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DR2-Positive Monozygotic Twins Discordant for Narcolepsy

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Summary: Narcolepsy runs in families, and recent research has revealed the human leukocyte antigen (HLA) DR2 to be a genetic marker closely associated with the disease. But, as indicated by family studies, other factors contribute to the pathogenesis of narcolepsy. The investigation of monozygotic twins is the most specific research tool for distinguishing between a multigenetic and a multifactorial pathogenetic model. We present clinical and sleep polygraphic data from two pairs of monozygotic twins, and in addition, from some of their first-degree relatives. In both pairs only one twin suffered from the clinical symptoms of narcolepsy/cataplexy. Only in these subjects did night sleep recordings and a multiple sleep latency test reveal both multiple sleep onset rapid-eye-movement periods (SOREMPs) and short mean sleep onset latencies. However, in two of the asymptomatic, HLA $DR2^+$ relatives, short mean sleep onset latencies during the multiple sleep latency test (MSLT) were observed, and one, HLA $DR2^-$ relative showed REM sleep two times during the MSLT. Our results strongly favor a multifactorial pathogenetic model for narcolepsy. **Key Words:** Narcolepsy—Genetics—Sleep disorders—Familial.

The nearly perfect association between narcolepsy and the human leukocyte antigen (HLA) DR2 (1,2) confirmed the long-standing assumption that genetic factors are involved in the pathogenesis of the disease (3–6). While ~99% of all narcoleptic patients studied turned out to be $DR2^+$, the percentage is only 30–35% in the general population (7). Thus, the presence of the HLA-DR2 or an adjacent gene seems to be involved in the development of the illness. Since 50% of the first-degree relatives of a patient share with him the critical gene, but only 5% develop the disease (5), one has to assume that other genetic and/or environmental factors are necessary for the development of narcolepsy.

The investigation of monozygotic twins is at present the most specific research tool to distinguish between a multigenetic and a multifactorial pathogenetic model, whereby the latter postulates the synergistic effect of at least one genetic and one environmental factor.

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Due to the low prevalence of the disease, there are few reports on narcolepsy in monozygotic twins in the literature. Until now only one pair could be demonstrated to be concordant according to clinical *and* polygraphical criteria (8). These twins were HLA DR2$^-$. In the twins reported to be concordant by Imlah (9), clinical diagnosis is doubtful in both twins. Sleep attacks were atypical and cataplectic attacks were not provoked by emotions; polygraphic sleep recordings were not performed. One of the twins claimed to be concordant for narcolepsy by Mamelak et al. (10) suffered only from mild daytime drowsiness and fatigue at the time of investigation. No sleep abnormality was obvious during a 48-h polygraphic recording. Some years before, however, clinical symptoms including cataplexy were present. Schrader et al. (11), Montplaisir and Poirier (12), and Guilleminault et al. (13) all reported monozygotic twins discordant for narcolepsy according to clinical and polygraphical criteria.

Recently we had the opportunity to investigate two pairs of monozygotic twins by means of polygraphic night sleep recordings and the multiple sleep latency test (MSLT). In each pair only one twin suffered from the clinical symptoms of narcolepsy. In addition, the parents of one pair and a sister of the other were studied with the same protocol. All of these relatives were free of narcoleptic symptoms.

METHODS

The pedigrees including the first-degree relatives of the twins are given in Fig. 1. In family A the twins (A/T1 and A/T2, 50 years) and one sister (A/S, 44 years) took part in our investigation. Their mother (A/M, 82 years) had HLA typing, but polygraphic sleep recording could not be performed. In family B the twins (B/T1 and B/T2, 20 years), their father (B/F, 44 years) and their mother (B/M, 39 years) were investigated.

In all subjects HLA typing was done using standard methods. In the twins, 28 blood group systems were determined additionally in order to confirm monozygoticity.

