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Narcolepsy Variant Presented with Difficult Waking

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■ ABSTRACT

Objectives Summary: A 20 - year - old man was presented with a history of difficult waking for 10 years. He suffered from morning headache, chronic fatigue and mild daytime sleepiness but had no history of irresistible sleep attack, cataplexy, hypnagogic hallucination or sleep paralysis.

Methods: Night polysomnography (PSG), multiple sleep latency test (MSLT) and HLA - typing were carried out.

Results: The PSG showed short sleep latency (4.0 min) and REM latency (2.5 min), increased arousal index (15.7/hour), periodic limb movements during sleep (PLMS index=8.1/hr) with movement arousal index 2.1/hr and normal sleep efficiency (97.5%). The MSLT revealed normal sleep latency (15 min 21 sec) and 4 times sleep - onset REM (SOREM). HLA - typing showed DQ6 - positive, that corresponded at the genomic level to the subregion DQB1*0601, which was different from the usual locus in narcolepsy patients (DQB1*0602 and DQA1*0102).

Conclusion: Differential diagnosis should be made with circadian rhythm disorder and other causes of primary waking disorder. The possibility of a variant type of narcolepsy could be suggested with an unusual clinical manifestation and a new genetic marker. **Sleep Medicine and Psychophysiology 2000 ; 7(2) : 115-119**

Key words: Difficult waking · HLA DQ6 · DQB1*0601 · Circadian rhythm disorder · Narcolepsy variant.

INTRODUCTION

Primary waking disorder encompasses various conditions of excessive daytime sleepiness and/or increased nighttime sleep, that is of unknown origin. It occurs most often in adolescence and has chronic or recurrent natural history (1). Well-known causes of this condition are circadian rhythm disorders, disturbance of night sleep from various sleep disorders, narcolepsy and idiopathic hypersomnia and so on. This case report is on a 21-year-old man who has had waking difficulty for 10 years.

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METHODS

The daytime sleepiness was measured by Stanford Sleepiness Scale (2) and Epworth Sleepiness Scale (3). The Stanford Sleepiness Scale is the brief measure of subjective activation simply consisting of a series of sentences. The subject is required to check the one that most accurately describes the current state, but comparatively coarse scale. The Epworth Sleepiness Scale is an objective and quantitative index of the sleep propensity indicating how likely an examinee is to doze off or fall asleep in the various situations. The total numbers for the eight different situations which are each scored from 0 to 3 are added together to give a global score between 0 and 24.

The night polysomnography (PSG) was performed using standard techniques and sleep scoring methods. Electroencephalogram (EEG) (C3-A2, C4-A1, O1-A2 and O2-A1), electrooculogram (EOG : 4 channels), electromyogram (EMG of chin, intercostal and tibialis anterior muscles), electrocar-diogram (EKG), nasal and oral airflow, respiratory movements of the chest and abdomen and oxygen saturation using pulse oximeter (Healthdyne Technologies)

were recorded by digital polysomnography (Alice 3, Healthdyne Technologies). Multiple sleep latency test (MSLT) was performed on the next day following the night PSG recording to provide accurate documentation of sleep during the preceding night. The patient was asked to nap at 2-hour intervals, beginning at 9 a.m., five times throughout the day.

Blood sample was obtained for routine laboratory study and HLA-typing.

CASE REPORT

A 21-year-old man was first seen at the sleep disorder clinic of Samsung Medical Center for the evaluation of difficult waking for 10 years. He went to bed at around 1 am. The patient had the same waking difficulty even after falling asleep early on the last night. He has never been able to wake up with an alarm clock. His mother always struggled with him every morning for several hours to wake him. He is away from home to study abroad, and has missed college lectures every morning. His parents tried making international calls to wake him in the morning. But it was of no use. His mother even asked neighbors to visit him in the morning, but pounding on the door didn't wake him. He had mild snoring without sleep apnea, severe morning heada-che occasionally, chronic fatigue and mild daytime sleepiness. He had fatty liver, but no history of irresistible sleep attack, cataplexy, sleep paralysis and hypnagogic hallucination. His father had been treated for hypertension, and there were no family history of narcolepsy or any other diseases. The Stanford Sleepiness Scale was 6 (sleep, prefer to lie down, woozy) (2). The Epworth Sleepiness Scale was 8 which was not so high (3).

