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Original Article

Effect of levothyroxine on prolonged nocturnal sleep time and excessive daytime somnolence in patients with idiopathic hypersomnia

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ABSTRACT

Objective: This study aims to examine the effect of levothyroxine, a thyroid hormone, on a prolonged nocturnal sleep and excessive daytime somnolence (EDS) in patients with idiopathic hypersomnia.
Methods: In a prospective, open-label study, nine patients were enrolled. All subjects met criteria for idiopathic hypersomnia with long sleep time defined by the International Classification of Sleep Disorders, 2nd edition (ICSD-2). Subjects with sleep apnea syndrome, obesity or hypothyroidism were excluded. Sleep architecture and subjective daytime somnolence were estimated by polysomnography (PSG) and Epworth Sleepiness Scale (ESS), respectively. After baseline examinations, levothyroxine (25 μg/day) was orally administered every day. Mean total sleep time, ESS score at baseline were compared with those after treatment (2, 4 and 8 weeks).
Results: Mean age of participants was 23.8 ± 13.7 years old. At baseline, mean total sleep time (hours) and ESS score were 12.9 ± 0.3 and 17.8 ± 1.4, respectively. Mean total sleep times after treatment were 9.1 ± 0.7 and 8.5 ± 1.0 h at 4 and 8 treatment weeks, respectively. Mean ESS scores were 8.8 ± 2.3 and 7.4 ± 2.8 at 4 and 8 treatment weeks, respectively. One patient dropped out at the 2nd week due to poor effect. No adverse effects were noted.
Conclusions: After treatment with levothyroxine for over 4 weeks, prolonged sleep time and EDS were improved. Levothyroxine was effective for hypersomnia and well tolerated.

1. Introduction

Idiopathic hypersomnia was formerly characterized as prolonged sleep episodes, excessive sleepiness, or excessively deep sleep, which lasted for over 6 months. The International Classification of Sleep Disorders, 2nd edition (ICSD-2) has separated idiopathic hypersomnia into two entities [1]. The two conditions are referred to as idiopathic hypersomnia with long sleep time and that without long sleep time. The former is characterized by excessive daytime somnolence (EDS), prolonged nocturnal sleep and difficulty in awakening, and is considered to be polysymptomatic, primary, essential idiopathic hypersomnia. The latter is, on the other hand, remarkable only for EDS, and appears to be monosymptomatic. In both subtypes of idiopathic hypersomnia, multiple sleep latency test (MSLT) reveals reduced mean sleep latency and less than two sleep onset rapid eye movement (REM) sleep periods (SOREMPs). In contrast to narcolepsy, idiopathic hypersomnia lacks specific clinical features such as cataplexy and characteristic polysomnographic features indicating alterations in rapid eye movement (REM) sleep.

Previous reports involving cerebrospinal fluid (CSF) analyses in idiopathic hypersomnia patients have revealed that cell counts, cytology, and proteins were not altered [2]. A decrease in dopamine and indoleacetic acid in the CSF was identified in patients with hypersomnia including narcolepsy and idiopathic hypersomnia [3]. Another study demonstrated a dysregulation of the dopamine system in narcolepsy and of the norepinephrine system in hypersomnia [4]. While there have been reports on the pathologies of idiopathic hypersomnia, its pathogenesis has not been sufficiently discussed, and a strategy for its treatment has not been established. While narcolepsy is treated with psychostimulants for excessive daytime sleepiness and antidepressants for cataplexy and abnormal REM sleep [5], psychostimulants such as methylphenidate are not effective for excessive daytime sleepiness in most patients with idiopathic hypersomnia [2]. Naps are of no

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; ICSD-2, International Classification of Sleep Disorders, 2nd edition; MSLT, multiple sleep latency test; REM, rapid eye movement; SOREMP, sleep onset rapid eye movement sleep period; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone (thyrotropin).

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use because they are lengthy and not refreshing. A strategy treating EDS in patients with idiopathic hypersomnia has not yet been established, and investigation to identify an appropriate strategy for pharmacological intervention is necessary.

This study aims to investigate the effect of a thyroid hormone on prolonged nocturnal sleep and excessive daytime somnolence in patients with idiopathic hypersomnia. It is well known that patients with hypothyroidism usually exhibit daytime sleepiness. Sleep apnea and its related arousal at night may cause reduction in quality of nocturnal sleep and daytime somnolence. Therefore, patients with hypothyroidism or sleep apnea syndrome were excluded. We previously reported two cases with latent hypothyroidism who presented prolonged daytime somnolence and EDS. They were successfully treated with levothyroxine [6]. In the present study, subjects with latent hypothyroidism were also excluded.

2. Methods

2.1. Study design

This study was a prospective, open-label study design to assess the therapeutic effect of levothyroxine. Data were collected between April 2008 and September 2010.

