Appl Psychophysiol Biofeedback (2015) 40:1–8
DOI 10.1007/s10484-014-9267-4

Effect of Neurofeedback Training on Depression and Fatigue in Patients with Multiple Sclerosis

Azadeh Choobforoushzadeh · Hamid Taher Neshat-Doost · Hossien Molavi · Mohammad Reza Abedi

Published online: 2 November 2014

Abstract Depression and fatigue are common symptoms of multiple sclerosis (MS) and are the primary determinants of impaired quality of life in this demyelinating neurological disease. Untreated depression is associated with suicidal ideation, impaired cognitive function and poor adherence to immunomodulatory treatment. For these reasons, systematic screening and management of depressive symptoms and fatigue is recommended for all patients with MS. The objective of this study was to evaluate the effectiveness of neurofeedback in treating depression and fatigue in persons with MS. We conducted a randomized trial with 24 MS patients with primary fatigue and depression. Participants were randomized into two groups: neurofeedback training group (16 sessions of NFB) or treatment as usual. Participants were evaluated at 3 time points (baseline, end of the treatment, and 2-month follow-up) using the Fatigue Severity Scale and Depression subscale of the Hospital Anxiety and Depression Scale as outcome measures. A repeated measures analysis of variance was used to examine differences between the groups. NFB significantly reduced symptoms of depression and fatigue in patients with MS patients, compared to treatment as usual ($p < .05$), and these effects were maintained the 2-month follow-up ($p < .05$).

Keywords Multiple sclerosis · Fatigue · Depression · Neurofeedback · Fatigue Severity Scale · Hospital Anxiety and Depression Scale

Introduction

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system that affects women and men in a ratio of 3:2 and which often develops in young people between 20 and 40. The generally accepted hypothesis as to etiology and pathogenesis is that this disease results from activation of the immune system by one or more viruses in a genetically predisposed individual (Sevène et al. 2009). Although MS is quintessentially a progressive disabling neurological disease, patients' experience of their disease extends beyond neurological disability to many other aspects of suffering, notably symptoms of fatigue, depression, and pain. Neurologists have tended to focus on therapeutic strategies that aim to reduce the risk of relapses and of disability progression. However, it is important to realize that physicians and patients may well have divergent opinions on what is important in MS and this needs to be taken into account in developing a comprehensive approach to treatment. MS is associated with a series of symptoms that include sensory and motor loss, fatigue, blindness, difficulties with balance, pain, cognitive impairment, and depression (Aronson 1996; Goodkine 1992; Williams et al. 2005; Minden et al. 1987; Siegert and Abernethy 2006). Physical illness and mental disorders often co-occur (Hendin 1999; Stenager et al. 2000).

A. Choobforoushzadeh (✉) · H. T. Neshat-Doost · H. Molavi
Department of Psychology, University of Isfahan, Isfahan, Iran
e-mail: azadechoobforoush@yahoo.com

H. T. Neshat-Doost
e-mail: h.neshat@edu.ui.ac.ir

H. Molavi
e-mail: hsmolavi@edu.ui.ac.ir

M. R. Abedi
Department of Counseling, University of Isfahan, Isfahan, Iran
e-mail: mr.abedi@edu.ui.ac.ir

Iwasaki et al. (2005) reported that depression, which is common in patients with MS, contributes to cognitive dysfunction. High rates of anxiety, depression, and substance use disorders have been documented as risk factors for suicidal ideation in medical patients. Depression in people with chronic physical illness may exacerbate functional disability and may lead to increased use of health care services (Stein et al. 2006), and reduced quality of life (Rickards 2005). Despite the high prevalence of these disorders, depression remains under-diagnosed and inadequately treated (Marrie et al. 2009; Sollom and Kneebone 2007; Mohr et al. 2006; Feinstein 2002). As reported in most of the works, depression occurs at a rate of 27–54 % in MS (McGuigan and Hutchinson 2006; Minden et al. 1987; Nocentini 2006). The consensus view of key mechanisms of depression in MS favors a multifactorial origin, including genetic, immunological, and psychosocial factors. Actually, a genetic predisposition has been suggested (Patten et al. 2000), but seems uncertain up to now, and a correlation has been found between depression and brain inflammatory markers, evidenced by the presence of gadolinium-enhanced lesions in brain magnetic resonance imaging (MRI) and of pleocytosis in the cerebrospinal fluid (Fassbender et al. 1998) in addition, support has been obtained for the role of perceived psychosocial stressors (Aikens et al. 1997). In spite of these findings, the identification of specific brain locations to underpin depression in MS remains an unsolved question; rather complex interactions between brain pathology and environmental factors may likely determine psychological and psychiatric symptoms in MS (Foong and Ron 2003). Depression has been associated with a variety of physical, cognitive and behavioral difficulties in persons with MS. For example, sleep disturbance and poor energy, which are characteristics of major depression disorder, have the potential to worsen primary symptoms of MS, including fatigue (Clark et al. 1992).

