Sleep Medicine 53 (2019) 88–93

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Longitudinal study of narcolepsy symptoms in first, second, and third-degree relatives of simplex and multiplex narcolepsy families

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ARTICLE INFO

Article history:
Received 22 March 2018
Received in revised form
27 June 2018
Accepted 28 June 2018
Available online 6 July 2018

Keywords:
Narcolepsy
Genetic
Hypersomnolence

ABSTRACT

Objective: To assess the evolution of narcolepsy symptoms in first-, second, and third-degree relatives and to compare multiplex and simplex families.
Methods: A total of 4045 family members and 362 narcoleptic individuals were entered in the study; with 3255 family members interviewed twice, five to seven years apart. A control group (n = 178) composed of spouses or housemates was also interviewed twice. Family members were divided according to their blood relationship with the probands and further divided into multiplex (ie, more than one narcolepsy cases) and simplex (only one narcolepsy case) families. Telephone interviews were conducted with the help of the Sleep-EVAL system; narcolepsy probands were evaluated and diagnosed by a Sleep Specialist in a Sleep Clinic Center.
Results: A total of 1123 family members from 72 families were identified as members of multiplex families while the rest of the sample were a part of simplex families (n = 2132). Multiplex families had higher incidence and chronicity of hypersomnolence than the simplex family members and the control group. For cataplexy-like symptoms, only prevalence at the time of the first assessment distinguished multiplex (5.5%) and simplex (2.9%) families. Prevalence of sleep paralysis was higher among the first- and second-degree relatives coming from multiplex families, while incidence was the highest among second- and third-degree relatives. Hypnagogic hallucinations had similar prevalence between multiplex and simplex families but the incidence and chronicity were significantly higher among multiplex families. For each symptom, predictive factors were also determined in simplex and multiplex families.
Conclusions: Our results show that individuals coming from multiplex families are at greater risks of a broad range of narcolepsy symptoms compared to simplex families.

1. Introduction

Narcolepsy, a lifelong debilitating neurological disorder, has been known for more than a century [1]. The disorder is characterized by hypersomnolence, sleep fragmentation and manifestations of various REM sleep abnormalities (cataplexy, sleep paralysis, and hypnagogic hallucinations). Its prevalence is established at around 0.05% worldwide [2–4].

The importance of genetic factors in narcolepsy has been recognized for more than 60 years [5]. Results of prior studies suggest that 6 to 40 percent of narcoleptic individuals have a close relative with the disease [6–11]. The risk for narcolepsy has been estimated to be between 10 and 40 times higher among families with a narcoleptic member than in the general population [6]. Family studies of narcoleptic individuals have reported increased prevalence of other sleep disorders among

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https://doi.org/10.1016/j.sleep.2018.06.015
1389-9457/

family members such as hypersomnolence or idiopathic hypersomnia, suggesting the existence of a narcolepsy spectrum. Aside from greater risks for the disease among the first-degree relatives of narcoleptic individuals, little is known about whether specific symptomatic markers exist that could characterize multiplex families or whether there is an evolution of narcolepsy symptoms in these families.

This study examined the nature and potential evolution of narcolepsy symptoms among first-, second- and third-degree relatives of individuals with narcolepsy by comparing multiplex and simplex families.

2. Methods

2.1. Participants

A total of 4045 family members of the 362 individuals with narcolepsy included in our study were interviewed at least once. Of these, 3255 family members and 300 narcoleptic individuals had initially been interviewed between mid-2005 and the end of 2007. The second interview was between December 2011 and January 2015.

Family members who were interviewed twice consisted of:

231 sons/daughters; 442 fathers/mothers; 521 siblings; 437 grandfathers/grandmothers; 588 uncles/aunts; 297 nephews/nieces, 277 first-degree cousins; 88 great grandfathers/grandmothers 97 great-uncles/aunts, and 277 second-degree cousins.

A total of 178 spouses/housemates were also interviewed twice and were used as a control group.

Family members were divided according to their blood relationship with the probands:

The first-degree relative group includes blood relatives who are the proband's parents, full siblings, and children.

