabenazine on Computerized Dynamic Posturography in Huntington disease patients

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Abstract

Background—Impairment in computerized dynamic posturography scores has been documented in Huntington disease patients. Tetrabenazine is approved to treat chorea in Huntington disease, but its effect on posturography scores, and balance in general, is unknown.

Materials and Methods—We designed a study to test computerized dynamic posturography performance while taking tetrabenazine and after stopping tetrabenazine for at least three days.

Results—10 Huntington disease patients were studied both ON and OFF tetrabenazine. The composite score was statistically different between ON and OFF conditions and both conditions were significantly worse than reference scores. There was no significant difference between ON and OFF trials in the number of falls. A significant improvement on Sensory Orientation Test conditions 3 (sway-referenced vision) and 5 (sway-referenced motion of the support surface and eyes closed) was seen while ON tetrabenazine. Strategy scores 1–3 were also significantly different while ON tetrabenazine.

Conclusion—These findings suggest that tetrabenazine aided patients in gating out of abnormal visual cues when other sensory modalities were available, as well as in gating out abnormal kinesthetic cues when visual cues were not available. It could not help with gating out of simultaneous abnormal visual and somatosensory cues. Thus, tetrabenazine can improve postural stability when one sensory modality is irrelevant, but this effect is not sustained when multiple abnormal sensory modalities are present. This is the first study supporting the use of any medicine to treat balance problems in Huntington disease.

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Keywords

Huntington disease; posturography; tetrabenazine; postural stability

Introduction

Postural instability and falls are major features in Huntington disease (HD), and stability abnormalities have been demonstrated in computerized dynamic posturography (CDP) [1]. This finding is true even in otherwise pre-symptomatic HD. HD gene-positive patients estimated to be within 5 years of symptom onset showed worse performance than gene-negative controls. Symptomatic HD patients had the most difficulty [2].

Tetrabenazine is a dopamine depleting drug which functions by inhibition of vesicular monoamine transporter-2 (VMAT-2) [3]. The drug reduces Huntington disease chorea [4]. The effect of tetrabenazine on postural instability has not been previously investigated.

Falling due to postural instability is a major morbidity in HD, however the nature of balance changes in HD patients remains poorly understood. In the present study we sought to determine the effect of tetrabenazine on the performance of HD patients on computerized dynamic posturography testing, including their ability to deal with variations in visual and kinesthetic information, including the number of falls, in order to help determine whether it improves, worsens, or has no effect on balance.

Materials and Methods

Participants were active patients at a tertiary referral movement disorders center who had documented HD (via HD gene CAG repeat testing greater than 40), and who were treated with a stable dose of tetrabenazine for at least three months. They were prospectively recruited for the study over a 14 month period (March 2010–May 2011) during clinic visits and via telephone calls to a database listing of active HD patients taking tetrabenazine who resided in geographic proximity (Texas and Louisiana). All study subjects were able to walk independently or with minimal assistance (use of cane or walker) when they were on tetrabenazine. Patients with psychiatric symptoms severe enough to interfere with medicine compliance or with the testing protocol were excluded. The study was approved by the Institutional Review Board for Human Subjects Research for Baylor College of Medicine and Affiliated Hospitals. All subjects gave informed consent prior to data gathering.

Subjects were tested under two medication conditions under an open label design: They were initially tested while taking their clinically adjusted tetrabenazine dose. They were then tested after having stopped the tetrabenazine for 3–4 days. Unified Huntington Disease Rating Scale - Motor rating was performed by RF. Subjects were tested using the Equitest computerized dynamic posturography system (Neurocom International, Clackamas, OR, USA). In that system the sensory orientation test (SOT) has six subconditions. An equilibrium score (EQT), a falls score, and a strategy score (Strat) is provided for each condition and for the average or Total score. Higher equilibrium scores correspond to less postural sway, while higher strategy scores correspond to greater use of ankle strategy compared to hip strategy for maintaining balance [5]. The conditions consist of SOT1: eyes open and stable support surface, SOT2: eyes closed and stable support surface, SOT3: eyes open but visual cues rendered unreliable with motion of the visual surround in phase with postural sway (sway-referenced motion) and stable support surface, SOT4: eyes open, visual feedback reliable, somatosensory feedback unreliable due to sway-referenced support surface motion, SOT5: eyes closed making vision unavailable and somatosensory feedback unreliable due to sway-referenced support surface, presumably requiring reliance on

vestibular information, SOT6: eyes open but sway referenced motion of the visual surround and the support surface made vision and somatosensory feedback unreliable [2].

Staff at the Center for Balance Disorders provided instructions and set up each test, but posturography results were rated directly by the CDP apparatus and software supplied by the manufacturer (Neurocom, versions 3 and 4).

