Published in final edited form as:

Parkinsonism Relat Disord. 2014 December ; 20(12): 1423–1426. doi:10.1016/j.parkreldis.2014.09.029.

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.

Keywords

myoclonus; dystonia; tetrabenazine; blinded; dopamine

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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 benzotropine [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 nonsurgical 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 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 hrs 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 hrs 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 hrs after tetrabenazine (Table 1). Before her morning dose of tetrabenazine, Patient 2 was functionally impaired (Video Segment 1). In the “on” state, 1.5 hrs 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).

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 -dihyrotetrabenazine. 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 -dihyrotetrabenazine was approximately 1 hr [8]. The terminal half-lives ($t_{1/2}$) for tetrabenazine, α -dihyrotetrabenazine and β -dihyrotetrabenazine were 2.1, 7.6 and 5.9 hrs, 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 greater with GPi-DBS than VIM-DBS [4]. Compatible with these clinical findings, significantly higher levels of striatal dopamine and its metabolites were found in a knockout mouse model of M-D [9]. Conversely, molecular, neurophysiological and imaging studies indicate that the clinical manifestations of M-D may be due to cerebellar or cerebellothalamocortical pathway dysfunction [10–12]. Given that (1) the cerebellum and striatum are disynaptically connected through the thalamus and subthalamic nucleus and (2) the cerebellothalamocortical pathways exert widespread effects on cortex and corticostriate projections [13], it is conceivable that surgical or pharmacological manipulations of basal ganglia output could compensate for abnormalities of cerebellar signaling. Tetrabenazine also depletes norepinephrine and, consequently, may also modify cerebellar output by reducing noradrenergic transmission in cerebellar cortex. In this regard, alterations in noradrenergic projections to the cerebellum have been described in rodent models of dystonia [14,15]. Continued study of M-D in humans and model systems may provide additional insights into the network biology of myoclonus and dystonia and point to novel forms of treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial disclosures relevant for the present article

Dr. LeDoux serves on the speakers' bureaus for Lundbeck, UCB Pharma and TEVA; serves on advisory boards for TEVA, Lundbeck and USWorldMeds; serves as a consultant for the Mayo Clinic; receives research support from the National Institutes of Health (NIH), Prana, Omeros, Auspex, USWorldMeds and CHDI; and receives royalty payments from Elsevier.

Dr. Jinnah has received research grant support from the NIH, the Atlanta Clinical & Translational Science Institute, the Emory University Research Council, the Lesch-Nyhan Syndrome Children's Research Foundation, the Dystonia Medical Research Foundation, the Bachmann-Strauss Dystonia & Parkinson's Foundation, and the Benign Essential Blepharospasm Research Foundation. He also is principal investigator for the Dystonia Coalition, which receives the majority of its support through NIH grant NS065701 from the Office of Rare Diseases Research in the National Center for Advancing Translational Sciences and National Institute of Neurological Disorders and Stroke. The Dystonia Coalition receives additional material or administrative support from industry sponsors (Allergan, Ipsen Biopharm, Medtronic, and Merz) as well as private foundations (The American Dystonia Society, The Bachmann-Strauss Dystonia and Parkinson Foundation, BeatDystonia, The Benign Essential Blepharospasm

Foundation, Dystonia Europe, Dystonia Ireland, The Dystonia Medical Research Foundation, The Dystonia Society, The Foundation for Dystonia Research, The National Spasmodic Dysphonia Association, and The National Spasmodic Torticollis Association). Dr. Jinnah serves on the Scientific Advisory Boards for Cure Dystonia Now, the Dystonia Medical Research foundation, Tyler's Hope for a Dystonia Cure, the Lesch-Nyhan Syndrome Children's Research Foundation, and Lesch-Nyhan Action France.

Dr. Pfeiffer serves on the speakers' bureaus for TEVA, UCB, and USWorldMeds; has served on advisory boards for Pfizer, Chelsea, and Acadia; has received research support from UCB; receives royalty payments from CRC Press and Humana Press for books edited and payment from Elsevier for journal editing.

