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Mood Disturbance in a Large Kindred With a High Prevalence of Narcolepsy and Isolated Sleepiness

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These findings suggest that genetic haplotypes associated with narcolepsy may create a liability for the development of depression and anxiety in patients with narcolepsy as well as their sleepy kindred.

KEY WORDS: narcolepsy; chronic-illness; psychosocial; subjective sleepiness; familial.

INTRODUCTION

The present study concerns mood disturbance and psychosocial well-being in a multigenerational African-American family with an unusually large number of family members with either a complaint of both excessive daytime sleepiness and cataplexy (narcolepsy) or a complaint of excessive daytime sleepiness (EDS) without cataplexy. At the time of study, the family was comprised of a 76-year-old male (research proband) with at least 14 children, 36 grandchildren, and 34 great grandchildren. Data were obtained from 31 family members (see Fig. 1). The proband and five additional family members complained of severe and chronic daytime sleepiness and described episodic muscle weakness when hearing or telling a joke, when laughing, or when angry. Description of episodic muscle weakness under these conditions is strongly suggestive of cataplexy (Anic-Labat et al., 1999). Cataplexy is pathognomonic for narcolepsy, a central nervous system disorder characterized by daytime sleepiness and abnormal features of REM sleep (Bassetti & Aldrich, 1996). Epidemiologic studies suggest the prevalence of narcolepsy with cataplexy is within a range of 0.02–0.18% (Mignot, 1998). Familial narcolepsy with cataplexy is considered rare in that no more than 10% of patients are able to identify other family members with the disorder (Mignot, 1998). A family with six narcoleptic members is extraordinarily rare.

In addition to the family members with complaints of EDS and cataplexy, 12 family members complained of EDS while denying cataplexy (isolated sleepiness). Isolated sleepiness has been reported in family members of patients with narcolepsy in several studies (Mignot, 1998). The relationship between isolated sleepiness and narcolepsy is unclear. A genetic factor in family members of patients with narcolepsy predisposing them to isolated sleepiness has not been established (Mignot, 1998).

The principle concern of the present report is whether narcolepsy with cataplexy and isolated sleepiness are related to the symptoms of depression and anxiety reported by members of this unusual family. Mood disorders are common among patients with narcolepsy (Ganado, 1958; Kales et al., 1982; Lindsley & Crawford, 1996; Merrit, Cohen, & Smith, 1992). It has typically been assumed that mood disturbance is a consequence as opposed to a feature or precipitant of narcolepsy. The sleepiness of the narcolepsy patient is chronic, often resistant to treatment, and at times severe to the point of debilitation (Broughton et al., 1983). Reduced functioning has been reported in most aspects of everyday life including recreation, employment, education, and interpersonal relations

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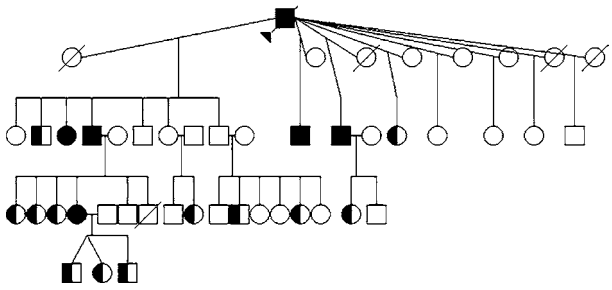

Fig. 1. Partial Pedigree of family with branches containing symptomatic members. *Arrow*, proband; *black symbols*, Narcolepsy/Cataplexy Family group; *half-filled symbols*, Sleepy-only Family group; and *white symbols*, Asymptomatic Family group.

(Broughton et al., 1981; Daniels, King, Smith, & Shneerson, 2000; Douglas, 1998; Kales et al., 1982). The relationship between mood disturbance and sleepiness associated with narcolepsy may be mediated by factors such as a loss of family support (Alaia, 1992; Beutler, Ware, Karacan, & Thornby, 1981; Broughton et al., 1981; McMahon, Walsh, Sexton, & Smitson, 1982), adoption of ineffective coping mechanisms, and/or perceptions of low self-efficacy.

