Parkinsonism and Related Disorders xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

A randomized study of botulinum toxin versus botulinum toxin plus physical therapy for treatment of cervical dystonia

Wei Hu[a], Valerie Rundle-Gonzalez[a], Shankar J. Kulkarni[b], Daniel Martinez-Ramirez[a], Leonardo Almeida[a], Michael S. Okun[a], Aparna Wagle Shukla[a,*]

[a] Center for Movement Disorders and Neurorestoration, Department of Neurology, University of Florida, Gainesville, FL, USA
[b] Shands Rehabilitation Service, University of Florida, Gainesville, FL, USA

ARTICLE INFO

Keywords:
Botulinum toxin
Dystonia
Physical therapy
Cervical dystonia

ABSTRACT

Background: Physical therapy (PT) for cervical dystonia is not well studied, and the underlying physiological effects are not known.

Methods: We enrolled 26 subjects comprising of 16 cervical dystonia and 10 healthy controls for normative physiological data. We randomized cervical dystonia patients who reported suboptimal benefits on botulinum toxin (BoNT) injections to BoNT alone (BoNT arm) or BoNT plus PT (PT-BoNT arm). PT-BoNT arm received manual PT on the injection day followed by six weeks of home-exercise program. Home-exercise program comprised of stretching, range-of-motion and isometric exercises. The primary outcome was change from baseline in Toronto Western spasmodic torticollis rating scale (TWSTRS) that was recorded six weeks after exercise program. TWSTRS was video evaluated by blinded raters. We probed sensorimotor plasticity with transcranial magnetic stimulation (TMS) using a paired associative stimulation (PAS) paradigm.

Results: TWSTRS score improved (severity 31%, $p = 0.002$; pain 28%, $p = 0.01$) and PAS plasticity decreased ($p = 0.01$) in PT-BoNT arm compared to BoNT arm. PAS values for PT-BoNT arm were found to approach values of healthy control values. Change in PAS measure correlated significantly with TWSTRS change (severity, $r = 0.56$, $p = 0.04$; pain, $r = 0.61$, $p = 0.03$. TWSTRS disability score only approached significance ($p = 0.14$) when comparing the two treatment arms.

Conclusion: PT is a potential adjunct in patients with cervical dystonia who report suboptimal benefits with BoNT therapy. PT related benefits in cervical dystonia are likely mediated through modulation of sensorimotor plasticity.

1. Introduction

Cervical dystonia (CD), a focal form of dystonia is a frequent source of disability [1], depression, and a diminished quality-of-life [2]. The first line of treatment for CD is botulinum toxin (BoNT) injection therapy administered approximately at every 12 weeks. The clinical improvements from BoNT can often be suboptimal, and these improvements commonly wane by 8–10 weeks [3]. Thus, meaningful adjunctive treatments are often warranted in these patients. There is scant literature on the use of physical therapy (PT) in dystonia [4–6], and there is no consistency in the dose, type, and duration of exercises. None of these studies have examined the effects of PT in the CD population who specifically show refractoriness or suboptimal response to BoNT therapy. None of these studies have also examined physiological changes underlying the PT related benefits.

We aimed to compare the clinical outcomes of BoNT versus BoNT plus PT in a well-defined population of CD patients who reported suboptimal response to BoNT therapy. Since multiple transcranial magnetic stimulation (TMS) studies have shown enhanced sensorimotor plasticity in dystonia, we employed this approach in both study arms to probe the underlying physiological change and its relationship to clinical improvement [7].

2. Methods

CD subjects receiving suboptimal benefits despite a regular schedule of BoNT injections every 12 weeks participated. Diagnosis of CD was established using standard criteria [8] and suboptimal benefits were defined as less than 30% improvement in dystonia symptoms and/or BoNT benefits lasting only 8–9 weeks out of 12 week cycle. Subjects

* Corresponding author. UF Center for Movement Disorders & Neurorestoration, 3450 Hull Road, Gainesville, FL, 32607, USA.
E-mail address: Aparna.shukla@neurology.ufl.edu (A. Wagle Shukla).

https://doi.org/10.1016/j.parkreldis.2019.02.035
Received 29 November 2018; Received in revised form 12 February 2019; Accepted 20 February 2019

Table 1
Demographics and clinical profile of participating cervical dystonia subjects.

