Environmental factors in the development of narcolepsy with cataplexy. A case-control study

Rosa Peraita-Adrados, Rafael del Río-Villegas, Antonio Vela-Bueno

Introduction. Epidemiological studies suggest the importance of environmental factors in the etiology of narcolepsy-cataplexy in genetically predisposed subjects.

Aim. To assess the role of environmental factors in the development of narcolepsy-cataplexy, using a case-control design with control subjects being matched for ethnicity and age.

Patients and methods. All patients were recruited through two outpatient clinics at the community of Madrid, ant the diagnosis of narcolepsy fulfilled the criteria of the International Classification on Sleep Disorders-2005. A questionnaire, including 54 environmental psychological stressor life events and 42 infectious diseases items, was administered to 54 patients. We specifically assessed the stressful factors and infectious diseases that occurred in the year preceding the onset of the first symptom of narcolepsy (excessive daytime sleepiness and/or cataplexy). The same questionnaire was administered to 84 control subjects recruited from non-related family members of the same community.

Results. Fifty four patients (55.6% males) answered the questionnaire, The mean age at onset of the first symptom was 21.6 ± 9.3 years, and the mean age at diagnosis was 36.5 ± 12.4 years. The main finding in narcoleptic patients as compared to control subjects was major changes in the 'number of arguments with partner, family, or friends' (odds ratio: 5.2; 95% confidence interval: 1.8-14.5). This can be interpreted as having a protective function and it suggests that psychological mechanisms are present since the beginning of the disease. As for the infectious factors, chickenpox was the most frequently reported. No significant differences were found in terms of total numbers of stress-related and infectious factors between cases and controls.

Conclusion. Prospective studies regarding the interaction between environmental and genetic factors are warranted.

Key words. Environmental factors. Epidemiology. Infectious diseases. Life events. Narcolepsy with cataplexy. Stress factors.

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Introduction

Narcolepsy is a chronic sleep disorder caused by a deficiency in hypothalamic hypocretin neurotransmission, through a selective loss of hypocretin producing neurons [1-3]. This very specific mechanism of neural destruction potentially points to an autoimmune process. The hypothesis that narcolepsy has an autoimmune etiology is based on its tight association with HLA-DQB1*06:02 [4] representing an almost necessary, but not sufficient, risk factor for narcolepsy since approximately 20% of the general healthy population carries the same haplotype. The autoimmune hypothesis fits also with onset of excessive daytime somnolence (EDS) in the juvenile-peripubertal period in many cases; also, the presence of environmental factors and the selective destruction of hypocretin-containing neurons, although no direct evidence is available, support that hypothesis.

The prevalence of narcolepsy with cataplexy has been assessed in many studies and falls between 25 and 50 per 100,000 people [5]. Information on incidence is limited, with one study finding the incidence of narcolepsy with cataplexy to be 0.74 per 100,000 person-years [6]. Luca et al [7] emphasized the extremely long diagnostic delay in Europe with age and gender substantially affecting symptoms.

Most patients suffer from the non-familial (or sporadic) form of narcolepsy, but genetic factors still play a role. The monozygotic twin concordance rate for narcolepsy is 36% [8,9]. Evidence indicates that narcolepsy with cataplexy is a complex disorder with genetic and environmental contributions.

Epidemiological studies emphasize the importance of environmental risk factors in the etiology of narcolepsy-cataplexy (NC) in genetically predisposed patients. Orellana et al [10] were the first to study systematically the major life psychological stressors that occurred in the previous year to the onset of NC symptoms onset using a structured questionnaire. The results showed that 84% of narcolepsy patients reported one or more life stressful

events in the year prior to symptoms onset compared with 36% in a matched year for the control group. In another case-control study –using a self-administered questionnaire– among the infectious disorders examined, only flu infections and unexplained fevers carried a significant risk [11]. Several of the life stressors carried a significant risk including a major change in sleep habits, a finding that replicated those of previous studies [10-12].

The search for etiologic factors has yet to yield important associations as these factors are suspected to act as cumulative triggers. Identification of modifiable risk factors will help to prevent the disease [13].

Recent studies have reported associations with infections by *Streptococcus pyogenes* [14-17], upper airway infections [18], including those with seasonal and annual patterns such as H1N1 influenza [19], as well as with H1N1 vaccinations [20, 21]. Thus, hypocretin neurons might become damaged in subjects with genetic predisposition triggered by environmental factors. The autoimmune response could be an acute one with symptoms of narcolepsy appearing when most neurons are damaged, and this explains the absence of inflammatory signs or autoantibodies once the condition is diagnosed, in most cases 10 or more years later [7].