All subjects (except A/M) slept for two consecutive nights in the sleep laboratory. Polygraphic sleep recording [electroencephalogram (EEG), electrooculogram (EOG),

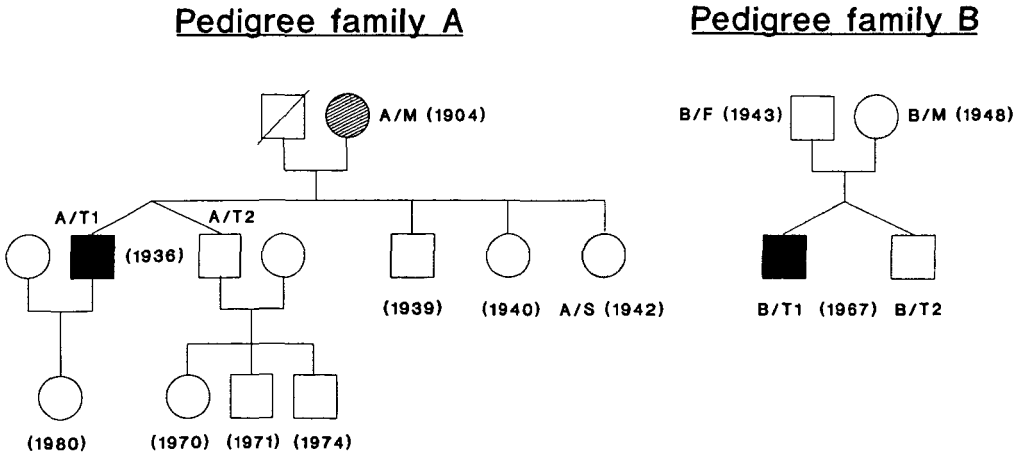

FIG. 1. Pedigrees of the families investigated. All first-degree relatives of the twins are represented. Figures in parentheses indicate year of birth. Subjects investigated are marked by the code used in the text. Filled symbols represent subjects suffering from clearcut narcolepsy/cataplexy. Hatched symbols represent subjects with a probable diagnosis of narcolepsy.

and electromyogram (EMG)] was performed and scored according to standard criteria. The parameters common in sleep research were computed (see Results).

On the day following one of the night sleep recordings an MSLT was performed in all subjects except A/M. The original procedure (14) was slightly modified (15). The subjects went to bed every 2 h five times per day beginning at 9:00 a.m. and were instructed to sleep; polygraphic recording was finished 30 min later, irrespective whether they slept or not. Sleep latency and REM latency were determined according to standard criteria (16).

RESULTS

Clinical findings

If not stated otherwise, medical history was uneventful and physical examination did not reveal any abnormality in all subjects.

Family A. A/T1 was the first born twin. He experienced daytime sleepiness for the first time at the age of 12. At the age of 16, he was confined to bed for about 2 weeks because he suffered from severe parotitis epidemica. Nothing is known about concomitant encephalitis. Immediately thereafter, irresistable sleep attacks, hypnagocic hallucinations, sleep paralysis, and cataplexy, typically provoked by emotions, appeared. At the time of investigation, drowsiness occurred about three times a day in quite regular intervals. Sleep attacks could be controlled effectively by a planned nap. Cataplectic attacks were provoked only when the patient was telling a joke; muscle weakness was confined to the face and to the speech muscles. Hypnagogic hallucinations occurred two to three times a week. Sleep paralysis very rarely occurred at the time of sleep onset. Automatic behavior was not reported. Night sleep was characterized subjectively by a very short sleep onset latency and difficulties in maintaining sleep. To control daytime sleepiness A/T1 was using fenityllin irregularily for 25 years with a maximum dosage of 50 mg per day. He had never used anticataplectic drugs (tricyclic antidepressants or MAO-inhibitors). Medication was discontinued 1 week before the investigation.

A/T2, the second born twin, had no history of sleep attacks, cataplexy, hypnagocic hallucinations, sleep paralysis, or automatic behavior. He described himself as a very good sleeper. Subjectively, sleep latency was very short, and sleep was undisturbed and refreshing. During the day he would take a nap of ~20 min almost every day around noon, and sometimes a second short nap in the late afternoon. At the age of 36 A/T2 was confined to bed for 1 week due to parotitis epidemica.

A/S, the sister of the twins, did not report any narcoleptic symptoms. Her sleep habits were as follows. She subjectively reported sleep latency to be short, and sleep was refreshing and of good quality. Since the age of 40 she awoke normally at about 3:00 a.m., remained awake for about half an hour and then returned back to sleep without problems. She took a nap of ~20 min around noon, but did not suffer from excessive daytime sleepiness if she skipped the nap.

A/M, the mother of the twins, could not be seen at our sleep laboratory. All family members reported that she had suffered from sleep attacks and cataplexy since her youth.