Second-degree relative group consists of blood relatives who are the proband's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

Third-degree relative group includes blood relatives who are first and second-degree cousins, great-uncles or great-aunts, great-grandparents and great grandchildren.

Family members were further divided into families with a single case of narcolepsy (simplex families) and families with two or more cases of narcolepsy (multiplex families). Family side carrying the narcolepsy gene was identified with a diagnosis of narcolepsy already made by a sleep specialist in a family member. Blood results were also used to help identify the side that carries the gene when the second narcoleptic was a sibling or a child.

We identified 72 multiplex families. Narcolepsy was observed in the father's side in 41 instances and in the mother's side in 31 families. A total of 1123 family members belonged to multiplex families, including 431 first-degree relatives, 432 second-degree relatives and 260 third-degree relatives. All family members with narcolepsy were removed from the analyses.

The study was approved by the Institutional Review Board of Stanford University.

2.2. Instrument

The Sleep-EVAL knowledge-based expert system was used in this study to conduct the interviews [12,13]. This computer software and its questionnaire were specially designed to conduct epidemiological studies in the general population.

Interviews lasted on average 71 (±38.44) minutes, with a median duration of 60.51 min. The shortest interview lasted 22 min and the longest 4 h and 24 min (completed over several interview sessions).

The Sleep-EVAL system is composed of a non-monotonic, level-2 inference engine, two neural networks, a mathematical processor, the knowledge base and the base of facts. The system-directed interview began with a series of questions asked of all the participants. Questions were read aloud by the interviewer as they appeared on the interviewer's computer screen. These questions were either closed-ended (eg, yes/no, five-point scale, multiple choice) or open-ended (eg, duration of symptom, description of illness).

Once this information was collected, the system began the diagnostic exploration of psychiatric conditions. On the basis of responses provided by a subject to this second set of questions, the system formulated an initial diagnostic hypothesis that it attempted to confirm or to reject it by asking supplemental questions or by deductions. Concurrent diagnoses are allowed in accordance with the DSM-IV-TR [14] and the Classification of Sleep Disorders or ICSD-II [15]. The system terminated the interview once all diagnostic possibilities were exhausted.

The differential process is based on a series of key rules allowing or prohibiting the co-occurrence of two diagnoses. The questionnaire of the expert system is designed such that decisions about the presence of a symptom is based upon the interviewee's responses rather than on the interviewer's judgment. This approach has proven to yield better agreement between lay interviewers and psychiatrists on the diagnosis of minor psychiatric disorders [16]. The system has been tested in various contexts in clinical psychiatry and sleep disorders medicine. In psychiatry, overall kappa between psychiatrists and the system was 0.71 [17]; kappas have ranged from 0.44 (schizophrenia disorders) to 0.78 (major depressive disorder). In sleep medicine, kappas between sleep specialists and Sleep-EVAL have ranged from 0.78 (RLS) to 0.94 (breathing-related sleep disorder) [18–20]. During the first wave of this study, the agreement between the Sleep-EVAL system and four sleep specialists was tested on 60 randomly selected participants. The kappa on the diagnosis of narcolepsy was very high: 0.96; with a sensitivity of 94.7% and a specificity of 100%. A sub-sample of 284 participants in this study also completed the Stanford Sleep Inventory. Correlations between the two instruments, administered within a six-month interval, were good: $r = 0.77$ on cataplexy; $r = 0.80$ on sleep paralysis; $r = 0.62$ on hypnagogic and/or hypnopompic hallucinations and 0.62 on automatic behaviors. A Kappa of 0.84 was obtained between the two instruments on the narcolepsy diagnosis. Sleep-EVAL has a sensitivity of 82.7% and a specificity of 98.4%.

2.3. Variables

Information collected as follows by the system included a complete description of symptoms of narcolepsy in the four weeks prior to the interview:

- Daytime sleepiness was assessed with a series of questions covering severity of the sleepiness, frequency per week and per day, situations when the sleepiness occurred (for example, during conversations, at work, quiet situations); age of onset, and consequences on daytime functioning.
- Cataplexy: description of affected muscles, situations triggering an episode; frequency, age of onset, and moment of last episode.
- Hypnagogic and hypnopompic hallucinations: types of hallucinations, frequency, age of onset, moment of the last hallucination.
- Sleep paralysis: frequency, age of onset, moment of the last episode.