Fatigue is a common and disabling symptom in MS, but it was overlooked for a long time probably because the measurement of this subjective symptom was difficult. Patients perceive fatigue as an abnormal and excessive symptom different from their prior experience without disease (Freal et al. 1984; Murray 1985; Krupp et al. 1988). Fatigue can be defined in a number of ways—as a lack of physical or mental energy or a feeling of tiredness (Multiple Sclerosis Council for Clinical Practice Guidelines 1998). Fatigue is reported in all clinical phenotypes of MS and affects patients of all ages (Comi et al. 2001). This symptom is an integral part of the disease process, which is usually present at the time of diagnosis and in some cases represents one of the reasons for which patients originally consult a neurologist. Fatigue is not closely related to physical signs of disability or with MRI markers of disease activity, although it does seem to increase when the patient experiences relapses (Fisk et al. 1994). Fatigue may be directly related to the disease mechanisms (primary fatigue) or may be secondary to non-specific factors. The most commonly proposed mechanisms of primary fatigue involve central nervous system factors and immunological factors, while secondary fatigue could be related to depression, sleep disorders, or other comorbidities (Braley and Chervin 2010; Kaminska et al. 2011).

Fatigue has a significant negative impact on daily work, family life, and social activities in persons with MS and is associated with the perception of an impaired general health, mental state and quality of life (Janardhan and Bakshi 2002). Previous studies on fatigue in MS have found significant correlations between higher fatigue and higher disability (Colosimo et al. 1995; Bergamaschi et al. 1997; Kroencke et al. 2000; Heron et al. 1999), progressive rather than relapsing remitting disease (Colosimo et al. 1995; Bergamaschi et al. 1997), and higher depression (Kroencke et al. 2000; Bakshi et al. 2000; Provinciali et al. 1999; Ford et al. 1998; Flachenecker et al. 2002; Ziemssen 2009).

Depression and fatigue are extremely important facets of a patient's experience of MS and represent major determinants of quality of life. It is important to investigate these symptoms carefully at the time of diagnosis and throughout the course of the disease. The variable and unpredictable nature of symptom relapse associated with MS imposes significant lifestyle challenges for individuals with the disease, their family members, and others in their sphere of contact. Decreasing the frequency and severity of relapse is an important goal of management and research, not only in terms of the pathophysiology of the disease, but in light of the needs of all those affected by MS. By moderating the physical and psychological impact of MS, one can sustain the hopes and dreams of individuals and families and bring new and realistic hope to their lives (Halper 2007).

Neurofeedback (NFB), the approach chosen for this trial, offers an alternative therapy for enhancing and supplementing treatment for MS, targeting often overlooked problems, such as depression, anxiety, and cognition, by treating the person's brain directly (http://www.sinhaclinic.com/). NFB has been employed for various clinical applications, such as migraine, epilepsy, attention deficit hyperactivity disorder, alcohol abuse and post traumatic stress disorder (Kayıran et al. 2010). More directly it has been found to be useful for depression (Putman 2001), anxiety and affective disorders (Hammond 2005b; Vanathy et al. 1998), fibromyalgia (Muller et al. 2001), and obsessive compulsive disorder (Hammond 2003), and also to enhance attention and memory performance in healthy subjects (Lubar 1997; Wilson et al. 2006; Hanslmayr et al. 2005; Egner et al. 2002; Vernon et al. 2003).

For degenerative problems, including MS, Parkinson's, or Alzheimer's, reports suggest NFB may help stabilize function, slow the process, or may help optimize brain function with whatever resources still exist. Thus, the focus rests more on "quality of life" training than an attempt to remediate the problem. Improved quality of life can significantly benefit the client (http://www.aboutneurofeedback.com/).