In summary, one of the twins in family A (A/T1) suffered from clearcut narcolepsy/cataplexy according to clinical criteria, whereby the full picture appeared after a parotitis epidemica. In addition, it is probable that the mother of the twins also suffered

from narcolepsy/cataplexy. The sister investigated did not complain of any symptom of narcolepsy, and there was no other known family member afflicted with the disease.

Family B. B/T1, the first born twin, first experienced excessive daytime sleepiness at the age of 15. Since that time imperative sleep attacks and automatic behavior occurred. At the age of 17 he experienced a cataplectic attack for the first time. Cataplexy was triggered by emotions and confined to the muscles of the knees and the arms. The attacks occurred about once a week. He suffered from hypnagogic hallucinations only during a treatment trial with gamma-hydroxy-butyrate, which he took for ~1 month at the age of 15. Sleep paralysis never occurred. Night sleep was characterized subjectively by a very short sleep onset latency and disturbed sleep continuity. Medication with mazindol was discontinued 1 week before the investigation. B/T1 in addition suffered from mild allergic asthma, which never required drug treatment.

B/T2, the second born twin, did not complain of any symptom of narcolepsy. He usually did not nap during the day. Reported sleep onset latency was ~30 min, and night sleep was undisturbed and refreshing. He too suffered from allergic asthma, but more severely than his twin brother. He took 600 mg of theophylline in the evening and fenoterol spray two to four times a day. This medication could *not* be stopped during the investigation.

B/F, the father of the twins, did not complain of any symptom of narcolepsy. He took a planned nap of 1 hour every day in the afternoon. Night sleep was subjectively undisturbed and refreshing.

B/M, the mother of the twins, did not complain of narcoleptic symptoms. She usually did not nap during the day, and night sleep was undisturbed and refreshing.

In summary, one of the twins in family B (B/T1) suffered from clearcut narcolepsy/cataplexy according to clinical criteria. The first-degree relatives investigated were asymptomatic and there was no other known family member suffering from narcolepsy.

HLA typing, blood group testing

The results of the HLA typing are summarized in Table 1. In both families the twins were HLA identical and HLA-DR2$^+$. In addition, subject A/S was HLA identical to her brothers. Table 2 shows the results of blood group testing in the twins. All results were

TABLE 1. *HLA phenotypes*

Family A						
A/T1;A/T2	A1	B8	Cw7	DR3	DRw52	DQw2
	A3	Bw57	Cw6	DR2		DQw1
A/S	A1	B8	Cw7	DR3	DRw52	DQw2
	A3	Bw57	Cw6	DR2		DQw1
A/M	A3	Bw57	Cw6	DR2		DQw1
	A2	—	—	DR4	DRw53	DQw3
Family B						
B/T1;B/T2	A1	B8	—	DR3	DRw52	DQw2
	A24	Bw57	Cw6	DR2		DQw1
B/F	A1	B8	—	DR3	DRw52	DQw2
	A3	B7	Cw7	DR1		DQw1
B/M	A3	B7	Cw7	—	—	DQw1
	A24	Bw57	Cw6	DR2	—	DQw1

TABLE 2. *Results of blood group testing*

Marker	A/T1;T2	B/T1;T2	Marker	A/T1;T2	B/T1;T2
ABO	A1	0	AK	1	1
MNSs	NSs	MSs	ADA	1	1
Rh	CcD.ee	CcD.ee	6-PGD	A	A
Cw	—	—	GPT	2-1	2
K	kk	kk	EsD	2-1	2-1
Fy	a+b−	a+b+	GLO	1	2
Jk	a−b+	a+b+	Gt	1	2-1
Lu	a−b+	a−b+	C3	S	S
Hp	1−1	2−1	Tf	C2-1	C2-1
Gc	2−1S	1F−1S	Bf	S	S
Gm	1−2−10+	1+2−10−	PI	M1	M1
Km	1+	1−	PlG	2-1	2-1
acP	B	AB	F-XIIIB	3-1	3-1
PGM1	1+1+	1−2−	A2-HS	2-1	2-1

identical for the respective twin pairs. For family A the probability for the twins to be monozygotic is 0.99999, for family B the probability is 0.999994.