Table 1. The results of night polysomnography and multiple sleep latency test

Night Polysomnography	
Total sleep time	398.0 min
Sleep latency	4.5 min
REM latency	1.5 min
Sleep efficiency	97.5%
Arousal index	15.7/hour
Respiratory disturbance index	2.5/hour
Hypopnea	0.1/hour
SaO2-hypopnea	2.4/hour
PLMS index	8.1/hour
Movement arousal index	2.1/hour
Multiple sleep latency test	
Numbers of SOREM	4 times out of 5 trials
Mean sleep latency	15 min 21 sec
Mean REM latency	2 min 45 sec

SaO_2-hypopnea : >3% decrease of O_2 saturation and arousal without >50% decrease of airflow, PLMS : periodic limb movements during sleep, SOREM : sleep onset REM, REM : rapid eye movement sleep

RESULTS

1. Sleep evaluation

The results and hypnograms of night PSG and MSLT are summarized in Table 1 and Fig. 1. The data showed 398.0 minutes of total sleep time (TST), short sleep latency (4.0 minutes), sleep onset REM (SOREM) with 1.5 minutes of REM latency, normal sleep efficiency (97.5%), normal range of respiratory disturbance index (RDI) with 2.9/hour of hypopnea and SaO_2-hypopnea (>3% decrease of SaO_2 and arousal without >50% decrease of airflow), slightly increased arousal index (AI=15.7/hour), and 8.1/hour of PLMS (periodic limb movement during sleep) index with 2.1/hour of movement arousal index (MAI). The patient had a relatively normal sleep architecture which consisted of 5.9% of stage 1, 52.5% of stage 2, 15.8% of slow wave sleep (SWS), 74.2% of total non-REM sleep and 25.8% of REM sleep. The MSLT showed normal mean sleep latency (15 minutes 21 seconds), and four times of sleep onset REM

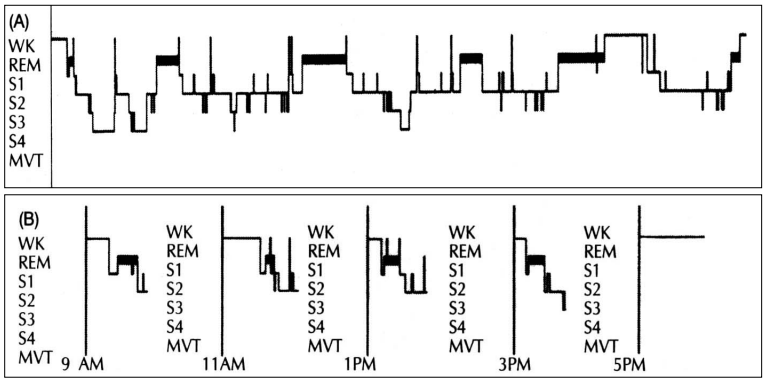

Fig. 1. The hypnograms of night polysomnography (A) and multiple sleep latency test (B). The PSG showed relatively normal sleep pattern during the night, and the MSLT revealed four times of sleep onset REM, which was compatible with the narcolepsy (WK : wake, REM : rapid eye movement, S1 - S4 : stage 1 - 4 of non-REM sleep, MVT : movement time).

(SOREM) out of five trials (REM latency=2 minutes 45 seconds).

2. Genetic study

The patient had the haplotype of HLA-DQ6. It corresponded at the genomic level to the subregion DQB1*0601 on chromosome 6, which was different from the typical marker of narcolepsy, DQB1*0602 and DQA1*0102.