Information was also collected on sleep habits, sleep quality, medication, hospitalizations and sleep and psychiatric disorders diagnoses according to the DSM-IV and ICSD classifications.

2.4. Analyses

First, the relationship between each narcolepsy symptom and family relationship at Wave 1 (W1) was examined, calculating

crude odds ratios and then adjusted odds ratios controlling for age and gender. Second, sleep and narcolepsy symptoms, psychiatric disorders at W1 were used to predict each narcolepsy symptom at Wave 2 (W2), first examining crude odds ratios and then adjusted odds ratios controlling for the same covariates.

The estimated odds ratios and their 95% confidence limits were calculated using logistic regression procedures and Taylor series approximation to compute the standard error of the odds ratio.

3. Results

The demographic characteristics of the narcoleptics' families are presented in Table 1. As expected, first and third-degree relatives were younger than second-degree relatives. Interviewed individuals from multiplex families were younger than simplex families for the first-degree (mean: 44.96 y.o. ± 17.05 vs. 48.76 y.o. ± 16.91; respectively $p < 0.0001$) and the second-degree relative groups (mean: 51.84 y.o. ± 16.08 vs. 56.93 y.o. ± 16.30; respectively $p < 0.0001$).

There were fewer males in the second-degree multiplex family group compared to simplex families (33.3% vs. 54.0%; respectively $p < 0.001$) and more males in the third-degree multiplex narcolepsy group compared to simplex families (52.9% vs. 37.0%; respectively $p < 0.001$).

Prevalence of DSM-IV psychiatric disorders are depicted in Table 2. Overall, Mood and anxiety disorders were more prevalent among multiplex family members than in simplex families and the control group.

3.1. Prevalence, incidence and chronicity of hypersomnolence

Table 3 depicts prevalence, incidence and chronicity of hypersomnolence according to blood relationships and multiplex versus simplex families. As shown, at W1, prevalence of hypersomnolence was comparable between the various groups with the exception of the control group where the lowest prevalence was observed. At W2, incidence of hypersomnolence was significantly higher among first- and second-degree relatives from multiplex families compared to those coming from simplex families. Chronicity (ie, presence of hypersomnolence at W1 and W2) was higher in all multiplex narcolepsy groups compared to the simplex family members. Chronicity was extremely low among the control group while the incidence was similar to the incidence rates observed in families with a single narcolepsy case.

Compared with the control group, the relative risk of reporting hypersomnolence at W2 was 4.1 [3.2–5.4] among first-degree and 1.7 [1.3–2.3] among second-degree relatives of multiplex families after adjusting for age, gender and health status.

When examining the predictive factors for hypersomnolence at W2, the following factors were found among multiplex families: reporting a poor health status at W1 (RR 2.0 [1.0–4.0]; $p = 0.04$), having a psychiatric disorder at W1 (RR 2.3 [1.4–3.9]; $p = 0.002$) and greater body mass index (RR 1.1 [1.0–1.2]; $p = 0.01$). Thus, for each one unit increase in the body mass index, the risk of developing hypersomnolence at W2 increases by a factor of 1.1.

Among simplex families, predictive factors for hypersomnolence at W2 were being younger than 25 y.o. at W1 (RR 4.9 [2.2–11.1]; $p < 0.0001$), having cataplexy-like symptoms (RR 2.7 [1.3–5.5]; $p = 0.006$), and greater body mass index (RR 1.1 [1.0–1.1]; $p = 0.009$).

3.2. Prevalence, incidence and chronicity of cataplexy-like symptoms

Non-narcoleptic family members reporting cataplexy-like symptoms were infrequent. Therefore, it was not possible to analyze them by blood relationship. As shown in Table 4, prevalence of cataplexy-like symptoms was higher at W1 in multiplex families compared to simplex families. Incidence and chronicity were comparable between groups. None of participants of the control group reported these symptoms.