The extraordinary prevalence of narcolepsy and isolated sleepiness in the family described here provided an opportunity to examine psychosocial functioning and mood disturbance in groups of affected and unaffected individuals remarkably homogeneous with respect to genetic and socioeconomic factors. A battery of tests was administered to four groups defined as (a) family members with complaints of narcolepsy/cataplexy (Narcolepsy/Cataplexy Family group), (b) family members with a complaint of sleepiness only (Sleepy-only Family group), (c) family members with no complaints of sleepiness or cataplexy (Asymptomatic Family group), and (d) nonfamily members with the same ethnic and socioeconomic background (Community Control group). It was expected that, in keeping with previous findings (Ganado, 1958; Kales et al., 1982; Lindsley & Crawford, 1996; Merrit et al., 1992; Mosko et al., 1989), family members with sleepiness plus cataplexy (narcolepsy) would evidence greater mood disturbance than nonsleepy groups. Under the assumption that sleepiness is the primary psychosocially debilitating feature of narcolepsy (Broughton, 1992), it was also expected that family members with sleepiness without cataplexy would also evidence greater mood disturbance relative to the Asymptomatic Family group and the Community Control group. Finally, it was anticipated that the sleepy groups (Narcolepsy/Cataplexy group and Sleepiness only group) would differ from the nonsleepy groups (Asymptomatic Family group and Community Control group) with regard to psychosocial factors that might mediate a sleepiness/mood disturbance relationship. Specifically, sleepy groups were expected to have reduced perceptions of family support, poor coping response styles, and perceptions of low self-efficacy.

METHOD

Subjects

The proband for this African-American family was a 76-year-old male with a diagnosis of narcolepsy with cataplexy. Fourteen children by 8 different mates were identified along with 36 grandchildren and 34 great grandchildren. All available and consenting members of the family over the age of 15 years were assessed. Data were obtained from 8 children, 16 grandchildren, and 7 great grandchildren. Community Control group members were primarily volunteering spouses, stepchildren, and friends of the kindred. Contributions were made to a local church in exchange for the cooperation of some of the Community Control group members. An institutional review board approved the research and a signed informed consent form was obtained from each participant in the study.

Narcolepsy/Cataplexy Family group

During clinical assessment by a diplomate of the American Board of Sleep Medicine, six family members described symptoms of narcolepsy including cataplexy. Five members of this group were evaluated at an accredited sleep disorders center with a polysomnogram (PSG) and a Multiple Sleep Latency test (MSLT). Four members had a mean MSLT sleep onset latency of less than 8 min and two or more sleep onset REM periods. Epworth Sleepiness scale (ESS) scores ranged from 20 to 24 ($M = 22.3$, $SD = 2.1$). Psychosocial data were obtained from four individuals in this group (two males and two females) who ranged in age from 38 to 51 years ($M = 44.8$, $SD = 7.2$) at the time of evaluation (see Table I).

Sleepy-Only Family Group

The 12 members of this group (4 males and 8 females) complained of excessive daytime

Table I. Narcolepsy-Related Symptomology

Symptoms	Narcolepsy/Cataplexy Family group ($n = 4$)	Sleepy-only Family group ($n = 12$)	Asymptomatic Family group ($n = 15$)	Community Control group ($n = 17$)
Hypnogoic hallucinations	4 (100)	9 (75)	9 (60)	5 (29)
Sleep paralysis	4 (100)	5 (42)	4 (27)	6 (35)
Automatic behaviors	4 (100)	5 (42)	6 (40)	4 (24)
Disturbed sleep	4 (100)	8 (67)	2 (13)	4 (34)

Note. The values given in parenthesis are expressed in percentage.

sleepiness but not cataplexy and had ESS scores of 15 or higher. The ESS scores for this group ranged from 15 to 22 ($M = 18.1$, $SD = 2.5$). The group age range was from 15 to 63 years ($M = 27$, $SD = 9.6$). Laboratory evaluation for two members resulted in unremarkable polysomnograms and mean MSLT sleep onset latencies of 5.6 and 1.6 min. Neither had two or more sleep onset REM periods. Medical and sleep histories for the remaining subjects in this group yielded no indication of sleep apnea, restless legs, or periodic limb movements, however, PSG and MSLT data were not obtained.

Asymptomatic Family Group

The 15 members (7 males and 8 females) of this group had no complaint of sleepiness or cataplexy. ESS scores ranged from 0 to 13 ($M = 8.9$, $SD = 4.1$). The group ranged in age from 14 to 68 years ($M = 28.2$, $SD = 14.6$).

