閉塞型に移行するものであればMSAとする（図2）。

2）低呼吸

前後の安定した呼吸に比べ、気流が10秒以上明らか（50%以下）に減少するとともに、基準値から3ないしは4%以上のSpO_2低下、もしくは覚醒反応を伴う場合に低呼吸と定義する。

3）呼吸努力関連覚醒反応（respiratory effort related arousal：RERA）

無呼吸・低呼吸だけでなく、フローリミテーション（flow limitation）*6が観察できる状態や食道内圧の変動幅の増大で表される呼吸努力の増加によって生じる覚醒反応のこと。

OSASの重症化とともにEDSを伴うようになる一方、無呼吸や低呼吸がないにもかかわらず、RERAの著しい増加に伴う睡眠障害を認める場合、前述したUARSの可能性がきわめて高い。UARSの確定診断には食道内圧（＝胸腔内圧）測定が不可欠なため、睡眠呼吸障害を専門的に診療する医療機関の受診を勧めるとよい。

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*6 フローリミテーション：
気道の狭小化に伴って特に吸気時の抵抗が上昇するため、吸気の流量波形が平坦化する現象のこと。

〈添付資料〉

睡眠に関するさまざまな変数とその定義

睡眠科学研究および睡眠臨床で用いられる睡眠パラメータについての定義を参考として列挙する。

1）全記録時間(total recording period：TRP)：記録開始から終了までの時間。
2）全就床時間(time in bed：TIB)：就床から起床までの時間。
3）全睡眠時間(total sleep time：TST)：入眠から翌朝の最後の覚醒までの時間のうち中途覚醒を除いた時間。
4）睡眠効率(sleep efficiency)：TST÷TIB×100%
5）睡眠期間(sleep period time：SPT)：入眠から翌朝の最後の覚醒までの時間。
6）睡眠段階出現時間：全記録時間において、各睡眠段階の占める時間。
　　TS1：段階１(Non-REM睡眠stageⅠ)の占める時間。
　　TS2：段階２(Non-REM睡眠stageⅡ)の占める時間。
　　TS3：段階３(Non-REM睡眠stageⅢ)の占める時間。
　　TS4：段階４(Non-REM睡眠stageⅣ)の占める時間。
　　TSR：段階REM(REM睡眠)の占める時間。
7）睡眠段階出現率
　(a) SPTにおける各睡眠段階出現率
　　%SW：覚醒段階の占める割合。
　　%S1：段階１の占める割合。
　　%S2：段階２の占める割合。
　　%S3：段階３の占める割合。
　　%S4：段階４の占める割合。
　　%SR：段階REMの占める割合。
　(b) TSTにおける各睡眠段階率
　　%S1：段階１の占める割合。
　　%S2：段階２の占める割合。
　　%S3：段階３の占める割合。
　　%S4：段階４の占める割合。
　　%SR：段階REMの占める割合。
8）中途覚醒(wake time after sleep onset：WASO、intermittent awakening)：睡眠期間(SPT)内での覚醒時間。
9）覚醒回数(number of arousals)：睡眠期間(SPT)内での覚醒回数。
10）睡眠段階移行数(stage shifts)：睡眠段階の移行した回数。
11）入眠潜時、睡眠潜時(sleep latency)：記録開始から入眠までに要した時間。
12）REM潜時(REM latency)：入眠からREM睡眠の出現するまでに要した時間。
13）REM活動(REM activity)：単位時間内に急速眼球運動が１回以上出現した場合を出現とみなし、その出現単位総数をいう。
14）REM密度(REM density)：単位時間内に急速眼球運動が１回以上出現した場合を出現とみなし、その出現単位数をREM睡眠の単位時間の総数で除した比率をいう。あるいは単位時間当たりのREMの出現頻度をいう場合もある。
15）REM睡眠段階数(number of REM periods)：睡眠期間(SPT)内でのREM睡眠回数(REM睡眠の中断が15分未満であれば１つのREM睡眠とする)。
16）睡眠周期(sleep cycle)：入眠より最初のREM睡眠の終わりまで、その後はREM睡眠の終了より次のREM睡眠の終了までの時間。
17）REM睡眠間隔(REM sleep interval)：REM睡眠が終わった時点から次のREM睡眠が始まるまでの時間で、この間の中途覚醒は除く場合もある。

薬物を使わない治療

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睡眠時無呼吸症候群の非薬物治療

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睡眠時無呼吸症候群，特にその患者人口の9割を占める閉塞性睡眠時無呼吸症候群（OSAS）に対して，1980～90年代前半まで，数多くの薬物療法が試みられてきたが，残念ながらそのほとんどに十分な効果が確認されず，今日ではほとんど用いられることがなくなった．本症候群での治療にあたっては，上気道内径を拡大するという物理的な視点に立脚した手法が主体になっており，確実な効果を収めている．

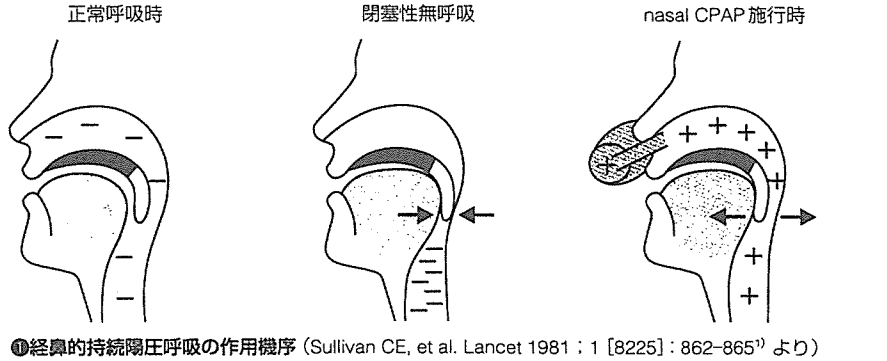
経鼻的持続陽圧呼吸（nasal CPAP）が第1選択

1981年に開発された手法であり，現時点でOSAS治療のfirst lineとして全世界的に認知されており，わが国でも推定8万人以上のCPAP使用患者が存在するという．本治療は❶[1]に示したように，鼻マスクから陽圧気流（4～20 cm H_2Oの範囲）を負荷して，睡眠中の上気道閉塞を抑制する，いわば“空気の副子”である．本治療の原理は極めて単純で，陽圧水準を調整すれば，呼吸障害をほぼ完全に抑止できるという点では，絶対の強みがある．本治療は，鼻呼吸ができないケース，極端な肥満などのために最大20 cm H_2Oまで圧レベルを上昇させても呼吸障害を抑止できないケースを除けば，確実な効果が得られる．本治療は無呼吸低呼吸指数（単位時間あたりのこれらの数；AHI）が20/時以上の症例については医療保険の適応を得ているので，終夜睡眠ポリグラフィ（PSG）を行いながら，適切な圧を検索し在宅使用する方法が一般化している．

nasal CPAPの副作用は，鼻閉，乾燥感（これらについては，加湿器で対応可能），気流による胸部・咽頭不快感（気流の水準を調整して対応する），マスクの違和感などである．本治療は，根治的な治療ではないので，これらの副作用に配慮しながら長期使用する必要がある．nasal CPAPのコンプライアンスは，4時間以上かつ観察期間中の70%以上使用することが目安となるが，不眠傾向の強い症例では苦痛を感じやすいので，耐えられないことも少なくない．nasal CPAP治療は，およそ1～2割程度の患者がドロップアウトすることに注意すべきで，この場合には後述する口腔内装置が適応になる．

口腔内装置（oral appliance；OA）の有効率は70%

睡眠時に，下顎を前方移動（4～10 mm程度）させるマウスピース（❷）を装着し，上気道虚脱を抑制する治療法で，2004年以来OSASに対する保険適応を得ている．OAを装着すると，舌骨の位置が上昇するし，咽頭筋のトーヌスも上昇して，気道開大保持性に働くこともわかっている[2]

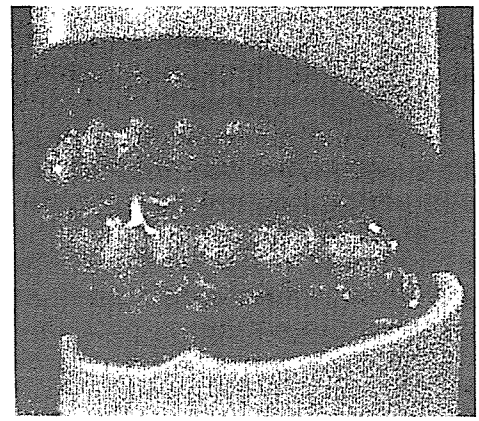


❶**経鼻的持続陽圧呼吸の作用機序**（Sullivan CE, et al. Lancet 1981；1［8225］：862-865[1]より）
－は咽頭内の陰圧を示し，＋は陽圧を示す．

