Research article

Functional electrical stimulation as a component of activity-based restorative therapy may preserve function in persons with multiple sclerosis

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Objective: To examine the effect of functional electrical stimulation (FES) cycling on disability progression in persons with multiple sclerosis (MS).

Design: Retrospective cohort, 40 participants with mean follow-up of 15 months.

Setting: International Center for Spinal Cord Injury at Kennedy Krieger Institute in Baltimore, a rehabilitation referral center.

Participants: Forty consecutive persons with MS undergoing rehabilitation from 2007 to 2011, with at least two evaluations based on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).

Interventions: FES cycling as part of activity-based restorative therapy interventions.

Outcome measures: Change in Expanded Disability Status Scale (EDSS) and ISNCSCI motor, light touch, and pin prick scores from baseline to latest evaluation.

Results: In 71% of patients, activity-based rehabilitation included FES cycling. There was no disability progression on the EDSS. Lower extremity motor scores improved or stabilized in 75% of patients with primary progressive MS (PPMS), 71.4% with secondary progressive MS (SPMS), and 54.5% with relapsing remitting MS (RRMS). Among patients with improved or stabilized lower extremity motor function, PPMS recorded a mean 9% improvement, SPMS 3% and RRMS 6%. In PPMS, use of FES showed trend towards improvement in motor scores ($P = 0.070$).

Conclusions: FES as part of activity-based rehabilitation may help preserve or improve neurological function in patients with MS.

Keywords: Activity-based restorative therapy, Functional electrical stimulation, Multiple sclerosis, Disability

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) of mostly unknown etiology. MS affects ~400 000 persons in the USA and is the most common non-traumatic cause of neurological disability in young adults.^{1,2} MS may be classified as relapsing remitting MS

(RRMS), primary progressive MS (PPMS), or secondary progressive MS (SPMS).^{3,4} Persons with MS usually accrue progressive disability over time. Whereas persons with PPMS experience a gradual progressive accumulation of disability, those with RRMS experience periods of relapses and remission of disease over several years following which they may progress into a phase of progressive disability accrual known as SPMS.⁴

Pharmacotherapy in MS is mainly effective in the RRMS stage. To date, disability accrual in the progressive

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stage of the disease has not been successfully reduced by pharmacological agents. The majority of disability in MS is generally thought to be caused by spinal cord dysfunction.⁵ The neurodegenerative processes of MS disability have been associated with axonal damage, inflammation, and demyelination.⁶⁻⁸

Most of the cellular mechanisms of CNS regeneration are activity-dependent. Findings suggest that activation of the CNS is important in influencing the cellular mechanisms associated with regeneration, particularly re-myelination, and axonal growth. The role of activity may be even more important in conditions where normal activity is reduced, as in inflammatory spinal cord injury (SCI).⁹ Examples where neural activity plays a critical role in development and plasticity include activity-dependent gene expression,^{10,11} modification of synaptic strength (e.g. long-term potentiation),^{12,13} synapse elimination,¹² myelination and maintenance of myelination,¹⁴⁻¹⁶ and axonal growth.¹⁷

Because both development and plasticity in the CNS depend on neural activity, optimizing neural activity might also be important for regeneration.^{14,18} Increased neural activity has been shown to enhance multiple components of spontaneous regeneration while decreased activity inhibits regeneration.^{19,20}

In patients with (SCI) including MS, a novel way of increasing activity in the injured CNS is by activity-based restorative therapy (ABRT). ABRT is a life-long intervention aiming at function restoration, utilizing principles based on activity-dependent neural plasticity, where changes in the nervous and muscular system are driven by repetitive activation of the neuromuscular system above and below the level of injury.^{21,22} ABRT also involves interventions that result in neuromuscular activation below the level of the lesion to promote recovery of motor function with the activation driven by the nervous system such as in epidural stimulation. ABRT interventions include functional electrical stimulation (FES), locomotor training, weight loading, patterned and non-patterned motor and sensory activation above and below the level of spinal lesions.^{15,23} The use of FES has been established in traumatic SCI rehabilitation.^{24,25} However, there are limited clinical data available on the use of FES in MS. The majority of that data are derived from FES bracing. Long-term FES bracing for foot drop has been shown to increase strength and walking speed suggesting that FES strengthens activation of motor cortical areas and their residual descending connections in patients with MS.²⁶ It has been shown to be a cost-effective intervention.²⁷

