BETASLEEP
Sleep Quality, Fatigue and Functional Health Status among Betaferon® treated MS patients
Design of an observational study

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Abstract

Background: *Patients with multiple sclerosis (MS) frequently suffer from comorbid conditions with sleep disorders affecting about 50% of patients. Further, sleep disorders may cause fatigue, a prominent MS–symptom, in up to 80% of patients. Available studies on the role of sleep disorders in MS are heterogeneous and prospective studies also investigating potential underlying reasons for sleep disorders among MS patients are lacking. Sleep disorders may represent a disease–specific feature among MS patients or may be confounded by comorbid conditions, MS treatment, and duration of treatment. Finally, data on diagnostic and treatment patterns of comorbid conditions in MS patients with sleep disorders and the impact of treatment on sleep disorders over time are unavailable.*

Aim: *Better understanding the characteristics, comorbidities, diagnostic and treatment patterns, and course of sleep disorders in MS patients in a real–life setting in Germany. The primary objective is to investigate the correlations between sleep quality, fatigue, and functional health status among MS patients treated with Interferon beta–1b (Betaferon®).*

Methods: *BETASLEEP is a prospective, non–interventional, multi–center, observational cohort study conducted in neurological offices/neurology departments throughout Germany specialized in MS treatment. Patients with RRMS or CIS and EDSS score≤5, who have been treated with Betaferon® ≤6 months and are tolerating Betaferon® according to their attending physician, may be enrolled. Treatment with any other disease–modifying drugs (DMD) or MS specific drugs is not permitted. It is planned to enroll a total of 300 patients, which will be followed up over 2 years with desired documentation every 6 months. Assessment tools for the comorbid conditions include the Pittsburgh Sleep Quality Index (PSQI), the Modified Fatigue Impact Scale (MFIS), the Short Form–36 (SF–36), the Epworth Sleepiness Scale (ESS), the Hospital anxiety and depression scale (HADS), the Hamburg Pain Adjective List (Hamburger Schmerz Adjektiv Liste (HSAL)), and the IRLSS group rating scale. All analyses will be exploratory and of descriptive character. The BETASLEEP study started in December 2012. At present 132 patients (August 2014) have been enrolled in centers throughout Germany. Enrollment is ongoing and will continue until December 2014. Hence, follow–up will last until December 2016.*

Discussion: *Analysis of the characteristics and comorbidities of MS patients with sleep disorders as well as the diagnostic and treatment patterns of these sleep disorders and their course may facilitate individualized and targeted treatment in the future.*

Key words: multiple sclerosis, sleep, fatigue, interferon beta-1b, restless-legs-syndrome, comorbidities, observational study

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Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating and degenerative disorder of the central nervous system, primarily affecting young adults [1]. MS patients frequently suffer from

comorbid conditions including depression, anxiety, sleep disturbances, pain, cognitive impairment, and fatigue, which may severely impair patients' quality of life [2].

Sleep disorders in particular affect approximately 50% of MS patients [3] and may present as difficulties falling asleep as well as frequent awakenings from sleep [4, 5]. Further, frequent arousals may result in impaired sleep efficiency [6] and fatigue [7].

Available studies investigating the association between MS and sleep disorders cannot be directly compared due to heterogeneity in study design, methodology, and number of patients. Further, studies investigating the underlying reasons for sleep disorders among MS patients are lacking. The underlying reasons for sleep disorders are likely complex and may result from other comorbid conditions, MS treatment, and duration of treatment [8].

Considering the high prevalence of sleep disorders in MS patients, better understanding the characteristics, comorbidities, diagnostic and treatment patterns, and course of sleep disorders in these patients is important for future individualized and targeted treatment. Hence, we decided to conduct a prospective observational study of sleep quality, other MS specific symptoms, and functional health status in patients with MS. We restricted our study to a homogeneous group of MS patients stabilized on treatment with interferon beta–1b (Betaferon®) in order to avoid biases on sleep and sleep–related variables introduced by different types of interferones and different rhythms of medication application.

Methods

Study objectives

The **primary objective** of the BETASLEEP study is to investigate the correlations between

- sleep quality,
- fatigue,
- functional health status

among MS patients treated with Betaferon®.

Secondary objectives are to investigate the correlations between sleep quality and

- daytime sleepiness,
- depression and anxiety,
- pain,
- RLS

among MS patients treated with Betaferon®.