	Physical therapy arm	No-Physical Therapy arm	p value
Age in years	64.8 ± 7.4	67.3 ± 7.2	0.51
Gender	4 Females: 4 Males	5 Females: 3 Males	0.06
Cervical dystonia duration in years	10.1 ± 5.4	8.7 ± 5.3	0.14
BoNT therapy duration in years	5.1 ± 4.9	4.1 ± 1.1	0.32
BoNT dose in units	235 ± 70.3	245 ± 55.1	0.41
Average duration of BoNT benefits per cycle (in weeks)	8.8 ± 4.1	9 ± 5.4	0.36
TWSTRS severity score at baseline	18.4 ± 8.7	22.2 ± 11.2	0.13
TWSTRS pain score at baseline	8.7 ± 7.2	7.1 ± 6.7	0.12
VAS pain score at baseline	6.7 ± 5.7	6.9 ± 5.8	0.46
SF-36 quality of life			
Physical component score at baseline	54.6 ± 26.4	47.1 ± 25.9	0.11
Mental component score at baseline	58.1 ± 21.9	62.3 ± 23.6	0.44
Inclinometer findings at baseline			
Range of Flexion	45.1 ± 25.4	42.7 ± 23.8	**0.05**
Range of Extension	37 ± 22.3	36.1 ± 24.2	0.32
Range of Rotation to right	45 ± 21.1	48.1 ± 19.3	0.12
Range of Rotation to left	40.1 ± 24.2	42.4 ± 26.5	0.56
Range of Lateral flexion to right	36.2 ± 16.2	18.7 ± 14.5	**0.03**
Range of Lateral flexion to left	37.2 ± 15.1	17.1 ± 13.2	**0.02**
TMS rest motor threshold	49.3 ± 6.8	50.1 ± 5.4	0.56
TMS active motor threshold	46.2 ± 9.1	48.1 ± 8.2	0.45

Plus-minus values are means ± SD.
BoNT: botulinum toxin.
TWSTRS: Toronto Western torticollis rating scale.
VAS: visual analogue scale.
TMS: transcranial magnetic stimulation.
There were no significant differences between groups except the p values in bold.

with acute spondylitis, unhealed fractures, and joint or ligamentous laxity were excluded. Participating subjects signed an IRB approved consent form. We registered the study protocol at the clinicaltrials.gov (NCT02177617). There were 22 subjects screened for the study, however, three declined to participate and three did not meet the inclusion criteria (Supplemental flowchart). Participating subjects were randomized to receive BoNT alone (BoNT arm) or BoNT plus PT (PT-BoNT arm). We used a block randomization method with a block size of 4 for assignment of patients to the two treatment arms. All injections were performed by the same provider using EMG guidance (AWS). We initiated the PT program on the day (baseline, Visit 1) patient presented for botulinum toxin injections. Upon completion of the injection procedure, subjects underwent a manual 60-min session of deep massage, myofascial elongation, and stretching of the cervical muscles that was supervised by the same physical therapist (SK). Once this session was completed, we provided training to subjects to perform a home exercise program for six weeks. Our physical therapy department prepared a list, an instructional DVD and a pictorial guide for the home exercises that every participant in the PT-BoNT arm received. Exercises consisted of stretching, active range-of-motion (ROM), and isometric exercises for the neck muscles. Subjects were required to exercise 15 min every day for 5 days-a-week and instructed to maintain an exercise log at home. Adherence to exercises was ensured through weekly telephone calls and/or emails. Age and gender-matched healthy controls were enrolled for normative physiological data.

The Toronto Western torticollis rating scale (TWSTRS) measures consisting of physician-rated motor severity and patient-reported pain and disability was employed at baseline (before injections, visit 1), after completion of six week exercises, (about the time of peak dose effect of BoNT, visit 2), and at the time of next injections (12 weeks, visit 3). The TWSTRS motor severity was video-recorded for blinded rating by two independent movement disorder neurologists. A visual analogue scale (VAS) for pain consisting of a numerical 0–10 scale with 0 as no pain and 10 as the worst pain and SF-36 scale for quality-of-life (QoL) was applied at each visit. In addition, an inclinometer recommended by the American Medical Association (for measurement of impairment related to spinal movement) to record the ROM for the neck muscles was applied.