FES cycling has been associated with improved spasticity without improvement in strength and walking

speed in a pilot trial with 12 MS patients who underwent FES cycling (three sessions/week for 2 weeks).²⁸ In a pilot trial in persons with MS, Ratchford *et al.*²⁹ showed improvements on a broad array of functional and neurological outcome measures including gait, upper extremity (UE) dexterity, and quality of life. Further, analysis of cerebrospinal fluid before the start of FES and 3 months after initiating FES cycling suggested a potential neural repair program (increased cerebrospinal fluid transforming growth factor beta 3 (CSF TGF- β 3)) and a reduced inflammatory environment within the CNS (decreased interferon- γ , IL-7, IL-8).

FES delivered by epidural spinal cord stimulation has been associated with improved motor control, spinal spasticity, and bladder function in MS.³⁰ The exact mechanism, by which spinal cord stimulation changes occur, is not well understood yet. Inhibition of excessive spinal reflex activity, augmentation or modulation of ascending and descending tracts, and modulation of the central excitatory state and neurotransmitter release have been proposed.³¹

We performed a retrospective review of the effect of long-term FES as part of ABRT on disability and neurological function in persons with MS who were referred to the International Center for Spinal Cord Injury at Kennedy Krieger Institute in Baltimore, MD, USA. Because MS is associated with a progressive decline in neurological function, we hypothesized that persons with MS undergoing ABRT would experience preservation of neurological function.

Methods

We reviewed the medical records of all patients with MS who underwent ABRT with or without FES at our Center between July 2007 and August 2011. Persons were referred to our facility for ABRT interventions based on chronic progression of disease outside the context of obvious relapses, and were free of relapse within 3 months prior to referral to our Center. ABRT was integrated into a traditional physical therapy (PT) program. Whereas traditional PT promotes compensation and usually involves low intensity activation of the nervous system above the level of the lesion by non-patterned movements, ABRT interventions target restoration and employ high intensity practice using patterned and non-patterned movements to activate the nervous system above and below the level of the lesion. ABRT interventions included FES, locomotor training, weight loading, patterned and non-patterned motor and sensory activation (strengthening, endurance, and balance training). Weight loading interventions

included standing, and gait training. All participants attending our Center are evaluated by the treating SCI specialist (neurologist and physiatrist) and physical and occupational therapists for use of FES as part of the ABRT regimen. Based on the functional goals to be achieved, a joint decision is made whether or not to use the FES modality as part of the ABRT program.

Patients with a diagnosis of PPMS, SPMS, and RRMS with at least two evaluations based on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) by a treating neurologist were included in this analysis. The ISNCSCI evaluates motor and sensory function and comprises motor scores (maximum 100), pin prick (PP) scores (maximum 112), and light touch (LT; maximum 112).³² As part of the ISNCSCI examination, anal and perianal testing was completed on all subjects for LT and PP sensation. The ISNCSCI is an internationally recognized clinical and research tool in SCI with high content validity.³² However, psychometric testing of this scale in MS has not been performed. Because disability in MS is mainly a result of spinal cord dysfunction,⁵ the ISNCSCI may be useful in assessing the level of impairment in MS.

A total of 69 persons with MS were evaluated at our Center during the study period of whom 25 (36.2%) had not received a follow-up neurologist examination at the time of these analyses because of non-continuation of therapy. Reasons for non-continuation of therapy at the Center were mainly because of transportation difficulties and non-coverage by insurance. We excluded these patients who had not yet received a follow-up ISNCSCI examination by the treating neurologist. We also excluded a diagnosis of neuromyelitis optica ($n = 2$) and patients with no record of receiving PT visits ($n = 2$). Forty participants were included in our analyses. This study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

Data abstracted from patient records included the number of PT sessions and use of FES cycling in the therapy regimen. The duration of PT during the study period was obtained from units of PT services billed (1 unit of PT corresponding to 15 minutes of PT). One neurologist certified in assessing disability on the Expanded Disability Status Scale (EDSS) estimated patient disability using the treating physician's evaluation from the last ABRT session. The EDSS is a MS disability quantifying scale that ranges from 0 to 10 in 0.5 point increments.³³ EDSS measures the following functional systems vision, brainstem, pyramidal, cerebellar, sensory, bladder, bowel, and mental function. The EDSS is a sum of functional system scores on a

scale of 0 (no disability), 1.0–1.5 (no disability, minimal signs in one or more functional systems), 2.0–4.5 (minimal-to-moderate disability in one or two functional systems), 5.0–9.5 (severe disability and impaired mobility), and EDSS of 10.0 being death due to MS.