本治療は，明らかにnasal CPAPに比べて簡便で，携行性に優れているが，有効率（AHIが50%以上かつ10/時以下まで低下することを基準とする）は70%程度にとどまる．したがって，現在の位置づけは，nasal CPAPに次ぐsecond lineというところである．本治療のresponderについての検討も数多く行われており，結論は得られていないものの，重症者，極端な肥満者には効果が乏しいようである．また副作用として，下顎前方移動による疼痛が生じることがある（前方移動距離の調整で，ある程度対応可能である）．

上気道手術：扁桃肥大を背景とするものには絶対適応

軟口蓋・口蓋垂・咽頭形成術（UPPP）[3]が一般によく知られている．本手術は，主に中咽頭部の開大効果を期待するものであるが，その有効性は50%程度と低く，第1選択とはなりえない．これは，UPPPが主に咽頭前後径を拡大する治療法であり，側方向から閉塞する症例には無効であること，さらには舌根部以下の閉塞には効果を発揮しないことなどが関与している．しかし，小児の扁桃肥大を背景として発症するOSASでは，その切除手術は著効することが多いので，絶対適応となりうる．近年では，顎を前方移動させる手術治療も考案されているが，適応が明らかにされておらず，美容上の問題もあるため，まだ実用性は低い．



❷歯科装具治療に用いるマウスピース

文献

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薬物療法

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適切な薬物の選び方——開始と中止の目安

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日本は世界有数の睡眠薬大国であり，薬剤の選択肢は極めて多い．しかしながら，薬剤選択の一定の基準は設けられておらず，しかも重要な問題として，薬物療法開始と中止のメリハリが不明瞭で，漫然と長期投与されがちである．睡眠問題を主訴に外来受診する症例は今後も増加することが予測されるので，この点には十分配慮する必要がある．

開始基準：服薬は強制せず患者の希望を取り入れる

必要な睡眠量には個人差があるので，睡眠時間の長さを含めて，薬剤投与開始の数量的な基準は設けにくい．また，患者の時間感覚が不正確で，入眠に要する時間や，中途覚醒時間が，実際の値と主観値に隔たりが生じている場合も少なくない（特に睡眠状態誤認が存在する場合）．不眠治療はあくまで，日中の活動性低下，作業機能低下，気分変化（いらいら感，不安など）や疲労感などが数日以上持続する場合に開始するべきである．

また，服薬の強制は避けるべきで，患者が睡眠衛生の調整などで対応したいという場合はこれに沿うべきであるし，認知行動療法的アプローチを優先したいという場合も同様である（もちろん，認知行動療法と薬物療法を併用し，症状が安定してから薬剤の減量・中止を図るという方法もある）．

睡眠薬の中止基準：ポイントは2つ

①不眠症状が十分改善されている，②不眠に対する恐怖感（不安感）が消失している，の2点が重要である．①に関しては，まったく症状がないか，ときおり不眠が生じるとしても苦痛の強い重篤なものでないことが原則となる．②に関して，特に精神生理性不眠症患者では，薬物への依存は恐いし，一方でこれなしには眠れないという両価的な心情を示すことが少なくないが，このような状況下で薬剤の副作用を恐れて無理にやめようとすると，症状が悪化することが多いので，避けるべきである．最も中止をスムーズに進められるのは，症状が改善していて，ときおり服薬を忘れるようになっている場合（あるいは，服用する前に眠ってしまうために，飲まなくなっている場合）である．このような状態になったら，睡眠薬の用法を定期服用から頓用に変える，あるいは用量を減らすなどの操作を行ってよい．

初期段階で治療のアウトラインを示すとよい

臨床場面での基本姿勢として，薬剤投与開始・中止についての考えを患者自身に理解させ，治療のアウトラインを示すことである（増量もしくは変更の根拠も示しておくとよい）．繰り返しになるが，睡眠薬の安易な長期投与は避けるべきなので，治療開始前ないし初期治療の段階で，治療終結までの展望を伝えておきたい．患者の安心感を得ることができれば，これが寝室環境での緊張感緩和，つまりは症状軽減にもつながる．また，薬剤の投与量は最少量で最大の効果を目指すという姿勢を明らかにすることも肝要であろう．

睡眠薬の長期連用は本当に悪いのか？

全世界的に，ベンゾジアゼピン系薬剤の長期使用は問題視されており，臨床用量依存の問題点が指摘されている．なお，非ベンゾジアゼピン系薬剤は，ベンゾジアゼピン類ほど危険視されていないが，これはこの群に属する薬剤の開発の歴史が新しく長期連用の問題点についての研究が多くないことと，半減期が短いために比較的離脱が容易なためであり，長期使用の問題点という点ではほぼ同様であろうと思われる．筆者も基本的にはこの考えに賛成だが，かといって難治性の慢性例についても薬剤を中止しなくてはいけないかどうかという点については疑問が残る．過去の報告をみても，長期使用による副作用（精神作業機能低下が多い）は，転倒や筋力低下などの一般的な副作用が生じやすい高齢者に関するものが圧倒的に多く，若年～中年期の患者については明らかな問題点はみられない．連用による耐性形成，用量増加は絶対避けなくてはいけないが，これに注意して薬剤を使いこなす（悪化すれば再開し，改善すれば休薬するというフレキシブルな対応が望ましい）ことが，患者の不眠によるQOL低下を防ぐうえでも重要なように思える．実際のところ，慢性の精神生理性不眠症で服薬が長期化する前に中止可能な症例は，全体の半数に満たない．薬剤の連用と中止に関する，さらなるエビデンスの集積を待ちたい．

Sleep and Biological Rhythms 2005; **3**: 99–105

ORIGINAL ARTICLE

Emotional states and quality of life in patients with obstructive sleep apnea

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Abstract

The aim of this study was to assess the substantial impact of obstructive sleep apnea (OSA) on emotional states and quality of life (QOL) along with the effect of treatment with continuous positive airway pressure (CPAP). Patients with any psychiatric disorders and serious physical diseases were excluded from the study. Thirty-one OSA patients and 63 healthy controls were asked to complete Profile of Mood States (POMS) and QOL-26 questionnaires at the commencement of the study, and then again after 3 months of CPAP treatment. The OSA group scored significantly higher (worse) in five mood factors and significantly lower (worse) in four QOL domains than the control group. Continuous positive airway pressure treatment produced significant improvement in the majority of emotional states and QOL after 3 months. These findings suggest that sleep apnea is at least partially responsible for emotional changes and reducing QOL. Furthermore, we found significant correlations between the apnea–hypopnea index (AHI) and tension-anxiety as well as fatigue-inertia and the physical QOL domain after 3 months of CPAP treatment. Some OSA patients had residual sleep apnea in spite of CPAP treatment due to severe obesity and tonsillar hypertrophy, and their mood states and QOL did not improve. Thus residual sleep apnea may impede improvement in emotional states and QOL in OSA patients. We believe that the frequency of apnea and hypopnea during sleep needs to be brought as close as possible to zero with intensive and combined therapy to improve emotional states and QOL in OSA patients.

Key words: continuous positive airways pressure (CPAP) treatment, emotional states, obstructive sleep apnea, quality of life (QOL).

INTRODUCTION

Sleep apnea, particularly obstructive sleep apnea (OSA), often results in excessive daytime sleepiness due to frequent awakening and sleep deprivation caused by repeated obstruction of the upper airway during sleep, while repetitive apnea causes deprivation of rapid eye movement (REM) sleep and stages 3 and 4 of non-REM (NREM) sleep.[1,2] Obstructive sleep apnea may result in various psychological changes, behavioral changes, and disturbances in quality of life (QOL).[3,4] Many studies have investigated the impact of sleep apnea on QOL and emotional states including depression and anxiety.[5–7] Regarding QOL, there is general agreement that QOL is disturbed in OSA patients and that it improves after continuous positive airway pressure (CPAP) treatment.[8–10] There is also almost consensus regarding emotional changes, including depression and anxiety, in OSA patients.[11–13] Various studies[12–14] have focused on the relationship between depression and sleep apnea, and

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Accepted for publication 9 March 2005.

some have considered depression to be a frequent symptom of sleep apnea. However, the majority of these studies failed to agree upon the prevalence rate of this symptom.[11] Lee stated that throughout the literature the importance of depression symptoms on sleep apnea had been overemphasized.[15] It is not apparent whether sleep apnea directly results in emotional changes such as depression, anxiety, and irritability, or indirectly results in these mood changes due to excessive daytime sleepiness and reduced QOL. Furthermore, the effect of CPAP treatment on psychological states in OSA patients remains controversial.[5,12–14,16] In this study, we excluded possible psychiatric disorders, mainly depression and anxiety disorder, and serious physical diseases affecting the OSA patients, and investigated the substantial impact of OSA on emotional states and QOL and the effect of CPAP treatment on these states.

