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Improvement of multiple sclerosis-associated tremor as a treatment effect of natalizumab

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Abstract

Background: Tremor is among the most physically disabling symptoms associated with MS. The effect of MS disease modifying therapies (DMTs) on the severity of MS tremor is unclear.

Objective: To compare the change over time in scores reflecting tremor severity between subjects treated with natalizumab and other disease modifying drugs.

Methods: Questionnaires were sent to North American Research Committee on MS registrants reporting mild or greater tremor on semiannual updates. Respondents on natalizumab and other MS therapies completed a survey which included tremor-specific scales to indicate tremor severity both currently and when the current therapy was initiated. Differences between natalizumab and non-natalizumab groups were compared using ANOVA.

Results: Surveys were returned by 567 registrants, including 202 taking natalizumab. Subjects on natalizumab were more likely to report tremor improvement (29.6%) than those never (15.2%) or previously (14.8%, $p=0.0002$) on natalizumab. Over a mean recall period of 6.2 ± 4.6 years, the Tremor Related Activities of Daily Living score worsened by 1.8 points among natalizumab-treated subjects, 3.3 points among those previously on natalizumab, and 5.3 points among those who never took natalizumab ($p=0.009$).

Conclusion: Respondents taking natalizumab were more likely to experience tremor improvement than those taking other MS disease modifying therapies.

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1. Introduction

Tremor ranks among the more physically disabling symptoms caused by multiple sclerosis (MS). Between 25% and 58% of MS patients are affected by tremor (Alusi et al., 2001;

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Pittock et al., 2004), and tremor is frequently associated with ataxia, another disabling MS symptom. Since tremor disproportionately affects the upper extremities, it interferes with many routine activities even in the absence of weakness. MS tremor and ataxia have also been shown to correlate with overall disability and dependence on caregivers (Weinshenker et al., 1991), and both are associated with high risk of respiratory impairment (Grasso et al., 2000) and poorer overall prognosis (Weinshenker et al., 1991).

A common attribute of MS-associated tremor has been its resistance to symptomatic therapy. Pharmacological interventions such as intrathecal baclofen (Weiss et al., 2003), isoniazid (Bozek et al., 1987; Hallett et al., 1985), levetiracetam (Striano et al., 2006), and cannabis (Fox et al., 2004; Wade et al., 2004; Zajicek et al., 2003) have been studied for their ability to lessen the effects of tremor, but results have been negative, not duplicated, or underpowered to draw clinically meaningful conclusions. Surgical interventions such as thalamotomy have shown benefit in numerous case series (Koch et al., 2007), but the effects are often temporary, and the treatment is expensive, highly specialized, and not practical for many patients.

The immune modulating drugs collectively referred to as the MS disease modifying therapies (DMTs) are not intended to reverse established MS symptoms, but rather to slow the accumulation of neurological disability through the prevention of relapses (IFN β Multiple Sclerosis Study Group, 1993; Jacobs et al., 1996; PRISM Study Group, 1998; Johnson et al., 1995; Hartung et al., 2002; Polman et al., 2006; Kappos et al., 2010). However, we observed marked regression of tremor and ataxia in two severely disabled patients after initiation of natalizumab, so we undertook to explore whether natalizumab might be associated with tremor regression across a broad cohort of MS patients.

Due to the infrequent presentation of severely ataxic or tremulous patients in a single clinic, we queried the North American Research Committee on Multiple Sclerosis (NARCOMS) registry to identify patients with subjective MS tremor and concurrent use of natalizumab or other MS DMTs. The NARCOMS registry includes more than 36,000 participants (Consortium of Multiple Sclerosis Centers, 2013) who provide demographic information and periodic updates about their treatments and subjective experience of MS symptoms. Participants who indicated the presence of tremor or ataxia were invited to complete a separate survey focused specifically on tremor and its effects on daily life.

2. Materials and methods

We designed a survey-based, case-control study to compare respondent impression of change in tremor symptoms over time. The primary hypothesis was that natalizumab treatment would be associated with greater likelihood of tremor improvement as measured by the Tremor Related Activities of Daily Living (TRADL) questionnaire (Bain and Findley, 1993). Cases were defined as subjects currently taking natalizumab, and controls were divided into two groups: (1) subjects who had never taken natalizumab and (2) subjects previously on natalizumab but now taking another DMT.

2.1. Study population

NARCOMS maintains the confidentiality of its registrants by acting as an intermediary between investigators and the registry. Local Internal Review Board approval was obtained prior to data collection. Subjects were identified within NARCOMS according to the following criteria: (1) subjects must have indicated a Tremor and Coordination Scale (TACS) (Marrie and Goldman, 2011) score of 2 or greater (indicating mild or worse impairment) on the Fall 2010, Spring 2011, or Fall 2011 semi-annual updates; and (2) subjects must have reported current use of an approved MS DMT, and have remained on the DMT for at least 6 months. All subjects who indicated current or previous treatment with natalizumab were mailed a survey, as well as a random selection of participants using other MS DMTs. In total, 777 surveys were sent to prospective participants. The surveys did *not* indicate to participants that their past or current DMT was a criterion for their inclusion in the study.

The prior-natalizumab control group was included for two reasons: first, since natalizumab treatment may signify more aggressive or treatment-refractory disease, including this subset would ensure we included respondents with similar disease characteristics to the current natalizumab group. Second, respondents in this group would be able to compare symptom experience between their current DMT and natalizumab.

2.2. Survey design and outcome measures

All invited participants were mailed a paper survey along with pre-paid return mailing materials. Respondents answered descriptive questions about the natural history of their tremor, parts of the body affected, family history of tremor, current DMT and duration of use, and the use of symptomatic treatments for tremor. Respondents also completed questionnaires assessing various aspects of tremor (Table 1). The TRADL questionnaire was selected to assess the primary endpoint, because it asks about a wide range of functional activities affected by tremor, and lends itself to generation of a summary score to reflect overall tremor severity. Also included in the survey were the Tremor Related Handicap (TRH) (Bain and Findley, 1993) scale, which asks “yes/no” questions about tremor-related physical disability and embarrassment in several common scenarios, and a Visual Analog Scale (VAS) on which respondents report their overall tremor severity. Respondents were asked to complete the TRADL, TRH, and VAS scales twice: once to reflect current symptom experience and a second time to recall their symptoms at the time their current DMT was initiated (a recalled “baseline”). Differences in these questionnaires were used to estimate change in symptom severity over time. Change in the TRADL scale and VAS could be positive or negative: negative scores indicate decreasing symptom burden over time, while positive scores indicate worsening symptoms. For all the tremor-focused outcome measures, lower scores represent less severe tremor or impairment.

The survey also adapted a Clinical Ataxia Rating Scale (CARS) (Bain and Findley, 1993), which was intended for use as a physician-administered tool for describing severity of ataxia and tremor, but was adapted for survey respondents using language understandable to non-clinicians. Finally, respondents were asked to draw two Archimedes spirals, one with each hand,

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