Statistical analysis

Baseline characteristics of subjects were compared across MS groups using χ^2 test for categorical variables and one-way analysis of variance (ANOVA) with Bonferroni corrections for continuous variables. We examined the change in ISNCSCI test scores for upper and lower extremity (LE) motor function, LT, and PP sensory scores between initial examination and latest follow-up using the Wilcoxon signed-rank test. Higher scores or an increase in test scores represent improvement in neurological function.

Because MS is associated with progressive disability accrual, we defined response in any functional domain (motor, LT, and PP) as an increase or no change in ISNCSCI scores. We restricted analysis of improvement in ISNCSCI scores to participants with impaired function in a specific functional domain at baseline. Further examination of the association between FES with ABRT and improvement in motor, LT, and PP scores was performed. We evaluated the change in EDSS after ABRT. Because the average follow-up was 15 months, we considered a 1.0 point increase in EDSS as sustained progression or increased disability, whereas a 1.0 point decrease in EDSS represents improved function.

At our Center, FES was delivered using several devices including FES ergometer RT-300 (Restorative Therapies Inc., Baltimore, MD, USA), MotoMed FES ergometer (RECK-Technik GmbH & Co. KG, Betzenweiler, Germany), portable neuromuscular electrical stimulation units 300PV (Empi, St Paul, MN, USA), and SWISS Stim (Valmed, Sion, Switzerland) among others. At least 1 hour of FES was provided during an average PT session. Statistical analysis was conducted using Stata Statistical Software (Release 10, 2007; Stata Corp., LP, College Station, TX, USA).

Results

Forty patients underwent ABRT at our Center during the study period; 12 PPMS, 14 SPMS, and 14 RRMS. The mean age was 54.7 years with 64.3% being females. Mean duration of illness at presentation was 19.8 years for patients with PPMS, 22.2 years for SPMS, and 8.7 years for RRMS (Table 1). The mean (range) EDSS at baseline was 6.4 (3.5–7.5) for PPMS;

Table 1 Baseline characteristics of study participants with MS, International Center for Spinal Cord Injury, Kennedy Krieger Institute, 2007–2011 (N = 40)

	Total (N = 40)	PPMS (n = 12)	SPMS (n = 14)	RRMS (n = 14)	P-value
Female, n (%)	27 (64.3)	6 (50.0)	11 (68.8)	10 (71.4)	0.523
Age, years, mean (SD)	54.7 (12.0)	60.8 (8.2)*	58.5 (9.5)*	45.5 (11.9)	<0.001
FES therapy, n (%)	30 (71.4)	11 (91.7)	12 (85.7)	7 (50.0)	0.026
Duration of illness, mean (SD) years	16.8 (12.7)	19.8 (16.3)*	22.2 (9.3)*	8.7 (7.8)	0.008
No. of therapy visits, mean (SD)	26.4 (22.5)	27.7 (24.8)	31.5 (23.8)	20.2 (19.1)	0.415
Hours of PT, mean (SD)	65.6 (61.8)	63.5 (80.0)	78.0 (49.5)	54.9 (57.6)	0.620
Duration of follow-up, mean (SD), months	15.1 (11.9)	11.7 (9.5)	22.2 (13.0)**	10.8 (9.4)	0.015
Impaired function at Baseline, n (%)					
UE motor	21 (52.5)	7 (58.3)	11 (78.6)	3 (21.4)	0.888
LE motor	37 (92.5)	12 (100.0)	14 (100.0)	11 (78.6)	0.354
LT	34 (85.0)	9 (75.0)	12 (85.7)	13 (92.9)	0.420
PP	33 (82.5)	8 (66.7)	12 (85.7)	13 (92.9)	0.298
EDSS					
Mean (SD)	6.0 (1.4)	6.4 (1.0)	6.2 (1.1)	5.4 (1.9)	0.197
(Range)	(2.5, 7.5)	(3.5, 7.5)	(3.5, 7.5)	(2.5, 7.5)	

EDSS, Expanded Disability Status Scale; FES, functional electrical stimulation; UE, upper extremity; LE, lower extremity; PPMS, primary progressive MS; SPMS, secondary progressive MS; RRMS, relapsing remitting MS; PT, Physical Therapy; SD, Standard deviation.