SUBJECTS AND METHODS

Thirty-one OSA patients, 28 males and 3 females, with a mean age of 47.4 ± 12.1 years, and 63 healthy sex-and age-matched controls, 57 males and 6 females with a mean age of 48.8 ± 9.1 years, were examined. The average body mass index (BMI) in the OSA group was 29.4 ± 5.5 and was significantly higher than that in the control group of 23.5 ± 4.2 ($P < 0.0001$). All subjects were evaluated by face-to-face screening, which included a medical examination, medical interview, and a structured clinical interview for DSM-IV.[17] Potential subjects for this study were excluded if they exhibited psychiatric disorders including major depression, anxiety disorder, schizophrenia, substance abuse/dependence, or other types of sleep disorders. No subject was on psychotropic medications and none had a serious physical disease. Before beginning this study, three major depression disorders and one panic disorder were excluded. All OSA patients were generally in good health with the exception of their sleep disorder. The control subjects were also generally in good health and had no habitual snoring or apnea during sleep according to their family members. The diagnoses of all OSA patients were confirmed by standard polysomnography. At the time of establishing diagnosis for sleep apnea, the criterion used was an apnea–hypopnea index (AHI) of above 5. Sleep stages were assessed according to Rechtschaffen and Kales,[18] and respiratory disorders during sleep were evaluated according to approved criteria.[19] Daytime sleepiness was evaluated using the Epworth sleepiness scale (ESS).[20] The AHI and ESS at baseline in the OSA group were 53.7 ± 26.4 and 16.3 ± 5.0, respectively. Informed consent was obtained from all subjects. The subjects in both groups were asked to complete Profile of Mood States (POMS)[21,22] and QOL-26[23,24] questionnaires during face-to-face interviews, where all questionnaires were performed in the morning between 09.00 and 11.00 hours. All interviews were conducted by the same investigator, who was not aware of the goals of the study and the difference between the two groups. The six mood factors evaluated in the POMS questionnaire included tension-anxiety (T), depression-dejection (D), anger-hostility (A), vigor-activity (V), fatigue-inertia (F), and confusion-bewilderment (C), while the five QOL domains evaluated in the QOL-26 questionnaire included physical, psychological, social relationships, environment, and general, and the average QOL value was subsequently calculated. We compared differences in all subscale scores for the POMS and QOL-26 questionnaires between the OSA and control groups by analysis of variance, to assess the substantial influence of sleep apnea on emotional states and QOL. After CPAP titration at 4–15 cm H_2O was conducted, all OSA patients were treated with CPAP and were asked to complete the POMS and QOL-26 questionnaires again after 3 months of treatment, always at the same time in the morning between 09.00 and 11.00 hours. All subscale scores in the POMS and QOL-26 before and after CPAP treatment were compared by the paired *t*-test to assess the effect of CPAP treatment on emotional states and QOL. Also, the subscale scores were correlated with the AHI, ESS, and various other sleep parameters using Pearson's test. The sleep parameters included total sleep time (TST), wake time after sleep onset (WASO), percentage of Stage 1 sleep (% Stage 1), percentage of Stage 2 sleep (% Stage 2), percentage of slow-wave sleep (% SWS), and percentage of rapid eye movement sleep (% REM). Furthermore, we analyzed the correlations among the improvements in the AHI rate, ESS score, changes in various sleep parameters, and improvement in all subscale scores in the POMS and QOL-26 questionnaires using Pearson's test to understand what factors during CPAP treatment determined improvement in emotional states and QOL.

RESULTS

The impact of OSA on emotional states and QOL

The OSA group scored significantly higher (worse) than the control group in five mood factors: tension-anxiety

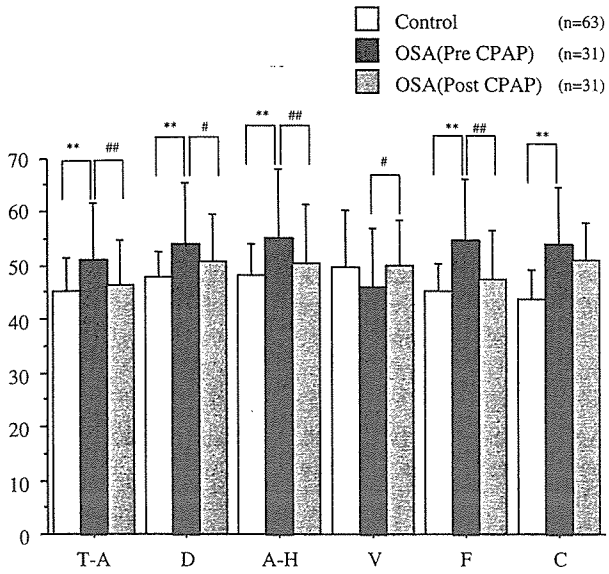

Figure 1 Mean T scores for the six mood factors evaluated in the Profile of Mood States (POMS) questionnaire for the control group ($n = 63$), and before and after continuous positive airway pressure (CPAP) treatment for the obstructive sleep apnea (OSA) group ($n = 31$). The six mood states are tension-anxiety (T-A), depression-dejection (D), anger-hostility (A-H), vigor-activity (V), fatigue-inertia (F), and confusion-bewilderment (C). **The difference is statistically significant ($P < 0.01$) between the control and the OSA groups by one-way ANOVA. # and ## indicate that the difference is statistically significant ($P < 0.05$ and $P < 0.01$, respectively) between before and after CPAP treatment in the OSA group by the paired *t*-test.

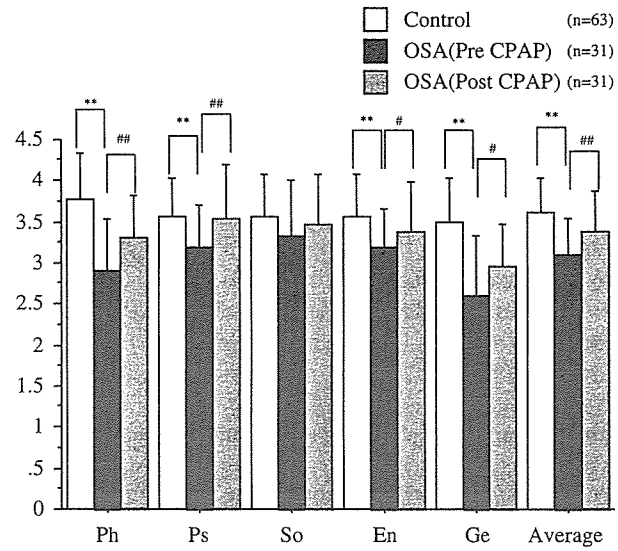

Figure 2 Mean quality of life (QOL) scores for five QOL domains and the average value of QOL evaluated in the QOL-26 questionnaire for the control group ($n = 63$), and before and after continuous positive airway pressure (CPAP) treatment for the obstructive sleep apnea (OSA) group ($n = 31$). The five QOL domains are physical (Ph), psychological (Ps), social relationships (So), environment (En), and general (Ge). The average value of QOL is represented on the right side of the figure. **The difference is statistically significant ($P < 0.01$) between the control and the OSA groups by one-way ANOVA. # and ## indicate that the difference is statistically significant ($P < 0.05$ and $P < 0.01$, respectively) between before and after CPAP treatment in the OSA group by the paired *t*-test.

(T-A); depression-dejection (D); anger-hostility (A-H); fatigue-inertia (F); and confusion-bewilderment (C) (all $P < 0.01$). Unexpectedly, there was no significant difference for vigor-activity (V) between the two groups (Fig. 1). The OSA group scored significantly lower (worse) than the control group in four QOL domains, physical (Ph), psychological (Ps), environment (En), and general (Ge), as well as in the average values of QOL (all $P < 0.01$; Fig. 2). Also, there were significant negative correlations between AHI and the physical and general QOL domains, as well as between ESS and the physical QOL domain at baseline in the OSA group ($R = -0.39$, $P < 0.05$, $R = -0.50$, $P < 0.01$, and $R = -0.43$, $P < 0.05$, respectively; Table 1). There were no correlations between AHI or ESS and all subscale scores in emotional states evaluated in POMS (Table 1), and there were no correlations between the various sleep parameters and the subscale scores in the POMS and QOL-26 questionnaires.