The aim of the present study was to evaluate potential exposition to life stressful events and/or infectious disorders in the year preceding the onset of narcolepsy in a case-control study, using controls matched for the age at onset of the first symptom (which has not previously taken into account).

Patients and methods

The study was conducted at the Sleep Disorders Unit of the University Hospital Gregorio Marañón and the Sleep Unit of La Paz University Hospital of the Community of Madrid (Spain). We included 54 white patients with narcolepsy with cataplexy diagnosed in our Sleep Units during the last 20 years, and with an outpatient follow-up of at least once a year. A questionnaire was administered to patient and control participants. We specifically asked about 54 environmental stressor factors and 42 infectious diseases taking place in the year preceding the onset of the first symptom suggestive of NC: excessive daytime somnolence (EDS) and/or cataleptic attacks. The list of the potentially stressful life events was a slightly modified translation of an adaptation of the Social Readjustment Rating Scale [22] by Picchioni et al [11]. The list of infectious factors derived from published recommendations of the questionnaire assessment of environmental risk factors for multiple sclerosis [23] (Table I).

The data from the questionnaires were collected in a database and matched for age at the onset of symptoms with those of 84 white control participants recruited from non-related family members and the same local community members than the patients. The study was performed during the period between November 1st 2011 and December 31st 2012, and was approved by the local ethic committees. A written informed consent was obtained from all subjects participating in the study.

Diagnostic procedure

The evaluation of patients with NC consisted of a careful clinical history, complete physical (including anthropometric measurements such as weight, height and BMI) and neurological examinations, Epworth Sleepiness Scale (ESS) and Ullanlinna Narcolepsy Scale. The diagnosis of narcolepsy was made according to the International Classification of Sleep Disorders (ICSD-2) [24]. The diagnostic criteria included the presence of EDS ≥ 3 months and typical cataplexy not explained by other medical or psychiatric disorders. Diagnosis was confirmed by an overnight video-polysomnographic recording (EEG, EOG, EKG, submental and tibialis anterior EMGs, nasal-oral air flow, thoracic and abdominal effort, and SaO2) followed by a MSLT (sleep latency ≤ 8 minutes, ≥ 2 SOREMPs). The procedures were completed with the HLA class II molecular typing for DQB1*06:02. Whenever possible the levels of Hcrt-1 were obtained from the CSF (cut-off ≤ 110 pg/mL).

Control group assessment

For the assessment of the control group (CG) 84 control participants were recruited from non-related family members and matched for age. The questionnaire were self-administered and subjects were asked about the pertinent conditions appearing the year before the interview. Cases and controls were interviewed in person by one of us.

Statistical analysis

Data are reported as mean ± SD. The Mann-Withney and squared chi tests were used for the comparison of parametric variables. Differences were considered as statistically significant if $p < 0.05$. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI).

Results

Fifty-four narcoleptic patients answered the questionnaire (55.6% males). The mean age at the onset of excessive sleepiness and/or cataleptic attacks was 21.6 ± 9.3 years (range: 6-36 years) and the mean age at diagnosis was 35.3 ± 14.5 years (range: 18-61 years). Controls were more likely to be women (64.3%) and older (36.58 ± 12.4 years) than the patients at the onset of the disease, although non-significantly. There were no significant differences in the number of stressors or infections between cases and controls.

Psychological stress related factors

Univariate logistic regression analysis showed statistically significant differences on 'trouble at school' and 'major change in sleeping habits' items in NC compared with controls.

Multivariate logistic regression analysis showed significant difference between groups was found for the item 'major change in the number of arguments with partner, family, or friends' was a protective factor and increased 5.2 fold (95% CI: 1.8-14.5) in narcoleptic patients (Table II).

Infectious diseases

In univariate logistic regression analysis, among the 42 infectious conditions of the questionnaire, only chickenpox occurred more common among the subjects with NC in the year before onset, compare with control

Multivariate logistic regression analysis adjusted for gender and age (first symptom in patients and age of interview in controls) did not show any significant differences between narcoleptics and controls regarding infectious factors.

Discussion

There is limited evidence to support the view that the environmental risk factors are of major importance in the etiology of NC. However, twin studies report only 25-31% of concordance suggesting a major contribution of environmental factors.