3.3. Prevalence, incidence and chronicity of sleep paralysis

Table 5 presents the prevalence, incidence and chronicity of sleep paralysis. As seen, prevalence was higher in first- and second-degree relatives from multiplex families compared with simplex families. Incidence was the highest among second- and third-degree relatives from multiplex families. Sleep paralysis was chronic for about one third of first- and second-degree relatives regardless of whether they were from a multiplex or simplex family.

Table 1
Demographic characteristics of the Narcolepsy family cohort.

	First-degree relatives		Second-degree relatives		Third-degree relatives		Control	
	W1%	W2%	W1%	W2%	W1%	W2%	W1%	W2%
Sex								
Male	39.2	39.2	41.3	41.3	46.1	46.1	39.8	39.8
Female	60.8	60.8	58.7	58.7	53.9	53.9	60.2	60.2
Age categories								
<24 y.o.	14.6	5.3	1.6	1.6	26.8	3.9	19.9	4.8
25–44 y.o.	25.1	27.8	19.1	5.2	61.6	57.7	45.2	39.8
45–64 y.o.	47.6	41.8	56.9	46.6	3.9	34.5	34.9	30.1
>=65 y.o.	12.7	25.1	22.4	46.6	7.7	3.9	0.0	25.3
Marital Status								
Single	21.8	20.5	14.6	21.7	39.1	35.3	10.2	1.0
Married	62.5	66.7	66.0	62.8	51.1	54.1	88.0	98.1
Sep/Div	11.3	7.7	8.2	8.9	3.8	4.6	1.9	1.0
Widowed	4.5	5.0	11.2	6.6	6.0	6.0	0.0	0.0
Occupation								
Working	63.6	62.2	52.5	56.9	70.1	81.6	69.1	62.8
Not working	36.4	37.8	47.5	43.1	29.9	18.4	33.9	37.2
Ethnicity								
White	88.2	88.2	88.3	88.3	86.4	86.4	88.8	88.8
Black	4.5	4.5	3.7	3.7	3.8	3.8	1.4	1.4
Hispanic	2.6	2.6	5.5	5.5	4.5	4.5	4.7	4.7
Asian	1.5	1.5	0.0	0.0	0.0	0.0	0.8	0.8
Mixed race	3.2	3.2	2.4	2.4	1.6	1.6	4.3	4.3

Table 2
One-month prevalence of the most frequent DSM-IV psychiatric disorders.

	First-degree relatives		Second-degree relatives		Third-degree relatives		Control	
	W1%	W2%	W1%	W2%	W1%	W2%	W1%	W2%
Persistent depressive disorder								
Multiplex families	2.1	1.9	0.0	1.4	0.0	2.3	0.0	0.0
Simplex families	1.2	1.0	1.1	0.8	0.0	2.2	1.9	0.0
Major depressive disorder								
Multiplex families	8.1	8.7*	10.4	4.2	0.0	4.6	0.0	0.0
Simplex families	4.9	3.4	7.7	2.5	10.0	8.6	2.7	1.0
Bipolar I disorder								
Multiplex families	1.9	2.5*	1.9	2.8	3.1*	4.6	0.0	0.0
Simplex families	2.7	1.6	1.9	0.9	0.7	0.0	0.7	3.4
Total Mood Disorders								
Multiplex families	12.1	13.1*	12.3	8.4*	13.1	11.5	0.0	0.0
Simplex families	8.8	6.0	10.7	4.2	10.7	11.0	5.3	4.4
Generalized anxiety disorder								
Multiplex families	6.7	4.8	7.0*	2.8	0.7	4.3	1.8	0.0
Simplex families	4.6	3.4	2.2	4.2	0.7	0.0	6.4	5.1
Obsessive-compulsive disorder								
Multiplex families	0.6	0.6	3.5*	0.0	2.9	2.3	0.0	0.0
Simplex families	1.1	1.0	0.5	0.0	2.9	4.3	4.6	1.0
Posttraumatic stress disorder								
Multiplex families	2.4	3.5	3.8	4.2	1.8	0.0	0.0	0.9
Simplex families	1.9	3.4	3.1	2.6	3.1	2.3	2.7	1.9
Social anxiety disorder								
Multiplex families	11.4*	8.7*	7.4	1.4	10.7	2.3	0.0	0.0
Simplex families	2.9	5.2	2.6	5.9*	5.0	0.0	5.9	2.4
Agoraphobia								
Multiplex families	2.5	2.7	0.9	4.2	3.1	2.3	0.0	0.0
Simplex families	2.3	1.2	2.6	0.9	0.0	1.2	1.8	3.4
Panic Disorder								
Multiplex families	7.4*	7.3*	5.6	8.4*	3.1	6.9	0.0	0.0
Simplex families	4.2	3.1	4.5	3.4	2.2	4.6	2.4	6.9
Total Anxiety Disorders								
Multiplex families	28.5*	23.8*	19.1*	14.0	14.9*	6.1	1.8	0.9
Simplex families	12.6	12.7	11.5	11.3	6.1	8.4	16.7*	11.3*

