Published in final edited form as:
J Sleep Res. 2010 March ; 19(1 Pt 1): 80–86. doi:10.1111/j.1365-2869.2009.00756.x.

Medical exposures in youth and the frequency of narcolepsy with cataplexy: a population-based case-control study in genetically predisposed people

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SUMMARY

Epidemiological observations suggest that exposures in youth may trigger narcolepsy in genetically predisposed individuals. In this population-based case–control study, we sought to identify all prevalent cases of narcolepsy with cataplexy aged 18–50 years as of 1 July 2001, in King County, Washington. The 45 eligible cases who were DQB1*0602-positive were compared with 95 controls with this allele, identified through random-digit dialing and buccal smears. Cases and controls were interviewed in person about physician-diagnosed infectious and non-infectious illnesses, immunizations, head trauma and parasomnias or psychiatric problems during youth. Narcolepsy with cataplexy was more frequent in African-Americans and in poorer households. Adjusting for these factors, the condition was 5.4-fold more common [95% confidence interval (CI) = 1.5–19.1] among people reporting a physician-diagnosed strep throat before the age of 21 years. No other significant associations with childhood diseases, immunizations or head trauma were found. However, prevalence was increased 16.3-fold (95% CI = 6.1–44.1) in subjects who reported having had ‘night terrors’. Strep throat may be related to narcolepsy with cataplexy in genetically susceptible individuals. The association with night terrors could simply reflect early symptoms of narcolepsy, or they could be a prodromal sign of disturbed sleep physiology. keywords epidemiology, head injuries, immunization, narcolepsy, night terrors, streptococcal infections

Keywords

epidemiology; head injuries; immunization; narcolepsy; night terrors; streptococcal infections

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DECLARATIONS OF INTEREST
None.

INTRODUCTION

Narcolepsy affects an estimated 25–50 per 100 000 people in the United States (Longstreth *et al.*, 2007). Although rarely fatal, this chronic condition can interfere with quality of life and increase the risk of injuries (Aldrich, 1989; Dauvilliers *et al.*, 2007). Available treatments help to control excessive daytime sleepiness and cataplexy but they do not cure the underlying disease and often carry side effects. Hence, ways to prevent narcolepsy are worth seeking.

The clinical, epidemiological and pathological features of narcolepsy offer some clues about where to look for potentially modifiable risk factors. A known strong association with histocompatibility complex, class II, DQ beta 1 (HLA-DQB1* 0602), especially in cases with cataplexy, suggests that some people have a genetic predisposition that may involve the immune system (Chabas *et al.*, 2003; Mignot *et al.*, 1995). Nonetheless, very few carriers of this relatively common allele develop narcolepsy, implying that other genetic or environmental cofactors must be involved. Twins are also often discordant for the disease (Chabas *et al.*, 2003). The first symptoms of narcolepsy usually begin in adolescence or early adulthood (Dauvilliers *et al.*, 2007; Silber *et al.*, 2002), suggesting that a precipitating exposure would typically have to occur early in life. This possibility is supported further by variation in the risk of narcolepsy according to month of birth in some studies, with a higher risk for those born in March and a lower risk for those born in September (Dauvilliers *et al.*, 2003; Picchioni *et al.*, 2004). Such a pattern might result from exposure during gestation or in early infancy to some seasonal environmental factor, possibly an infectious disease. Loss of hypocretin-producing cells in the lateral hypothalamus appears to be a critical pathological lesion (Wurtman, 2006). What triggers this selective cell death is unknown, but an analogy with selective neuronal loss in Parkinson's disease has raised suspicion that a specific neurotoxin might be involved.

We conducted a population-based case–control study of narcolepsy with cataplexy, investigating a wide range of exposures in early life that might be contributing causes among genetically predisposed individuals. Included in this exploratory search were childhood illnesses (infectious and non-infectious), immunizations, head trauma and parasomnias or psychiatric conditions.

METHODS

Cases and controls were recruited in King County, Washington, the state's most populous county, with a population of about 1.81 million in 2005 (Washington State Office of Financial Management, 2006).