Community Control Group

The 17 members (6 males and 11 females) of this group had no complaint of cataplexy. The ESS scores ranged from 2 to 19 ($M = 9.1$, $SD = 5.0$). The group ranged in age from 16 to 57 years ($M = 35.9$).

Instruments

All subjects completed a battery of instruments including the Stanford Sleep Inventory for narcolepsy (Anic-Labat et al., 1999), Epworth Sleepiness scale (Johns, 1991), Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988), Profile of Mood States (McNair, Lorr, & Droppleman, 1971), Generalized Self-Efficacy scale (Tipton & Worthington, 1984), Family Environment scale (Moos & Moos, 1986), and Quality of Life Index (Ferrans, 1990).

Statistical Analyses

Unless otherwise indicated, analysis of variance (ANOVA) was used to compare group mean differences. The Tukey's Honestly Significant Difference procedure was used for post hoc comparisons.

RESULTS

Mood Disturbance

Figure 2 presents the mean scores for the four groups obtained from the Beck Depression Inventory (BDI). The mean scores for the Narcolepsy/Cataplexy ($M = 17.3$, $SD = 6.1$) and the Sleepy-only Family ($M = 15.8$, $SD = 8.1$) groups on the BDI are consistent with mild to moderate depression (Beck & Beamesderfer, 1974). The Asymptomatic Family and the Community Control groups mean scores, 6.1 ($SD = 4.9$) and 6.0 ($SD = 5.5$), respectively, were within the normal range. Analysis of variance of the Global BDI scores was significant, $F_{3,44} = 9.6$, $p < .001$. Follow-up tests revealed that the Narcolepsy/

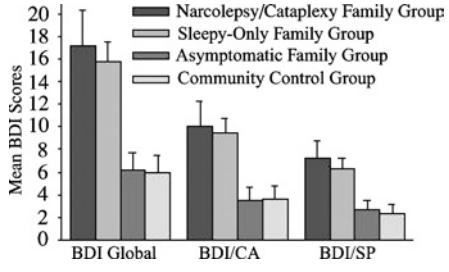

Fig. 2. Mean Beck Depression Inventory global, cognitive/affective, and somatic/performance scores for the Narcolepsy/Cataplexy Family, Sleepy-only Family, Asymptomatic Family, and Community Control group.