*$p < 0.001$.

Compared to the control group, the relative risk of having sleep paralysis at W2 was 2.3 [1.7–3.1] among first-degree, 1.8 [1.3–2.4] among second-degree and 4.7 [3.4–6.6] among third-degree relatives from multiplex families.

Among multiplex families, the predictive factors for sleep paralysis at W2 were: reporting hypnagogic hallucinations at W1 (RR 2.4 [1.3–4.4]; $p = 0.007$), having cataplexy-like symptoms at W1 (RR 4.0 [1.9–8.7]; $p < 0.0001$), sleeping more than 7 h per night (RR 2.7 [1.0–7.3]; $p = 0.04$) and having a sleep apnea syndrome at W1 (RR 3.3 [1.3–8.0]; $p = 0.01$).

Predictive factors for sleep paralysis at W2 in simplex families were similar to those for multiplex families. At W1, reporting hypnagogic hallucinations (RR 3.9 [2.2–7.1]; $p < 0.0001$), hypnopompic hallucinations (RR 5.5 [2.5–12.2]; $p < 0.0001$), having cataplexy-like symptoms at W1 (RR 2.9 [1.4–6.3]; $p = 0.04$) and sleeping more than 7 h per night (RR 3.0 [1.4–6.3]; $p = 0.004$) were predictive of sleep paralysis at W2.

3.4. Prevalence, incidence and chronicity of hypnagogic hallucinations

Prevalence, incidence and chronicity of hypnagogic hallucinations are presented in Table 6. Prevalence was comparable between multiplex and simplex families but all were at least four times higher than the control group. As stated previously, incidence and chronicity were significantly higher among

Table 3
Prevalence and stability of hypersomnolence.

	Prevalence at W1	W1–W2 changes		
		Total Incidence	Chronic	Remitted
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
First-degree				
Multiplex families (n = 431)	28.1 [23.9–32.3]	26.5 [22.3–30.7]*	28.1 [23.9–32.3]*	71.9 [67.7–76.1]
Simplex families (n = 763)	24.3 [21.3–27.3]	11.1 [8.9–13.3]	6.9 [5.1–8.7]	93.1 [91.3–94.9]
Second-degree				
Multiplex families (n = 432)	21.5 [17.6–25.4]	16.8 [13.3–20.3]*	12.9 [9.7–16.1]*	87.1 [83.9–90.3]
Simplex families (n = 890)	22.5 [19.5–25.5]	9.7 [7.6–11.8]	3.3 [2.0–4.6]	96.7 [95.4–98.0]
Third-degree				
Multiplex families (n = 260)	26.9 [22.7–31.1]	11.1 [8.1–14.1]	22.9 [18.9–26.9]*	77.1 [73.1–81.1]
Simplex families (n = 479)	26.3 [23.2–29.4]	8.2 [6.3–10.1]	5.6 [4.0–7.2]	94.4 [92.8–96.0]
Control (n = 178)	9.6 [5.3–13.9]	8.3 [4.2–12.4]	1.1 [0.0–2.6]	98.9 [97.4–100]

W1: Wave 1; W2: Wave 2.
*$p < 0.001$.