Cases

The parent study sought to identify all prevalent physician-diagnosed narcolepsy cases who were aged 18 years or older and residing in King County as of 1 July 2001. The search for qualifying cases extended from July 2001 to June 2005. Eligible cases and controls had to be aged 18–50 years, speak English and test positive for the DQB1*0602 allele. Cases were identified by (i) surveillance through all 10 sleep disorder clinics; (ii) monthly letters to all sleep center clinicians and neurologists; (iii) one-time letters to all family medicine physicians, community clinic physicians and psychiatrists; (iv) presentations at local narcolepsy support groups; (v) flyers in area pharmacies; and (vi) advertisements and public service announcements.

Of the 425 cases aged 18 years or older who were eligible for the parent study, 78 could not be located, 10 could not be interviewed due to language and 58 declined, leaving 279

completed interviews. Of these, 138 (49%) were positive for the DQB1*0602 allele, and 67 were in the 18–50 year age range with a confirmed physician diagnosis of narcolepsy.

Because it was not feasible to require diagnostic confirmation through sleep studies on all cases countywide to minimize diagnostic misclassification the case–control comparisons reported here were restricted further to 45 cases with cataplexy. For 29 of these cases, medical records were available, and cataplexy was documented therein by a physician. For the remaining 16 cases the presence of cataplexy was based on interview responses, following the algorithm of Anic-Labat *et al.* (1999). Specifically, subjects were asked 'Do you currently experience, or have you ever experienced, episodes of muscle weakness, such as weakness in your legs or buckling of your knees, during the following situations: (i) when you tell or hear a joke or (ii) when you laugh?'. Cataplexy was classified as present when the respondent answered yes to (i) or no to (i) but yes to (ii).

Controls

Controls were recruited by random-digit telephone dialing. From August 2002 to May 2004, each randomly generated telephone number was called up to nine times. For working residential numbers, the household was screened to determine whether an adult aged 18–50 years resided there. If so, one was chosen at random. Then an age- and gender-specific selection probability was used to determine whether that adult was invited to participate.

From May 2004 to March 2005, the more efficient Mitofsky–Waksberg method was used to select telephone numbers to be called (Waksberg, 1978). For working residential numbers, a household census of adults aged 18–50 years was taken. Selection probabilities were then applied to all age-eligible adults. If one was selected, the caller attempted to recruit that person. If more than one were selected, one was chosen at random and invited to participate.

Within-household sampling of potential controls used the randomized recruitment method (Weinberg and Sandler, 1991). Age- and gender-specific sampling fractions were applied to potential controls to make the distribution of controls resemble the projected distribution of cases on age and gender. Sampling fractions ranged from 0.352 for males aged 36–40 years to 1.000 for females aged 36–40 years.

Of the 61886 telephone numbers called, 9399 numbers were found to be working residential numbers and 5108 numbers had unknown residential status. After distributing the numbers with unknown residential status between those eligible (residential) and ineligible (non-residential) in the same proportions as among those with known eligibility status, we estimated the number of working residential phone numbers to be 10244. Of these, 3999 telephone numbers (39%) furnished the necessary information about household demographic composition. Of the 1202 controls in these households who were eligible to participate in the study, 520 declined participation at the initial telephone contact, 84 could not be located subsequently and 150 refused later when contacted by a study coordinator. The remaining 448 completed interviews. The overall response rate of those screened and eligible who completed the survey was 37%.

Data collection

Cases and controls were interviewed in person by a trained interviewer using a standardized questionnaire. Respondents completed a life-events calendar to record salient events such as graduating from school and births of siblings or children. Subjects who reported having been diagnosed by a physician as having a medical condition were asked which medications, if any, they had taken for it. Head trauma episodes were counted only if they occurred before onset of narcolepsy symptoms among cases or at a comparable age among controls. During

the interview, 99% of cases and controls provided a buccal smear for DNA which was tested for HLA-DQB1*0602, as described elsewhere (Gersuk and Nepom, 2006).

Analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). For control i, a final sampling probability, P_i, was incorporated into the logistic model using $-\ln(P_i)$ as an offset term (Weinberg and Sandler, 1991). Exposure prevalences reported for controls were weighted estimates, using weight $w_i = 1/P_i$ for control i; ns shown were unweighted.

As shown below, age and gender proved not to be important confounders, but strong associations were found with African-American race and socioeconomic status, particularly annual household income. Income data were missing for four cases and seven controls. Rather than drop these subjects from analysis, we multiply imputed household income for them (van Buuren *et al.*, 1999; Rubin and Schenker, 1991). The imputation model for income included age, black race, education, interview year and case–control status as predictors, using the 'mice' package in the r statistical language (R Development Core Team, 2006). This process resulted in five imputed income values for each case or control with missing income data. The main analyses were then run in parallel on five datasets that differed only in their imputed income values. The five sets of results were then combined using standard formulas according to Rubin and Schenker (1991).

All analyses were conducted with R version 2.5 (R Development Core Team, 2006). The study was reviewed and approved by the University of Washington Institutional Review Board.

RESULTS

Cases and controls were similar on age and gender (Table 1). However, cases were more likely to be African-American (OR = 7.6, 95% CI = 1.9–30.9), to have lower educational attainment and to come from households with significantly lower annual income. Nearly all cases (96%) reported having been treated with amphetamines or other nervous system stimulants, 56% with antidepressants, 7% with gamma hydroxybutyrate (GHB) and 16% with other drugs.

Table 2 shows no evidence of higher prevalence of narcolepsy with cataplexy when the subject was known to have had low birth weight, although the CI was wide. Although the condition was less common among individuals born in July–September, the association with season of birth fell short of statistical significance.

Cases and controls were asked whether they had ever been diagnosed by a physician with various infectious illnesses before they attained the age of 21 (Table 3). Most conditions were uncommon in both groups. However, significantly more cases (90%) reported strep throat (adjusted OR = 5.2, 95% CI = 1.6–16.8). No significant associations were found with specific antibiotics for any of these conditions (not shown).

Table 4 compares cases and controls on various physician-diagnosed non-infectious conditions before age 21 years. Two cases and one control reported having had arthritis as a child, leading to a significantly elevated OR. A follow-up question asked was 'Did a physician ever diagnose you with rheumatic fever?', but no cases or controls answered affirmatively to this question. No other statistically significant associations were found.

Table 5 compares cases and controls on frequency of immunizations before age 21. Similarly high proportions of cases and controls reported vaccination against polio, diphtheria, tetanus, pertussus, measles, mumps and rubella. Vaccination against hepatitis or varicella were uncommon but similar between cases and controls.

Approximately 28% of cases and 30% of controls reported at least one head trauma episode, and narcolepsy status was not related significantly to number of head trauma episodes (Table 6). Similarly, approximately the same proportion of cases as controls reported several indicators of more severe head trauma: loss of consciousness, receipt of medical care or residual disability.

Finally, Table 7 compares the groups on history of parasomnias or psychiatric problems before 21 years. The most striking association was found with night terrors: more than half of cases reported having had night terrors, compared with fewer than 12% of controls (adjusted OR = 14.9, 95% CI = 5.7–39.0).

DISCUSSION

In this population-based case–control study of narcolepsy with cataplexy, we found a fivefold increase associated with a history of physician-diagnosed strep throat before age 21 and a 15-fold increase with night terrors. Narcolepsy was also more common among African-Americans, and was associated negatively with education and annual household income.