P-value for χ^2 tests and one-way ANOVA.

*P < 0.05 for comparison with the RRMS group.

**P < 0.05 for comparison with both the PPMS and RRMS group.

6.2 (3.5–7.5) for SPMS; and 5.4 (2.5–7.5) for RRMS. On average, the number of PT visits was 27.7 for PPMS, 31.5 for SPMS, and 20.2 for RRMS.

Although a higher proportion of patients with PPMS (91.7%) and SPMS (85.7%) received FES as part of their ABRT regimen compared to RRMS (50%), this was not statistically significant. Persons with RRMS had lower disability (mean EDSS 5.4) compared to persons with

progressive MS, although not statistically significant. In total, 71.4% patients underwent FES as part of the prescribed ABRT regimen. The average prescribed 12-month ABRT program consisted of two 3-hour sessions per week administered in two blocks of 4 weeks each. The duration of PT obtained from PT hours billed for service was on average 65.6 hours over 15 months follow-up, representing 4.4 hours of therapy per month.

Figure 1 Proportion showing response or stable ISNCSCI classification by MS type in (A) LE motor; (B) UE motor; (C) LT; and (D) PP sensation after 15 months follow-up (N = 40; PPMS = 12, SPMS = 14, and RRMS = 14).

ISNCSCI examination changes

At baseline, 52.5% of all participants had some degree of impairment in UE motor function compared to 92.5% with impaired LE motor function (Table 1). LT and PP sensation were similarly impaired at baseline in 34 and 33% of all participants, respectively.

Motor function

Response or stable LE motor ISNCSCI scores were observed in 75% of patients with PPMS, 71% with SPMS, and 55% with RRMS (Fig. 1). However, the changes in LE motor ISNCSCI scores were not statistically significant. Mean LE motor ISNCSCI scores in PPMS showed a 9% increase from baseline (Table 2).

UE function at baseline showed minimal disability with a mean motor score of 45.7 of 50, and was the least disabled functional domain (Table 2). There was little to no change in UE motor function at the end of follow-up.

LT sensation

LLT sensation measured by the ISNCSCI is a summation of upper and lower extremity LT function. At baseline, the mean LT score was 96 out of 112 (Table 2). The average LT improvement in all patients was 3.7%. The largest improvement in LT was observed in RRMS, 7.5%.

PP sensation

The mean PP ISNCSCI score at baseline was 92 out of 112 (Table 2). At the end of follow-up, a mean of 9.8% improvement in PP function was observed. The largest improvement in PP function was seen among SPMS, 18.6%. RRMS patients showed an average of 10% improvement in PP function, whereas PPMS showed no significant change.

Effect of FES

The use of FES was associated with response in LE ISNCSCI motor scores, 76.7% compared to 50% response among participants who did not receive FES ($P = 0.014$) (Table 3). Response in LT scores was observed in 76% of FES users compared to 44.4% of non-FES users ($P = 0.083$). Improvements in UE motor function and PP sensation were not associated with FES therapy.

EDSS changes

The combined baseline disability measured on the EDSS averaged 6.0 (SD = 1.4) and ranged from 2.5 to 7.5. We did not observe an increase in disability among SPMS patients who underwent ABRT over the mean duration of 15 months. On average the EDSS

score decreased by 0.3 in PPMS, increased by 0.07 in RRMS, and remained unchanged in SPMS.

Discussion

In this evaluation of the effect of FES as part of ABRT in persons with advanced MS disease, we observed that the neurological function of many patients remained stable. We determined improvements in motor and sensory function as measured by the ISNCSCI examination. Participants who underwent FES interventions showed better responses as compared with those who did not receive FES.

We did not observe progression of disability as measured by the EDSS after a mean follow-up of 15 months. In fact, the EDSS scale showed no difference in the functional changes that we were able to document on the ISNCSCI examination, especially considering the range of our patient population. The ISNCSCI examination, which is typically used for patients with traumatic SCI, was able to identify motor and sensory changes as they are typically subjectively reported by the patients who undergo this type of novel neurorehabilitative intervention. The lack of a true functional outcome measure that could determine change in this study may be a perceived limitation of this report.