Birth order and early childhood infections may play a role in autoimmune diseases, and both factors may be involved in the etiology of narcolepsy [25]. The month of birth has been proposed as a risk factor for narcolepsy [26-28] suggesting a harmful influence of factors acting during early development. Several authors have described an excess of

Table I. List of stressors and infectious factors included in the questionnaire [11].

Stressors factors	Infectious diseases
1 Change in the number of arguments between your parents	1 Measles
2 Your parent lost his/her job when you were a child	2 Mumps
3 Change in your acceptance by your peers	3 Rubella
4 Divorce of parents	4 Chickenpox
5 Jail term of close friend or family member	5 Scarlet fever
6 Parent remarried	6 Diphtheria
7 Trouble at school	7 Mononucleosis
8 Change in alcohol or drug use	8 Whooping cough
9 Changed schools	9 Impetigo
10 Began or ended an intimate relationship	10 Conjunctivitis
11 Beginning or ceasing formal schooling	11 Encephalitis
12 Engagement or broken engagement	12 Meningitis
13 Change in independence	13 Hand-foot-and-mouth disease
14 Changing course of study	14 Reye syndrome
15 Marriage	15 Dancing eyes syndrome
16 Trouble with the boss	16 Herpangina
17 Detention in jail or other institution	17 Pleurodynia
18 Death of a close friend or family member	18 Myopericarditis
19 Major change in sleeping habits	19 Hepatitis A
20 Major change in eating habits	20 Hepatitis B
21 Foreclosure on a mortgage or loan	21 Hepatitis C
22 Revision of personal habits	22 Pyelonephritis
23 Ticketed for a minor violation of the law	23 Neuritis
24 Arrested for a major violation of the law	24 Tonsillitis
25 Outstanding personal achievement	25 Herpes zoster
26 You or your partner gave birth to a child	26 Tuberculosis
27 Major change in the health of a close friend or family member	27 Urinary tract infection
28 Sexual adjustment problems	28 Osteomyelitis
29 Trouble with in-laws	29 Pneumonia
30 Major change in number of family gatherings	30 Typhoid fever
31 Major change in financial state	31 Gastroenteritis
32 Addition of a new family member	32 Ear infection
33 Change in residence	33 Strep throat
34 Your child leaving home	34 Rabies
35 Marital or partner separation	35 Lyme disease
36 Marital or partner reconciliation	36 Unexplained fever
37 Major change in religious activities	37 Frequency of the common cold
38 Fired from a job	38 Frequency of flu infections
39 Divorce	39 Frequency of sinus infections
40 Changed jobs	40 Colds in the year before onset
41 Major change in the number of arguments with your partner, family, or friends	41 Flu infections in the year before onset
42 Major change in responsibilities at work	42 Sinus infections in the year before onset
43 Partner began or ended a job	
44 Major change in working hours or conditions	
45 Major change in recreational activities	
46 Began a mortgage	
47 Major personal injury or illness	
48 Major business readjustment	
49 Major change in social activities	
50 Major change in living conditions	
51 Major vacation	
52 Retirement	
53 Diagnosis of depression, anxiety, or other mental illness	
54 Head injury that caused a loss of consciousness or required medical attention	

Table II. Statistical analysis (univariate and multivariate logistic regression).

			p	Odds ratio	Min-Max
Univariate logistic regression	Psychological stressor factors	Trouble at school	0.01 [a]	7.13	1.45-35.00
		Major change in sleeping habits	0.03 [a]	2.59	1.05-6.35
		Major change in the number or arguments with your partner, family or friends	0.002 [b]	0.25	0.10-0.60
	Infectious diseases	Chickenpox	0.05	4.18	0.99-12.18
Multivariate logistic regression adjusted for gender and age	Psychological stressor factors	Major change in the number or arguments with your partner, family or friends	0.002 [b]	0.19	0.06-0.54

[a] $p < 0.05$; [b] $p < 0.01$

births in March in those who developed narcolepsy later in life, although studies in this realm-lack appropriate statistical analyses [29, 30]. Careful matching and statistical analysis, however, found no effect of birth month on the occurrence of narcolepsy [31]. Therefore, this aspect remains controversial. It has been hypothesised that exposure to pathogens in utero may increase the risk of the disease. Against this hypothesis is the mentioned the high rate of discordance in monozygotic twins [8,9].