Polygraphic night sleep recordings

The results of the polygraphic night sleep recordings are given in Table 3. In family A the narcoleptic twin (A/T1) showed a short sleep onset latency (SOL) in the second night, low sleep efficiency, high percentages of stage 1 sleep and wake, and a very low percentage of sleep stages 3 and 4 in both nights. During night 1 a sleep onset REM period (SOREMP) was observed. His healthy twin brother (A/T2) showed a high percentage of stage 1 sleep and an absence of sleep stages 3 and 4 during both nights. The sister (A/S) did show a short SOL in the second night; in all other aspects her sleep was normal.

In family B the narcoleptic twin (B/T2) showed a short SOL in the second night and SOREMPs during both nights. Percent stage 1 sleep was high in both nights. In his twin

TABLE 3. *Results of polygraphic night sleep recordings*

	A/T1		A/T2		A/S		B/T1		B/T2		B/M		B/F
Subject	1[a]	2	1	2	1	2	1	2	1	2	1	2	2
TIB (min)	484.5	474.0	479.5	478.5	473.0	474.5	484.5	479.5	484.5	480.0	460.0	479.5	480.5
SPT (min)	470.5	453.5	472.0	469.0	461.5	472.5	477.5	460.0	471.0	471.5	442.0	468.0	472.5
SEI (% of SPT)	64.4	76.5	91.5	95.0	91.4	96.4	96.6	97.6	98.0	96.9	96.7	94.4	96.3
N of awakenings	32	40	40	22	18	12	10	8	10	6	13	22	13
SOL (min)	14.0	2.0	7.5	9.5	11.5	2.0	7.0	3.5	13.5	8.5	18.0	11.5	7.5
REM latency (min)	0.0	194.5	139.0	106.5	88.0	91.5	0.0	0.0	160.5	48.5	80.0	46.5	52.0
Stage % of SPT													
Awake	35.6	23.5	8.5	5.0	8.6	3.6	3.4	2.4	2.0	3.1	3.3	5.6	3.7
REM	7.0	9.3	14.6	14.1	19.7	24.2	21.9	14.5	18.0	27.1	15.6	18.9	17.8
1	16.6	12.7	28.0	24.4	7.3	5.7	15.5	20.3	7.4	11.9	13.6	12.3	13.7
2	40.2	53.1	48.8	56.5	52.8	53.2	39.7	37.6	57.4	38.4	61.2	61.2	56.7
3	0.2	1.1	0.0	0.0	10.1	9.7	6.2	10.1	10.9	11.5	5.2	1.1	6.5
4	0.0	0.0	0.0	0.0	0.2	2.2	11.4	12.2	1.9	5.4	0.2	0.0	0.0
MT	0.4	0.3	0.1	0.0	1.4	1.3	0.8	2.1	2.2	1.7	0.9	0.1	1.7

TIB, Time in bed; SPT, sleep period time; SEI, sleep efficiency index; SOL, sleep onset latency (time between lights off and first occurrence of stage 2, 3, 4 or REM). Night 1 of subject B/F could not be evaluated for technical reasons.
[a] Night number.

brother (B/T2), as well as in their mother (B/M) and in their father (B/F), sleep was normal in all aspects.

MSLT

The results of the MSLT are summarized in Table 4. All members of family A showed shortened mean SOLs in comparison to normative data (16). The narcoleptic twin (A/T1) had four SOREMPs (REM latency between 0.5 and 4.0 min), and his sister (A/S) had one SOREMP (REM latency 7.0 min). In family B the narcoleptic twin showed a very short mean SOL and five SOREMPs (REM latency between 1.5 and 4.5 min), whereas his twin brothers and their parents' mean SOL was within normal limits. In B/M one SOREMP occurred (REM latency 9.5 min). In B/F two naps contained REM sleep (REM latency 15.5 and 12.0 min).

DISCUSSION

The results underline the important role of exogenous factors in the pathogenesis of narcolepsy/cataplexy. In both identical twin pairs investigated, only one twin presented clinical symptoms of the disease, and only in the afflicted one did the MSLT reveal multiple SOREMPs and short mean SOLs. The twins of family A can be assumed to be discordant for narcolepsy, since it is very unlikely that the unaffected twin will develop the disease beyond the age of 50. In family B, on the other hand, the twins were only 20 years old at the time of investigation. Thus, the unaffected twin is still at the age of risk and one cannot be sure that they will remain discordant. Nevertheless, one can assume that out of eight twins investigated up to now at least half of them were discordant. These data favor a multifactorial model for the pathogenesis of narcolepsy (4,5,17). In terms of this model, both the HLA DR2 or a nearly adjacent gene, and one or more exogenous factors are necessary to precipitate the disease.