Several study limitations should be noted. First, the number of cases was small, in part because the study was confined to genetically predisposed individuals. Confidence limits were wide, and modest associations might have escaped detection. Second, although we used multiple means to identify cases, we cannot be sure that all eligible cases were captured. In other analyses (Longstreth *et al.*, 2008) we found that narcolepsy was somewhat less common than was reported for Olmsted County, MN, where surveillance through medical records was possible (Silber *et al.*, 2002). Third, it was not possible on a population scale to confirm the diagnosis of narcolepsy through formal sleep studies. The relatively low prevalence (49%) of the HLA-DQB1*0602 allele among all cases identified originally may imply that the condition is over-diagnosed. However, restricting the case group in this analysis to cases with cataplexy should have minimized diagnostic misclassification. Fourth, reflecting the growing difficulty of randomdigit dialing, the estimated response rate for controls was less than 40%. We sought to minimize bias by controlling statistically for African-American race and annual household income, which have been associated with survey participation (Groves *et al.*, 1988). Fifth, the study relied on self-report for exposure ascertainment. We sought to avoid false-positive reports by asking specifically about physician-diagnosed illnesses. Finally, in order to generate new hypotheses about causes, we explored multiple potential etiological exposures which creates a multiple-testing problem. Attempts to confirm or refute these findings elsewhere may be especially worth-while.

The association between narcolepsy and strep throat observed here could simply reflect chance, in light of the multiple exposures considered. Previous studies of anti-strep-tococcal antibodies, such as against streptolysin O and deoxyribonuclease B, and narcolepsy have yielded inconsistent results (Billiard *et al.*, 1989; Montplaisir *et al.*, 1989; Mueller-Eckhardt *et al.*, 1990). By analogy, Sydenham's chorea is a delayed complication of certain Group A streptococcal infections (Stollerman, 2001). Because of the long delay in onset of symptoms and diagnosis after the initial streptococcal infection, streptococcal antibody titers are often normal and cannot be used to verify this exposure. Clinical manifestations also vary among streptococcal strains, as defined by their M protein and associated superantigenic moieties,

and by genetic make-up. Patients with the DRB1*1501/DQB1*0602 haplotype have been found to respond differently to Group A streptococcal infections than do other patients (Kotb *et al.*, 2002). Perhaps this haplotype which is a strong genetic marker for narcolepsy presents the superantigens of the M proteins in a manner that triggers an autoimmune response and leads to selective neuronal loss. Sydenham's chorea and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections appear to provide biological precedents for such a mechanism (Dale, 2005; Longstreth *et al.*, 2007). Other still unidentified cofactors may also be required, which could explain why controls with the same genetic marker and a strep throat history remained unaffected. In any case, the association observed with arthritis appears to be unrelated, as no cases or controls reported having had rheumatic fever. The arthritis finding may simply be an artifact of small numbers.

One of the strongest associations we observed was between a self-reported history of night terrors and narcolepsy. The interviewee was asked only 'Before you turned 21, did you ever have problems with night terrors?'. In other studies, the reported frequency of night terrors has been found to depend strongly upon the specific wording of questions about them (Hublin *et al.*, 1999). Some respondents in the present study may have reported as 'night terrors' early symptoms of narcolepsy itself: hypnagogic or hypnopompic hallucinations, which can be perceived as threatening and can interrupt sleep (Dauvilliers *et al.*, 2007). Some may have reported as 'night terrors' symptoms of rapid eye movement behavioral disorder, which can involve violent motor behavior during sleep and has been reported to accompany some cases of early narcolepsy (Nevsimalova *et al.*, 2007). Occurrence of night terrors could also be an early sign of disturbed sleep physiology that in some cases may precede more characteristic symptoms of narcolepsy. In any case, this result agrees with the high prevalence of several forms of parasomnia found in a series of 41 patients with narcolepsy and definite cataplexy at a Swiss sleep clinic (Sturzenegger and Bassetti, 2004). A recent review of disturbed sleep patterns in narcolepsy with cataplexy also noted that over 60% of cases in some series report 'vivid and frightening dreams' (Plazzi *et al.*, 2008).