TMS techniques were used at each visit to record the underlying physiology. For the TMS test, subjects were seated comfortably with the forearms resting in a semi-prone position to facilitate complete relaxation of the muscles. A figure-of-eight shaped TMS coil (diameter of 9 cm) coil was attached to the Magstim 200[2]. Significant background EMG area for about 500 ms period before the delivery of TMS pulse was rejected. We recorded the rest motor threshold (RMT), the active motor threshold (AMT) and the sensorimotor plasticity measured with a standard paired associative stimulation (PAS) protocol. In this PAS protocol, median nerve stimulation at the wrist was paired at an interstimulus interval of 25 ms with TMS pulse delivered to the motor cortex (90 pairs delivered) [9]. The mean PAS (PAS_{mean}) motor evoked potential (MEP) recorded from the surface EMG of the abductor pollicis brevis muscle was determined immediately, at 15 min and at 30 min after completion of the PAS protocol to compare with baseline MEP [9].

The primary outcome was the change from baseline in TWSTRS measures at visit 2 compared between two arms. Secondary outcomes included change from baseline in VAS measure, SF-36 scores, inclinometer readings and TMS measures. Secondary outcomes also included a change from baseline in all outcome measures at visit 3. We applied last observation carried forward for imputation of missing data. The sample size was determined based on parameters of moderate effect size, a power of 80% and type I error at 0.05. The between-group differences in change in scores were examined with SPSS software version 24, either using a *t*-test or Wilcoxon rank-sum test which was Bonferroni corrected for multiple comparisons. Spearman test was used for correlation. Non-parametric tests were applied since the values were not normally distributed ($p < 0.05$, Kolmogorov Smirnov test). All tests were 2-sided set at p value < 0.05.

3. Results

16 CD subjects and 10 healthy controls participated in the study. CD subjects (7 males, 9 females) were randomized to the two treatment arms. The mean age ± standard deviation (SD) was 64.5 ± 5.4 years and the mean disease duration was 14.4 ± 10.9 years. All CD

