Epilepsy & Behavior 26 (2013) 114–117

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Tobacco habits in nocturnal frontal lobe epilepsy

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ARTICLE INFO

Article history:
Received 20 July 2012
Revised 27 September 2012
Accepted 11 October 2012
Available online 12 December 2012

Keywords:
Nocturnal frontal lobe epilepsy
Case–control study
Tobacco habits
Nicotine receptor
Cholinergic system

ABSTRACT

The beneficial effect of nicotine has been reported in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) patients, but not tested in sporadic cases. Recently, a nicotine defect in the arousal pathway has been hypothesized even in sporadic NFLE patients and their relatives. This case–control family study was designed to test whether NFLE subjects were more likely to use tobacco than controls, as an indirect marker of cholinergic arousal system dysregulation. At least four relatives were included for each NFLE proband and control. Each subject was questioned about tobacco habits; 434 individuals were recruited. Moreover, we compared NFLE patients with age- and sex-matched controls to determine whether they are more likely to use tobacco. We found a slightly higher trend of tobacco use in NFLE probands compared to that in control subjects; we did not find any significant difference in the distribution of tobacco use among NFLE group compared to that in the control group.

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1. Introduction

Nocturnal frontal lobe epilepsy (NFLE) is a focal epilepsy characterized by bizarre motor seizures recurring during sleep [1,2]. Large pedigrees with an autosomal dominant inheritance and sporadic cases have been described [1,3,4] without clinical differences [5]. Mutations in the *CHRNA4*, *CHRNB2*, and *CHRNA2* genes respectively encoding the α4, β2, and α2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR) have been reported in less than a quarter of families with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [4]. Mutations in CHRNA4 and CHRNB2 have been found even in sporadic cases [6–12].

Willoughby et al. [13] described one ADNFLE patient with a CHRNA4 mutation whose seizures were refractory to standard antiepileptic therapy and improved after treatment with nicotine transdermal patches. The beneficial effect of nicotine on seizure frequency was later reported in 9 out of 22 subjects from two ADNFLE Norwegian pedigrees with CHRNA4 mutations [14]. These data suggest that nicotine consumption is an environmental factor reducing susceptibility to seizures in ADNFLE patients and, hence, that transdermal nicotine should be considered in pharmacoresistant NFLE cases [13,14].

The pathogenetic role of nicotine has yet to be clarified in NFLE [4,15]. Experimental data on animals showed that nicotine injection induced a pathological locomotor activity and an escape reaction by binding to nAChR in the cells of the ventral tegmental area (VTA). The VTA is part of the ascending arousal system, and it could be argued that its abnormal functioning could trigger automatic exploratory behaviors related to arousal, like sleepwalking and epileptic nocturnal wandering [16]. This might suggest that nicotinic 'overactivity' of the mutated receptors is responsible for the arousal phenomena in humans and would contradict the idea of a therapeutic effect of nicotine. However, the chronic use of nicotine has been documented to desensitize nAChR [17], and this would account for the beneficial effect demonstrated in ADNFLE patients with known nAChR mutations [13,14].

Recently, we hypothesized that sporadic NFLE patients also have a molecular dysfunction in the pathways regulated by nACh receptors that is inherited by their relatives or even transmitted across the unaffected relatives [18]. This pathogenetic hypothesis originated from our finding of a higher frequency of arousal parasomnias not only in NFLE patients but also in their unaffected relatives, suggesting an inherited dysregulation of the nicotine mediated cholinergic arousal pathway [18].

A dysregulation of the cholinergic system has also been documented on the basis of proneness to tobacco use by experimental data on animals and humans [19–21].

Nicotine is the principle addictive component driving continued tobacco use despite users' knowledge of the dangerous consequences. This substance initiates addiction by directly involving the neural circuitry that normally reinforces reward-seeking behaviors [22]. Mesocorticolimbic circuitry that includes the dopaminergic pathway originating in the VTA and projecting to the nucleus accumbens is recognized as vital for reinforcing behaviors during the initiation of nicotine addiction [19,23–25]. In the midbrain, nACh receptors are essential for nicotine-induced reinforcement and release of dopamine [19,26].

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http://dx.doi.org/10.1016/j.yebeh.2012.10.014

All these findings supported the hypothesis that proneness to tobacco consumption should be an indirect marker of a dysfunction of the cholinergic ascending arousal system because of the reward process and of a possible beneficial effect both on seizures and/or on arousal disorders.

We recently designed a case–control family study to explore the frequency of arousal parasomnias in NFLE patients and their relatives [18]. Our present study is an ancillary investigation. Its primary aim was to test whether the NFLE group was more likely than the control group to use tobacco, as an indirect marker of a dysregulation of the cholinergic arousal system. The secondary aim was to compare NFLE patients with age- and sex-matched controls to determine whether they are more likely to use tobacco for a possible beneficial effect on seizures.

2. Methods

The study was conducted at the Department of Neurological Sciences, University of Bologna after approval by the local Ethical Committee was obtained on 16th July 2002, patient recruitment finished on 16th July 2006. This was a case–control family study [27,28] with direct collection of data from each subject involved ("family study" technique). Nocturnal frontal lobe epilepsy probands were recruited if they had at least one hypermotor/asymmetric tonic seizure or two paroxysmal arousals recorded by video-polysomnography (VPSG).