Tertiary objectives are to describe

- comorbidities among patients with and without impaired sleep quality,
- diagnostic and treatment patterns of these comorbidities,
- the course of comorbidities, sleep quality, fatigue, and functional health status in relation to the initiated treatments for comorbidities

among MS patients treated with Betaferon®.

Study design

The BETASLEEP study is a prospective, non–interventional, multi–center, observational cohort study. It is conducted in private neurological offices and neurology departments throughout Germany specialized in the treatment of MS patients. Recruitment started in December 2012. It was planned to collect valid documentations of 300 patients over a 1–year period; however, due to slow patient accrual the recruitment period has been extended until December 2014. The study has been approved by the Ethics Committee of the Medical Faculty of the University of Göttingen, Germany, and is registered at Clinicaltrials.gov (NCT01766063). All participants are required to give written informed consent. The decision upon treatment with Betaferon® is made at the discretion of the attending physician, according to the medical practice. Every patient will be followed–up for 24 months with desired documentation at baseline and every six months thereafter.

Inclusion and exclusion criteria

In order to minimize treatment–related effects on sleep quality patients will be required to be on stable treatment with Betaferon®; however, duration of treatment should not be longer than six months.

Specifically, to be included into the BETASLEEP study patients (1) must have relapsing–remitting MS (RRMS) or a clinically isolated syndrome (CIS) with a score on the Expanded Disability Status Scale (EDSS) of ≤ 5 and (2) must be on treatment with Betaferon® and tolerate Betaferon® according to the investigator's evaluation, but should not have received Betaferon® longer than six months. Patients may not be included in the BETASLEEP study (1) if they do not tolerate Betaferon® according to the investigator's evaluation or have been treated with Betaferon® for more than six months or (2) if they receive any other disease–modifying drug or MS specific treatment or (3) if they have contraindications of Betaferon® as described in the Summary of Product Characteristics.

Outcome variables and assessment tools

The **primary outcome** variables are

- sleep quality, measured with the Pittsburgh Sleep Quality Index (PSQI) [9],
- fatigue, measured with the Modified Fatigue Impact Scale (MFIS) [10], and
- functional health status, measured with the Short Form–36 (SF–36) [11].

The **secondary outcome** variables include:

- daytime sleepiness, measured with the Epworth Sleepiness Scale (ESS) [12],
- depression and anxiety, measured with the Hospital anxiety and depression scale (HADS) [13],
- pain, measured with the Hamburg Pain Adjective List (Hamburger Schmerz Adjektiv Liste (HSAL) [14],
- severity of RLS, measured with the International Restless Legs Syndrome Study (IRLSS) group rating scale [15].

Additional variables to be collected include demographics, employment status, education, medical history, medication, disease course, Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), clinical diagnosis of RLS as well as results from polysomnography and magnetic resonance imaging (MRI), if available.

The desired variable collection schedule is summarized in Table 1.

Sample Size

Study aim is to collect valid documentations of 300 patients. This number is based on the following considerations: First, about 50% of MS patients will be expected to have impaired sleep quality. In order to be able to reliably estimate the prevalence with 95% confidence intervals of impaired sleep quality (defined by PSQI≥5) in the overall group of MS patients as well as in certain patient strata (CIS/RRMS, women/men, etc.) a solid number of patients in each of these subgroups is needed. For example, in order to estimate the proportion of patients with impaired sleep quality within plus/minus 10 percentage points with confidence 95%, a sample of 100 patients would be sufficient. Inclusion of 300 patients guarantees that the two–sided 95% confidence interval will not be wider than plus/minus 6.3% percentage points (allowing for 20% drop out). These calculations are based on an expected proportion of 50%.

Second, for the tertiary aim it is planned to explore comorbidities and sketch treatment patterns of comorbid conditions and one focus will involve comorbid conditions that may account for impaired sleep quality. If we conservatively assume that in MS patients depression, RLS, and pain each account for 30% of impaired sleep quality and that these conditions are independent, there will be approximately 40 Patients in each of the groups. This is a solid number to document treatment patterns and disease course for each of the conditions and still leaves room to detect other underlying causes.

Statistical Analysis

Statistical analyses will be explorative and of descriptive nature thus have a hypotheses generating character. All statistical issues including derived variables for analysis, handling of missing data and proposed format and content of tables will be detailed in the Statistical Analysis Plan.

Funding

The BETASLEEP study is conducted und funded by Bayer Vital GmbH, Germany.