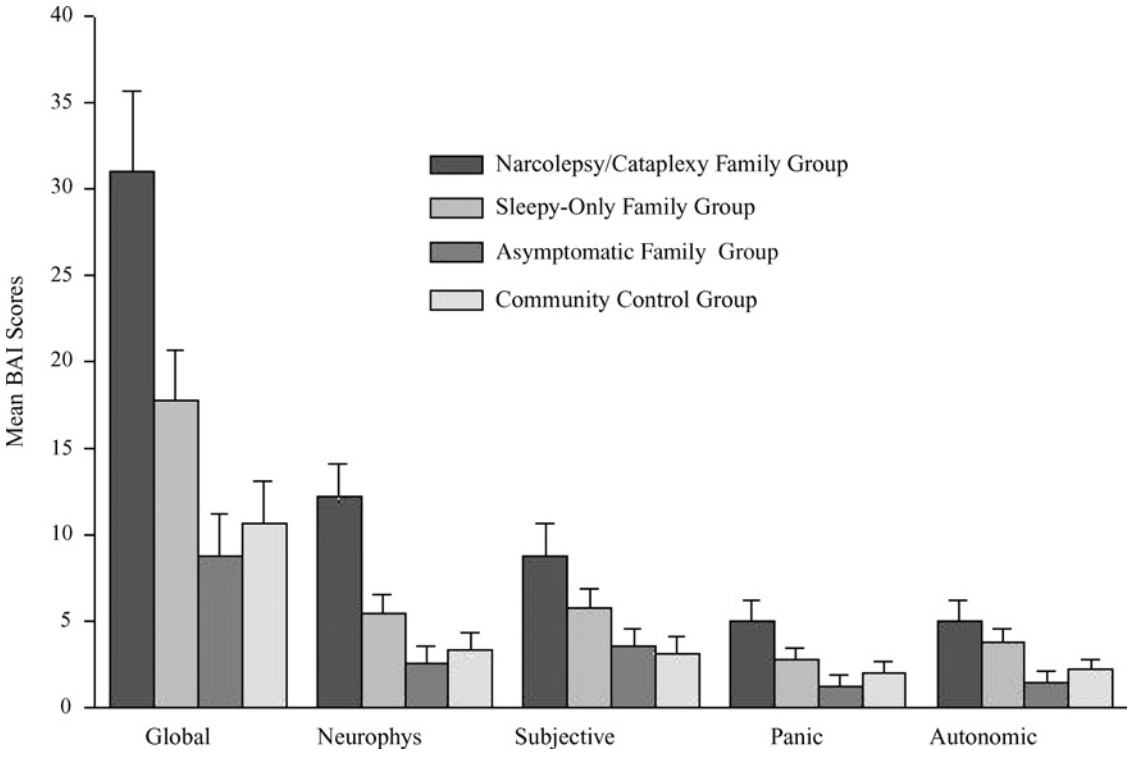

Fig. 3. Beck Anxiety Inventory global, neurophysiological, subjective, panic, and autonomic scores for the Narcolepsy/Cataplexy Family, Sleepy-only Family, Asymptomatic Family, and Community Control group.

Cataplexy Family and the Sleepy-only Family group means did not differ significantly, while both groups differed significantly ($p < .01$) from the Asymptomatic Family and Community Control group means. Analysis of variance also yielded significance for the Cognitive–Affective (CA) $F_{3,44} = 6.3$, $p < .001$, and Somatic–Performance (SP) $F_{3,44} = 6.6$, $p < .001$, subscales of the BDI. The CA and SP subscale means were statistically comparable for the Narcolepsy/Cataplexy Family ($M = 10, SD = 3.2$; $M = 7.3, SD = 3.3$) and the Sleepy-only Family group ($M = 9.4$, $SD = 6.9$; $M = 6.3$, $SD = 4.1$) and both were significantly higher than means for the Asymptomatic Family ($M = 3.5$, $SD = 3.1$; $M = 2.7$, $SD = 2.4$) and the Community Control group ($M = 3.7$, $SD = 3.6$; $M = 2.4$, $SD = 2.6$).

Figure 3 presents mean scores for the four groups obtained from the BAI. The mean global score for the Narcolepsy/Cataplexy Family ($M = 31$, $SD = 12.4$) and the Sleepy-only Family ($M = 17.8$, $SD = 10.2$) groups on the BAI are consistent with moderate anxiety (Beck & Steer, 1993). The means for the Asymptomatic Family ($M = 8.4$, $SD = 9.6$) and the Community Control ($M = 10.4$, $SD = 8$) groups were in the minimal anxiety range. Significant group differences were found on the BAI, $F_{3,42} = 7.1$, $p < .001$. The Narcolepsy/Cataplexy Family group scored significantly higher ($p < .05$) on the BAI than all other groups. The Sleepy-only Family group scored higher ($p < .05$) than the Asymptomatic Family group, but not the Community Control group. The Asymptomatic Family and Community Control groups did not differ significantly. Group differences were found on the Neurophysiological $F_{3,42} = 8.149$ ($p < .001$), Subjective $F_{3,42} = 3.24$ ($p < .05$), Panic $F_{3,42} = 2.795$ ($p < .05$, and Autonomic $F_{3,42} = 3.328$ ($p < .05$) subscales of the BAI. The Narcolepsy/Cataplexy Family group scored significantly higher ($p < .01$) than the other groups on the BAI Neurophysiological subscale. The Narcolepsy/Cataplexy Family group scored significantly higher ($p < .05$) than the Asymptomatic Family and Community Control groups on the BAI Subjective and Panic subscales. Both the Narcolepsy/Cataplexy Family and the Sleepy-only Family group scored higher ($p < .05$) than the asymptomatic group on the BAI Autonomic subscale.