3. Clinical course

The patient denied any sleeping difficulty in sleep initiation. He was educated to try sleep hygiene and to go to bed earlier around 10 p.m. for a period of four weeks. Although he was able to fall asleep early at night, waking difficulty in the morning did not change. Several drugs such as pemoline, methylphenidate and their combination had been tested. These drugs, however, turned out to aggravate the waking difficulty because the drug affected and disturbed only the night sleep. A loud alarm clock did not help him. Finally, a bright light box (Apollo, Bright Light 4, 10,000 Lux) was placed 66 cm in front of his eye 30 minutes before the alarm clock rang. The patient woke on his own by the sound of the alarm.

DISCUSSION

The causes of primary wake disorder are somewhat variable. Considering the differential diagnosis is an important step in the diagnosis of primary wake disorder. Well-known causes of this condition are circadian rhythm disorders such as delayed sleep phase syndrome or wake schedule disorder, night sleep disturbances from various causes, narcolepsy and idiopathic hypersomnia.

The delayed sleep phase syndrome has the following characteristics : (a) chronic inability to fall asleep at a desired set time ; (b) when not on a strict schedule, the patients have a normal sleep pattern, and after a normal length of sleep, they awaken spontaneously and feel refreshed ; and (c) a long history of unsuccessful attempts at treating the problem (4). So for the diagnosis of delayed sleep phase syndrome, it is important to confirm the history or PSG finding of long sleep latency. In this patient, sleep latency was abnormally short (4.5 minutes), trials to advance the sleep cycle was not effective on difficult waking. Wake schedule disorder is a condition that makes waking from sleep profoundly difficult. This disorder is commonly found in shift workers with the exclusion of any possibility of other sleep disorders in sleep study (5).

Night sleep disturbances can be associated with various conditions such as sleep apnea syndrome, periodic limb movements during sleep (PLMS), and insomnia etc. This patient had a few hypopnea and PLMS. The PSG showed 2.5/hour of hypopnea and SaO 2-hypopnea and 8.1/hour of PLMS index with low movement arousal index (2.1/hour) and normal ranges of sleep efficiency (97.5%). So this patient's night sleep did not seem to have been disturbed.

Narcolepsy is usually associated with two major clinical features, irresistible episodes of sleep, sleep onset REM periods and an almost constant association with HLA DR2-DQ1. Concerning genetics, the HLA DQB1*0602 gene is known to predispose to narcolepsy. The recently proposing diagnostic criteria for idiopathic hypersomnia include : (a) very long night sleep, (b) difficulties waking up in the morning or at the end of a nap, (c) more or less constant excessive daytime sleepiness, (d) total sleep time per day exceeds 10 hours ; (e) absence of cataplexy ; (f) does not meet the criteria for other sleep disorders that account for the excessive daytime sleep episodes (6). The diagnostic criterias of idiolothic hypersomnia, however, are not clear enough and overlaps with those of narcolepsy in some patients. Idiopathic hypersomnia has no special features in PSG or immunogenetic findings and is ten times less frequent. A strong genetic component is suggested by the high proportion of familial cases, but no association with HLA has been evidenced to date (7). This patient did not have excessive daytime sleepiness nor narcolepsy but was manifested only as difficult waking. But the sleep study met the diagnostic criteria for narcolepsy. Furthermore, the HLA-typing showed DQ6-positive which is found in 95 to 100% of narcolepsy patients.

