General Hospital Psychiatry 37 (2015) 360–364

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Smoking increases the risk of delirium for older inpatients: a prospective population-based study

Johannes Baltasar Hessler, M.Sc. [a,*], Monika Brönner, M.D. [a], Thorleif Etgen, M.D. [a,b], Othmar Gotzler, M.D. [c], Hans Förstl, M.D. [a], Holger Poppert, M.D. [d], Dirk Sander, M.D. [e], Horst Bickel, Ph.D. [a]

[a] Department of Psychiatry and Psychotherapy, Technische Universität München Klinikum Rechts der Isar, Ismaninger Strasse 22, 81675 Munich, Germany
[b] Department of Neurology, Kliniken Südostbayern–Klinikum Traunstein, Cuno-Niggl-Strasse 3, 83278 Traunstein, Germany
[c] INVADE Study Group, Karl-Böhm-Strasse 32, 85598 Baldham, Germany
[d] Department of Neurology, Technische Universität München Klinikum Rechts der Isar, Ismaninger Strasse 22, 81675 Munich, Germany
[e] Department of Neurology, Benedictus Krankenhaus Tutzing, Bahnhofstrasse 5, 82327 Tutzing, Germany

ARTICLE INFO

Article history:
Received 26 November 2014
Revised 13 March 2015
Accepted 13 March 2015

Keywords:
Acetylcholine
Nicotine
Withdrawal
Prevention
Hospital

ABSTRACT

Objectives: To investigate the association between smoking in the older population and the risk of inpatient delirium, which is common and has adverse consequences.
Method: Participants (N=3754) were insurants aged ≥55 years of the largest German statutory health insurance company, who enrolled in a 6-year prospective population-based study. Baseline smoking, adjusted for age, sex, depressive symptoms, cognitive impairment and alcohol consumption, was analyzed as risk factor of inpatient delirium. Results are presented as hazard ratios (HRs) and 95% confidence intervals (95% CIs).
Results: Three-hundred seventy-three (10.0%) participants were smokers at baseline, 865 (23.0%) were quitters and 2516 (67.0%) were lifelong abstainers. Mean pack-years of smokers and quitters were 23.8 (S.D.=22.4). Sixty-one (1.6%) received a diagnosis of inpatient delirium. Smokers had an increased risk of delirium compared to abstainers in the fully adjusted model (HR=2.87, 95% CI 1.24–6.66). Quitters and abstainers did not differ (HR=0.79, 95% CI 0.37–1.72). Comparing smokers and quitters, current smoking status (HR=3.22, 95% CI 1.20–8.62) but not pack-years [residual $\chi^2(1)=0.25$, $P=.874$] were associated with inpatient delirium.
Conclusion: Only current smoking but not being a quitter and the lifetime amount smoked were associated with inpatient delirium, indicating that acute nicotine withdrawal may represent a relevant pathogenic mechanism.

1. Introduction

Delirium describes acute brain failure that causes impairment of attention and other cognitive functions [1]. The occurrence of delirium appears to result from the interplay of a wide range of precipitating noxious events and predisposing factors [2]. Among others, high age; cognitive, functional and sensory impairment; infection; physiological abnormalities; a history of physical and mental disease; drug use; alcohol misuse; physical constraints; anesthesia; use of a bladder catheter; urgent or trauma admission and intensive care unit (ICU) stay can contribute to the etiology of delirium [3,4]. Delirium is most common among older hospital patients [5], with the highest incidence rates in surgical and ICU patients [3]. Given the high costs, prolonged hospital stays and increased rates of morbidity and mortality associated with delirium [1], as well as the poor cognitive and functional prognosis for those affected [6], the investigation of means to reduce its incidence in older hospital patients is of vital importance.

Several multicomponent prevention strategies have been proven effective in reducing the incidence of delirium in hospitalized older people [7,8]. Surprisingly, since being a common habit, smoking has not been considered in this context. This neglect is possibly due to the sparse and inconsistent evidence on the role of smoking in the pathogenesis of delirium [9]. In some studies, current smoking was found to increase the risk of delirium in the hospital [10–13], yet others found no effect [14–17].

