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ScienceDirect

Neuromuscular Disorders 24 (2014) 245–249

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Excessive risk of cancer and in particular lymphoid malignancy in myasthenia gravis patients: A population-based cohort study

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Received 23 September 2013; received in revised form 8 November 2013; accepted 14 November 2013

Abstract

The exact relationship between myasthenia gravis (MG) and extrathymic malignancies has not been established thus far. Occasional cases of MG have been reported in association with lymphoma or other lymphoproliferative disorders. To determine the risk of extrathymic malignancy with particular attention on lymphoid malignancy for MG patients in a large cohort representing 99% of the Taiwan population, claims data from the Taiwan National Health Insurance Database were used to conduct retrospective cohort analyses. The study cohort comprised 3671 MG patients who were 10-fold frequency matched by age and sex, and assigned the same index year without MG. Cox proportional hazard regression analysis was conducted to estimate the risk of cancer. The MG cohort had a 1.74-fold increased risk of developing cancer compared to the comparison cohort (HR = 1.74, 95% CI = 1.47–2.05). After adjusting for confounders and relative to the cohort, patients with MG had a 2.27-fold increased risk of developing lymphoid malignancies (HR = 2.27, 95% CI = 1.06–4.88) and a 118.47-fold increased risk of thymus cancer (HR = 118.47, 95% = 42.57–329.71). This population based retrospective case-control study confirms and extends previous observations on the association between MG and lymphoid malignancies.

Keywords: Lymphoma; Leukemia; Myasthenia gravis; Thymus cancer; Thymic carcinoma

1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by an impaired neuromuscular transmission caused by a circulating antibody [1]. In total, 10–15% of patients with MG have concurrent thymoma [2]. Although extrathymic malignancies were reported to be relatively common (15%) in patients with MG in one series [3], to date, the exact relationship between MG and extrathymic malignancies has not been fully established [4–8]. By contrast, occasional cases of MG have been reported in association with lymphoma or other lymphoproliferative disorders [9,10]. Although such associations could be coincidental, certain genetic or environmental factors could have possibly predisposed these patients to both diseases [11]. The 2 illnesses occurred concomitantly, and lymphoid malignancy treatment typically improved MG symptoms or induced remission, suggesting a paraneoplastic association [9,10]. This study uses a large

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http://dx.doi.org/10.1016/j.nmd.2013.11.007

cohort representing 99% of the Taiwan population to determine the risk of extrathymic malignancy with particular addition to lymphoid malignancy of MG patients.

2. Materials and methods

2.1. Data source

The Taiwanese government established a universal, single-payer health insurance program in 1995, which comprises nearly 99% of the Taiwan population. The National Health Insurance Research Database (NHIRD) contains the annual original claims data for reimbursement, and is maintained by the National Health Research Institutes (NHRI). To protect personal privacy, all personal identification information was encrypted before being released for research. The NHRI created scrambled and anonymous identification numbers to link each patient's information, including sex, birth date, and the registry of medical services. In addition, this study was also approved by the Ethics Review Board at China Medical University (CMU-REC-101-012).

For this study, we collected the disease records from inpatient and catastrophic illness registry files. The disease was defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2. Study population

This research is a population-based retrospective cohort study. The case cohort was constructed according to newly diagnosed MG (ICD-9-CM 358.0) during 2000–2009 from the catastrophic illness registry. We established a comparison cohort from patients without an MG diagnosis in the NHIRD, who were 10-fold frequency-matched by age (per 5 years), sex, and assigned the same index year. We excluded patients with a cancer diagnosis, or those who had developed cancer within half a year of enrollment in the research because of more clinical visits and examinations resulting in coincidental increasing detection of cancers after the diagnoses of MG. The event of interest in our study was cancer development (ICD-9-CM 140-208, from the catastrophic illness registry). The patient cases were followed until the patient withdrew from the national health insurance, developed cancer, or until December 31, 2010.

We also investigated the cancer site risk between the comparison cohort and the MG group. The cancer site was separated into liver cancer (ICD-9-CM 155), colorectal cancer (ICD-9-CM 153 and 154), stomach cancer (ICD-9-CM 151), lung cancer (ICD-9-CM 162), breast cancer (ICD-9-CM 174), cervical cancer (ICD-9-CM 180, women only), head and neck cancer (ICD-9-CM 140-149), lymphoma and leukemia (ICD-9-CM 200-208), thymus cancer (ICD-9-CM 164), and others.

Cancer-associated comorbidities were considered confounding factors. Comorbidities and the disease record from the inpatient file included hypertension (ICD-9-CM 401-405) and diabetes (ICD-9-CM 250) before the index date.

2.3. Statistical analysis

The distributions of the comparison and MG cohorts were displayed as the mean and standard deviation (SD) for continuous variables and the number and percentage of each category variable. To test the differences between these cohorts, we applied the t test for continuous variables and the chi-square test for category variables. We calculated the total developing cancer incidence, and also the incidence of different cancer sites between the comparison and MG cohorts. We used the product-limit method to estimate the cumulative developing cancer incidence curve between these 2 cohorts. The log-rank test was performed to assess differences between these 2 incidence curves. Relative to the comparison cohort, we employed Cox's proportional hazards regression model with adjusted potential confounding factors to estimate the hazard ratio (HR) and the confidence interval (CI) of the MG cohort.

We used SAS 9.3 software (SAS Institute, Cary, NC, USA) to manage and analyze the data. The cumulative incidence curves were drawn using R software (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at less than .05 for the 2-sided P value.

3. Results

The study comprised a 3671 MG patient cohort and a comparison cohort of 36,710 patients with a similar average age (44 years) and sex ratio (women: 59%; Table 1). The proportion of comorbidities, hypertension, and diabetes in the MG cohort was considerably higher than that of the comparison cohort ($P < .0001$).

The developing cancer incidence in the MG cohort was 91.08 per 10,000 person-years, and the incidence was nearly 1.71-fold greater than in the comparison cohort (53.35 per person-years; Table 2). The cumulative cancer incidence curves (Fig. 1) showed that the cancer incidence curve in the MG cohort was significantly higher than in the comparison cohort (log-rank test <.0001). After adjusting the potential confounding factors, the MG cohort had a 1.74-fold increased developing cancer risk compared to the comparison cohort (HR = 1.74, 95% CI = 1.47–2.05).

Table 2 shows the risk of developing the type of cancer between the study cohorts. The results revealed that patients with MG were significantly associated with increased lymphoid malignancies and thymus cancer. After adjusting for confounders, relative to the comparison cohort, patients with MG had a 2.27-fold increased risk of developing lymphoid malignancies