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Short communication

Treatment of myoclonus-dystonia syndrome with tetrabenazine

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ABSTRACT

Background: Many cases of myoclonus-dystonia (M-D) are due to mutations in *SGCE* (DYT11). For the majority of patients, myoclonus is relatively more severe than dystonia and can lead to significant functional disability. Deep brain stimulation has been chosen as a treatment option in some patients given that M-D often responds poorly to oral pharmacotherapy.
Methods: Two siblings with M-D due to the same *SGCE* deletion mutation were evaluated with the Global Dystonia Rating Scale (GDRS), Fahn-Marsden Rating Scale (FM) and Unified Myoclonus Rating Scale (UMRS) on and off tetrabenazine.
Results: Both subjects showed marked improvement in myoclonus and mild-to-moderate improvement in dystonia with tetrabenazine. In addition, the response to tetrabenazine has been sustained for years.
Conclusions: A therapeutic trial of tetrabenazine should be considered in patients with M-D, especially before consideration of deep brain stimulation. An adequately powered multi-center, double-blind study of tetrabenazine will be required to determine the relative contributions of tetrabenazine therapy to myoclonus, dystonia, quality of life, and activities of daily living in patients with M-D.

1. Introduction

Myoclonus-dystonia (M-D) due to mutations in *SGCE* (DYT11, OMIM 159900) is typically characterized by the combination of myoclonus and dystonia. Myoclonus can be quite severe and functionally disabling. Dystonia is not evident in all cases and, when present, most frequently affects the neck and arms. Psychiatric co-morbidities including depression, anxiety and obsessive-compulsive disorder have been described in some families with M-D [1]. M-D usually appears within the first two decades of life and may plateau, abate or progress in severity during adulthood.

SGCE is maternally imprinted. A wide array of nonsense, missense, indel and large deletion mutations in *SGCE* has been causally associated with M-D [2]. Although M-D genotype–phenotype correlations have not been overtly evident, subjects with very large deletions that extend beyond the boundaries of *SGCE* may exhibit intellectual disability and extra-neural manifestations. To date, there have been no reported associations between genotype and response to treatment.

A broad collection of oral medications has been used to treat M-D including benzodiazepines (clonazepam, lorazepam, diazepam), valproic acid, gabapentin, levetiracetam, tizanidine, sodium oxybate, levodopa, trihexyphenidyl and benztropine [3]. In general, the responses to these drugs are minimal, at best. Dystonia may benefit from injections of botulinum toxin. Myoclonus and, to a lesser degree, dystonia characteristically improve with consumption of alcohol which, in some patients, contributes to the development of alcohol dependence. More severe cases of M-D, refractory to non-surgical treatment, may benefit from deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) and/or ventral intermediate thalamic nucleus (VIM) [4].

2. Methods

The subjects of this study were two siblings (Patient 1, a 28 year old right-handed male, and Patient 2, a 31 year old right-handed female) with the same previously described *SGCE* deletion mutation of Exons 4 and 5 [2]. Genetic, clinical and videotape analyses were approved by the University of Tennessee Institutional Review Board. Patient 1 refused videotape examination. Patient 2 consented to videotape examination and publication of her video. Both patients were evaluated

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with the Global Dystonia Rating Scale (GDRS), Fahn-Marsden Rating Scale (FM) and Unified Myoclonus Rating Scale (UMRS) "on" and "off" tetrabenazine. At the time of formal ratings, both patients had been treated with tetrabenazine (25 mg PO TID) for over 3 years without apparent adverse effects. Normally, both patients have taken their first dose of tetrabenazine shortly after arising in the morning and last dose approximately 4 h before bedtime. Neither patient has been genotyped for CYP2D6 metabolizer status. Ratings scales initially were completed by M.S.L. during face-to-face assessments with each patient on two separate clinic days (Table 1). Patient 2 then held her morning dose of tetrabenazine before her a third clinic visit. The Dystonia Coalition (www.rarediseasesnetwork.org/dystonia) and UMRS [5] videotape exam protocols were utilized and three blinded raters (H.A.J., R.F.P., and D.D.T.) scored videotapes of Patient 2 with the GDRS, FM and UMRS "off" and "on" tetrabenazine. Assessments were completed in the early morning shortly after the patients arrived in clinic. The raters were blinded to genotype and treatment.

3. Results

Both patients showed a positive response to tetrabenazine. Patient 1 was on no additional medications. Patient 2 was taking montelukast and mometasone furoate for asthma, omeprazole for gastroesophageal reflux, and diltiazem for hypertension. The results of single examiner unblinded ratings of Patient 2 were similar to those of the three blinded raters. In both patients, myoclonus improved to a greater degree than dystonia.

Three hours after taking tetrabenazine, Patient 1 showed moderate reductions in dystonia with changes in GDRS and FM scores from 17 and 22 to 11 and 10, respectively (Table 1). Similar degrees of change were noted in myoclonus at rest and during action. Handwriting was more cohesive but Archimedes spirals became slightly more constricted (Fig. 1). No changes were noted in patient or rater assessments of global disability related to myoclonus.