Among the 42 infectious conditions of the questionnaire, chickenpox and sore throat were the most frequently found in the year preceding NC onset, although not in a significant manner. The hygiene hypothesis supports the idea that microbial infections play an important role in the maturation of the immune system, regulating the risk of allergy. This idea has been extended to autoimmune diseases, suggesting that infections may protect against both by a common mechanism [32]. This mechanism would be related to the induction of immune regulation by infections in early childhood, and a reduced exposure to microbes could lead to an over-reaction of immune responses involved in both autoimmune and allergic disorders. That could explain why allergic and autoimmune diseases coexist more frequently than expected. The association between NC and immune-pathological disorders has recently been addressed [33], indicating that the prevalence of comorbid immunopathological diseases is high in NC. In addition, the age of diagnosis is earlier and cataplexy is significantly more severe than in patients without comorbidities.

The stress related factor –'major change in the number of arguments with partner, family, or friends'– appears to be a 'protective factor' for susceptible individuals and is more than fivefold in our NC series. Our data suggest that individuals may start to feel changes at a subclinical level and try to protect themselves by avoiding the disturbing effects of interpersonal conflicts that might trigger the full-blown symptoms. This is in agreement with the observation of Kales and his group that patients with NC are 'overly concerned with emotional control' which may lead to 'their generalized lack of expressiveness and tendency to build-up emotional pressure' [34].

There are several limitations to our study. The controls were not HLA-DQB1*06:02 matched to the cases. There are no epidemiological studies in the Spanish population concerning the prevalence of NC, but there are studies on the prevalence of HLA-DQB1*06:02 in controls that demonstrate the presence of this allele in 15% of the population in our area far less from the figures of northern European populations [35]. The probability that a DQB1*06:02 negative subject develops NC is very low in our community. The control sample included more women than men and they were older when interviewed, compared with age at onset of first symptoms of the disease in narcolepsy patients, therefore this factor was minimized with the multivariate statistical adjustment.

Further studies, including the ongoing prospective epidemiological studies in Europe are warranted for a better understanding of the implication of risk

factors in the etiopathogeny of narcolepsy. The control of many of these factors can prevent the disease.

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Factores ambientales en la etiología de la narcolepsia-cataplejía. Estudio de casos y controles de una serie

Introducción. Los estudios epidemiológicos subrayan la importancia de los factores ambientales en la etiología de la narcolepsia con cataplejía en pacientes genéticamente predispuestos.

Objetivo. Evaluar el papel de los factores ambientales en la etiología de la narcolepsia-cataplejía utilizando un diseño de casos y controles comparados por edad y etnia.

Pacientes y métodos. Todos los pacientes fueron diagnosticados en nuestras unidades de sueño, según los criterios de la Clasificación Internacional de los Trastornos del Sueño de 2005. Utilizamos un cuestionario consistente en 54 preguntas relacionadas con acontecimientos psicológicos estresantes y 42 enfermedades infecciosas en 54 pacientes. Evaluamos específicamente la presencia de factores estresantes y/o infecciosos en el año previo al comienzo del primer síntoma de narcolepsia-cataplejía (somnolencia excesiva diurna y/o cataplejía). El mismo cuestionario se administró a 84 controles, miembros de la misma comunidad, sin relación de parentesco.

Resultados. Respondieron el cuestionario 54 pacientes (55,6%, hombres) (edad media del primer síntoma: 21,6 ± 9,3 años; edad media del diagnóstico: 36,5 ± 12,4 años) y 84 controles. El principal hallazgo fue un cambio importante en el 'número de discusiones con la pareja, la familia o los amigos' (*odds ratio*: 5,2; intervalo de confianza al 95%: 1,8-14,5) en los narcolépticos, lo que sugiere que los mecanismos psicológicos están presentes desde el comienzo de la enfermedad con una función protectora. La varicela fue el factor infeccioso más frecuente. No se obtuvieron diferencias significativas en el número de factores psicológicos estresantes e infecciosos entre los pacientes narcolépticos y los controles.

Conclusión. Estudios prospectivos epidemiológicos en series de individuos susceptibles genéticamente están justificados para aclarar la implicación de los factores ambientales en la etiopatogenia de la narcolepsia-cataplejía.

Palabras clave. Acontecimientos vitales estresantes. Enfermedades infecciosas. Epidemiología. Factores medioambientales. Narcolepsia con cataplejía.