Our findings shed light on a potential disability stabilizing or reducing therapy that may be beneficial in persons with MS who invariably are faced with disability progression over time. Within 15 years after onset of the disease, about 50% of all patients will require a walking assistive device.^{3,4} Although the ISNCSCI examination is validated in traumatic SCI and not in the MS population, it may be applicable to patients with MS because the disability in MS is thought mainly to occur as a result of secondary spinal cord dysfunction.²⁶ Based on the baseline patient characteristics of our study, we consider a 3–5% change in motor function, and 5–10% change in sensory function a meaningful response.

When interpreted in the light of the average of 4.4 hours of ABRT with FES received per month, and taken in the light of our clinical experience, we speculate that a higher frequency of ABRT would improve outcomes in persons with MS. Research on the frequency, duration, and intensity of ABRT in MS is yet to be performed. We observed significant differences in the changes in ISNCSCI scores of patients who showed response to ABRT. This may suggest that there might be specific characteristics that determine which persons would benefit the most from FES as part of an ABRT regimen. These characteristics need to be investigated further in larger studies in order to optimize resource

Table 2 Change in ISNCSCI classification scores by functional domain and MS type

ISNCSCI scores	PPMS (n = 12)	SPMS (n = 14)	RRMS (n = 14)	Total (N = 40)
LE motor, mean (SD)				
Baseline	27.9 (15.5)	34.0 (14.0)	36.4 (15.6)	33.0 (15.1)
Follow-up	30.3 (14.3)	32.3 (14.8)	36.6 (14.7)	33.2 (14.5)
Change	2.4 (4.8)	-1.7 (7.4)	0.3 (4.0)	0.23 (5.7)
t Score (P-value)	-1.746 (0.109)	0.863 (0.404)	-0.271 (0.791)	-0.248 (0.806)
UE motor, mean (SD)				
Baseline	45.9 (5.8)	44.8 (8.0)	46.4 (11.2)	45.7 (8.6)
Follow-up	45.8 (6.3)	45.4 (7.3)	46.3 (11.1)	45.9 (8.4)
Change	-0.1 (2.9)	0.6 (3.4)	-0.1 (2.6)	0.2 (2.9)
t Score (P-value)	0.100 (0.922)	-0.715 (0.487)	0.103 (0.919)	-0.381 (0.706)
LT, mean (SD)				
Baseline	96.7 (14.8)	95.8 (15.7)	89.2 (16.9)	96.1 (14.6)
Follow-up	98.3 (9.0)	95.7 (15.9)	94.6 (17.7)	96.1 (14.6)
Change	1.7 (9.9)	-0.1 (9.0)	5.3 (14.1)	2.35 (11.2)
t Score (P-value)	-0.584 (0.571)	0.030 (0.977)	-1.421 (0.179)	-1.322 (0.194)
PP, mean (SD)				
Baseline	100.4 (10.8)	90.9 (28.4)	87.0 (21.6)	92.4 (22.1)
Follow-up	99.3 (9.3)	95.9 (18.2)	93 (17.0)	95.9 (15.4)
Change	-1.1 (6.0)	4.9 (16.8)	6.0 (12.5)	3.5 (12.9)
t score (P-value)	-0.629 (0.542)	1.096 (0.293)	1.797 (0.096)	1.719 (0.094)
EDSS, mean (SD)				
Baseline	6.4 (1.0)	6.2 (1.1)	5.4 (1.9)	6.0 (1.4)
Follow-up	6.1 (1.5)	6.2 (1.2)	5.5 (1.7)	5.9 (1.5)
Change	-0.3	0.0	0.1	-0.1
t score (P-value)	1.431 (0.180)	<0.001 (1.000)	-0.563 (0.583)	0.829 (0.412)

UE, upper extremity; LE, lower extremity; PPMS, primary progressive MS; SPMS, secondary progressive MS; RRMS, relapsing remitting MS; SD, Standard deviation.

utilization and provide the best chance of maintaining or improving function in patients with MS.