A particularly robust body of research, summarized by Davidson (1998a), has documented that depression is associated with an activation difference between the right and left prefrontal cortex. A large number of EEG studies, reviewed in earlier papers by Davidson (1992, 1995, 1998a), have established that the left frontal area is associated with more positive affect and memories, whereas the right hemisphere is more involved in negative emotion. A biologic predisposition to depression exists when there is a frontal asymmetry in brain wave activity, with more left frontal alpha activity. This imbalance (with increased left frontal alpha) means that the left frontal area is less activated. Such persons may be less aware of positive emotions, while at the same time being more in touch with the negative emotions that are associated with the right hemisphere (Davidson 1998b; Baehr et al. 1997; Rosenfeld et al. 1995). Researcher reveals that when the left hemisphere is basically ''stuck'' in an alpha idling rhythm, there is not only a deficit in positive affect but also more withdrawal behavior. This biologic predisposition to depression is also firmly documented in research findings that have shown that infants of depressed mothers display this same reduced left frontal EEG activation (Dawson et al. 1992a, b). Additional research has provided evidence that individuals suffering from Depression have increased amounts of alpha activity in the left frontal region (Henriques and Davidson 1991). Other evidence from work by Sterman (1999), Sterman and Kaiser (2001) suggests that the area anterior to electrode site F3 also appears to be hypoactive in depression.

Although a large number of NFB studies have been published, we could not find any systematic investigations exploring outcomes for psychological symptoms after receiving EEG biofeedback in MS patients. However, such information is important to assess the overall effects of biofeedback training. Thus, the purpose of this study was to evaluate the effectiveness of NFB in reducing symptoms of depression and fatigue in MS patients.

Methods

Participants and Procedure

The study was conducted at Shahid Sadooghi Hospital, of the Yazd University Medical School, in Yazd, Iran, between August 2013 and January 2014. The institutional review board approved the protocol. Twenty-four (24) participants with relapsing-remitting MS, followed as outpatients at the MS Society (at Shahid Sadooghi Hospital) were recruited for the study. All participants were clinically diagnosed following the McDonald et al. (2001) criteria and were in a stable phase of the disease, without relapsing in the last 2 months. All participants were above 18 years of age and also experienced primary fatigue and depression. The exclusion criteria were (1) the use of medication that could potentially interfere with fatigue, (2) acute relapse of MS within the last month, and (3) or the presence of additional neurological or psychiatric disorders, epilepsy and other chronic diseases.

Written informed consent was obtained from all participants, following a thorough description of the study procedures and requirements. The participants were then randomized into two groups, each containing 12 patients. Participants assigned to NFB received 16 sessions of training and continued their regular care. The remaining participants continued to receive treatment as usual and constituted the control group. At a baseline visit, basic demographic data and disease history information were recorded and a complete neurological examination was performed, which included assessment of neurological impairment by using the EDSS. Table 1 shows the general characteristics of the study participants.

Experimental Procedure

Treatment as Usual (TAU)

Participants in this group received only medical treatment that was prescribed by a neurologist.

Neurofeedback Training (NFB)

Biofeedback was provided by a Procomp2 Infiniti system. Patients were comfortably seated with their head and arms at rest. Electroencephalic activity was recorded with one

Table 1 General characteristics of the study participants

Characteristic	All (N = 24)	NFB Group (N = 12)	TAU Group (N = 12)
Age (years)	36.27 ± 9.11	34.28 ± 8.17	33.39 ± 7.72
Gender (male/female)	12/12	6/6	6/6
Disease duration (years)	7.24 ± 4.98	6.91 ± 4.52	6.24 ± 4.3
EDSS	4 ± 1.6	3.8 ± 1.5	3.9 ± 1.4

Values are mean ± standard deviation for age, disease duration, EDSS

scalp electrode placed on the position F3 (International 10–20 system) with a left-ear reference (A1). The right earlobe was connected to circuit ground. Based on the evidence from a review of the literatures, particularly depression protocol Hammond (2000, 2005b), the patient was trained to decrease the production of theta (4–8 Hz) and alpha (8–12 Hz) wave activity, during reinforcement of 15–18-Hz beta for the first 20 min of each training session, after which the reinforcement frequency band was changed to 12–15 Hz for the final 10 min of each session. Biofeedback training consisted of a visual game on the computer screen and audio at the same time. The EEG signal controlled the status of the game and the audio in real-time. The game and or the audio were active only when the beta activity was higher than the preset threshold and the theta or alpha activity was lower than another preset threshold, which constituted the reward procedure. The patient was told to be simply relaxed and keep the game and the audio active. This recommendation serves to reduce EEG artifacts caused by muscle tension.