In regards to genetics in narcolepsy, the observation of the familial cases of narcolepsy with a suggested autosomal-dominant inheritance pattern points to a genetic substrate of the disease (8). After discovering a close association between HLA-DR2 and narcolepsy-cataplexy (9), studies have shown that, in white and Japanese patients, the strongest association which is about 95% to 100% of the cases occurred with the haplotypes DR15 (a subtype of HLA-DR2) and DQ6 (a subtype of HLA-DQ1) (10). On the other hand, 40% of narcoleptic African-Americans are DR15-negative, whereas 95% of them are DQ6-positive. Currently, it is thought that DQ6, which corresponds at the

genomic level to the subregion DQB1*0602 and DQA1*0102 on chromosome 6, is a better marker for narcolepsy across all ethnic groups (10, 11). The existence of rare DQ6-negative cases of both idiopathic and symptomatic narcolepsy, however, suggests that the narcoleptic gene may be linked closely to but is not identical to the DQ6 haplotype. Other genes not linked to the HLA locus also may confer narcoleptic susceptibility (12). Concerning clinical manifestation and HLA-typing, the linkage with the DQ6 haplotype can be related to the expression of cataplexy, as its presence is less common in patients who meet the diagnostic criteria for narcolepsy but do not have cataplexy (13, 14). Similarly, patients with sleep paralysis without hypersomnia are often DR15-negative (13, 15). In this case, one hypothesis for the unusual manifestation of difficult waking might be related to DQB1*0601, a new genetic marker in chromosome 6 of a variant type of narcolepsy. This however may have many debated opinions.

SUMMARY

A 20-year-old man with a difficult waking for 10 years was presented here. He had no history of irresistible sleep attack, cataplexy, hypnagogic hallucination or sleep paralysis. Night polysomnography (PSG), multiple sleep latency test (MSLT) and HLA-typing were done. The PSG showed short sleep latency (4.0 min) and short REM latency (2.5 min), increased arousal index (15.7/hour), periodic limb movements during sleep (PLMS index=8.1/hr) with movement arousal index 2.1/hr and normal sleep efficiency (97.5%). The MSLT revealed normal sleep latency (15 min 21 sec) but four times of sleep-onset REM (SOREM). HLA-typing showed DQ6-positive, that corresponded at the genomic level to the subregion DQB1*0601, which was different from the usual locus in narcolepsy patients (DQB1*0602 and DQA1*0102). The possibility of a variant type of narcolepsy could be suggested with an unusual clinical manifestation and a new genetic marker.

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초 록

각성장애로 발현한 기면증의 변종

이 향 운·홍 승 봉

목 적 : 십년 이상 각성장애를 보인 20세 남자환자를 분석하였다. 환자는 두통, 만성피로, 경한 주간졸리움증을 호소하였으나 조절할 수 없는 수면발작, 탈력발작, 입면시 환각이나 수면마비의 병력은 없었다.

방 법 : 야간 수면다원검사 (PSG), 반복적 수면잠복기 검사 (MSLT) 및 조직적합성 유전자검사 (HLA - typing)를 시행하였다.

결 과 : PSG상 수면잠복기가 짧고 (4분), 렘수면잠복기도 감소하였고 (2.5분), 각성지표 (arousal index)가 시간당 15.7로 약간 증가되었으며, 수면 중 주기적 사지운동지표 (PLMS index)가 시간당 8.1로 관찰되었으나 운동과 연관된 각성지표 (movement arousal index)는 시간당 2.1로 높지 않았다. 잠효율은 (sleep efficiency)는 97.5%로 정상이었다. MSLT상 수면잠복기는 15분 21초로 정상이었으나 sleep - onset REM (SOREM)은 5회의 낮잠 시도 중 4회에서 관찰되었다. HLA - typing에서 DQ6 - 양성이었는데, 이는 기면증 환자에서 대개 관찰되는 유전자 위치인 DQB1*0602, DQA1*0102와는 다른 DQB1*0601 부위에 상응하였다.

결 론 : 일차성 각성장애의 원인이 되는 여러 질환 특히 일주기리듬장애나 기면증, 원발성 다면증과의 감별진단이 필요하며, 수면검사와 유전자검사 상 기면증의 새로운 변종일 가능성을 배제할 수 없다.

중심 단어 : 각성장애 · HLA DQ6 · DQB1*0601 · 24시간 주기장애 · 기면증 변종.