2.2. Patients

Nine patients with idiopathic hypersomnia with long sleep time were enrolled in this study. The diagnosis of idiopathic hypersomnia was made according to the criteria established by ICSD-2 [1].

Patients were eligible if (i) they were aged <60 years old; (ii) their body mass index was <25 kg/m^2; (iii) they had not been treated for hypersomnia and had not been medicated with psychotropic agents such as psychostimulants, narcotics and antidepressants; (iv) no other drugs were prescribed during levothyroxine treatment; and (v) serum tri-iodothyronine (T_3), thyroxine (T_4) and thyrotropin (TSH) were within normal range. Patients were excluded for pregnancy or breast-feeding, for having contraindications to levothyroxine, for comorbidity with psychiatric disorders or medical illness. Psychiatrists diagnosed psychiatric comorbidity using the Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) [7]. To exclude medical disorders, clinical interview and laboratory examinations were carried out. Patients were also excluded from this study if the baseline polysomnography demonstrated the existence of other sleep disorders or a high apnea-hypopnea index (AHI) (>10).

The local institutional research boards approved this study. All patients gave informed consent according to institutional guidelines and the tenets of the Declaration of Helsinki.

2.3. Treatment

After the baseline examination, 25 μg/day of levothyroxine was administered in the morning. To examine whether adverse effects including symptoms due to an alteration in thyroid function were present, we examined the patients carefully and laboratory data were also examined.

2.4. Measurements

2.4.1. Polysomnography and multiple sleep latency test

Each patient received a standardized evaluation including a medical history, physical, and neurological examinations. At the baseline, polysomnography (PSG) was carried out following the adaptation night. Electrodes for polysomnogram were attached at 16:30. The patients entered their rooms at 18:00. Room lights were put off when patients required. Our staff checked and recorded the time. Nocturnal PSG was measured for 12 h (19:00 to 07:00). We performed overnight PSG by means of standard procedures that included recording a sleep electroencephalogram (C3-A2, C4-A1), bilateral eye movements, submental electromyography (EMG), an electrocardiogram, pulse oximetry, bilateral tibialis anterior EMG, nasal air flow by a pressure sensor, as well as rib cage and abdominal excursions. The sleep stage was scored according to standard criteria [8]. Sleep efficiency and the lengths of stages I, II, III, IV, and REM were obtained independently. Periodic limb movements during sleep (PLMs) and the apnea-hypopnea index (AHI) were also estimated.

To evaluate the sleep latency and sleep onset REM periods (SOREMPs), the MSLT was performed following overnight PSG according to the standard guideline [9]. Sleep latency was calculated from the results obtained by five sleep latency tests that were repeated at 2 h intervals (08:00, 10:00, 12:00, 14:00, and 16:00). A SOREMP was defined as the appearance of an epoch of REM sleep during the first 15 min of naps on the MLST.

2.4.2. Evaluation of symptoms

Mean daily sleep time, daytime somnolence and symptom severity were evaluated at baseline and treated for 2, 4, and 8 weeks. Mean daily sleep time indicates nocturnal plus daytime sleep, and was calculated with sleep logs and interview. Values were means of 7 days till each evaluation point. The subjective daytime somnolence was determined by the Epworth Sleepiness Scale (ESS) [10].

2.4.3. Laboratory data

Blood samples were collected before breakfast. Serum free T_3, free T_4, and TSH were evaluated.

2.4.4. Observation of adverse effect

To examine whether adverse effects including symptoms due to an alteration in thyroid function were present, we examined the patients carefully at each visit, and laboratory data were also examined.

2.5. Data analysis

To assess changes in scores on the mean daily sleep time and the ESS score, we used a Wilcoxon's signed rank test. Calculation was carried out with software PASW Statistics 18.0™. When the p value is less than 0.05, we considered the difference statistically significant.

3. Results

3.1. The demography and baseline characteristics of subjects (Table 1)

Nine patients were enrolled in this study (four males and five females). All patients met criteria for idiopathic hypersomnia with long sleep time. The mean age of diagnosis was 23.8 ± 13.7 years old (14–59 years old). Prolonged nocturnal sleep and excessive daytime somnolence began in their teens, and the mean age of symptom onset was 15.1 ± 1.1. The mean duration of hypersomnia was 8.1 ± 13.3 years (1.0–44.0 years). The mean body mass index was 21.2 ± 2.5 kg/m^2. The mean serum levels of fT3, fT4 and TSH were 3.00 ± 0.42 pg/mL (normal range, 2.2–4.1 pg/mL), 1.17 ± 0.15 ng/mL (normal range, 0.88–1.81 ng/mL) and 1.71 ± 0.95 μ-IU/mL (normal range, 0.35–3.73 μ-IU/mL), respectively. No subjects exhibited an altered thyroid function at baseline.