The lack of association seen here between narcolepsy with cataplexy and several other exposures may be viewed as pertinent negatives. No significant association was found for any form of vaccination, which might be suspected as a possible trigger for autoimmunity. Previous head trauma was no more common or more severe among people with narcolepsy than among controls. Much of the evidence for the existence of 'post-traumatic narcolepsy' comes from case reports or case series (Bruck and Broughton, 2004; Ebrahim *et al.*, 2005; Good *et al.*, 1989; Lankford *et al.*, 1994), which cannot account for the possibility of a spurious co-occurrence of head trauma and narcolepsy (Silber, 2005). In agreement with another study, narcolepsy was not associated with migraine (DMKG Study Group, 2003). There was a trend towards lower prevalence among people born during the summer months, in general agreement with other studies (Dauvilliers *et al.*, 2003; Picchioni *et al.*, 2004), but the observed variation in relation to season of birth fell short of statistical significance.

We also found incidentally that narcolepsy was more common among African-Americans and those with lower education and household income. These observations argue against the possibility that variations in the apparent frequency of narcolepsy merely reflect differences in access to sleep centers where the diagnosis is made. The observed association with race is also unlikely to be due solely to racial differences in willingness to participate in telephone surveys, from which our controls were derived, because a separate analysis found higher prevalence in African-Americans using denominators from census data (Longstreth *et al.*, 2008).

The discovery of DQB1*0602 as a strong genetic risk factor for narcolepsy has created new opportunities to focus the search for environmental risk factors on genetically predisposed individuals. Given the probable importance of genetic– environmental interactions in the etiology of narcolepsy, future case–control studies may profit from considering HLA status when trying to confirm these findings and when searching for new environmental risk factors.

Acknowledgments

The authors thank Dr Vivian Gersuk and Dr Gerald Nepom for assistance with HLA genotyping and Ms Audrey Hendrickson and Ms Sarah Velde for study coordination. This work was supported by grant R01 NS38523 from the National Institute of Neurological Disorders and Stroke.

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J Sleep Res. Author manuscript; available in PMC 2012 May 05.

Table 1

Sociodemographic characteristics

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Odds ratio		P for trend
			Estimate	95% CI	
Age group (years)					0.14
18–25	28.9	18.0	1.0	Reference	
26–30	17.8	18.2	0.6	0.2–1.9	
31–35	20.0	17.7	0.6	0.2–1.9	
36–40	6.7	15.8	0.2	0.0–0.8	
41–45	11.1	17.2	0.3	0.1–1.2	
46–50	15.6	13.0	0.7	0.2–2.2	
Gender					
Male	26.7	41.9	1.0	Reference	
Female	73.3	58.1	1.6	0.7–3.7	
Race					
White	80.0	92.1	1.0	Reference	
African-American	13.3	1.4	8.1	1.9–34.3	
Asian American	2.2	0.9	2.0	0.2–23.0	
Hispanic	2.2	0.5	4.1	0.2–66.8	
Other	2.2	5.1	0.4	0.0–4.4	
Education					0.068
High school or less	33.3	24.3	1.0	Reference	
College	55.6	54.8	0.7	0.3–1.5	
Graduate school	11.1	20.9	0.3	0.1–1.1	
Annual income (imputed)					<0.001
Under $20K	40.9	18.2	1.0	Reference	
$20K–40K	24.9	23.3	0.4	0.1–1.1	
$40K–60K	18.7	11.7	0.5	0.2–1.7	
$60K +	15.6	46.8	0.1	0.0–0.3	

CI: confidence interval.

Table 2

Low birth weight and season of birth

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.	
			Estimate	95% CI	Cases	Controls
Low birth weight (below 2500 g)	5.6	5.8	0.9	0.1–6.1	9	19
Season of birth						
Winter (January–March)	24.4	20.4	1.0	Reference	0	0
Spring (April–June)	24.4	24.1	0.8	0.3–2.6		
Summer (July–September)	22.2	31.4	0.5	0.1–1.4		
Fall (October–December)	28.9	24.1	0.9	0.3–2.8		

CI: confidence interval.

*Adjusted for African-American race, annual income (four categories, multiply imputed).