Changes in sleep measures after CPAP treatment

Table 2 shows the mean values and standard deviations for the 31 OSA patients, including the apnea–hypopnea index (AHI), mean oxygen saturation (mean SaO_2), Epworth sleepiness scale (ESS), total sleep time (TST), wake time after sleep onset (WASO), percentage of Stage 1 sleep (% Stage 1), percentage of Stage 2 sleep (% Stage 2), percentage of slow-wave sleep (% SWS), and the percentage of REM sleep (% REM), before and after CPAP treatment. Continuous positive airway pressure breathing (4–15 cm H_2O) resulted in a remarkable decrease of AHI from 53.7 ± 26.4 to 8.1 ± 10.2 ($P < 0.0001$). However, six patients had residual sleep apnea with a range of 10–40 episodes of apnea–hypopnea per hour of sleep, in spite of CPAP breathing, due to severe obstruction of the upper airway caused by severe obesity and tonsillar hypertrophy. Continuous positive airway

pressure breathing also resulted in improvements in mean SaO_2, ESS, and sleep architecture, where mean SaO_2 improved from 90.2 ± 5.8 to 96.5 ± 1.5 ($P < 0.0001$). The ESS improved from 16.3 ± 5.0 to 7.0 ± 4.7 ($P < 0.0001$), and total sleep time increased from 394.5 to 428.8 min ($P < 0.05$). The % Stage 1 value decreased from 31.8 to 12.9% ($P < 0.0001$), % Stage 2 increased from 33.6 to 49.0% ($P < 0.01$), % SWS increased from 1.1 to 3.4% ($P < 0.001$), and % REM increased from 14.1 to 19.4% ($P < 0.001$; Table 2).

Table 1 Correlations between the apnea–hypopnea index (AHI) and the subscale scores in the QOL-26 and POMS questionnaires, as well as between the Epworth sleepiness scale (ESS) and scores at baseline before CPAP treatment in the obstructive sleep apnea (OSA) group

	AHI	ESS
Quality of life in the QOL-26		
Physical domain (Ph)	−0.39	−0.43
Psychological domain (Ps)	NS	NS
Social relationships (So)	NS	NS
Environment (En)	NS	NS
General domain (Ge)	−0.50	NS
The average value of QOL	NS	NS
Emotional states in the POMS		
Tension-anxiety (T-A)	NS	NS
Depression-dejection (D)	NS	NS
Anger-hostility (A-H)	NS	NS
Vigor-activity (V)	NS	NS
Fatigue-inertia (F)	NS	NS
Confusion-bewilderment (C)	NS	NS

POMS, profile of mood stages; QOL, quality of life.

The effects of CPAP treatment on emotional states and QOL

In the OSA group, five mood factors, tension-anxiety, depression-dejection, anger-hostility, vigor-activity, and fatigue-inertia, significantly improved after 3 months of CPAP treatment. However, the score for confusion-bewilderment did not significantly improve after 3 months of treatment (Fig. 1). In the OSA group, four QOL domains, physical, psychological, environment, and general, and the average QOL values, significantly improved after 3 months, but the score for social relationships did not (Fig. 2). There were significant negative correlations between the physical QOL domain and the AHI, as well as ESS after 3 months of CPAP treatment ($R = -0.40$, $P < 0.05$, and $R = -0.41$, $P < 0.05$, respectively; Table 3), and there were significant positive correlations between the AHI and the score for tension-anxiety, as well as the score for fatigue-inertia after treatment ($R = 0.43$, $P < 0.05$, and $R = 0.39$, $P < 0.05$, respectively; Table 3). Finally, there were no correlations between the various sleep parameters and all subscale scores in the POMS and QOL-26 questionnaires after 3 months of CPAP treatment.

Factors that determine the improvement of emotional states and QOL

To understand what factors during CPAP treatment determine the improvement of mood states and QOL, we analyzed the correlations among the improvement in the AHI rate, the ESS score, changes in various sleep parameters, and improvement in all subscale scores in the POMS and QOL-26 using Pearson's test. There were

Table 2 Mean values and standard deviations for 31 obstructive sleep apnea (OSA) patients

	Pre-treatment		Post treatment	
	Mean	SD	Mean	SD
Apnea–hypopnea index	53.7	26.4	8.1	10.2
Mean oxygen saturation	90.2	5.8	96.5	1.5
Epworth sleepiness scale	16.3	5.0	7.0	4.7
Total sleep time	394.5	88.9	428.8	62.8
Wake time after sleep onset	104.2	58.9	79.3	36.2
Percentage of Stage 1 sleep	31.8	14.8	12.9	6.9
Percentage of Stage 2 sleep	33.6	19.5	49.0	9.6
Percentage of slow wave sleep	1.1	2.6	3.4	3.6
Percentage of REM sleep	14.1	6.4	19.4	6.7

REM, rapid eye movement.

significant correlations between the improvement in the ESS score and the physical QOL domain, as well as the improvement in the vigor-activity score in the POMS questionnaire ($R = 0.45$, $P < 0.05$, and $R = 0.44$, $P < 0.05$, respectively), while there were no correlations between the improvement in the AHI rate and in all subscale scores in the POMS and QOL-26 questionnaires (Table 4). Also, we did not find any correlations between the changes in various sleep parameters and the improvement in all subscale scores in the POMS and QOL-26 questionnaires.

Table 3 Correlations between the apnea–hypopnea index (AHI) and the subscale scores in the QOL-26 and POMS questionnaires, as well as between the Epworth sleepiness scale (ESS) and scores after 3 months of continuous positive airway pressure (CPAP) treatment in the obstructive sleep apnea (OSA) group

	AHI	ESS
Quality of life in the QOL-26		
Physical domain (Ph)	−0.40	−0.41
Psychological domain (Ps)	NS	NS
Social relationships (So)	NS	NS
Environment (En)	NS	NS
General domain (Ge)	NS	NS
The average value of QOL	NS	NS
Emotional states on the POMS		
Tension-Anxiety (T-A)	0.43	NS
Depression-deiection (D)	NS	NS
Anger-hostility (A-H)	NS	NS
Vigor-activity (V)	NS	NS
Fatigue-inertia (F)	0.39	NS
Confusion-bewilderment (C)	NS	NS

POMS, profile of mood stages; QOL, quality of life.

DISCUSSION

The results of our study, as well as those of previous studies[4–7] indicate that OSA patients had more disturbed mood states and lower quality of life (QOL) than did the healthy controls. Regarding QOL, there is general agreement that QOL is disturbed in OSA patients and that it improves after CPAP treatment.[7–10] Young *et al.*[7] investigated the effects of sleep apnea on QOL in patients with and without OSA using the Medical Outcomes Study SF-36 Health Survey, after adjusting for differences in age, gender, body mass index, and the number of comorbid conditions, and reported that sleep apnea has a negative impact on several QOL domains. In addition, Jenkinson *et al.*[10] investigated the effects of therapeutic CPAP on subjective sleepiness, objective sleepiness, and QOL using the SF-36 questionnaire, compared with those of subtherapeutic CPAP of 1 cm H_2O. They found that therapeutic CPAP significantly reduces excessive daytime sleepiness and improves QOL, compared with subtherapeutic CPAP. In this study, we also observed that OSA patients had lower QOL than did healthy controls and that CPAP treatment produced significant

Table 4 Correlations between improvement in the apnea–hypopnea index (AHI) rate and improvement in the subscale scores in the QOL-26 and POMS questionnaires, as well as between improvement in the Epworth sleepiness scale (ESS) score

	AHI rate improvement	ESS score improvement
Quality of life in the QOL-26		
Physical domain (Ph)	NS	0.45
Psychological domain (Ps)	NS	NS
Social relationships (So)	NS	NS
Environment (En)	NS	NS
General domain (Ge)	NS	NS
The average value of QOL	NS	NS
Emotional states on the POMS		
Tension-anxiety (T-A)	NS	NS
Depression-deiection (D)	NS	NS
Anger-hostility (A-H)	NS	NS
Vigor-activity (V)	NS	0.44
Fatigue-inertia (F)	NS	NS
Confusion-bewilderment (C)	NS	NS

POMS, profile of mood stages; QOL, quality of life.

