European Journal of Internal Medicine 26 (2015) 534–539

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original Article

Risk of psychiatric disorders following gastroesophageal reflux disease: A nationwide population-based cohort study

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ARTICLE INFO

Article history:
Received 15 March 2015
Received in revised form 4 May 2015
Accepted 12 May 2015
Available online 26 May 2015

Keywords:
Gastroesophageal reflux disease
Psychiatric disorders
Depression disorder
Anxiety disorder
Sleep disorder

ABSTRACT

Background: Recent studies have shown that the peripheral inflammation may cause the up-regulation of central nervous system inflammation and therefore possibly plays a vital role in the pathophysiology of subsequent psychiatric disorders.
Objective: We explored the relationship between gastroesophageal reflux disease (GERD) and the subsequent development of psychiatric disorders including schizophrenia as well as bipolar, depressive, anxiety, and sleep disorders.
Methods: We investigated patients who were diagnosed with GERD according to the data in the Taiwan National Health Insurance Research Database. A comparison cohort comprised patients without GERD who were matched according to age and sex. The incidence rate and the hazard ratios (HRs) of subsequent new-onset psychiatric disorders were calculated for both cohorts, based on the diagnoses of psychiatrists.
Results: The GERD cohort consisted of 3813 patients, and the comparison cohort comprised 15,252 matched control patients without GERD. The risks of depressive disorder (HR = 3.37, 95% confidence interval [CI] = 2.49–4.57), anxiety disorder (HR = 2.99, 95% CI = 2.12–4.22), and sleep disorder (HR = 2.69, 95% CI = 1.83–3.94), were higher in the GERD cohort than in the comparison cohort. In addition, the incidence of newly diagnosed depressive, anxiety, and sleep disorders remained significantly increased in all of the stratified follow-up durations (0–1, ≥1 year).
Conclusions: GERD may increase the risks of subsequent depressive, anxiety, and sleep disorders. These psychiatric disorders have a negative effect on people's quality of life. Clinicians should pay a particular attention to psychiatric comorbidities in GERD patients.

1. Introduction

Gastroesophageal reflux disease (GERD) is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications [1]. It is one of the most common gastrointestinal (GI) disorders with a prevalence of 8.1%–27.8% in North America, 8.8%–25.9% in Europe and 0.69%–25% in Taiwan [2,3]. Typical GERD symptoms affect patients' quality of life and overall work productivity, and have caused health care costs to increase in Asian countries [4–6].

Psychiatric disorders often coincide with chronic medical conditions such as cardiovascular diseases and GI disorders (e.g., GERD) and increasing research has been conducted on the interplay between psychiatric disorders and chronic medical illness. In a clinical setting, symptomatic presentations of GERD are associated with various psychosocial factors, such as chronic stress, sleep disorders, and emotional dysfunction. Patients with GERD have been reported to exhibit an increased risk of psychiatric disorders [7–10]. In addition, studies have shown that patients with psychiatric disorders tend to exhibit GERD [11,12]. This indicates a bidirectional relationship.

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http://dx.doi.org/10.1016/j.ejim.2015.05.005
0953-6205/

The mechanisms involved in the pathogenesis of GERD symptoms have not been comprehensively determined. Studies have reported that in patients with GERD, the esophageal mucosa exhibits significantly higher amounts of various cytokines and chemokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), platelet-activating factor (PAF), and reactive oxygen species (ROS), than it does in healthy people [13,14]. These inflammatory cytokines and chemokines activate immune cell recruitment and migration and may play a crucial role in the generation of GERD symptoms; in other words, GERD can be considered a chronic inflammatory process [13,15]. Studies have shown that peripheral inflammation is associated with the upregulation of central nervous system (CNS) inflammation [16]. In addition, studies have reported that chronic inflammation plays a critical role in the pathophysiology of common mental disorders [17] including depression, sleep, and anxiety disorders [18–20].

Several cross-sectional and case-control studies have discussed GERD and psychiatric disorders [7–12]. However, no nationwide and longitudinal perspective study has been conducted; therefore, it has not been possible to observe the incidence and sequential risk of psychiatric disorders among GERD patients. In addition, in several of the aforementioned cross-sectional studies, psychiatric disorders have been evaluated by using rating scales such as the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory, Epworth Sleepiness Scale, and Pittsburg Sleep Quality Index, rather than a diagnosis by a psychiatrist.

In response to the lack of national data and few longitudinal studies concerning the association between GERD and the subsequent risk of psychiatric disorders, and on basis of the hypothesis that GERD might entail a high risk for developing subsequent psychiatric disorders, we designed a nationwide-population-based study to investigate the incidence of psychiatric disorders among patients with GERD.