Patient 2 showed no significant reduction in GDRS and FM unblinded scores 3 h after taking tetrabenazine (Table 1). In contrast, UMRS rest and action myoclonus were markedly reduced. Motor function, including handwriting, improved and the UMRS function score improved by >50% (Fig. 1). More substantial improvements in dystonia and myoclonus were identified by blinded ratings 1.5 h after tetrabenazine (Table 1). Before her morning dose of tetrabenazine, Patient 2 was functionally impaired (Video Segment 1). In the "on" state, 1.5 h after tetrabenazine, Patient 2 showed considerable improvements in handwriting and overall motor function with overt reductions in rest and action myoclonus. Changes in dystonia were more modest (Video Segment 2).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.09.029.

4. Discussion

Despite limitations of study design and small sample size, our findings suggest that therapy with tetrabenazine should be considered as a therapeutic option in patients with M-D. Uncontrolled, retrospective case series have provided data supporting use of tetrabenazine for various forms of myoclonus and dystonia [6,7]. Future studies of tetrabenazine in M-D must be double-blinded, multi-centered, unbiased, and take the pharmacokinetics of tetrabenazine into full consideration. Tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2). VMAT2 is also inhibited by the two major metabolites of tetrabenazine, α-dihyrotetrabenazine and β-dihydrotetrabenazine. Recent pharmacokinetic analyses of six healthy controls found that the time to attainment of maximum plasma concentration (t_{max}) for tetrabenazine, α-dihyrotetrabenazine, and β-dihydrotetrabenazine was approximately 1 h [8]. The terminal half-lives ($t_{1/2}$) for tetrabenazine, α-dihyrotetrabenazine and β-dihydrotetrabenazine were 2.1, 7.6 and 5.9 h, respectively. Therefore, the overall effects of tetrabenazine on quality of life may be limited, at least in part, by pharmacokinetics, and the timing of clinical assessments will be critical in future studies. In addition, use of tetrabenazine in M-D and other disorders can be compromised by adverse reactions such as sedation, fatigue, insomnia, depression, akathisia, anxiety, and nausea.

Other limitations of our study should be noted. First, the findings in our patients with a defined *SGCE* deletion mutation may not extrapolate to patients with other *SGCE* mutations on different genetic backgrounds. Second, the validity and reliability of the GDRS and FM rating scales have not been carefully assessed in M-D or other non-primary dystonias. Thirdly, although inter-rater reliability may be better with videotape than in-person examinations, traditional videotape assessments are inherently two-dimensional and may be less accurate than in-person binocular three-dimensional assessments. Lastly, we cannot exclude experimental bias since the two patients in our study were not blinded to treatment.

The positive responses of both myoclonus and dystonia to GPi-DBS and tetrabenazine suggest that abnormal striatal signaling may be involved in the pathophysiology of M-D. A recent literature review of 40 published neurosurgically-treated cases of M-D found that improvements in myoclonus and dystonia were similar for GPi-DBS and VIM-DBS whereas improvements in dystonia were

Table 1
Dystonia and myoclonus rating scale scores "on" and "off" tetrabenazine.

	Patient 1[a]	Patient 1	Patient 2[b]	Patient 2	Patient 2	Patient 2	Patient 2
Tetrabenazine (25 mg)	Off	On	Off	On	Off	On	% Improvement blinded ratings
Time since last dose of tetrabenazine	15 h	3 h	15 h	3 h	15 h	1.5 h	
Rater(s)	MSL	MSL	MSL	MSL	(HAJ, RFP, DDT)	(HAJ, RFP, DDT)	
Rater(s) blinded to treatment	Yes	Yes	No	No	Yes	Yes	
Rater(s) blinded to diagnosis	No	No	No	No	Yes	Yes	
GDRS	17	11	12	12	14 ± 4.0[c]	2.0 ± 1.0	86%
FM	22	10	19	18.5	9.3 ± 0.4	4.5 ± 1.9	52%
UMRS-patient questionnaire	6	2	16	7	16	3	81%
UMRS-patient global disability	1	1	3	2	2	1	50%
UMRS-myoclonus at rest	47	27	68	25	50 ± 1.2	4.0 ± 1.2	92%
UMRS-stimulus sensitivity	5	2	13	8	6.7 ± 2.2	6.0 ± 1.2	10%
UMRS-action	45	31	83	24	47 ± 13	2.7 ± 1.8	94%
UMRS-function	6	6	17	8	13 ± 0.3	1.0 ± 0.0	92%
UMRS-global disability	1	1	2	1	2.3 ± 0.3	0.3 ± 0.3	87%
UMRS-negative myoclonus	0	0	0	0	0	0	NA

[a] 28 year old right-handed male.
[b] 31 year old right-handed female.
[c] Mean ± standard error of the mean (SEM) for blinded ratings.

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