For each NFLE proband, one healthy subject (control) of the same sex, age (±5 years), education (±3 years), and area of residence was recruited. The control subject was chosen directly by the proband among his or her acquaintances according to an order of priority (neighbors, colleagues, and friends). Alternatively, after at least three failed attempts, we asked general practitioners (randomly selected from a list provided by the Local Medical Council) for a control subject among their patients. If this method also failed, we selected control subjects from the population register.

At least four members (first and further degrees) of the proband and control families were recruited. Eighty-nine NFLE relatives were first-degree, 75 were second-degree, and 18 were third-degree; 94 control relatives were first-degree, 74 were second-degree, and 20 were third-degree.

An ad hoc trained young doctor (IN), blinded to the hypothesis of the study and the group to which each subject belonged, administered a standardized interview regarding life-long recurrence of parasomnias including a part specifically devised for smoking habits. All enrolled relatives of probands and controls were interviewed by telephone, whereas probands and control subjects were interviewed directly.

One hundred and seventy-five out of 182 NFLE relatives (96.2%) and 170 out of 188 control relatives (90.4%) had suffered from at least one type of arousal disorder. In particular, arousal parasomnias had occurred in 23 NFLE relatives (7 confusional arousals, 13 sleepwalking, and 3 sleep terrors) and in six control subjects (1 confusional arousal and 5 sleepwalking) (Table 1).

2.1. Exposure assessment

Data on smoking habits were collected at the time of recruitment to the study using a lifestyle questionnaire. All subjects were asked for the following information: i) smoking status at recruitment: a) "never smokers": people who have never smoked, b) "former smokers": people who smoked at least 1 cigarette/day for at least 6 months and stopped smoking at least 3 months before the recruitment, and c) "current smokers": people who are still smoking at least 1 cigarette/day for at least 6 months); ii) when they started smoking; and iii) when they quit smoking. We defined "under-age subjects" as individuals under 18 years.

2.2. Statistical analysis

Sample size was calculated to test the hypothesis of a higher frequency of arousal parasomnias in NFLE patients and their relatives compared to that in families of matched population controls [18]. Thus, the present study must be considered exploratory.

The demographic characteristics of the four groups were analyzed by sex; differences between the NFLE group and the healthy control group were assessed with two tests for categorical variables and a *t* test for continuous variables. In particular, age at study recruitment, highest educational qualification obtained, marital status, and employment were analyzed as potential confounders.

Smoking habits were analyzed for men and women separately in the NFLE group and in the control group. The number of years spent smoking was calculated as the following: age at recruitment (for current smokers) or age at quitting smoking (for former smokers) minus age at starting smoking. Similarly, time since quitting smoking was calculated as follows: age at recruitment minus the age at quitting smoking for former smokers only.

Table 1
Clinical features and tobacco habits in NFLE probands and their relatives compared with control subjects and their relatives.

	NFLE probands N = 33	Control subjects N = 31	p	NFLE relatives N = 182	Control relatives N = 188	p
Smokers n (%)						
Any age	15 (45.5)	12 (38.7)	0.621	90 (49.5)	83 (44.1)	0.348
>18 years	15/30[a](55.6)	12/28[a] (44.4)	0.610	85/165[a] (51.5)	80/155[a] (51.6)	1
Smoking status n (M/F, %)						
Never smoker	18 (10/8; 54.5)	19 (9/10; 61.2)		92 (19/73; 50.5)	105 (39/66; 55.8)	
Former smoker	9 (6/3; 27.3)	3 (1/2; 9.6)		45 (27/18; 24.7)	39 (22/17; 20.7)	
Current smoker	6 (2/4; 18.1)	9 (6/3; 29.0)		45 (23/22; 24.7)	44 (20/24; 23.4)	
Mean years spent smoking (range yr, SD)						
Former smoker[b]	11 (3–20; 7.5)	8 (4–15; 6.1)		21.6 (2–59; 16.2)	21.6 (1–53; 13.4)	
Current smoker[c]	8.6 (2–15; 4.9)	13.3 (6–30; 8.3)		21.6 (0–51; 14.7)	24.5 (1–57; 17.15)	
Time since quitting smoking: mean yr, (SD)[d]	10.4 (12.8)	17.3 (10.1)		14.8 (13.3)	15.8 (13.9)	
Parasomnias n (%)				175 (96.2)	170 (90.4%)	
Arousal disorder n				23	6	
Confusional arousal				7	1	
Sleepwalking				13	5	
Sleep terror				3	0	

Legend: N = number; M = male; F = female; SD = standard deviation; yr = years.
[a] Number of smokers aged >18 years/number of subjects aged >18 years within the group.
[b] Data missing for 3/96 (3.1%) subjects.
[c] Data missing for 7/104 (6.7%) subjects.
[d] For former smokers only (n = 96/434): year in which the study was conducted minus the year of quitting smoking.

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