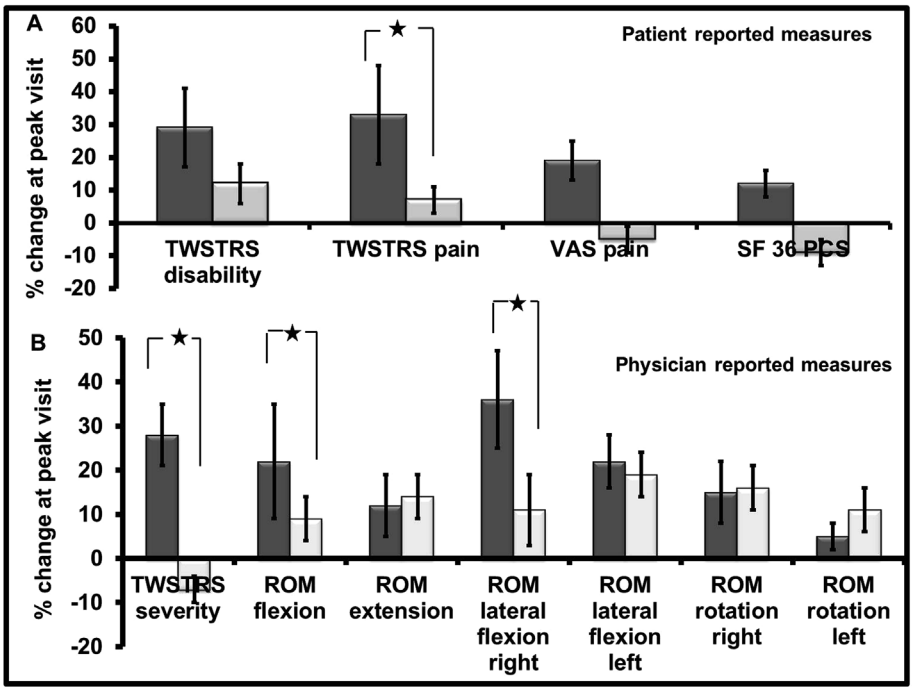

Fig. 1. Group average data on patient reported measures. The difference in scores between visit 1 and visit 2 is expressed as a percentage change. A positive change indicates improvement and a negative change indicates worsening. Dark grey bar represents the physical therapy arm and light grey bar represents no physical therapy arm. Error bars represent standard errors. Asterisks between the bars indicates significant difference between the groups. *P < 0.05. A significant difference is seen for the TWSTRS pain measure. **B:** Group average data on physician reported measures. The difference in scores between visit 1 and visit 2 is expressed as a percentage change. A positive change indicates improvement and a negative change indicates worsening. Dark grey bar represents the physical therapy arm and light grey bar represents no physical therapy arm. Error bars represent standard errors. Asterisks between the bars indicates significant difference between the groups. *P < 0.05. ROM is range-of-motion. A significant difference is seen for the TWSTRS severity measure, Range-of-motion flexion and range-of-motion flexion to the right.

participants received stable (not changed in previous two cycles) doses of onabotulinum toxin type A (BOTOX) and at the time of visit 2, the usual peak benefits related to BoNT were confirmed. Participating CD subjects scored moderately at baseline on severity and pain measures. Most of them had a mixed combination of torticollis, laterocollis, and retrocollis. The two treatment arms were balanced for mean age, gender distribution, disease duration, duration of BoNT therapy, BoNT dose, TWSTRS severity, TWSTRS pain, VAS pain, and SF-36 QoL scores and TMS thresholds except for the flexion ROM in the sagittal plane and the lateral flexion motion in the coronal plane. (Table 1). An email or phone log documented that participating subjects in the PT-BoNT arm maintained compliance with the home exercises. There were no adverse effects reported. One subject dropped out after randomization from the BoNT arm due to a family emergency. One subject from PT-BoNT arm did not follow up at visit 2 and one subject from the BoNT arm did not follow-up at visit 3 for TMS assessment part. The inter-rater agreement for video assessment was moderately high (Cohen's kappa 0.65).

The change from baseline in primary outcome variable (TWSTRS severity and pain measures) at visit 2 was significantly greater in the PT-BoNT arm compared to the BoNT arm (Fig. 1). The TWSTRS severity score improved by 31% (mean change 3 ± 0.5 points; $p = 0.002$) in the PT-BoNT arm compared to the BoNT arm. The TWSTRS pain score improved by 28% (1.8 ± 1.1; $p = 0.01$) in the PT-BoNT arm compared to the BoNT arm. There was also a significant decrease in PAS_{mean} at visit 2 for the PT-BoNT arm which was not seen in the BoNT arm (mean difference 35%; $p = 0.01$). The PAS_{mean} values for the PT-BoNT arm were noted to approach values of healthy control values. There was a positive correlation between the change in PAS_{mean} and the change in TWSTRS severity measure ($r = 0.56$; $p = 0.04$). Similarly change in PAS_{mean} also correlated with TWSTRS pain measure ($r = 0.61$; $p = 0.03$).

TWSTRS disability score (16%; $p = 0.14$) and VAS pain scores (21%; $p = 0.09$) improvements in the PT-BoNT arm approached significance compared to BoNT arm. Improvement in SF-36 physical component scale also approached significance in the PT-BoNT arm (23%; $p = 0.09$) whereas the mental component did not achieve significance ($p = 0.23$). The inclinometer findings were not statistically different between the two arms except for the range of flexion in the sagittal plane (27%; $p = 0.03$) and lateral flexion (26%, $p = 0.01$). There were no statistical differences between the two arms for RMT ($p = 0.8$) and AMT ($p = 0.67$). The change from baseline at visit 3 was not significant for any of the outcome measures ($p > 0.05$, supplemental table).