Table 4
Prevalence and stability of cataplexy-like symptoms[a].

	Prevalence at W1	W1–W2 changes		
		Total Incidence	Chronic	Remitted
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Multiplex families (n = 1123)	5.5 [4.2–6.8]*	1.3 [0.6–2.0]	3.2 [2.2–4.2]	96.8 [95.8–97.8]
Simplex families (n = 2132)	2.9 [2.2–3.6]	0.7 [0.3–1.1]	2.4 [1.8–3.0]	97.6 [97.0–98.2]
Control (n = 178)	0	0	0	0

W1: Wave 1; W2: Wave 2.
*p < 0.001.
[a] Self-reported cataplexy defined as an episode of muscle weakness triggered by a strong emotion.

Table 5
Prevalence and stability of sleep paralysis.

	Prevalence at W1	W1–W2 changes		
		Total Incidence	Chronic	Remitted
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
First-degree				
Multiplex families (n = 431)	22.2 [18.3–26.1]*	15.8 [12.4–19.2]	34.2 [29.7–38.7]	65.8 [61.3–70.3]
Simplex families (n = 763)	9.0 [7.0–11.0]	10.3 [8.1–12.5]	46.4 [42.9–49.9]	53.6 [50.1–57.1]
Second-degree				
Multiplex families (n = 432)	13.6 [10.4–16.8]*	36.8 [32.3–41.3]*	33.3 [28.9–37.7]	66.7 [62.3–71.1]
Simplex families (n = 890)	8.3 [6.5–10.1]	6.0 [4.4–7.6]	33.3 [30.2–36.4]	66.7 [63.6–69.8]
Third-degree				
Multiplex families (n = 260)	7.7 [4.5–10.9]	25.9 [20.6–31.2]*	20.0 [15.1–24.9]	80.0 [75.1–84.9]
Simplex families (n = 479)	8.2 [5.7–10.7]	2.4 [1.0–3.8]	0.0	100.0
Control (n = 178)	6.2 [2.7–9.7]	9.2 [5.0–13.4]	11.1 [6.5–15.7]	88.9 [84.3–93.5]

W1: Wave 1; W2: Wave 2.
*p < 0.001.

multiplex families with the exception of incidence among second-degree relatives.

The relative risk of having hypnagogic hallucinations at W2 was 3.8 [2.7–5.2] among first-degree and 2.9 [1.9–4.4] among third-degree relatives from multiplex families compared with the control group.

Predictive factors for hypnagogic hallucinations at W2 in multiplex families were presence of hypnopompic hallucinations at W1 (RR 2.4 [1.0–5.9]; p = 0.05) and cataplexy-like symptoms at W1 (RR 3.4 [1.5–7.8]; p = 0.004).

For simplex families, having hypnopompic hallucinations (RR 4.0 [1.9–8.8]; p < 0.004), reporting early morning awakenings (RR 1.3 [1.0–1.7]; p = 0.05) and being 65 y.o. or older (RR 5.3 [1.8–15.6]; p = 0.02) predicted hypnagogic hallucinations at W2.

4. Discussion

Our research is one of the first to study the longitudinal evolution of narcolepsy symptoms in family members of individuals with narcolepsy. Furthermore, we are one of the first to distinguish between multiplex and simplex families and to distinguish between, first-, second- and third-degree relatives. Interestingly, while for many cases, the additional family member(s) identified with narcolepsy was a first degree-relative, it was not uncommon, to find some narcolepsy cases among the second- and third-degree relatives. Compared with the control group, both multiplex and simplex family members presented higher rates of hypersomnolence. However, the long-term evolution of this symptom was comparable between simplex families and the control group (ie, incidence and chronicity were similar in both groups). Conversely, it was clearly different for multiplex families where the incidence was twice as high and the chronicity even greater, compared to simplex families and the control group. Other family studies [21–23] have reported a high number of first-degree relatives with hypersomnolence; up to 44% in one study [24].