All patients took part in 2 training sessions per week. Each training session consisted of the following sequence: approximately 2 min of baseline recording without feedback, in order to establish the thresholds; followed by approximately 30 min of feedback training including different games at different difficulty levels. We provided a short break to participants if they reported tiredness. NFB was conducted over 8 weeks.

Thresholds were set in a way that if subjects were able to maintain the reinforcement band above the threshold for 80 % of the time during at least .5 s, and the suppressed band under the threshold for 20 % of the time, they received more reinforcement of audio or visual NFB. If the patient was able to maintain the reinforced band higher than the defined threshold in 2 consecutive attempts at 90 %, the threshold was changed automatically so that it was closer to the optimal threshold.

Measures

The Expanded Disability Status Scale (EDDS), was used to rate the disability of the participants only at the beginning of the study. Instruments used for evaluation of outcomes were the Fatigue Severity scale (FFS) and depression subscale of the Hospital Anxiety and Depression Scale (HADS).

The EDDS, is the oldest and the most widely used rating system of clinical assessment in MS (Sharrack and Hughes 1996). The EDSS is rated by half point increments, from .0 (normal neurological examination) to 10.0 (death from MS complications). Following the neurological examination, the investigator is required to summarize the results in several ‘‘Functional System Scores’’, which are graded from normal (0) to maximal impairment (5 or 6). The Functional Systems are the following: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and ‘‘others’’. An overall score for the patient’s disability is then obtained by combining the different functional systems grades and the ability to walk, which has to be assessed separately, to provide a score on the full 20-point scale. EDSS steps 1.0–4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0–9.5 are defined by the impairment to ambulation (Hauser and Goodkin 2001).

The FSS is frequently used to measure fatigue level in patients (due to its simple and clinical nature). The FSS is a nine-item general fatigue questionnaire, where scores range from 1 (not fatigued at all) to 7 (very much fatigued) for each item (Krupp et al. 1989). Persian version of FSS has satisfactory psychometric properties and is applicable in research and clinical activities relating to MS patients. Internal consistency of FSS is high (Cronbach’s Alpha = .93). The coefficient of item-total correlation for each item ranges from .43 to .8 (Salehpoor et al. 2013).

Participants also completed the HADS (Zigmond and Snaith 1983) for assessment of depressive symptoms. The HADS is a self-report 14-question survey (Bjelland et al. 2002) used to identify anxiety and depression. The questionnaire has seven questions reflecting anxiety alternating with seven reflecting depression: HADS-A and HADS-D. Each item is answered on a four point (0–3) response category so the possible scores range from 0 to 21 for anxiety and for depression. Several questions are reversed scored. A score of 0–7 for either subscale could be regarded as being in the normal range, a score of 8–10 being suggestive of either mild anxiety or depression, a score of 11–14 a moderate degree of anxiety or depression and 15 and above indicating a more severe anxiety or depression. If participants registered scores of anxiety or depression above 14 the clinical nurse specialist at the relevant hospital was contacted and asked to follow up.

Assessment took place before treatment (T0), immediately after treatment (T1) and in a 2 months follow-up (T2). SPSS 19.0 (SPSS, version 19, Chicago, USA) was used for analyzing data.

Results

We first conducted descriptive statistics, including an examination of the distributions for all continuous variables. Two repeated measures analyses of variance (ANOVAs) (Treatment condition X Assessment Period) were next conducted to examine the effect of NFB on depression and fatigue in MS patients, respectively. Effect sizes were computed by using Cohen’s d.