2. Patients and methods

2.1. Data source

The National Health Insurance Research Database (NHIRD) in Taiwan, which contains registry files and all medical benefit claims for approximately 25.68 million enrollees, was established in 1998. Numerous researchers worldwide have used the NHIRD for published studies. The NHIRD contains substantial information regarding clinical visits, including date, prescription elements, and diagnostic codes using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD is a research database developed and managed by the National Health Research Institutes (NHRI), with confidentiality being maintained according to the directives of the Bureau of National Health Insurance.

The Longitudinal Health Insurance Database 2005 (LHID 2005) was used in this study. LHID 2005 contains all original claim data of 1,000,000 beneficiaries which were randomly sampled from the year 2005 Registry for Beneficiaries of the NHIRD, where registration data of everyone who was a beneficiary of the National Health Insurance program during the period of Jan. 1st 2005 to Jan. 1st, 2006 were drawn for random sampling. There are approximately 25.68 million individuals in this registry. All the registration and claim data of these 1,000,000 individuals collected by the National Health Insurance program constitute the LHID2005 and we have data of 1,000,000 individuals in LHID 2005 from 1996 to 2009. The NHRI affirms that there are no statistical differences in the distributions of age, sex, or health care costs between the data in the LHID 2005 and that of the NHIRD.

2.2. Ethics statement

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital. Written consent was not obtained from the study participants because the data were obtained from the LHID 2005, which contains deidentified data. In addition, the Institutional Review Board issued a formal written waiver of the need for consent.

2.3. Study population

We extracted data from the LHID 2005 for this retrospective cohort study, in which patients newly diagnosed with GERD between January 1, 2000 and December 31, 2008 were investigated. The patients with GERD were defined according to ICD-9-CM codes 530.11 or 530.81. To ensure diagnostic validity and patient homogeneity, we included only patients who were diagnosed by gastroenterologists and had at least two consensus GERD diagnoses. We excluded patients who were diagnosed with GERD between January 1, 1996, and December 31, 1999. In addition, we excluded patients who were diagnosed with psychiatric disorders (A codes: A210–A219; ICD-9-CM codes: 290–319) prior to GERD diagnosis. The index date was defined as the date when an eligible GERD patient was included in our GERD cohort. For each patient with GERD included in the GERD cohort, four age- and sex-matched patients without GERD and any psychiatric disorder were randomly selected from the LHID 2005 and included in the comparison cohort with the same index date. The random assignment procedures were performed by SAS statistical software and were based on the random numbers which were generated from the uniform distribution. Each member of the GERD and comparison matched pair was followed from the same index date and all participants were observed until they were diagnosed with schizophrenia (ICD-9-CM code: 295), depressive disorder (ICD-9-CM codes: 296.2 [Major Depressive Disorder, Single Episode], 296.3 [Major depressive disorder recurrent episode], 300.4 [Dysthymic disorder], and 311 [Depressive disorder, not elsewhere classified]), bipolar disorder (ICD-9-CM codes: 296.0 [Bipolar I disorder, single manic episode], 296.1 [Manic disorder recurrent episode], 296.4 [Bipolar I disorder, most recent episode (or current) manic], 296.5 [Bipolar I disorder, most recent episode (or current) depressed], 296.6 [Bipolar I disorder, most recent episode (or current) mixed], 296.7 [Bipolar I disorder, most recent episode (or current) unspecified], 296.8 [Other and unspecified bipolar disorders], 296.80 [Bipolar disorder, unspecified], and 296.89 [Other bipolar disorders]), anxiety disorder (ICD-9-CM codes: 300.0 [Anxiety states], 300.2 [Phobic disorders], 300.3 [Obsessive-compulsive disorders], 308.3 [Other acute reactions to stress], and 309.81 [Posttraumatic stress disorder]), or sleep disorder (ICD-9-CM codes: 780.5 [Sleep disturbances], 307.4 [Specific disorders of sleep of nonorganic origin]); or until death, withdrawal from the NHI system, or December 31, 2009. The primary clinical outcomes were psychiatrist-diagnosed schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, and sleep disorder. Furthermore, the comorbidities at the date of enrolment (the index date) were both identified in both cohorts. However, in psychiatry, there are only a few clearly defined and modifiable risk factors; consequently, most studies have focused on largely unmodifiable ones, such as age and sex. In addition, although many studies have indicated several comorbidities as risk factors for GERD (e.g., old age, female sex, lower education, gain in BMI, and ever tobacco smoking [21]), most of the factors are unavailable in the claims dataset. However, considering the relatively higher prevalence of physical comorbidities among the studied population, we selected only those cases involving typical physical comorbidities, such as diabetes mellitus, heart disease, liver disease, renal disease, lung disease and malignancy as potential confounding factors. The advantage is that we may avoid the influence of these physical illnesses that are possibly related to the occurrence of psychiatric disorders in the patients with GERD. For sensitivity analyses, we also conducted a cohort of newly diagnosed GERD patients who were diagnosed by gastroenterologists or non-gastroenterologists.