improvements in a majority of the QOL domains after 3 months, although our study was not based on controlled trials and we should have repeated the POMS and QOL-26 questionnaires for the control subjects after 3 months. We found significant negative correlations between the physical QOL domain and the ESS, as well as the AHI, at baseline and after 3 months of CPAP treatment. This suggests that not only the severity of sleep apnea but also subjective sleepiness significantly reduces the physical QOL domain in OSA patients. Regarding psychological states in OSA patients, some investigators reported correlations between the severity of sleep apnea and emotional states, while one has contradicted these findings. Watson *et al.*[13] investigated correlations between sleep apnea syndrome and depressive states using the Beck Depression Inventory and found a significant correlation between depression symptomatology and the frequency of apnea–hypopnea per hour of sleep, termed the apnea–hypopnea index (AHI). However, Pillar and Lavie[14] did not observe any relationship between anxiety and depression and the severity of sleep apnea. We also did not observe any correlation between emotional states and the severity of sleep apnea at baseline, although we found significant correlations after 3 months of CPAP treatment. There has also been disagreement regarding the effect of CPAP treatment on psychological states in OSA patients. Millman *et al.*[12] discovered that CPAP treatment improves depression symptomatology in some OSA patients, while Sanchez *et al.*[11] reported that CPAP treatment significantly improves depression and anxiety levels using the Beck Depression Inventory and the State-Trait Anxiety Inventory after 1 and 3 months of CPAP treatment. Previously, Derderian *et al.*[5] investigated seven men with OSA using the POMS questionnaire, and reported that two of the six mood factors, depression and fatigue, were significantly improved at least 2 months after CPAP treatment. We also observed that five of the six mood factors in the POMS questionnaire (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, and fatigue-inertia) were significantly improved after 3 months of CPAP treatment. However, Borak *et al.*[16] did not observe any improvement in the emotional states of patients with severe OSA after 3 months and 1 year of CPAP treatment. They explained that the difference between their findings and those of others might have resulted from the different populations studied and that the emotional states in their patients did not improve after CPAP treatment because they suffered from severe OSA, where the AHI was 67 ± 16. In this study, our subjects also suffered from severe OSA with an AHI of 53.7 ± 26.4, but the emotional states were significantly improved after CPAP treatment. We found, however, significant correlations between the AHI and tension-anxiety as well as fatigue-inertia and the physical QOL domain after 3 months of CPAP treatment. Six of the 31 OSA patients had residual sleep apnea, with a frequency of ten to forty episodes of apnea–hypopnea per hour of sleep, in spite of CPAP treatment due to severe obstruction of the upper airway caused by severe obesity and tonsillar hypertrophy. In particular, two male OSA patients for which the BMI was 36.8 and 41.7, and AHI was 126.8 and 100.5, respectively, had residual apnea and hypopnea with an AHI of 40.7 and 33.8 after CPAP titration due to severe obesity and tonsillar hypertrophy. Their mood states and QOL did not improve 3 months after CPAP treatment and remained at the pathological level. These results suggest that residual sleep apnea may impede improvement in emotional states and QOL in OSA patients. Therefore, we believe that the frequency of apnea and hypopnea during sleep needs to be brought as close as possible to zero with intensive and combined therapy including CPAP treatment, oral appliances, tonsillectomy, and weight reduction to improve emotional states and QOL in OSA patients. Regarding the factors that determine the improvement of emotional states and QOL, Derderian *et al.*[5] found that changes in depression are negatively correlated with the percentage change of total time spent in Stage 3 and 4 sleep ($R = -0.76$, $P < 0.05$), and that the change in fatigue is negatively correlated with the improvement in oxyhemoglobin saturation ($R = -0.81$, $P < 0.05$). In this study, we did not find any correlations between the improvement in the AHI rate and changes in various sleep parameters and the improvement in emotional states and QOL. However, we found correlations between improvement in the ESS score and improvement in the physical QOL domain, as well as improvement in the score for vigor-activity. We believe that we need to improve subjective sleepiness, as well as the frequency of apnea and hypopnea to improve emotional states and QOL in OSA patients. To date, various studies have focused on the relationships between depression and sleep apnea, and many investigators reported depression to be a frequent symptom of sleep apnea. However, the majority of these studies failed to agree upon the actual prevalence of this symptom. Lee stated that the importance of depression symptoms in terms of sleep apnea has been overemphasized.[15] Therefore, we excluded any psychiatric disorders, mainly depression and anxiety disorders, subjects who had received psychotropic medication, and those with

serious physical diseases from participation in this study. In spite of excluding those with psychiatric disorders, we observed more disturbed emotional states such as anxiety, depression, anger, fatigue, and confusion in the OSA patients than in the healthy controls, although emotional changes in the OSA patients were not indicative of a remarkably high score at the pathological level. We also observed that CPAP treatment produced a significant improvement in a majority of emotional states. These findings suggest that sleep apnea is at least partially responsible for emotional changes. However, it is still not apparent whether some OSA patients have only concomitant major depression, or if sleep apnea can result in major depression. Furthermore, it remains controversial whether depression in OSA patients is derived from biological mechanisms or from social maladjustment caused by persistent daytime sleepiness and reduced QOL. To solve these questions, we need to investigate the prevalence of major depression among the majority of the OSA population, and how CPAP treatment improves depression symptoms in OSA patients concomitant with major depression without applying any combined antidepressive therapy.

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Psychiatry and Clinical Neurosciences (2005), **59**, 223–225

Short Communication

Consecutive monitoring of sleep disturbance for four nights at the top of Mt Fuji (3776 m)

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Abstract The purpose of the present study was to conduct consecutive monitoring of sleep from the second to the fifth night at altitude. Three healthy male subjects climbed the top of Mt Fuji (3776 m) and stayed there for 6 days. Polysomnographic recordings were performed during this period and control recordings were made at sea level 1 month after the mountaineering. Disturbed sleep characterized by an increased number of arousals and/or long wake time was observed to persist through the fifth night in all subjects. These results suggest that sleep disturbance might persist during initial days at altitude despite cumulating sleep pressure due to poor night's sleep.

Key words acclimation, altitude, measurement on consecutive nights, periodic breathing, sleep.

INTRODUCTION

It is well-known that sleep disturbance is one of the major symptoms of acute mountain sickness.[1] Sleep disturbance at high altitude has been reported to be characterized by polysomnographic findings of frequent arousals and reduced amounts of both slow-wave sleep and rapid eye movement (REM) sleep, accompanied by poor subjective sleep quality.[1] Periodic breathing with a feeling of suffocation has also been reported when those accustomed to lower altitudes ascend to high altitudes.[1] Because the studies examining the polysomnographic characteristics of sleep at high altitudes have been conducted only for 1 night or several non-consecutive nights in high-altitude mountain areas,[2–4] adaptive sleep processes at high altitudes remain to be elucidated. Because sleep is known to be strongly affected by the conditions of the previous night's sleep, disturbed sleep at high altitudes would facilitate sleep on the following nights. Otherwise, cumulative sleep disturbance might adversely influence daytime activities,[5] leading to an increased risk of accidents during mountaineering. Taking the aforementioned issues into account, we investigated the sleep architecture of three healthy male subjects over the course of four consecutive nights, from the second to the fifth night at the top of Mt Fuji (the highest peak in Japan, at an altitude of 3776 m).

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Received 23 April 2004; revised 26 August 2004; accepted 29 August 2004.

METHODS

Three healthy male lowlanders (24, 27, and 39 years), who had no experience of climbing above 3500 m altitude in the past 1 year, participated in the study. The subjects were fully informed of the study and provided written consent before participation. The subjects climbed the top of Mt Fuji (3776 m altitude) and spent five nights in a meteorological observatory located there. On the day of ascending, the subjects arose at 04:30 hours, then rode to an altitude of 2380 m by car, from which point they started to climb on foot for 4.5 h to reach the summit. Except for the days on which they ascended and descended the mountain, all subjects spent each day conducting regular activities, for example domestic duties, preparing three meals and engaging in pedaling exercise for 30 min with moderate intensity. The time for sleep was set from 22:00 to 06:00 hours, and daytime napping was prohibited. The

room temperature and relative humidity in the observatory was kept at around 20°C and 60% throughout the period. The subjects slept in their own sleeping quarters free from noise and bright light.

Polysomnography (PSG) including electroencephalogram (C3-A2 and O1-A2), electrooculogram, electromyogram of mentalis muscle and electrocardiogram, was consecutively performed before and during their stay at the summit, using portable cassette recorders (Medilog 9000 and 9200 systems, Oxford Instruments, Oxford, UK). In two out of three subjects, respiratory monitoring using nasal air flow and chest movement were also included in the PSG recordings. Arterial oxygen saturation (SaO_2) was measured with a Biox II oximeter (Ohmeda, Boulder, USA) immediately upon waking each morning. More than 1 month after the climb, the subjects were measured with the PSG devices for two consecutive nights at sea level in the same manner as at the top of Mt Fuji. Control values were taken from the records during the second night at sea level.

Because the first night's sleep at the top of Mt Fuji was thought to be influenced by short sleep duration in the previous night (23:30–4:00) and climbing physical activities for 4.5 h, we investigated the content of sleep from the second to fifth night when nocturnal sleep period and daytime activity were kept constant. Sleep parameters were calculated from the results of visual scoring, in accordance with the method described by Rechtshaffen and Kales.[6]

The periodic breathing monitored in two subjects (1 and 2) was defined as a cyclic increase in the amplitude of respiratory air flow, followed by apneas/hypopneas.[7] Apnea was defined as a pause in respiration of >10 s, and hypopnea was defined as a decrease in the amplitude of recorded respiratory air flow to ≤50% of the baseline value. The frequency of apnea and hypopnea per hour, referred to as the apnea/hypopnea index (AHI), was then calculated.