Discussion

The BETASLEEP study aims at comprehensively investigating sleep related parameters among MS patients. The primary objective is to investigate the correlations between sleep quality, fatigue, and functional health status among MS patients treated with Betaferon®. Secondary objectives are to investigate correlations between sleep quality and daytime sleepiness, depression and anxiety, pain, as well as RLS. Further, tertiary objectives are to describe (1) comorbidities among patients with and without impaired sleep quality, (2) diagnostic and treatment patterns of these comorbidities, and (3) the course of comorbidities, sleep quality, fatigue, and functional health status in relation to the initiated treatments.

Sleep disorders affect approximately 50% of MS patients [3]. However, the term 'sleep disorders' does not adequately characterize the multi–faceted impairments patients are facing. For example, patients may have difficulties falling asleep or may suffer frequent awakenings from sleep [4, 5]. Further, frequent arousals may result in impaired sleep efficiency [6] and fatigue [7]. Available studies investigating the association between MS and sleep disorders are heterogeneous and do not allow to adequately acknowledge these multiple aspects. Investigated patients have a wide disease spectrum [5–7, 16] and investigators employed different methods to ascertain sleep disorders or surrogate markers for sleep disorders [6, 7, 17]. In addition, reasons for sleep disorders are not well understood, but are likely complex and may include other comorbid

Table 1. Variable collection

Visit Procedure	Initial Visit	Follow–up Visit 1 (after ~6moths)	Follow–up Visit 2 (after ~12 months)	Follow–up Visit 3 (after ~18 months)	Final Visit (after ~24 months)
Demographic data	X				
Employment status	X				
Education	X				
Medical history	X				
Betaferon® treatment	X	X	X	X	X
Concomitant medication	X	X	X	X	X
Disease course		X	X	X	X
EDSS	X	X	X	X	X
MSFC	X		X		X
RLS (clinical diagnosis)	X	X	X	X	X
RLS severity scale if RLS is present	X	X	X	X	X
Polysomnography results if available	X	X	X	X	X
MRI cerebral and spinal if available	X	X	X	X	X
Pittsburgh Sleep Quality Index (PSQI)	X	X	X	X	X
Epworth Sleepiness Scale (ESS)	X	X	X	X	X
Short Form–36 (SF–36)	X	X	X	X	X
Modified Fatigue Impact Scale (MFIS)	X	X	X	X	X
Hospital anxiety and depression scale (HADS)	X	X	X	X	X
Hamburg Pain Adjective List (HSAL)	X	X	X	X	X
Adverse Events		X	X	X	X

conditions [8]. For example, depression, RLS, and pain are common comorbidities among MS patients [18] and are known to cause sleep disorders. Further, most studies were of small sample size [6, 7, 16] and often had a cross–sectional design [5–7, 17], obviating investigation of causal associations and the direction of associations. Hence, sleep disorders may represent a disease–specific feature among MS patients or may be confounded by these comorbid conditions. Further, data on diagnostic and treatment patterns of comorbid conditions in MS patients with sleep disorders and the impact of treatment on sleep disorders over time are unavailable. Hence, the BETASLEEP study was designed to investigate both sleep quality, daytime sleepiness, and fatigue as well as potentially confounding comorbidities including depression, anxiety, pain, and RLS prospectively over two years in a large cohort of patients.

When investigating sleep disorders among MS patients it is pertinent to consider potential factors that may impact sleep quality. In addition to factors that are known to impair sleep quality including depression, pain, certain medication, etc. MS treatment specific factors need to be taken into account. For example, interferon beta–1b appears to play an important role in modifying the sleep–wake–cycle. In a rodent model a null mutation of the Interferon type I receptor gene, coding for the receptor mediating the effect of interferon beta, was shown to aggravate sleep fragmentation [19]. In humans a small study of 13 patients did not find an impact of interferon beta on fatigue and the sleep–wake–cycle in patients with MS [20]. However, other data suggest that interferon beta–1b treatment may have a modifying effect on sleep quality of MS patients depending on the duration of treatment [8]. Hence, studies on sleep disorders in MS patients should account for both treatment and duration of treatment. One aspect is to ensure that all subjects receive the same treatment and have been treated for a similar period of time. In addition, it is desirable to investigate patients that tolerate treatment in order to avoid early treatment termination, which would obviate evaluation of disease course and treatment effects over time. However, treatment should not be too long as his may have caused changes in disease activity and affected comorbidities. Hence, for the present study we decided only to include patients that tolerate treatment with Betaferon® and have not received Betaferon® longer than six months.