Figure 4 presents mean scores for the four groups obtained from the POMS. Group differences were

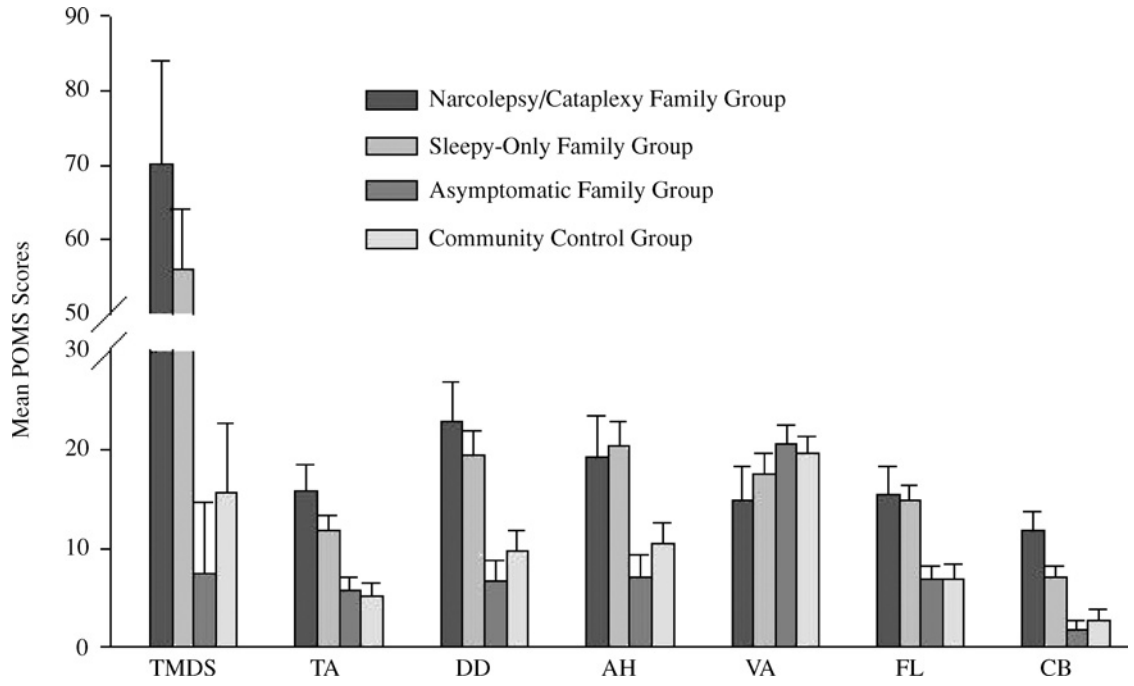

Fig. 4. Profile of Mood States total mood disturbance, tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, and confusion–bewilderment scores for the Narcolepsy/Cataplexy Family, Sleepy-only Family, Asymptomatic Family, and Community Control group.

found on the POMS Total Mood Disturbance Score (TMDS), $F_{3,43} = 10.94$, $p < .001$. Mean scores for the Narcolepsy/Cataplexy Family $M = 70.3$, $SD = 49.7$ and the Sleepy-only Family $M = 56.1, SD = 30.5$ groups were significantly ($p < .01$) higher than the Asymptomatic Family $M = 7.5, SD = 20.9$ and Community Control $M = 15.6$, $SD = 25.2$ groups. The Narcolepsy/Cataplexy Family and the Sleepy-only Family groups did not differ significantly. The Asymptomatic Family and Community Control groups also did not differ significantly. Group differences were found on the subscales Tension–Anxiety $F_{3,43} = 7.9$ ($p < .001$), Depression–Dejection $F_{3,43} = 8.0$ ($p < .001$), and Fatigue–Inertia $F_{3,43} = 7.3$ ($p < .001$). These results are similar to the POMS TMDS in that the affected family groups were statistically similar and elevated relative to the asymptomatic and Community Control groups. The POMS Anger–Hostility ($F_{3,43} = 7.0$, $p < .001$) subscale follows a similar pattern although the Narcolepsy/Cataplexy Family score elevation relative to the Community Control group did not reach statistical significance. Scores from the POMS Confusion–Bewilderment ($F_{3,43} = 9.9$, $p < .001$) subscale follow a pattern similar to the POMS TMDS with an additional statistically significant elevation of Narcolepsy/Cataplexy Family group relative to all other groups including the Sleepy-only Family group. No significant group differences were found for the POMS Vigor–Activity subscale.