Nothing is known to date about the nature of possible exogenous factors necessary for the development of the illness. The strong association with HLA-DR2 suggests the involvement of autoimmunological processes. But there is no clear evidence pointing in this direction. Langdon et al. (18) reported two cases of increased cerebrospinal fluid (CSF) immunoglobulin concentrations and one with oligoclonal bands out of 20 patients investigated. Honda et al. (19) could not find abnormalities in different

TABLE 4. *Results of the Multiple Sleep Latency Test (MSLT)*

Subject	mean SOL (min)	range (min)	SOREMPs (N)
Family A			
A/T1	3.7	2.5–5.0	4
A/T2	4.7	2.5–6.0	0
A/S	6.3	3.0–8.5	1
Family B			
B/T1	2.4	1.0–3.5	5
B/T2	10.4	4.0–20.0	0
B/M	13.0	4.0–20.0	1
B/F	11.0	8.0–16.0	1

If a subject did not fall asleep during a session of the MSLT, a value of 20 min was entered into the calculation of mean SOL; mean SOL is according to Carskadon et al. (16): time between lights off and first occurrence of stage 1, 2, 3, 4 or REM; SOREMPs = number of Sleep onset REM periods.

lymphocyte subsets. On the other hand, in ~10% of patients studied (18), the onset of the disease was in temporal relationship to an acute infection, as it was also at least in one of the cases reported here. Billiard et al. (20) reported significantly increased antibody titers to streptolysine 0 and DNase B in a group of 52 narcoleptic patients as compared with normal controls. However, control subjects were not matched for HLA-DR antigens, and elevation of antibody titers was present in less than half of the patients. Possibly immunological mechanisms involved in the pathogenesis of narcolepsy are of very local character and/or of limited duration and thus escape observation.

SOREMPs are the most typical polygraphic abnormality found in narcolepsy. In addition, multiple SOREMPs during the MSLT in combination with short mean SOLs seem to be highly specific (21). Other polygraphic findings such as reduced slow wave sleep and disturbed night sleep are more variable and seem to be nonspecific. Our results support the assumption that SOREMPs are the most typical polygraphic characteristic of narcolepsy, since in all other sleep parameters the twins investigated were much more similar to their respective healthy twin brother than to the other narcoleptic subject.

There are some surprising findings in the asymptomatic relatives of the twins. In family A the healthy twin as well as the HLA identical sister of the twins showed short mean SOLs during the MSLT, which, according to normative data (16), would indicate excessive daytime sleepiness. The father of the twins in family B who was HLA $DR2^-$ showed an unremarkable mean SOL during the MSLT, but one SOREMP and a second REM episode (REM latency 15.5 min) occurred. All these asymptomatic subjects reported taking one or two naps almost every day. In the literature there are no conclusive data on daytime sleep in relatives of narcoleptic subjects. In a preliminary report, Geisler et al. (22) could not find differences in night sleep or MSLT results between HLA $DR2^+$ and HLA $DR2^-$ first-degree relatives of narcoleptic patients. Two passing remarks concern the issue of sleep prospensity during the day: Mitler (14), in his review article on MSLT data, mentions two male offspring of a narcoleptic patient both showing unremarkable night sleep, but short mean SOLs during the MSLT. In addition, one of them showed one SOREMP and the other three SOREMPs during the MSLT. HLA typing was not done in these subjects. Carskadon (23) followed a narcoleptic patients child who developed the disease at the age of 14. As early as 2 years before the onset of the disease the MSLT indicated that she was sleepier than controls. The latter finding suggests that the MSLT may help to identify subjects before the onset of narcolepsy who later on may develop the disease. Contrary to this assumption our results seem to indicate that in asymptomatic relatives of narcoleptics short mean SOLs or even multiple SOREMPs during the MSLT may be without clinical significance. In our investigation all subjects showing such results were beyond the main age of risk, and the subject showing one SOREMP, and in addition, a second REM episode with a latency of 15.5 min during the MSLT, was HLA $DR2^-$.