RESULTS AND DISCUSSION

The values of SaO_2 after the control night at sea level stood at approximately 96% in all of the subjects. In contrast, morning SaO_2 values after the second to fifth night at the top of Mt Fuji were around 90% (ranging from 87% to 94%) with no obvious tendency to improve over the time spent at this altitude.

The deterioration in sleep architecture among subjects on Mt Fuji is shown in Table 1. Due to technical problems, there was no PSG recording corresponding to the third night for subject 3. The recordings at the top of Mt Fuji showed definite abnormalities in sleep-architecture variables (<80% or >120% of control values); these variations are indicated by the + and – characters in Table 1. The highest stage wake value, around 120 min, was observed on the second night in subjects 1 and 3, and on the fifth night in subject 2. The number of arousals on Mt Fuji increased for subjects 1 (53–79 times/night) and 2 (59–72 times/night) on all recording nights. In contrast, in subject 3, although sleep disturbance was milder than in subjects 1 and 2, longer sleep latency was observed on the fourth and fifth night. Decreased slow wave sleep was also seen on two nights for subject 2 and on three nights for subject 3. However, the amount of REM sleep did not change among subjects, except for the results on the fourth night of subject 3.

Both subjects 1 and 2 had no periodic breathing on the control night. The average value ± SD of AHI across the nights on Mt Fuji was 9.0 ± 5.4 and 4.0 ± 3.4 in subjects 1 and 2, respectively, and all of the disordered breathing events were of the central type. As it was consistent with the previous reports,[1] periodic breathing appeared mostly during light non-REM sleep, and there was no periodic breathing during REM sleep. In accordance with previous studies,[3,8] there were numerous awakening events without periodic breathing at the top of Mt Fuji.

Despite the small number of subjects, the present study first examined sleep architecture during consecutive nights at altitude. According to our previous study examining sleep under acute simulated altitude by using a hypobaric chamber, no sleep disturbance was observed below 3000 m altitude but sleep under 4000 m altitude was disturbed with increased wakefulness accompanied by a significant decrease in nocturnal SaO_2 compared with those below 3000 m.[8] Therefore, the altitude at the top of Mt Fuji seems to be critical to the appearance of sleep disturbance when lowlanders ascend to high altitudes. Our results indicate that sleep architecture at an altitude of 3776 m remained unacclimated through the fifth night. Although we could not measure SaO_2 during sleep, the lack of obvious improvement in morning SaO_2 values over the time spent on Mt Fuji may suggest that nocturnal hypoxemia might persist through the fifth night. Because Normand *et al.*[2] have reported no sleep disturbance after 3 weeks spent at an altitude of 3800 m, it might take 1–3 weeks for acclimation of sleep architecture atop Mt. Fuji (3776 m). As it is also seen in the present study, sleep disturbance at altitude is characterized by sleep fragmentation,[1] which is known to increase daytime sleepiness even when total sleep time is unaffected.[9] Considering the likelihood of increased daytime sleepiness caused by cumulative sleep deprivation, schedules of work and rest should be carefully planned during the initial week at such altitudes.

Table 1. Changes in sleep architecture from the second to fifth night at summit of Mt Fuji

	Second night	Third night	Fourth night	Fifth night	Control night
Subject 1					
Sleep latency (min)	13.7	2.0	5.7	9.0	36.3 +
No. arousals	79.0 + + +	75.0 + + +	73.0 + + +	53.0 + +	29.0
Stage wake percentage in SPT	25.0 + + +	14.3 +	13.6	23.3 + + +	11.6
Stage 1% in SPT	24.5 + +	26.2 + + +	21.6 + +	12.0	12.4
Stage 2% in SPT	25.4 – –	26.4 – –	31.6 –	34.8 –	46.5
SWS % in SPT	13.5	16.0	17.8	18.1	16.3
REM % in SPT	11.4	17.1	15.4	11.7	13.1
Total sleep time (min)	348.7	398.0	402.7	357.3	393.3
Subject 2					
Sleep latency (min)	8.0	7.3	2.3	12.3	11.7
No. arousals	70.0 + + +	59.0 + + +	69.0 + + +	72.0 + + +	21.0
Stage wake percentage in SPT	10.4 +	8.0	12.6 + +	19.8 + + +	8.2
Stage 1% in SPT	20.2 +	18.6 +	17.0	13.3	15.2
Stage 2% in SPT	36.4 –	45.9	34.0 –	32.2 –	48.2
SWS % in SPT	6.3 – –	7.5 –	12.0	11.4	10.6
REM % in SPT	26.6	20.0	24.4	23.4	17.8
Total sleep time (min)	423.7	422.7	409.0	371.3	430.0
Subject 3					
Sleep latency (min)	9.3		40.3 +	48.3 + +	3.3
No. arousals	41.0		44.0 +	35.0	36.0
Stage wake percentage in SPT	27.2 + + +		5.8 +	4.0	4.6
Stage 1% in SPT	7.2		28.5 + + +	13.6	14.0
Stage 2% in SPT	41.7		36.7	50.9 +	42.0
SWS % in SPT	3.1 – –		10.2 –	7.6 – –	13.6
REM % in SPT	20.7		18.8 –	23.9	25.8
Total sleep time (min)	336.7 –		400.3	407.7	457.3

SPT, sleep period time.

+/–, increases or decreases in each sleep parameter compared with that on the control night at sea level. + or –, change of ±20–40%; + + or – –, change of ±41–100%; + + + or – – –, change of >100% of the control value.

Sleep latency: +, 20–40 min; + +, 41–80 min.

ACKNOWLEDGMENTS

The authors are grateful for the valuable help of the staff of the meteorological observatory atop Mt Fuji. We dedicate this paper to our colleagues Drs N. Okudaira and K. Kikuchi who climbed Mt Fuji for this experiment but passed away in recent years.

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Psychiatry and Clinical Neurosciences (2005), **59**, 194–199

Regular Article

Difference in the characteristics of subjective and objective sleepiness between narcolepsy and essential hypersomnia

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Abstract The present study was conducted to investigate the difference in the characteristics of daytime sleepiness between narcolepsy and essential hypersomnia and to identify the relationship between the Epworth Sleepiness Scale (ESS) and the Multiple Sleep Latency Test (MSLT) in patients with these two disorders. Subjects consisted of 34 patients with essential hypersomnia (32.4 ± 11.0 years old), 52 patients with narcolepsy (29.0 ± 13.8 years old), and 45 control subjects (33.3 ± 6.6 years old). The subjects completed the ESS and underwent MSLT following a regular sleep-wake schedule for over 2 weeks. The ESS scores were pathologically high and mean sleep latency on MSLT was short, not only in narcolepsy but also in essential hypersomnia. With respect to sleep latencies on each MSLT session, both essential hypersomnia and control subjects had the smallest value at 14:00, while narcolepsy lacked any statistical change at this time period. The correlation between ESS and mean sleep latency on MSLT was higher in essential hypersomnia than in narcolepsy, and the correlation was strongest for the session performed at 14:00. Based on the ESS and MSLT results, the severity of excessive daytime sleepiness was significantly milder in essential hypersomnia compared with that in narcolepsy. The results also indicate that diurnal variation of sleepiness was maintained, and the correlation between subjective and objective sleepiness was relatively maintained in essential hypersomnia compared to narcolepsy. It is suggested that the mild disease severity of essential hypersomnia contributed to the formation of these characteristics.

Key words diagnosis, Epworth Sleepiness Scale, essential hypersomnia, Multiple Sleep Latency Test, narcolepsy.

INTRODUCTION

Both Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT) have been commonly used in clinical settings as quantitative methods of evaluating daytime sleepiness.[1,2] Although the MSLT has been widely accepted as the gold standard for measuring daytime sleepiness, this test is time- and labor-consuming. In contrast, the ESS is easy to perform, but the accuracy and validity of the test results have yet to be clearly established. To clarify this issue, the relationship between ESS and MSLT test results has been studied by several investigators.[3,4] Some reports have suggested that ESS is not appropriate for the diagnosis of pathological hypersomnia.[4,5] However, the previous studies consisted of heterogeneous subjects with hypersomnia, including obstructive sleep apnea hypopnea syndrome (OSAHS), periodic limb movements disorder (PLMD), primary insomnia, narcolepsy, idiopathic hypersomnia, and so forth.[4,5] Furthermore, the schedules of night-time sleep and daytime activities prior to

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Received 9 August 2004; revised 27 September 2004; accepted 1 November 2004.

the examination were not strictly controlled in most of the previous investigations.[3,6] Accordingly, the inconsistency between ESS and MSLT findings may have resulted from the heterogeneity of disease backgrounds and/or variations in sleep habits.