EQT composite scores were compared to the EquiTest normative scores using Student's t-test. Paired comparisons of ON and OFF conditions were performed using Wilcoxon matched pairs rank order test using STATA software (College Station, TX). Spearman's rank correlation coefficient was calculated to compare percentage change ($100 \times (\text{OFF} - \text{ON}) / \text{OFF}$) in UHDRS total chorea score and EQT composite score using Statview software (SAS Institute, Inc., Cary, NC).

Results

A total of 10 patients, 6 females and 4 males, with a mean age of 58 ± 11 years (range 43–73) and duration of motor symptoms for a mean of 8.4 ± 3.5 years, (range 2–13) were recruited (Table 1). The average CAG repeat number for 9 patients was 43.4 ± 1.9 ; one subject was reported to have a greater than 40 CAG repeats but the exact number was not available. There were no reported adverse events from withdrawing the medication except for worsening of chorea as anticipated. ON and OFF Unified Huntington Disease Rating Scale scores are shown in Table 1.

Tables 2, 3, and 4 provide average EQT, median number of falls, and average strategy scores. The overall average EQT was 42.7 ± 13.6 ON, 38.1 ± 16.4 OFF, average number of falls was 6.1 ± 3.6 ON, 7.2 ± 3.7 OFF, and average strategy score was 72.9 ± 8.0 ON and 63.5 ± 15.0 OFF.

EQT composite score was significantly worse in both ON ($p < 0.001$) and OFF ($p < 0.001$) tetrabenazine compared to EquiTest age matched normative score, which is consistent with prior observations of symptomatic HD patients [2]. There was a significant difference between ON and OFF evaluations on SOT conditions 3 (sway-referenced vision) and 5 (sway-referenced motion of the support surface and eyes closed) favoring tetrabenazine. In addition, there was a significant difference in the EQT composite score (SOT1–6) between ON and OFF tetrabenazine (Table 2).

The median number of falls in all conditions was 5.0 (range 2–13) in the ON state and 5.5 (range 3–15) in the OFF state (Table 3). Differences between ON and OFF number of falls approached significance in Condition 5 and the composite of all conditions via the Wilcoxon matched-pairs signed rank test. There was a significant difference in strategy scores for tests 1, 2, 3. There was no significant difference in strategy score for tests 4, 5, and 6 (Table 4).

Table 5 lists percentage change of the composite EQT scores compared to percentage improvement in chorea. Analysis via Spearman rank correlation coefficient yielded rho, with correction for ties, of -0.286 and $p = 0.3914$. Given this result, we believe that improvement in EQT score is not solely due to improvement in chorea. EQT reference ranges [5] are provided in Table 6.

Discussion

The baseline decrease in EQT composite scores of HD patients is consistent with prior reports [2]. Statistically significant differences in SOT3 and SOT5 between the ON and OFF tetrabenazine states suggest that tetrabenazine aided patients in gating out of abnormal

visual cues in SOT3 and abnormal somatosensory cues in SOT5, but could not help with gating out of combined simultaneous abnormal visual and somatosensory cues in condition 6. Thus, tetrabenazine can, theoretically, most improve postural stability when one sensory modality is irrelevant. This effect is not sustained with multiple abnormal sensory modalities. The beneficial effects carried over to the EQT composite scores (SOT1–6), which were statistically improved ON tetrabenazine.

The trend toward reduced falls ON tetrabenazine in condition 5 is interesting due to significant difference on SOT5. Improvement in gating out of abnormal somatosensory cues in SOT5 may contribute to the trend towards decreased falls in condition 5.

Strategy scores were significantly higher in conditions 1–3 and also in the composite score while ON tetrabenazine, indicating greater use of ankle strategy. Ankle strategy is considered to be associated with better postural stability than hip strategy [6]. In this setting, tetrabenazine helps in gating out unreliable visual cues in condition 3.

Impaired gating of somatosensory and visual cues has been reported in dysfunction of hand movements in HD. More specifically, reaching movements in HD commence normally, but deteriorate 300 milliseconds after initiation [7]. At that time, deranged somatosensory and visual correction mechanisms send the reaching movement off course. This phenomenon as well as mild impairments in posturography have been reported even in pre-symptomatic HD [2]. Consequently, they are thought to be independent of chorea. They most likely involve long-loop cortical sensorimotor pathways which pass through the thalamus and may be influenced by striatal dysfunction [7]. Improvements in postural stability in symptomatic HD patients through dopaminergic depletion are not limited to amelioration of chorea, but may also include a direct effect in visual and proprioceptive gating mechanisms. A somewhat analogous effect is observed in improvement on the classic Stroop test, which measures interference of visual stimuli, in a state of dopaminergic depletion [8] and haloperidol use in normal controls [9].