Table 2 Depression and fatigue scores in the NFB and WL groups

	Depression		Fatigue	
	NFB Mean ± SD	TAU group Mean ± SD	NFB Mean ± SD	TAU group Mean ± SD
T0	15.93 ± 4.39	15.37 ± 4.28	48.11 ± 13.81	47.91 ± 13.67
T1	11.25 ± 4.08	15.47 ± 4.32	37.56 ± 13.59	49.61 ± 13.65
T2	11.38 ± 4.27	15.75 ± 4.38	37.87 ± 12.87	50.72 ± 13.68

The mean ages of the patients were similar in the NFB and TAU groups (34.28 ± 8.17 and 33.39 ± 7.72, respectively; $p = .678$). *T* tests showed that the differences between NFB and TAU groups were not significant with regard to disease duration (6.91 ± 4.52 and 6.24 ± 4.36, respectively; $p = .598$) and EDSS (3.8 ± 1.6 and 3.9 ± 1.4, respectively; $p = .385$) No significant differences were found for gender between the two groups (6 males and 6 females in both groups).

Neither the assumption of normality (by the Shapiro–Wilk test) nor the equality of population variances (by Levene's test) were violated. The two groups also did not differ significantly at pre-test with regard to Depression and Fatigues [$t(22) = .19$, $p > .05$ and $t(22) = .21$, $p > .05$, for both measurements, respectively). The means of both dependent variables and standard deviations of pre-test(T0), post-test(T1), and follow-up tests (T2) are presented in Table 2.

The 2 repeated measures ANOVAs (Group: NFB vs TAU) × 3 (Time: pre vs post vs follow-up) with Depression as the outcome variable revealed a significant main effect of Time ($F(2, 21) = 6.5$; $p < .005$) and a significant interaction effect of Group and Time ($F(2, 21) = 13.7$; $p < .005$). Inspection of the means indicates that individuals in the treatment group improved on Depression, whereas control individuals remained stable across all time points. The largest improvement on depression scores was observed between T0 and T1; an independent samples *t* test with Depression change scores (post-test minus pre-test) as the dependent variable was significant [$t(22) = -2.3$, $p < .001$; mean change scores being −4.6 and .1 for the NFB and control group, respectively]. Between T1 and T2, the scores of both groups remained stable; that is, changes scores from T1 to T2 were not significantly different for both groups [$t(22) = .17$, $p > .05$; mean change scores being .13 and .27 for the NFB and control group, respectively], indicating that the NFB group's improvement persisted at follow-up whereas the control groups' relatively unchanged higher scores persisted.

The two-way repeated measures ANOVA with Fatigue scores as the outcome variable revealed a similar pattern: a significant main effect of Time [$F(2, 21) = 7.9$; $p < .01$] and a significant interaction effect of Group and Time [$F(2, 21) = 11.8$; $p < .01$]. Inspection of the means indicates that individuals in the NFB group improved on Fatigue whereas control individuals remained stable. Here, also, the largest improvement on fatigue scores was observed between pre-test and post test; a *t* test with fatigue change scores (post-test minus pre-test) as the dependent variable was significant [$t(22) = -4.2$, $p < .001$; mean change score being −10.4 and 1.7 for the NFB and TAU group, respectively]. Between post-test and follow-up, the scores of both groups remained stable; that is, changes scores from T1 to T2 were not significantly different for both group [$t(22) = .5$, $p > .05$, mean changes scores being .3 and 1.1, for the NFB and TAU condition, respectively], indicating that the NFB group's fatigue score improvement persisted at follow-up whereas the control groups' unchanged higher fatigue scores remained.

The effect size of NFB, as compared to TAU, was *Cohen's d* = .29 for depression and *Cohen's d* = .33 for fatigue. Overall the analyses showed that NFB had a significant incremental effect on reducing depression and fatigue in MS patients compared to treatment as usual.

Discussion

Neurofeedback was found to yield improvements in symptoms of depression and fatigue in patients with MS, above and beyond those obtained by standard care. The Association for Applied Psychophysiology (AAPB) rated NFB for MS as "Level 1 Efficacy: Not sufficiently investigated" (Yucha and Gilbert 2004) and this rating likely remains unchanged. Reports to date on the application of NFB for depression consist only of uncontrolled case reports that are not sufficiently rigorous to receive evidence-based support (rated more recently in Yucha and Montgomery 2008 as "possibly efficacious"). However these case and pilot studies (reviewed by Hammond 2005a, b; Walker 2007; Yucha and Montgomery 2008, with generally positive outcomes reported by Baehr et al. 1997, 1999, 2001, 2004) provide encouragement that NFB may hold potential for treating mildly to severely depressed patients and that, unlike medication, NFB may enduringly modify the functional brain abnormality associated with a biologic predisposition to depression.