We choose an observational study design in a real–life setting with patients recruited from private neurological offices and neurology departments across Germany to ensure representativeness of the data. Owing to the observational study design treatment with Betaferon® will be initiated according to the discretion of the attending physician.

Considering the high prevalence of sleep disorders in MS patients, better understanding the characteristics, comorbidities, diagnostic and treatment patterns, and course of sleep disorders in MS patients is important for future individualized and targeted treatment. Study results may also reveal underlying reasons and best therapy options for fatigue.

Conflicts of interest

- S. Kotterba received study grants from Bayer Health Care Germany and BiogenIdec, personal compensation as a speaker from Bayer HealthCare, BiogenIdec, UCB, Pfizer, and Novartis.
- S. Braune has received fees as a consultant from Bayer HealthCare Germany.
- M. Walther, B. Stollfuß, P. Bussfeld, T. Glaser and M. Schürks are full–time employees of Bayer HealthCare Germany.

Resumo

Fono

Gemalsanuloj kun multobla sklerozo (MS) ofte suferas de pliaj problemoj. Dormproblemoj koncernas ĉirkaŭ 50% de la pacientoj. Krome, dormproblemoj kaŭzas lacecon, oftan MS–problemon, en 80 % de la gemalsanuloj. Disponeblaj esploroj pri la rolo de dormĝenaĵoj je MS estas heterogenaj kaj mankas ankaŭ prospektivajn studaĵojn, kiuj esploras eventualajn kialojn de dormĝenaĵoj ĉe MS–pacientoj. Dormĝenaĵoj eble reprezentas MS–specifan trajton, aŭ eble estas efikoj de aliaj samtempaj malsanoj, MS–kuracado kaj daŭro de la kuracado. Fine, ni ne disponas pri datenoj koncerne paternojn de samtempaj malsanoj en MS pacientoj kun dormĝenaĵoj kaj la efiko de kuraciloj dum la tempo de la apliko.

Celo

Pli bone kompreni la karakteristikojn, samtempajn malsanojn, diagnozistikajn kaj kuracadajn paternojn kaj la sinsekvon de dormproblemoj de MS–gemalsanuloj kadre de la reala vivo en Germanio. La primara celo estas esplori la korelativecon inter la kvalito de dormo, laceco kaj la funkcia sanstato inter MS–pacientoj kuracataj per Interferon beta–1b (Betaferon®).

Metodoj

BETASLEEP estas prospektiva, ne–intervena, multcentra, observa kohorta studaĵo farita en neŭrologiaj praktikejoj kaj departementoj, kiuj estas specialigitaj por la kuracado de MS tra la tuta Germanio. Pacientoj, kiuj suferas de RRMS aŭ CIS kaj EDSS ≤ 5, kiuj estas kuracataj per Betaferon® ≤ 6 monatoj kaj kiuj bone toleras Betaferon® laŭ la informo de ilia kuracanta medicinisto, povas esti inkluzivotaj. Kuracado per alia DMD aŭ MS–specifaj kuraciloj ne estas permesata. Estas planita inkluzivi entute 300 pacientojn, kiuj estas sekvotaj dum 2 jaroj kun dezirita dokumentado ĉiun duonan jaron. Pritaksiloj koncerne la samtempajn aliajn malsanojn enhavas la Pittsburgh Sleep Quality Index (PSQI), la Modified Fatigue Impact Scale (MFIS), la Short Form–36 (SF–36), la Epworth Sleepiness Scale (ESS), la Hospital Anxiety and Depression Scale (HADS), la Hamburger Schmerz Adjektiv Liste (HSAL) kaj la IRLSS Group Rating Scale. Ĉiuj analizoj estos esploraj kaj de priskribanta karaktero. La BETASLEEP studaĵo komencis en decembro 2012. Estante 132 pacientoj (aŭgusto 2014) estas inkluzivitaj en la germanaj centroj. Inkluzivado daŭras kaj estos daŭrigata ĝis decembro 2014. Tial sekvado daŭros ĝis decembro 2016.

Diskuto

Analizo de la karakteristikoj kaj samtempaj aliaj malsanoj de MS–gemalsanuloj kun dormproblemoj kaj la diagnozaj kaj kuracadaj paternoj de tiuj dormĝenaĵoj kaj iliaj sinsekvoj eble faciligos individuajn kaj celitajn kuracadojn estontece.

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