In speculating on how FES and ABRT may translate into improved neurological function, one has to consider that MS is a progressive neurodegenerative disease associated with increasing disability as well as the current literature on disease modifying therapy for MS. There is anecdotal evidence from our Center that supports the clinical benefit of combining ABRT,

including FES, with disease modifying therapy in MS patients (unpublished data). This theory is supported by recent evidence that newer disease modifying therapies such as laquinimod may up-regulate serum brain-derived neurotrophic factor (BDNF) levels.³⁴ Interferon-beta and glatiramer acetate therapy have also been shown to up-regulate BDNF.^{35,36} BDNF plays a critical role in exercise-induced cell proliferation. On the other hand, exercise has been associated with an

Table 3 Association between FES therapy and improvement in ISNCSCI classification functional domains

Functional domain	FES use n (%)	No FES use n (%)	P-value*
LE motor ISNCSCI scores (N = 40)			
Responders	23 (76.7)	5 (50.0)	0.014
Non-responders	7 (23.3)	5 (50.0)	
UE motor ISNCSCI scores (N = 21)			
Responders	15 (83.3)	3 (100.0)	0.445
Non-responders	3 (16.7)	0	
LT ISNCSCI scores (N = 34)			
Responders	19 (76.0)	4 (44.4)	0.083
Non-responders	6 (24.0)	5 (55.6)	
PP ISNCSCI scores (N = 32)			
Responders	19 (76.0)	6 (75.0)	0.954
Non-responders	6 (24.0)	2 (25.0)	

*P-value for χ^2 analysis.

Response defined as no change in ISNCSCI scores or an increase in ISNCSCI scores over follow-up period.

No response: decrease ISNCSCI scores over follow-up period.

Analysis limited to participants with disability in functional domain at baseline.

increase in BDNF and its downstream effectors on synaptic transmission in the brain and spinal cord.^{37,38} Therefore, the combination of intense exercise with disease modifying therapies might hold promise for future research.

Our study limitations include the lack of a control group and the relatively small sample size. However, the observed response to ABRT with FES interventions holds promise in managing progressive MS which is associated with accrual of disability. FES use as evaluated in this study is limited because we were unable to evaluate FES duration and intensity. Our findings inform the design of future clinical trials to assess the efficacy of ABRT in persons with MS. Because we performed a retrospective study we were unable to assign duration and intensity of ABRT. This should be a consideration when designing future studies. Based on observed changes in ISNCSCI score but not in EDSS scores, it may be worth considering including the ISNCSCI and the EDSS as outcome measures in future MS trials. Future studies utilizing ABRT should also have a longer duration study intervention. Since progressive forms of MS seemed to have a bigger response to ABRT with FES interventions one might design trials towards this patient population. Also the time of instituting ABRT (early MS disease vs. progressive or late stage disease) needs to be considered in subsequent evaluation of the benefit of ABRT with FES interventions in MS. We estimated the amount of ABRT patients received by using data from billing department. Supplementary therapy, which may have been received at home or in other facilities, was not considered in this analysis. Additional limitations include having one un-blinded neurologist performing the examination, and estimated EDSS from chart review. Our findings are also limited because there are no reports on the validity of the ISNCSCI in the MS population. However in persons with SCI, the ISNCSCI has been shown to have good inter-rater reliability with an intra-class correlation for total motor and LT scores between two examiners exceeding 0.99, $P < 0.01$, and 0.97, $P < 0.01$ for PP scores.³⁹ We did not have information on disease relapse during the period of ABRT. If any participants had undocumented relapses during period of ABRT, then it is possible that the effect of ABRT may be underestimated in this report. The emphasis on our findings, however, is on stabilization of function which may be a reasonably informative step forward as compared to functional decline which would be expected in persons with MS during this follow-up period.

Conclusion

Our findings suggest that FES as part of ABRT may be associated with preservation of neurological function in persons with MS. The use of FES may play an integral part in neurological restoration of function possibly secondary to neuroregeneration. Observed improvements on the ISNCSCI examination with no disability progression measured on the EDSS may suggest some benefit in adopting the ISNCSCI examination for use in MS clinical trials. Randomized clinical trials administering higher doses of FES and ABRT may help provide the necessary evidence establishing any benefits in persons with MS.

Disclaimer statements

Contributors Conception and design: ERH and DB. Acquisition of data: ERH, ACR and DB. Data analysis: ERH and DB. Interpretation of data: ERH and DB. Drafting the article: ERH and DB. Critical revision of manuscript for important intellectual content: ERH, ACR, CLS and DB. Final approval of published manuscript: ERH, ACR, CLS and DB.

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