Two papers (Hammond, 2000, 2005b) have appeared on the NFB treatment of depression, both of which built on the same robust foundation of frontal asymmetry research. Hammond (2000) utilized a protocol in which electrodes are placed at Fp1 (on the left forehead) and F3 (approximately 2.5–3 inches straight above Fp1). During the training, slow brain wave activity is inhibited in the alpha and theta frequency bands during reinforcement of 15–18 Hz beta for the first 20–22 min of each training

session, after which the reinforcement frequency band is decreased to 12–15 Hz for the final 8–10 min of each session. Within one session the patient reported sensing an improvement. At the completion of treatment improvements were noted on various measures (scale 2 of the MMPI; somatic symptoms such as gastritis, headaches, achiness, and preoccupation with health; over-emotionality, anxiety and rumination, and fatigue), which were maintained at an 8.5 month followup. As a result of this successful case outcome this protocol has continued to be used. In total Hammond has treated at least three-dozen individuals using this depression protocol, with consistently positive results in an estimated 75–80 % of cases.

Frontal lobe dysfunction has been identified by neuropsychological tests as integral to depression. A study involving individuals experiencing from major depression and Melancholia, found evidence suggesting the presence of decreased alpha and increased beta activity in the right anterior regions of the brain (Kano et al. 1992). Baehr et al. (2001) successfully treated two depressed women, utilizing the alpha asymmetry protocol, for purposes of alleviating depression upon learning how to increase activation of the left hemisphere and/or decrease activation of the right hemisphere. Evidence is thus accruing to support the value of alpha asymmetry NFB as a treatment for depression and that this pathological asymmetry may be a trait marker of vulnerability to depression.

In the current investigation, symptoms of depression and fatigue evidenced significant reduction by the NFB group during post-treatment assessment; this suggests that improved mental energy may be related to treatment outcome. Regarding the relationship between depression and fatigue, decrease in one of these variables is associated with a reduction in the other one.

The exact mechanism of the NFB treatment is not clear. Although no data exist, the repetitive and concentrated practice performed in BF might be playing a role in brain plasticity (Dursun et al. 2004). However in a recently published study, there is evidence that EEG biofeedback promotes neuroplastic changes (Ros et al. 2010).

To illustrate the effectiveness of NFB in MS patients, it should be noted that MS is a remitting and relapsing condition. It is considered to be an idiopathic disease of possibly autoimmune origin. The person's immune system attacks the brain and spinal cord leading to demyelination. This causes disturbances in the communication networks within the brain and spinal cord. Like other organic brain conditions including degenerative disorders NBF's potential benefit as an alternative MS therapy is more easily understood. Training with EEG Biofeedback affects the neuronal resources, which are trainable—despite the damage present within the cortical and sub-cortical premises. Immune system regulation and improvement of symptoms, which might be secondary to the structural changes within the cortex such as mood changes, depression, fatigue and psychosis, may also explain an overall positive benefit from NFB for MS.

In summary, NFB appeared to be a relatively effective treatment for symptoms of depression and fatigue in patients with MS. NFB treatments, in general, aim to correct imbalances or abnormalities in brain electrical activity identified through statistical comparisons to a normative EEG database. As this treatment is postulated to affect multiple interconnected brain systems, improvements may be seen across a number of different measures following treatment. Unfortunately, we were not able to assess change in targeted EEG parameters. This is one important aspect that needs attention in future research. Also, the same therapist conducted treatment for all patients, which leaves us unable to rule out effects unique to the therapist. Finally, our sample was selective (e.g., relapsing-remitting MS) and small and our followup period limited.

The present study was novel in that it was the first attempt toward examining the effects of NFB for treating symptoms of depression and fatigue in persons with MS. Given certain limitations identified above, outcomes of this study should only be generalized to patients with relapsing-remitting MS. Further controlled studies, employing larger sample sizes, more extended followup, and a more thorough examination of treatment mechanisms seem warranted.

Acknowledgments The authors would like to thank all the patients for their participation, the Editor-in-Chief and the anonymous reviewers for their constructive and detailed comments that helped improve very much the quality of this paper.

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