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Receipt of thyroid hormone deficiency treatment and risk of herpes zoster

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SUMMARY

Objective: Thyroid hormone (TH) has been suggested to control herpes virus gene expression and replication in neurons via epigenetics through its nuclear receptors. It has previously been shown that patients with hypothyroidism are predisposed to herpes zoster (HZ), suggesting that the TH deficiency may be a risk factor for varicella zoster virus (VZV) reactivation. The aim of this study was to test the hypothesis that TH treatment will ameliorate the complication of HZ.
Methods: This study investigated the hypothesis by enquiring into a comprehensive medical database at Kaiser Permanente Southern California (KPSC) to verify whether patients taking TH medication experience a reduction in HZ occurrence.
Results: It was shown by Kaplan–Meier analysis that hypothyroidism patients taking TH medicines had a lower risk of HZ. The fully adjusted analysis indicated that patients receiving medication for the treatment of TH deficiency exhibited a reduced risk of HZ (hazard ratio 0.60, 95% confidence interval 0.51–0.71). This lower risk of HZ was significant in all age groups except the 18–39 years cohort. In addition, female patients taking TH treatment exhibited a lower risk than their male counterparts.
Conclusions: Together these findings support the hypothesis that a constant level of TH will provide a degree of protection from contracting HZ. More studies are underway to evaluate the laboratory data for an analysis of hormonal effects on individuals.

Introduction

Following the primary assault, varicella zoster virus (VZV) may establish a dormant state of infection within the dorsal root ganglia. Reactivation may occur decades later as herpes zoster (HZ, shingles), after the patient's initial exposure (varicella, chickenpox) (Dworkin et al., 2007). While usually a self-limited painful skin rash, shingles can be serious, with complications such as post-herpetic neuralgia (PHN), and the disease results in a significant economic burden (Blein et al., 2015). Common risk factors that may increase the chance of shingles are age older than 50 years, having a weakened immune system due to diabetes or HIV infection, suffering stress or trauma, and undergoing cancer treatment, etc (Shafran, 2016; Ogunjimi et al., 2015; Iglar et al., 2013; Forbes et al., 2016; Guignard et al., 2014). The relationship between thyroid hormone disruption and the pathophysiology of shingles has been mentioned previously, but this is not well-studied (Ajavon et al., 2015).

There are two forms of thyroid hormone (TH), depending on the number of iodine atoms per molecule: tri-iodothyronine (T_3) and thyroxine (T_4). These hormones are composed of two tyrosine molecules and are produced in the thyroid gland. They play significant roles in the regulation of metabolism, development, and immune responses. Common clinical complications due to TH disruptions are hyperthyroidism (caused by excess T_3 and T_4) and hypothyroidism (resulting from a hormone deficiency). Patients diagnosed with low thyroid hormones can be treated with levothyroxine, a synthetic thyroid hormone that is chemically identical to T_4 and is prescribed widely. Levothyroxine is included in the World Health Organization List of Essential Medicines, as it is one of the most important medications needed in a basic health

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system (WHO Expert Committee on the Selection and Use of Essential Medicines (19th: 2013: Geneva Switzerland) and World Health Organization, 2014).

It has been reported that thyroid hormones contribute, at least in part, to the replication and reactivation of herpes simplex virus type 1 (HSV-1), an alpha-herpes virus (Bedadala et al., 2010; Hsia et al., 2010; Hsia et al., 2011; Chen et al., 2014; Figliozzi et al., 2014; Hsia and Hsia, 2014; Chen et al., 2016). An epidemiology study at a rural medical center showed that patients with hypothyroidism were prone to shingles (Ajavon et al., 2015). The observation was based on a pilot cross-sectional analysis of existing medical records. This was the first report linking low TH to VZV reactivation and suggested that the hormone may protect patients from VZV reactivation. However, limitations impeded further discussions. For example, the National Drug Codes were not available, so it was not known whether/when the patients received TH medication. Furthermore, the cross-sectional study design was not able to disentangle the temporal relationship between TH treatment and the development of HZ.

This study was performed to test the hypothesis that TH treatment will ameliorate the complication of HZ. This was done by querying a large comprehensive database to determine whether patients taking TH medication exhibit a decreased occurrence of HZ.