Possible Mediating Variables

Family Support

No significant differences were found on a measure of familial social support, the Family Environment scale (FES), between any of the subject groups. The FES scores for the three groups appeared comparable to normative samples from nondistressed families (Moos & Moos, 1986; see Table II for overall means).

Coping Style

The Narcolepsy/Cataplexy Family, Sleepy-only Family, Asymptomatic Family, and Community Control groups did not significantly differ in level of utilization of any specific coping style as measured by the Coping Response Inventory (CRI). Further, no differences were found in utilization of general coping

Table II. Means and Standard Deviations of the FES

	Narcolepsy/Cataplexy Family group ($n = 4$)		Sleepy-only Family group ($n = 11$)		Asymptomatic Family group ($n = 14$)		Community Control group ($n = 15$)	
FES	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Cohesion	6.75	2.06	6.82	.87	7.20	2.18	7.07	1.33
Expressiveness	4.25	.96	5.18	1.78	5.07	1.59	4.40	1.30
Conflict	3.75	.50	3.27	1.68	3.92	1.82	3.47	1.51
Independence	6.50	2.08	7.00	1.18	7.29	1.44	6.07	1.67
Achievement	6.75	.96	6.55	1.21	6.71	.92	6.33	1.29
Int.-Cultural	6.5	2.65	5.00	2.32	5.43	2.59	5.67	2.06
Active–Recreation	6.25	2.75	6.36	1.29	5.71	2.02	4.8	1.93
Moral–Religious	8.25	.50	6.91	1.87	7.57	.65	7.93	.70
Organization	5.50	1.92	5.00	2.28	6.14	1.96	6.13	1.89
Control	5.75	1.26	5.09	1.92	5.29	1.82	5.87	1.41

styles of approach, avoidant, behavioral, or cognitive coping (see Table III for overall means).

Self Efficacy

No significant differences were found between Narcolepsy/Cataplexy Family, Sleepy-only Family, Asymptomatic Family, and Community Control group scores on the Generalized Self Efficacy scale (GSES) (see Table IV for overall means).

DISCUSSION

In the studied kindred, family members with narcolepsy/cataplexy (Narcolepsy/Cataplexy Family group) and with isolated sleepiness (Sleepiness-only Family group) scored significantly higher on measures of depression, anxiety, and mood state disturbance than did family members without sleepiness or cataplexy complaints (Asymptomatic Family group) and higher than nonfamily members (Community Controls). The Narcolepsy/Cataplexy Family group reported generally higher levels of anxiety than did the Sleepy-only Family group, but did not differ on any other psychosocial variable. There was no evidence of group differences on psychosocial variables that might mediate a relationship between narcolepsy/cataplexy and disturbed mood.

The findings of the present study suggest that sleepy members of families with narcolepsy patients may be prone to psychological disturbances and, with regard to family members with narcolepsy/cataplexy, are consistent with those of previous investigators in that narcolepsy/cataplexy is associated with psychological disturbance (Beutler et al., 1981; Kales et al., 1982; Lindsley & Crawford, 1996; Merrit et al., 1992; Broughton et al., 1981). It is reasonable to consider that, since sleepiness is a feature of depression,

Table III. Means and Standard Deviations of the Coping Response Inventory

	Narcolepsy/Cataplexy Family group ($n = 4$)		Sleepy-only Family group ($n = 10$)		Asymptomatic Family group ($n = 14$)		Community Control group ($n = 16$)	
CRI	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Approach	44	15.3	44.5	10.8	43.7	12.2	45.8	13.6
Avoidance	32.3	3.9	35.2	11.9	31.9	13.1	36.4	15.1
Cognitive	42.8	13.8	43	7.5	42	10.9	43.0	14.4
Behavioral	33.5	7.4	36.7	10.7	33.6	13.2	39.1	13.0
Logical analysis	9.25	5.12	10.8	3.85	11.4	3.50	11.25	3.97
Positive reappraisal	12.8	4.4	12.6	2.8	12.1	3.7	12.1	4.1
Seeking guidance and support	10.0	4.	10.0	3.3	8.4	4.3	9.7	3.7
Problem solving	12.0	3.6	11.1	3.3	11.9	3.4	12.8	3.8
Cognitive avoidance	10.0	4.7	9.9	3.9	10.6	3.2	10.4	4.6
Acceptance or resignation	10.8	2.8	9.7	3.5	8.0	4.2	9.3	4.4
Seeking alternative rewards	6.8	3.6	8.1	5.0	7.0	4.3	8.8	4.9
Emotional discharge	7.8	2.6	7.5	3.5	6.4	4.8	7.9	3.8