Despite the lack of clear evidence, there is a reason to believe that smoking could be a relevant factor in the development of delirium, both as predisposing factor and precipitating noxious event. Next to other factors (e.g., hypoxemia, increased carbon monoxide levels), smoking potentially increases the risk of delirium through the build-up of microvascular and atherosclerotic changes in the brain [11,18,19]. These changes are positively correlated with the number of cigarettes smoked and can persist for many years after quitting [20]. If vascular changes were the main agent behind the association between smoking and delirium, not current smoking status but the lifetime number of cigarettes smoked should predict the occurrence of delirium. Case

* Corresponding author. Department of Psychiatry and Psychotherapy, Klinikum Rechts der Isar der Technische Universität München, Ismaninger Strasse 22, 81675 Munich, Germany. Tel.: +49-89-4140-6183; fax: +49-89-4140-6379.
E-mail addresses: johannes.hessler@lrz.tum.de (J.B. Hessler), m.broenner@mnet-online.de (M. Brönner), thorleif@etgen.de (T. Etgen), gotzler-med@t-online.de (O. Gotzler), hans.foerstl@lrz.tum.de (H. Förstl), poppert@gmx.de (H. Poppert), d.sander@mac.com (D. Sander), h.bickel@lrz.tum.de (H. Bickel).

http://dx.doi.org/10.1016/j.genhosppsych.2015.03.009
0163-8343/

reports of heavily smoking hospital patients [21–24], however, point to an alternative or additional pathway from smoking to delirium. These patients had to stop smoking due to their treatment and developed delirium. The symptoms remitted within hours after the application of transdermal nicotine replacement. These reports suggest that acute nicotine withdrawal due to smoking cessation in the hospital may constitute a noxious event, which directly relates to the development of delirium. If nicotine withdrawal and not atherosclerosis were the critical factor linking smoking and delirium, current smoking status but not the number of cigarettes smoked should predict incident delirium.

The present study aimed to investigate the unclear association between smoking in the older population and the incidence of inpatient delirium, as well as explore possible underlying mechanisms. To this purpose, we analyzed data of almost 4000 individuals older than 54 years who were prospectively observed for an average of 6 years over the course of the INVADE trial (Intervention Project on Cerebrovascular Disease and Dementia in the District of Ebersberg [25]).

In particular, we examined two questions. (1) Do quitters and current smokers differ from abstainers in their risk of inpatient delirium? (2) Is smoking status or the lifetime amount smoked the better predictor of inpatient delirium among current smokers and quitters?

2. Method

2.1. Participants

The INVADE trial is a prospective and population-based cohort study in a geographically defined area. Participants were identified from the database of the statutory health insurance company Allgemeine Ortskrankenkasse (AOK). Membership in a health insurance is mandatory in Germany and AOK holds the largest market share, representing around 40% of the total population. In 2001, 11,317 insurants met the inclusion criteria of being 55 years or older, as well as living in the district of Ebersberg, and were invited to participate. Between 2001 and 2003, 3908 participants enrolled in the trial.

2.2. Procedure

The ethics committee of the Faculty of Medicine at the Technische Universität München approved the study protocol and all participants signed informed consent.

The participants were examined by their respective general practitioner (GP) at baseline and at follow-ups after 2, 4 and 6 years. At baseline, GPs asked the participants about their current and previous smoking habits. Based on this information, the participants were categorized into current smokers, quitters and lifelong abstainers. For smokers and quitters, the number of pack-years was determined as an indicator of the lifetime amount smoked. Pack-years are calculated by multiplying the number of packs a person smoked per day with the number of years the person has smoked. Further, the participants filled in questionnaires about sociodemographic data, subjective health, use of medical services, memory complaints and depressive symptoms (Geriatric Depression Scale or GDS [26]). GPs reported the patients' previous and current diagnoses, current medication, alcohol consumption, physical activity, body mass index (BMI), impairment of activities of daily living (Rankin Scale [27]), blood pressure, ankle-to-brachial index (ABI), and cognitive status (6-Item Cognitive Impairment Test or 6CIT [28,29]) and conducted an electrocardiogram. GPs also took fasting blood samples that were analyzed in a central laboratory with regard to total cholesterol, low- and high-density lipoprotein (LDL, HDL) cholesterol, triglycerides, serum glucose, glycosylated hemoglobin A_{1c} (HbA_{1c}), creatinine, homocysteine and high-sensitivity C-reactive protein (hsCRP). A detailed description of the INVADE trial and the baseline examination is published [25].