4. Discussion

The current study found adjunctive PT in CD in combination with BoNT therapy led to greater improvements in the TWSTRS scores compared to the BoNT alone. There were positive changes in the QoL evidenced on a generic measure, and a significant correlation between sensorimotor plasticity and clinical improvements suggest that the plasticity effects likely play a role in PT benefits, which needs a further mediation analysis [10]. Previous research has suggested, abnormal movement patterns in dystonia are stored due to excessive sensorimotor plasticity and BoNT therapy in CD likely modulates the plasticity at the time of peak injection benefits [11]. Interesting and unique to our study was that sensorimotor plasticity decreased in greater amounts at the time of peak BoNT benefits in patients who were randomized to the PT-BoNT arm compared to BoNT alone. Regular exercise training probably modulates the abnormal movement patterns in dystonia, and that sensorimotor plasticity may play a major role in the phenomenon. There is evidence to show exercise training in healthy adults and other neurological disorders such as Parkinson's disease, Multiple Sclerosis and stroke modulates brain circuitries with associated health benefits [12–14]. Exercises in animal models of Parkinson's disease have shown neuroprotective effects [15]. In dystonia, although there is growing clinical support, there is a lack of insight on pathophysiological mechanisms underpinning the clinical improvements.

We acknowledge our study had limitations such as the small size of the sample and the short length of exercise program. As a result, the benefits drawn from exercises in the first six weeks of cycle did not impact the wearing-off related to BoNT therapy measured at 12 weeks. Although a home exercise program that is more practical and cost-effective was employed, supervised PT sessions may have yielded greater improvements. We also cannot exclude the possibility of a “lessebo effect” as the BoNT arm did not receive an extra intervention. Additionally, there were minor differences at baseline between the groups in the inclinometer findings, and a larger study could address

this concern. However, the randomized design, blinded assessment of videos and large physiological change associated with positive benefits strengthen the premise that PT may be useful as an adjunct to BoNT therapy.

We conclude that PT in a CD population is a promising adjunctive treatment option and that there is preliminary physiological evidence supporting an important role for sensorimotor plasticity. Future studies should employ larger sample sizes, longer duration of exercises, and perhaps supervised PT sessions with multimodal rehabilitation strategies such as resistance training and biofeedback protocols. These studies may be better served using dystonia or movement disorders specific scale [16]. Structural and functional imaging studies in conjunction with TMS may also further elucidate the pathways underpinning the synergistic improvement.

5. Author roles

Wei Hu was involved in execution, review and critique of manuscript;

Valerie Rundle Gonzalez was involved in collection of data and critique of manuscript.

Shankar Kulkarni was involved in execution and collection of data.

Daniel Martinez-Ramirez was involved in collection of data and critique of manuscript.

Leonardo Almeida was involved in collection of data and critique of manuscript.

Michael S Okun was involved in review and critique of manuscript.

Aparna Wagle Shukla was involved in conception, organization and execution of research project, execution and critique of statistical analysis, review and critique of manuscript;

Acknowledgment

Drs. Wei Hu and Valerie Rundle-Gonzalez are the recipients of American Brain Foundation Clinical Research Training Fellowship in the Neurological Application of Neurotoxins Funded by the Allergan Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.035.

Financial disclosures

Wei Hu: employment - *University of Florida; American Brain Foundation*.

Valerie Rundle Gonzalez: *University of Florida; American Brain Foundation*.

Shanker Kulkarni- *Shands Rehabilitation service; University of Florida*.

Daniel Martinez-Ramirez- *University of Florida*.

Leonardo Almeida: employment- *University of Florida*.

Dr. Michael S. Okun – Serves as consultant for the National Parkinson's Foundation, and has received research grants from the National Institutes of Health, National Parkinson's Foundation, Michael J. Fox Foundation, Parkinson Alliance, Smallwood Foundation, Bachmann-Strauss Foundation, Tourette Syndrome Association, and UF Foundation. Dr. Okun has previously received honoraria, but in the past > 60 months has received no support from industry. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). Dr. Okun is an associate editor for New England Journal of Medicine Journal Watch Neurology. Dr. Okun has participated in CME and educational activities on movement disorders (in the last 36 months) sponsored by PeerView, Prime, Quantia, Henry Stewart, and the Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. Dr.

Aparna Wagle Shukla – Reports grants from the NIH and has received grant support from Benign Essential Blepharospasm Research Foundation, Dystonia coalition, Dystonia Medical Research Foundation, National Organization for Rare Disorders and grant support from NIH (KL2 and K23 NS092957-01A1).