Table IV. Means and Standard Deviations of the Generalize Self-Efficacy Scale

	Narcolepsy/Cataplexy Family group ($n = 4$)		Sleepy-Only Family group ($n = 11$)		Asymptomatic Family group ($n = 15$)		Community Control group ($n = 15$)	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
GSES global score	152	13.0	133.6	14.8	134.1	15.2	134.9	12.6

scores on depression inventories might be elevated in sleepy individuals because they would naturally endorse sleepiness-related items. This does not seem to be an issue here, however, in that elevations were found on both the Cognitive–Affective (CA) and Somatic–Performance (SP) subscales of the Beck Depression Inventory. These subscales are used for assessing depression in persons whose vegetative and somatic symptoms might lead to an overestimation of the severity of depression (Beck & Beamesderfer, 1974). It is of interest that the Narcolepsy/Cataplexy Family group scored higher on measures of anxiety (in the moderate anxiety range) relative to the Sleepy-only Family group. It is reasonable to consider that the pathophysiology associated with cataplexy involves regions of the central nervous system involved in anxiety regulation.

It appears from the present findings that the elevations on the screen measures of depression, anxiety, and mood state disturbance of the Narcolepsy/Cataplexy Family group and Sleepy-only Family group are independent of mediating psychosocial variables such as self-efficacy, social-support, and coping styles. Previous research (Alaia, 1992) failed to find evidence that loss of social support mediated a negative impact of narcolepsy on psychological well-being. Although reliance on specific coping styles by patients with narcolepsy has been suggested (Beutler et al., 1981), coping strategies of individuals suffering from narcolepsy have previously only been qualitatively examined (Rogers, 1984). It is possible that observed differences in mood are due to some uninvestigated mediating variable or variables that exacerbate or mitigate the disease state for the individual. The absence, however, of statistically significant group differences on all mediating variables studied here contrasts with the robust differences found with the measures of depression, mood, and anxiety.

It is possible that disturbed mood may be a trigger factor for narcolepsy and related disorders. A multifactorial etiological model including both genetic as well as environmental factors has been suggested (Partinen, Hublin, Kaprio, Koskenvuo, & Guilleminault, 1994). In this model, a genetic liability as well as psychological stressors or some environmental stressor are though to act in combination. In support of this model, Orellana et al. (1994) found that a significantly greater number of patients with narcolepsy recall potentially stressful life events in the year preceding onset of EDS (82%) and cataplexy (84%) than do healthy matched controls.

Rather than being precipitant or consequent to chronic illness, it could be argued that anxiety and depression are features of the narcolepsy syndrome. As proposed by Broughton et al. (1981) "the pathophysiology of narcolepsy may be endogenously expressed by depression as well as by the major sleep symptoms" (p. 103). In support of this proposal, Broughton et al. (1981) found that the life effects of narcolepsy and associated symptoms occurred regardless of cultural milieu or genetic pool. Particular genetic haplotypes are thought to predispose one to developing narcolepsy (Partinen et al., 1994). Similarly, these same genetic factors, or associated haplotypes, which manifest as cataplexy or isolated sleepiness, may create a liability for developing depression and anxiety.

The present study was particularly interesting with regard to the relative homogeneity of the gene pool, SES, and originating geographic region of the subjects. Although these factors may be advantageous with regard to control and focus, such homogeneity may limit generalizability. Future research investigating the families of patients with narcolepsy should prove useful in addressing this issue. An additional consideration is that of reliance on self-report of sleepiness for the subcomponent of data gathered in the field allowed the possibility of false positives and sleepiness due to occult sleep disorders. Clinical interviews did not rule out, but served to minimize these possibilities.

In the present study, both patients with narcolepsy and many of their sleepy close relatives were found to experience depression, anxiety, and mood disturbance. No evidence of mediating psychosocial variables was discovered. It is hypothesized that genetic haplotypes associated with narcolepsy may create a liability for the development of depression and

anxiety in patients with narcolepsy as well as their sleepy kindred.

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