Table 3

Childhood infectious diseases

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.	
			Estimate	95% CI	Cases	Controls
Strep throat	90.9	75.9	5.4	1.5–19.1	1	2
Pneumonia	18.2	19.9	1.0	0.3–3.0	1	0
Hepatitis	2.2	1.8	1.1	0.0–29.7	0	0
Infectious mononucleosis	15.6	14.1	1.6	0.5–5.0	0	0
Brain infection (e.g. meningitis or encephalitis)	6.7	0.0	Inf	0.0–Inf	0	0

CI: confidence interval.

*Adjusted for African-American race, annual income (four categories, multiply imputed).

Table 4

Non-infectious childhood medical conditions

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.	
			Estimate	95% CI	Cases	Controls
Heart problems	8.9	13.0	1.0	0.3–3.9	0	0
Arthritis	4.4	0.5	17.9	1.2–267.4	0	0
Diabetes	0.0	0.9	0.0	0.0–Inf	0	0
Severe headaches	8.9	7.2	1.9	0.4–9.1	0	1
Migraine	11.1	13.1	0.6	0.2–2.0	0	0
Seizures / epilepsy	8.9	3.3	4.3	0.7–27.8	0	0
Allergic / autoimmune condition	51.1	41.7	1.3	0.6–2.9	0	0
Radiation treatment to head	0.0	2.7	0.0	0.0–Inf	0	0
Other medical problem	57.8	46.8	1.4	0.6–3.2	0	0

CI: confidence interval.

*Adjusted for African-American race, annual income (four categories, multiply imputed).

Table 5

Childhood immunizations

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.	
			Estimate	95% CI	Cases	Controls
Polio	97.7	98.6	0.9	0.1–11.2	2	4
Hepatitis	29.7	24.8	1.0	0.4–2.5	8	13
Diphtheria	100.0	99.5	Inf	0.0–Inf	3	6
Pertussis	100.0	99.5	Inf	0.0–Inf	3	5
Measles	85.0	73.8	1.4	0.4–4.3	5	7
Mumps	85.0	70.6	2.0	0.7–6.0	5	6
Rubella	85.4	70.9	1.8	0.6–5.2	4	7
Varicella	2.3	5.7	0.3	0.0–2.8	2	2

CI, confidence interval.

*Adjusted for African-American race, annual income (four categories, multiply imputed).

Table 6

Head trauma prior to reference date

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.		P for trend
			Estimate	95% CI	Cases	Controls	
No. head injuries					0	0	0.9
0	71.1	69.7	1.0	Reference			
1	17.8	16.7	1.3	0.4–3.7			
2	6.7	10.3	0.6	0.1–2.7			
3+	4.4	3.4	1.4	0.1–14.2			
With loss of consciousness	11.1	10.5	1.0	0.3–3.8	0	0	
Had medical treatment	13.3	21.4	0.8	0.2–2.4	0	0	
With pierced skull	0.0	2.3	0.0	0.0–Inf	0	0	
With skull fracture	0.0	0.6	0.0	0.0–Inf	0	0	
Had stitches	8.9	8.1	2.3	0.5–9.7	0	0	
Had surgery	0.0	0.9	0.0	0.0–Inf	0	0	
With residual disability	2.2	0.0	Inf	0.0–Inf	0	0	

CI, confidence interval.

*Adjusted for African-American race, annual income (four categories, multiply imputed).

Table 7

Childhood parasomnias, behavioral and psychiatric conditions

Characteristics	% of cases (n = 45)	% of controls (n = 95)	Adjusted* odds ratio		Missing no.	
			Estimate	95% CI	Cases	Controls
Hyperactivity / ADD	6.7	4.8	1.2	0.2–7.0	0	0
Depression	22.2	14.0	1.4	0.5–4.0	0	0
Other psychiatric condition	11.1	2.6	5.4	0.9–32.2	0	0
Head-banging to go to sleep	2.2	0.9	1.6	0.1–27.4	0	0
Night terrors	59.1	11.8	16.3	6.1–44.1	1	1
Sleepwalking	26.7	14.6	1.8	0.7–0.6	0	2

CI, confidence interval; ADD, attention deficit disorder.

*Adjusted for African-American race, annual income (four categories, multiply imputed).