Overall tetrabenazine moderately improved balance as determined by computerized posturography. This finding may be directly due to improved chorea, which can dissociate the subject from their normal center of balance, or by some unknown effect possibly involving information processing. Weaknesses of the study include the small sample size and that the drug was prospectively withdrawn rather than added to de novo HD subjects. Nevertheless these results suggest that, at the least, the drug is not contraindicated in HD patients with falls, and possibly supports its use in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics

ID	Age	Sex	# CAG repeats	Age of Motor Sx onset	UHDRS chorea "off" TBZ	UHDRS chorea "on" TBZ	UHDRS total motor off	UHDRS total motor on
1	72	F	41	62	18	17	51	38
2	43	M	44	30	13	8	37	28
3	55	M	45	43	22	17	47	45
4	73	F	42	68	17	5	34	20
5	67	F	44	59	18	17	66	71
6	48	F	47	40	20	8	53	44
7	60	F	44	53	17	8	44	30
8	66	M	42	59	21	5	41	28
9	46	M	42	44	18	6	31	16
10	57	F	>40	45	20	17	50	41

Table 2

Mean Equilibrium scores for On and Off conditions, (standard deviations in parentheses).

Condition	SOT 1	SOT 2	SOT 3	SOT 4	SOT 5	SOT 6	Composite
On	73.8 (13.7)	70.8(16.1)	59.7(23.9)	29.9(25.0)	10.9(9.9)	10.8(13.2)	34.1(14.2)
Off	68.6(21.6)	65.5(23.1)	29.3(51.7)	33.1(25.9)	2.9(6.8)	7.0(10.7)	30.0(15.5)
p	0.329	0.102	0.032 *	0.719	0.043 *	0.186	0.036 *

* denotes significant difference by matched-pairs signed rank Wilcoxon test.

Table 3

Median number of falls per condition (ranges in parentheses).

Condition	SOT 1	SOT 2	SOT 3	SOT 4	SOT 5	SOT 6	Composite (total falls)
On	0 (0–1)	0 (0–1)	0 (0–2)	1 (0–3)	2 (0–3)	2.5 (1–3)	5.0 (2–13)
Off	0 (0–1)	0 (0–2)	0 (0–3)	0.5 (0–3)	3 (1–3)	3 (0–3)	5.5 (3–15)
p	0.317	1.000	0.157	0.659	0.056 *	0.180	0.059 *

* denotes trend approaching significance via Wilcoxon matched-pairs signed rank test.

Table 4

Mean strategy scores (standard deviations in parentheses).

Condition	SOT 1	SOT 2	SOT 3	SOT 4	SOT 5	SOT 6	Composite
On	89.7 (5.8)	90.8 (4.2)	85.6 (9.5)	59.3 (13.1)	58.1 (19.8)	53.6 (24.3)	72.8 (8.0)
Off	82.2 (16.4)	77.4 (20.1)	66.4 (26.0)	55.0 (16.5)	56.0 (13.9)	43.7 (20.3)	63.5 (15.0)
P	0.024*	0.005*	0.005*	0.386	0.959	0.139	0.059

* denotes significant difference by Wilcoxon test.

Table 5

Percent improvement of chorea and EQT composite score, calculated as $100 \times (\text{OFF} - \text{ON}) / \text{OFF}$.

ID	% improvement chorea	% change EQT
1	5.6	6.1
2	38.5	-9.1
3	22.7	-5.1
4	70.6	-3.0
5	5.6	-94.1
6	60.0	-13.3
7	52.9	-6.7
8	76.2	-121.1
9	66.7	-7.9
10	15.0	-5.5

Table 6

Reference ranges for the Equilibrium Test (EQT) and EQT composite score (by permission of NeuroCom, a division of Natus).

	Age (years)	Mean	Standard Deviation (SD)	Mean-1.67*SD
EQT1	20–59	93.991	2.35	90
	60–69	93.679	2.315	90
	70–79	89.483	11.374	70
EQT2	20–59	92.045	4.218	85
	60–69	91.025	2.98	86
	70–79	85.799	13.498	63
EQT3	20–59	91.494	3.335	86
	60–69	88.895	5.152	80
	70–79	88.202	3.888	82
EQT4	20–59	82.451	7.549	70
	60–69	85.185	4.944	77
	70–79	77.679	5.485	69
EQT5	20–59	69.196	10.437	52
	60–69	65.25	8.613	51
	70–79	61.631	10.193	45
EQT6	20–59	67.185	11.582	48
	60–69	64.731	9.332	49
	70–79	53.03	15.508	27
EQT composite	20–59	79.787	5.626	70
	60–69	77.589	5.995	68
	70–79	72.850	5.431	64