Among patients with primary hypersomnia, many patients exhibit narcolepsy-like sleepiness but do not exhibit cataplexy or rapid eye movement (REM)-related symptoms. These patients are termed as having essential hypersomnia,[7,8] narcoleptic idiopathic hypersomnia,[9] or monosymptomatic idiopathic hypersomnia.[10] Although these patients are categorized as having idiopathic hypersomnia in the International Classification of Sleep Disorders (ICSD),[11] symptomatic characteristics are clearly different from those of classical idiopathic hypersomnia syndrome, in which long naps and prolonged nocturnal sleep have been reported.[10] According to the revision of ICSD, idiopathic hypersomnia without long sleep, which is mostly consistent with essential hypersomnia, would be advocated. Although the severity of this kind of disorder has been suggested to be milder than typical narcolepsy,[8,9] detailed examinations using both subjective and objective measures of daytime sleepiness have not yet been conducted.

Taking the aforementioned issues into consideration, we conducted an investigation on the features of ESS and MSLT in normal controls and patients with essential hypersomnia or narcolepsy under a strictly controlled schedule of night-time sleep and daytime activities. Based on the results of this study, we discussed differences in the characteristics of daytime sleepiness in these two primary hypersomnias.

METHOD

Subjects

The study was approved by the ethical committee of Juntendo University.

Subjects of the present study were patients who visited the outpatient clinic of Japan Somnology Center from October 1999 to August 2002 and were diagnosed with narcolepsy or essential hypersomnia based on both clinical symptoms and MSLT findings. All of the patients with narcolepsy exhibited the typical clinical features of the disorder, that is, the presence of typical cataplexy; the presence of HLADQB1*0602; sleep paralysis and/or hypnagogic hallucinations. According to criteria previously proposed by our group, essential hypersomnia was diagnosed when the patients exhibited narcolepsy-like excessive daytime sleepiness, that usually improved after awakening from short naps, and the clear absence of narcoleptic symptoms including cataplexy, two or more sleep-onset REM periods, sleep paralysis and hypnagogic hallucinations.[7,8] A total of 52 patients with narcolepsy (27 women, 24 men, 29.0 ± 13.8 years old) and 34 patients with essential hypersomnia (18 women, 16 men, 32.4 ± 11.0 years old) were examined. The control subjects consisted of 45 healthy volunteers (23 women, 22 men, 33.3 ± 6.6 years old), all of whom gave their written informed consent. None of the subjects were night-shift workers, and individuals attesting to irregular sleep-wake cycles and/or extreme morning type or evening type[12] were excluded from the study. Patients with insufficient sleep syndrome, OSAHS and PLMD were also excluded. All subjects were free of any treatments and were not taking any medication. There were no significant differences in either age or gender distribution among the three groups, nor were there any significant differences in self-reported bedtimes and wake times (bedtime: $F_{2,128} = 1.31$, ns; wake time: $F_{2,128} = 0.43$, ns).

Procedure

The subjects were instructed to fulfill their sleep logs[13] for more than 2 weeks prior to the examination, and the regularity of their sleep-wake schedules was confirmed based on the findings. The ESS was then scored using systematic interviews, and standard form MSLT was given after confirming that subjects had slept for more than 7 h on the previous night using polysonmogram (PSG).[2,14] The PSG was performed from around 0:00 h to 8:00 h. Two hours after waking the following morning, the first session of MSLT was started at around 10:00 h and followed by sessions at around 12:00 h, 14:00 h, and 16:00 h in sequence.

Data analysis

The grouped data were statistically analyzed using StatView statistical software (Abacus Concepts, Berkely, CA, USA). The implementing factors of the group and MSLT sessions performed at 10:00, 12:00, 14:00, and 16:00 h were analyzed using an analysis of variance (ANOVA) for repeated measurements. The results of ESS data were compared among the three groups using a one-way ANOVA. When significant differences were found with the ANOVA, Scheffe's post-hoc analysis were conducted. Pearson's simple correlation coefficient was used to assess the relationships between ESS score and mean sleep latency on MSLT as well as sleep latencies at each session in the subject groups. The hypothesis rejection level for all tests was $P < 0.05$.

RESULTS

A statistically significant difference in both ESS score and mean sleep latency on MSLT was observed among the three subject groups (ESS: $F_{2,128} = 197.3$, $P < 0.0001$; MSLT: $F_{2,128} = 479.0$, $P < 0.0001$, Fig. 1). The ESS scores of narcolepsy was significantly higher than that of essential hypersomnia ($P < 0.001$) and that of control subjects ($P < 0.0001$). The value was also significantly higher in cases of essential hypersomnia than in control subjects ($P < 0.0001$). Mean sleep latency on MSLT of narcolepsy was significantly shorter than that of the other two groups ($P < 0.0001$, for both comparisons), and was significantly shorter in essential hypersomnia than in the control subjects ($P < 0.0001$).

All of the patients with narcolepsy had two or more sleep-onset REM periods on MSLT. In contrast, none of the patients with essential hypersomnia and none of control subjects had more than two sleep-onset REM periods.

When the difference in sleep latency at each MSLT session was assessed, an interaction between the subject groups and the session times was found ($F_{6,384} = 8.2$, $P < 0.0001$; Fig. 2). Post-hoc tests revealed that both narcolepsy and essential hypersomnia had shorter sleep latency than control subjects at every MSLT session ($P < 0.0001$, respectively). Furthermore, narcolepsy had shorter periods of sleep latency than essential hypersomnia at every session except for the value at 14:00 h (10:00 h, $P < 0.01$; 12:00 h, $P < 0.0001$; 16:00 h, $P < 0.05$).

Among the control subjects, sleep latency at 14:00 hours was significantly shorter than the value at 10:00, 12:00, and 16:00 h ($P < 0.0001$ for all comparisons). In the cases of essential hypersomnia, sleep latency was also shortest at 14:00 h. In contrast, no reduction in sleep latency at 14:00 h was observed among the narcolepsy patients, while the value at 10:00 h was significantly longer than the values at 12:00 h ($P < 0.05$) and 14:00 h ($P < 0.01$).

As shown in Fig. 3, the standardized regression coefficient between ESS score and mean sleep latency on MSLT for all subjects was −0.86 ($P < 0.0001$). Among the three groups, control subjects had the strongest association between the two variables ($r = -0.73$, $P < 0.0001$), with the second strongest association observed in the patients with essential hypersomnia ($r = -0.55$, $P < 0.001$). The association in the patients with narcolepsy was weakest among the three groups ($r = -0.34$, $P < 0.05$).

In the control subjects, a significant relationship between the ESS value and sleep latency at every session except at 10:00 h was recognized, with the strongest association being at 14:00 h ($r = -0.79$, Table 1). In contrast, in the patients with narcolepsy, r at 14:00 h was lowest among the three groups ($r = -0.35$). The r-value of the patients with essential hypersomnia at 14:00 h ($r = -0.48$) was higher than that in narcolepsy, while it was lower than that of the control subjects.

DISCUSSION

It is well known that mean sleep latency on MSLT is extremely short and ESS score is definitely higher in narcoleptic patients,[15–17] thus, the present results for narcoleptic patients are consistent with those of previous studies. Regarding essential hypersomnia, a systematic evaluation of the severity of excessive daytime

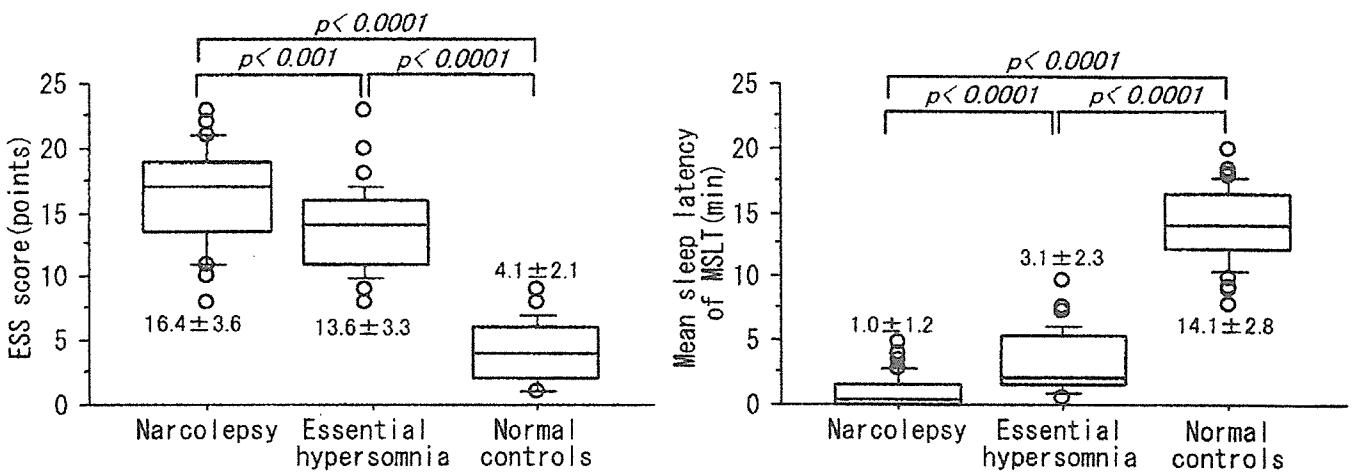
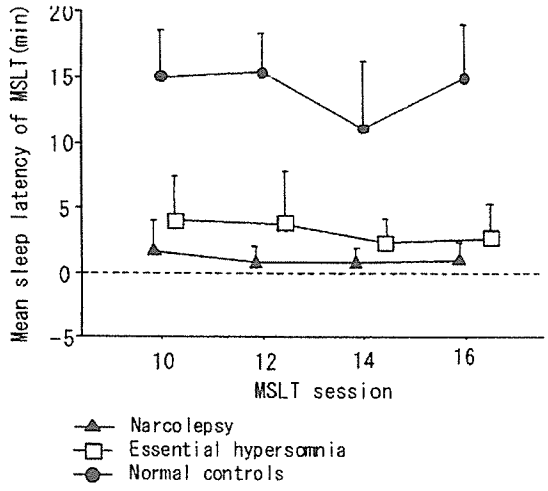