Cases of delirium not induced by alcohol and other psychoactive substances were identified by searching claims data of the AOK health insurance for *International Statistical Classification of Diseases* (*ICD*), *10th Revision* codes F05.0–F05.9 that were assigned during a hospital stay over the course of the 6-year period of the INVADE trial. If participants received more than one diagnosis of delirium over the course of the study, the first diagnosis was used as endpoint. Diagnoses of substance withdrawal state with delirium (F1×.4) were not considered.

2.3. Statistical analysis

In order to establish an independent association between smoking and inpatient delirium, the known risk factors age, sex, cognitive impairment (6CIT), depressive symptoms (GDS), alcohol consumption (GP), use of psychoactive drugs (GP) and functional impairment (Rankin Scale) [3] were employed as covariates in the regression analyses (Table 1). The robustness of the results was then tested again in a sensitivity analysis, with adjusting for a range of additional covariates that may contribute to the development of delirium. Medical history (diabetes, hypertension, coronary heart disease, hyperlipidemia, stroke, myocardial infarction, renal insufficiency), physical activity, physiological markers (blood pressure, total cholesterol, LDL, HDL, triglyceride, serum glucose, HbA_{1c}, hsCRP, creatinine), BMI and ABI were controlled for.

A Cox proportional hazards regression was performed to establish the risk of delirium for current smokers and quitters compared to lifelong abstainers after adjusting for other risk factors. In the first block, a trichotomous variable indicating the current smoking status at baseline (abstainer, quitter, current smoker), as well as age in years and sex, was simultaneously entered as predictors. In the second block, a forward selection method (Wald) was used to select the significant covariates of the variables shown in Table 1. As for all analyses, the dichotomous outcome variable indicated whether or not a participant received a diagnosis of delirium within the 6 years of the trial. For cases with incident delirium, the time variable was defined by the time between the date of the baseline examination and the date of the first diagnosis. For cases without incident delirium, the time variable

Table 1
Established risk factors used as covariates in the Cox proportional hazards regression models and incident delirium according to smoking status at baseline.

Descriptive	Smoking		
	Abstainers *N*=2516	Quitters *N*=865	Smokers *N*=373
Age, mean (S.D.)*	68.3 (7.9)	67.5 (7.6)	63.9 (6.1)
Sex, *N* (%)*			
Female	1875 (74)	237 (27)	127 (34)
Male	641 (26)	628 (73)	246 (66)
Cognitive impairment (6CIT), *N* (%)*			
0–7 errors	2265 (90)	762 (88)	326 (87)
8–12 errors	196 (8)	95 (11)	35 (9)
13–28 errors	55 (2)	8 (1)	12 (3)
Depressive symptoms (GDS), *N* (%)			
<6 symptoms	2279 (91)	786 (91)	327 (88)
≥6 symptoms	237 (9)	79 (9)	46 (12)
Alcohol consumption (GP), *N* (%)*			
No alcohol	1146 (45)	176 (20)	108 (29)
1–14 drinks per week	1328 (53)	626 (73)	212 (57)
≥15 drinks per week	42 (2)	63 (7)	53 (14)
Use of psychoactive drugs (GP), *N* (%)			
No	2210 (88)	782 (90)	327 (88)
Yes	306 (12)	83 (10)	46 (12)
Functional impairment (Rankin Scale), *N* (%)			
None (0)	2006 (80)	678 (88)	295 (79)
None despite symptoms (1)	337 (13)	126 (15)	50 (13)
Slight to severe (2–5)	173 (7)	61 (7)	28 (8)
Incident delirium, *N* (%)			
No	2476 (98)	854 (99)	363 (97)
Yes	40 (2)	11 (1)	10 (3)

Note: *P* values were calculated with analysis of variance for age and the χ^2 test for the remaining variables.
* Significant with $P<.05$.