To get more information about possible premorbid polygraphic sleep patterns and their significance for the pathogenesis of narcolepsy, longitudinal studies of night sleep and MSLT in young asymptomatic relatives are needed.

REFERENCES

1. Juji T, Satake M, Honda Y, Doi Y. HLA antigens in Japanese patients with narcolepsy. *Tissue Antigens* 1984;24:316–9.

2. Langdon N, Welsh KI, Dam MV, Vaughan RW, Parkes D. Genetic markers in narcolepsy. *Lancet* 1984;ii:1178–80.
3. Nevsimalova-Bruhova S, Roth B. Heredofamilial aspects of narcolepsy and hypersomnia. *Arch Suisses Neurochir Psychiatr* 1972;110:45–54.
4. Kessler S, Guilleminault C, Dement W. A family study of 50 REM narcoleptics. *Acta Neurol Scand* 1974;50:503–12.
5. Kessler S. Genetic factors in narcolepsy. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:285–302.
6. Honda Y, Asaka A, Tanimura M, Furusho T. A genetic study of narcolepsy and excessive daytime sleepiness in 308 families with a narcolepsy or hypersomnia proband. In: Guilleminault C, Lugaresi E, eds. *Sleep/wake disorders: natural history, epidemiology, and long-term evolution*. New York: Raven, 1983:187–99.
7. Baur MP, Neugebauer M, Deppe H, et al. Population analysis on the basis of deduced haplotypes from random families. In: Albert ED, Baur MP, Mayr WR, eds. *Histocompatibility testing 1984*. Berlin: Springer, 1985:333–41.
8. Douglas AB, Harris L, Pazderka F. Monozygotic twins concordant for the narcoleptic syndrome. *Neurology* 1989;39:140–1.
9. Imlah NW. Narcolepsy in identical twins. *J Neurol Neurosurg Psychiatry* 1961;24:158–60.
10. Mamelak M, Caruso VJ, Stewart K. Narcolepsy: a family study. *Biol Psychiatr* 1979;14:821–34.
11. Schrader H, Gotlibsen OB, Skomedal GN. Multiple sclerosis and narcolepsy/cataplexy in a monozygotic twin. *Neurology* 1980;30:105–8.
12. Montplaisir J, Poirier G. Narcolepsy in monozygotic twins. *Neurology* 1987;37:1089.
13. Guilleminault C, Grumer C, Mignot E, Masterson MB, Fry J. HLA transmission of narcolepsy. *Sleep Res* 1989;18:233.
14. Mitler MM. The multiple sleep latency test as an evaluation for excessive somnolence. In: Guilleminault C, ed. *Sleeping and waking disorders. Indications and techniques*. Menlo Park: Addison-Wesley, 1982:145–53.
15. Pollmächer T, Geisler P, Schulz H. Der multiple Einschlaflatenz-Test (MSLT) in der Differentialdiagnose der Narkolepsie. *Psycho* 1986;12:378–9.
16. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1986;9:519–24.
17. Thomson G. Narcolepsy: theoretical aspects of a genetic study. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976:303–10.
18. Langdon N, Lock C, Welsh K et al. Immune factors in narcolepsy. *Sleep* 1986;9:143–8.
19. Honda Y, Juji T, Matsuki K et al. HLA-DR2 and Dw2 in narcolepsy and in other disorders of excessive somnolence without cataplexy. *Sleep* 1986;9:133–42.
20. Billiard M, Laaberki MF, Reygrobellet C, Seignalet J, Brissaud L. Bacterial and viral studies in narcoleptic patients. In Horne J, Lavie P, eds. *Sleep'88. Proceedings of the 9th ESRS congress, Jerusalem 1988*. Stuttgart: G. Fischer, 1989:125–127.
21. Amira SA, Johnson TS, Logowitz NB. Diagnosis of narcolepsy using the multiple sleep latency test: analysis of current laboratory criteria. *Sleep* 1985;8:325–31.
22. Geisler P, Schulz H, Pollmächer T et al. Sleep in first degree relatives of narcoleptic patients. *Sleep Res* 1987;16:335.
23. Carskadon MA. The second decade. In Guilleminault C, ed. *Sleeping and waking disorders. Indications and techniques*. Menlo Park: Addison-Wesley, 1982:99–125.