Figure 1. Comparison of Epworth Sleepiness Scale (ESS) score (left panel) and mean latency of Multiple Sleep Latency Test (MSLT; right panel) among groups with narcolepsy, essential hypersomnia, and normal controls (mean ± SD).

Table 1. Standardized regression coefficient between ESS score and sleep latency of MSLT

	MSLT session			
	10:00 h	12:00 h	14:00 h	16:00 h
Narcolepsy ($n = 52$)	−0.238	−0.254	−0.351****	−0.270
Essential hypersomnia ($n = 34$)	−0.452***	−0.371****	−0.482***	−0.481***
Normal controls ($n = 45$)	−0.010	−0.512**	−0.787*	−0.609*

ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test.
*$P < 0.0001$; **$P < 0.001$; ***$P < 0.01$; ****$P < 0.05$.



Narcolepsy: Significance between 10:00 and 14:00 (*p<0.01*), 10:00 and 12:00 (*p<0.05*).
Essential hypersomnia: Significance between 10:00 and 14:00 (*p<0.05*).
Normal controls: Significance between 10:00 and 14:00, 12:00 and 14:00, 14:00 and 16:00 (*p<0.0001*).

10:00 Significance between narcolepsy and normal control, essential hypersomnia and normal controls (*p<0.0001*), narcolepsy and essential hypersomnia (*p<0.01*).
12:00 Significance between narcolepsy and normal control, essential hypersomnia and normal controls, narcolepsy and essential hypersomnia (*p<0.0001*).
14:00 Significance between narcolepsy and normal control, essential hypersomnia and normal controls (*p<0.0001*).
16:00 Significance between narcolepsy and normal control, essential hypersomnia and normal controls (*p<0.0001*), narcolepsy and essential hypersomnia (*p<0.05*).

Figure 2. Sleep latency of Multiple Sleep Latency Test (MSLT) in narcolepsy, essential hypersomnia, and normal controls. Values are expressed as mean ± SD.

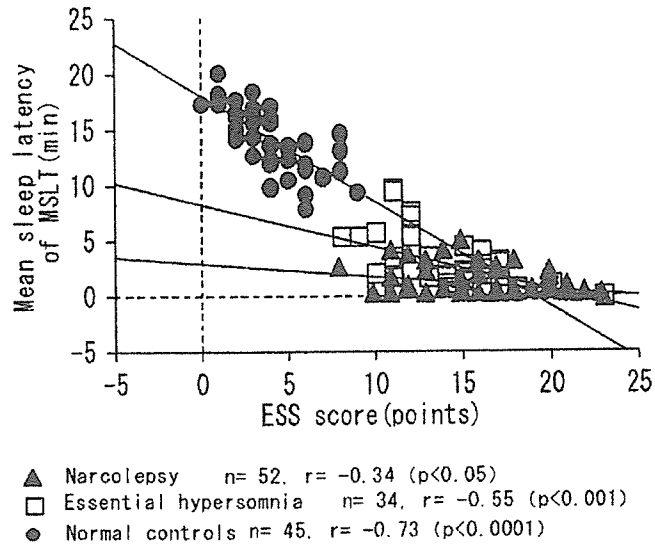


Figure 3. Relationship between the Epworth Sleepiness Scale (ESS) score and Multiple Sleep Latency Test (MSLT) in three subject groups.

sleepiness has not been performed except for a report by Bassetti and Aldrich.[18] However, the present study revealed that both subjective sleepiness and objective sleepiness estimated using ESS and MSLT are milder in patients with essential hypersomnia than in those with narcolepsy, although definite excessive daytime sleepiness was present in the former group.

Recent studies have shown that either a weak or no correlation exists between ESS and MSLT scores among patients with various hypersomnia disorders.[19,20] The ESS has also been reported to be an inadequate clinical replacement for MSLT, with a poor sensitivity and specificity.[17,20,21] However, the present results indicate that ESS and MSLT scores were strongly correlated in control subjects. This finding may indicate that a correlation between subjective and objective sleepiness is well-maintained in healthy subjects. In contrast, the correlation between ESS and MSLT was low in patients with narcolepsy, as the previous study suggested.[4] It is noteworthy that r was clearly higher in the group with essential hypersomnia than in the group with narcolepsy, although the correlation in the patients with essential hypersomnia was smaller than that in control subjects. The discrepancy between these two variables in narcoleptic subjects was thought to be attributable to the variation in subjective

sleepiness manifested on ESS, despite sleep latency on MSLT being extremely short in all the subjects in this group. Some patients with severe narcolepsy are known to lapse into sleep without being aware of their sleepiness; this phenomenon has been designated as a 'sleep attack'.[22,23] We speculate that the aforementioned discrepancy between subjective and objective sleepiness may contribute to the occurrence of this phenomenon.

Sleep latency on MSLT is widely accepted to be shorter in the afternoon in healthy subjects.[24] In the present study, the effect of time of day on sleep latency was seen not only in control subjects but also in patients with essential hypersomnia, and the length of sleep latency was shortest at 14:00 h. Judging from this finding, the diurnal variation in sleepiness appears to be maintained in patients with essential hypersomnia, despite the existence of pathological hypersomnia. In contrast, no increase in sleep propensity was noted at 14:00 h among the narcolepsy patients. This finding suggests that the sleepiness resulting from narcolepsy is so severe that the diurnal variation in sleep propensity is disrupted. Interestingly, sleep latency at 10:00 h was longer than at 12:00 and 14:00 h in the narcoleptic patients. The reason for this phenomenon is unclear. However, considering that daytime sleep propensity in narcoleptic patients was reported to be reduced by the extension of nocturnal sleep,[25] the decrease in sleep pressure found at 10:00 h might be due to the relatively short period since morning awakening.

Determining at which time of day the subjective estimation of sleepiness (assessed using ESS scores) is most strongly correlated with sleep latency on MSLT would be of immense interest. In the present study, ESS scores had the highest correlation with sleep latency at 14:00, especially in control subjects. This result was thought to be due to the characteristics of ESS items; specifically, the subjects tended to assume sleepiness at this time of day as a result of the inclusion of items in the ESS asking about sleepiness after lunch. That is, ESS items such as 'Lying down to rest in the afternoon when circumstances permit (question no. 5)' and 'Sitting quietly after lunch without alcohol (question no. 7)' elicit definite estimates of sleepiness during the afternoon hours.[1] Because of the strong impression of these items, the overall effect of the ESS would tend to remind the subjects of their sleepiness in the afternoon. In the present study, however, the correlation between sleep latency on MSLT at 14:00 h and ESS scores was lowest in the patients with narcolepsy. This finding was thought to be attributable to the disappearance of diurnal variation in sleepiness in narcolepsy. In patients with essential hypersomnia, however, the correlation was clearly higher than among the patients with narcolepsy, despite being lower than the correlation among the control subjects. This finding was thought to be related to the preservation of the diurnal variation in sleepiness in this group.

In conclusion, essential hypersomnia may be a milder disease condition than narcolepsy. Unlike narcolepsy, the diurnal variation in sleepiness was maintained in essential hypersomnia, and the correlation between subjective and objective sleepiness in essential hypersomnia was thought to be maintained relatively better, compared to narcolepsy. We speculated that the mild disease severity of essential hypersomnia may contribute to the formation of these characteristics.

ACKNOWLEDGMENT

This research was partly supported by a research grant from the Ministry of Health and Welfare of Japan (2001).

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