References

[1] K.K. Martikainen, T.H. Luukkaala, R.J. Marttila, Working capacity and cervical dystonia, Park. Relat. Disord. 16 (3) (2010) 215–217.
[2] L. Camfield, Y. Ben-Shlomo, T.T. Warner, Impact of cervical dystonia on quality of life. Movement disorders, Off. J. Mov. Disord. Soc. 17 (4) (2002) 838–841.
[3] D. Martinez-Ramirez, J.C. Giugni, E. Hastings, A. Wagle Shukla, I.A. Malaty, M.S. Okun, et al., Comparable Botulinum Toxin Outcomes between Primary and Secondary Blepharospasm: A Retrospective Analysis vol. 4, Tremor and other hyperkinetic movements, New York, NY, 2014, p. 286.
[4] C. Tassorelli, F. Mancini, L. Balloni, C. Pacchetti, G. Sandrini, G. Nappi, et al., Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia, Mov. Disord. Off J. Mov. Disord. Soc. 21 (12) (2006) 2240–2243.
[5] C. Counsell, H. Sinclair, J. Fowlie, E. Tyrrell, N. Derry, P. Meager, et al., A randomized trial of specialized versus standard neck physiotherapy in cervical dystonia, Park. Relat. Disord. 23 (2016) 72–79.
[6] M.F. Contarino, M. Smit, J. van den Dool, J. Volkmann, M.A. Tijssen, Unmet needs in the management of cervical dystonia, Front. Neurol. 7 (2016) 165.
[7] A. Wagle Shukla, D.E. Vaillancourt, Treatment and physiology in Parkinson's disease and dystonia: using transcranial magnetic stimulation to uncover the mechanisms of action, Curr. Neurol. Neurosci. Rep. 14 (6) (2014) 449.
[8] A. Albanese, K. Bhatia, S.B. Bressman, M.R. Delong, S. Fahn, V.S. Fung, et al., Phenomenology and classification of dystonia: a consensus update, Mov. Disord. Off. J. Mov. Disord. Soc. 28 (7) (2013) 863–873.
[9] K. Stefan, E. Kunesch, L.G. Cohen, R. Benecke, J. Classen, Induction of plasticity in the human motor cortex by paired associative stimulation, Brain J. Neurol. 123 (Pt 3) (2000) 572–584.
[10] D.P. MacKinnon, A.J. Fairchild, M.S. Fritz, Mediation analysis, Annu. Rev. Psychol. 58 (2007) 593–614.
[11] M. Kojovic, A. Caronni, M. Bologna, J.C. Rothwell, K.P. Bhatia, M.J. Edwards, Botulinum toxin injections reduce associative plasticity in patients with primary dystonia, Mov. Disord. Off. J. Mov. Disord. Soc. 26 (7) (2011) 1282–1289.
[12] J.L. Jensen, P.C. Marstrand, J.B. Nielsen, Motor skill training and strength training are associated with different plastic changes in the central nervous system (Bethesda, Md : 1985), J. Appl. Physiol. 99 (4) (2005) 1558–1568.
[13] B. Vahlberg, T. Cederholm, B. Lindmark, L. Zetterberg, K. Hellstrom, Short-term and long-term effects of a progressive resistance and balance exercise program in individuals with chronic stroke: a randomized controlled trial, Disabil. Rehabil. 39 (16) (2017) 1615–1622.
[14] N. Akbar, B.M. Sandroff, G.R. Wylie, L.B. Strober, A. Smith, Y. Goverover, et al., Progressive resistance exercise training and changes in resting-state functional connectivity of the caudate in persons with multiple sclerosis and severe fatigue: a proof-of-concept study, Neuropsychol. Rehabil. (2018) 1–13.
[15] N. Tajiri, T. Yasuhara, T. Shingo, A. Kondo, W. Yuan, T. Kadota, et al., Exercise exerts neuroprotective effects on Parkinson's disease model of rats, Brain Res. 1310 (2010) 200–207.
[16] J. Muller, J. Wissel, G. Kemmler, B. Voller, T. Bodner, A. Schneider, et al., Craniocervical dystonia questionnaire (CDQ-24): development and validation of a disease-specific quality of life instrument, J. Neurol. Neurosurg. Psychiatr. 75 (5) (2004) 749–753.