Methods

Subjects

This retrospective cohort study included censored data from January 1, 2011 through December 31, 2014, followed up to June 2015. The hypothyroidism medication cohort consisted of Kaiser Permanente Southern California (KPSC) members who were age 18 years or older and diagnosed with hypothyroidism (International Classification of Diseases, Ninth Revision (ICD-9) codes 244), who received TH disorder treatment, between January 1, 2011 and June 30, 2014; the first date of diagnosis was termed the index date. The non-hypothyroidism medication cohort consisted of randomly sampled KPSC members who were free of hypothyroidism and thyroid hormone disorder treatment. The non-hypothyroidism medication cohort patients were matched for age and sex to the hypothyroidism medication patients and recruited at a ratio of 3:1. The non-hypothyroidism medication individuals were assigned the same index dates as the matching hypothyroidism medication group individuals. The subjects in both cohorts were limited to individuals with continuous membership for 1 year before their index date. Individuals with the HZ vaccine code and who had been diagnosed with HZ prior to the index date were excluded from the analysis.

Exposure

The exposed cohort was the hypothyroidism medication patients who were diagnosed with hypothyroidism and had received orders of TH disorder treatment to treat hypothyroidism (Thyroid Disorder National Drug Codes) within 30 days of the diagnosis, between January 1, 2011 and December 31, 2014.

Outcomes

The incidence of HZ was defined by ICD-9 codes 053 from the hospital, outpatient, and emergency department settings during the study period (index date to June 2015). The subjects were followed passively by medical records until the diagnosis of HZ, vaccination with the HZ vaccine, or disenrollment from the health plan, whichever came first.

Covariates

Baseline demographic characteristics recorded included age, sex, race, health care utilization, and comorbid chronic diseases. Health care utilization was defined as the number of hospitalizations, outpatient or emergency department visits within 1 year before the index date. Chronic comorbid diseases were defined as one or more diagnoses for diabetes or for heart, lung, kidney, or liver disease within 1 year before the index date. Patients could be assigned multiple conditions.

Statistical analysis

Incidence was calculated by dividing the number of HZ cases by the total number of person-years. The 95% confidence intervals (CI) were estimated assuming that the occurrence of HZ follows a Poisson distribution. The hazard ratio (HR) is the chance of having shingles occurring in the hypothyroidism patients divided by the chance of the event occurring in the individuals without a history of hypothyroidism; the HRs and 95% CI were estimated for age, sex, race, and chronic comorbid diseases using Cox proportional hazards regression models (Spruance et al., 2004). Significance was set at 0.05 based on a two-sided test. The cumulative risk was measured by the Kaplan–Meier plot (Singh and Mukhopadhyay, 2011). SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Demographic analyses

A total 13 915 hypothyroidism medication patients and 41 745 non-hypothyroidism medication individuals were included in the study, with approximately 74% women in both groups (Table 1). Compared to the non-hypothyroidism medication cohort, the individuals in the hypothyroidism medication cohort were more likely to be white and to have attended more outpatient, inpatient, and emergency department visits in the 12 months prior to the index date. The hypothyroidism medication cohort had a higher prevalence of chronic conditions/diseases such as diabetes, kidney disease, and heart disease (Table 1).

Herpes zoster incidence

There were 884 cases of HZ identified in the study. Among the hypothyroidism medication and non-hypothyroidism medication cohorts, follow-up averaged 1.4 years; the HZ incidence yielded was 8.5 (95% CI, 7.3–9.9) per 1000 person-years in the hypothyroidism medication cohort and 12.4 (95% CI, 11.5–13.3) per 1000 person-years in the non-hypothyroidism medication cohort, by univariable analysis (Table 2). Among the non-hypothyroidism medication individuals, the HZ incidence varied by several factors.

Measurement of the hazard ratio and cumulative risk

In the fully adjusted analysis, taking medication to treat a TH deficiency was associated with a reduced risk of HZ (HR 0.60, 95% CI 0.51–0.71). The reduction in risk varied according to age at the index date, sex, race, and the presence of chronic diseases (e.g., diabetes). In general, patients taking medications, regardless of their sex, exhibited a significantly lower risk of HZ in all age groups except the 18–39 years group (Table 3). Of all the chronic conditions studied, diabetic patients received the greater protection from contracting HZ while using TH medication (HR 0.59, 95% CI 0.42–0.84, $p < 0.05$; Table 3).