Of note, BMI was among the significant predictors of hypersomnolence at the second evaluation: the heavier the family members were, the greater the risk of being hypersomnolent a few years later. A similar finding was obtained recently in the Sleep

Table 6
Prevalence and stability of hypnagogic hallucinations.

	Prevalence at W1	W1–W2 changes		
		Total Incidence	Chronic	Remitted
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
First-degree				
Multiplex families (n = 431)	20.1 [16.3–23.9]	13.6 [10.4–16.8]*	19.5 [15.8–23.2]*	80.5 [76.8–84.2]
Simplex families (n = 763)	16.0 [13.4–18.6]	6.7 [4.9–8.5]	8.1 [6.2–10.0]	91.9 [90.0–93.8]
Second-degree				
Multiplex families (n = 432)	16.0 [12.5–19.5]	6.6 [4.3–8.9]	5.8 [3.6–8.0]*	94.2 [92.0–96.4]
Simplex families (n = 890)	15.4 [13.0–17.8]	3.5 [2.3–4.7]	2.4 [1.4–3.4]	97.6 [96.6–98.6]
Third-degree				
Multiplex families (n = 260)	26.9 [21.5–32.3]	11.2 [7.4–15.0]*	17.1 [12.5–21.7]*	82.9 [78.3–87.5]
Simplex families (n = 479)	22.6 [18.9–26.3]	2.8 [1.3–4.3]	3.2 [1.6–4.8]	96.8 [95.2–98.4]
Control (n = 178)	5.7 [2.3–9.1]	4.6 [1.5–7.7]	5.3 [4.3–6.1]	94.7 [91.4–98.0]

W1: Wave 1; W2: Wave 2.
*p < 0.001.

Heart Health Study [25]. The authors found that weight gain had a detrimental effect on somnolence that could only be partially explained by the severity of OSA.

Cataplexy-like symptoms (ie, muscle weakness linked to strong emotions) were only reported by narcoleptic family members. The prevalence was higher in multiplex families but the incidence and the chronicity were comparable between multiplex and simplex families. Few studies have reported rates of isolated cataplexy among family members. One reported a rate of 5.9% among first-degree relatives [21].

Sleep paralysis was more common in multiplex families, and had a high incidence in second- and third-degree relatives of multiplex families. Unlike hypersomnolence, sleep paralysis was mostly chronic. As stated previously, the simplex families were similar in terms of incidence and prevalence. Sleep paralysis is a fairly common symptom among first-degree relatives with prevalence ranging from 5.1% to 21.9% [21,23].

Factors predictive of sleep paralysis were mostly symptoms suggestive of REM sleep abnormalities such as sleep-related hallucinations or cataplexy-like symptoms. This is in sharp contrast with hypersomnolence in which predictive factors were more physical and/or mental health related.

4.1. Limitations of the study

There were several limitations in our study. First, we did HLA typing for only a part of the family members (483 individuals, 51% of them were HLA-DQB1*0602 positive). We did not perform polysomnographic recordings on the family members. Therefore, we cannot guarantee with 100% certainty the characterization of simplex families since undiagnosed family members might have been present in families we identified as simplex. Nevertheless, the longitudinal data, the size of the sample and the ability to distinguish between close and extended families offered a unique opportunity to see how symptoms evolved overtime.

5. Conclusions

Our study demonstrates the value of independently investigating multiplex and simplex families rather than simply only characterizing family members according to the presence or absence of narcolepsy spectrum symptoms. Our results strongly suggest that individuals from multiplex families are at greater risk of a broad range of symptoms and may benefit from close follow-up.

Author contributions

MMO contributed to the conception and design of the study. MMO, JB, AK, CMS, TJS, RB and CCW contributed to acquisition and analysis of data and MMO, JB, AK, CMS, and TJS contributed to the drafting of the manuscript.

Acknowledgements

This study was supported by a grant from NIH (R01NS044199), the Arrillaga Foundation and unrestricted educational grant from Jazz Pharmaceuticals.

Conflicts of interest

Nothing to report.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.06.015.

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