Dr. Truong receives research support from AbbVie, Adamas, Auspex, Ipsen, Kyowa Hakko Kirin, Merz, the National Institutes of Health and Pfizer; and receives royalty payment from Cambridge Publishing Company, Demos and Wiley Blackwell.

Dr. Nance has received grant support for research from NIH, The Patient Centered Outcomes Research Institute (PCORI), the Park Nicollet Foundation, The National Parkinson Foundation, The Michael J. Fox Foundation, Neurosearch A/S, Prana Biotechnology, Auspex, TEVA, Huntington Disease Society of America, CHDI and for Centers of Excellence from the Huntington Disease Society of America and the National Parkinson Foundation. She has served on an Advisory Board from Lundbeck. Her husband owns stock in Fresca Corporation. She has received payment for educational program development from WebMD and Medscape, and royalties from Oxford University Press.

This research was supported by National Institutes of Health grants R01 NS069936, R01 NS082296 and U54 NS065701 to Dr. LeDoux. Dr. Jinnah's work related to dystonia has been supported in part by grants from private foundations including the Bachmann-Strauss Dystonia & Parkinson Foundation, the Benign Essential Blepharospasm Research Foundation, and the Dystonia Medical Research Foundation, and Tyler's Hope for a Cure. It also has been supported in part by research grants from the NIH (U54 NS065701, R01 NS040470, R01 HD053312), and the Emory University Research Council.

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- Many cases of myoclonus-dystonia are due to mutations in *SGCE* (DYT11).
- Two siblings with myoclonus-dystonia due to a deletion mutation in *SGCE* showed notable improvements in myoclonus and dystonia after treatment with tetrabenazine.
- 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.

Patient 1 - Off Tetrabenazine

Patient 1- On Tetrabenazine

Patient 2 - Off Tetrabenazine

today is a nice day

Patient 2 - On Tetrabenazine

today is a nice day

Figure 1.

Handwriting and Archimedes spirals “off” and “on” tetrabenazine.

Table 1

Dystonia and myoclonus rating scale scores “on” and “off” tetraabenazine

	Patient 1 ^a		Patient 1	Patient 2 ^b		Patient 2	Patient 2	Patient 2	Patient 2	Patient 2	% improvement blinded ratings
Tetraabenazine (25 mg)	Off	On	Off	On	Off	On	Off	On	On		
Time since last dose of tetraabenazine	15 hrs	3 hrs	15 hrs	3 hrs	15 hrs	3 hrs	15 hrs	15 hrs	1.5 hrs		
Rater(s)	MSL	MSL	MSL	MSL	MSL	MSL	(HAJ, RFP, DDT)	(HAJ, RFP, DDT)			
Rater(s) Blinded to Treatment	Yes	Yes	No	No	No	No	Yes	Yes	Yes		
Rater(s) Blinded to Diagnosis	No	No	No	No	No	No	Yes	Yes	Yes		
GDRS	17	11	12	12	12	12	14 ± 4.0 ^c	2.0 ± 1.0	2.0 ± 1.0	86%	
FM	22	10	19	18.5	16	7	9.3 ± 0.4	4.5 ± 1.9	4.5 ± 1.9	52%	
UMRS-Patient Questionnaire	6	2	16	7	3	2	16	3	3	81%	
UMRS-Patient Global Disability	1	1	3	2	68	25	50 ± 1.2	4.0 ± 1.2	4.0 ± 1.2	50%	
UMRS-Myoclonus at Rest	47	27	13	8	83	24	6.7 ± 2.2	6.0 ± 1.2	6.0 ± 1.2	92%	
UMRS-Stimulus Sensitivity	5	2	31	8	17	8	47 ± 13	2.7 ± 1.8	2.7 ± 1.8	10%	
UMRS-Action	45	31	6	6	2	1	13 ± 0.3	1.0 ± 0.0	1.0 ± 0.0	94%	
UMRS-Function	6	6	1	1	0	0	2.3 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	92%	
UMRS-Global Disability	1	1	0	0	0	0	0	0	0	87%	
UMRS-Negative Myoclonus	0	0	0	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.