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Herpes zoster is associated with herpes simplex and other infections in under 60 year-olds

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KEYWORDS
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Summary *Objectives:* We assessed the association between herpes zoster (HZ) and herpes simplex (HS) occurrence whilst controlling for risk factors of HZ.

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Herpes simplex;
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Methods: Using a Belgian general practitioner network, a retrospective cohort study with 3736 HZ patients and 14,076 age-gender-practice matched controls was performed, covering over 1.5 million patient-years. Multiple logistic regression was used with HZ as outcome and several diagnoses (malignancy, depression, diabetes mellitus, auto-immune diseases, asthma, multiple sclerosis, HIV, fractures), medications (systemic corticosteroids, biologicals, vaccination), HS and other infections as variables.
Results: HS was significantly associated with HZ for all analysed time intervals (up to five years) post HZ (OR of 3.51 [2.09 5.88] 95%CI one year post HZ) and to a lesser extent for time ranges pre HZ. Registration of other infections was significantly associated with HZ in all time intervals pre and post HZ (OR up to 1.37). Malignancy up to five years pre HZ, depression up to one year pre or post HZ, fractures up to two years pre HZ, asthma, auto-immune diseases, and immunosuppressive medication one year pre or post HZ were also associated with HZ.
Conclusions: HZ and HS occurrences are significantly associated and potentially share a common susceptibility beyond the known risk factors.

Introduction

Chickenpox is caused by primary infection with varicella-zoster virus (VZV), after which VZV remains latent in neural ganglia until reactivation. Symptomatic reactivation of VZV is known as herpes zoster (HZ) or shingles. Protection against HZ is assumed to be closely regulated by VZV-specific cellular immunity. Indeed, symptomatic VZV reactivation occurs frequently in known immunocompromised persons.[1] Furthermore, some studies found HZ to be predictive of a later diagnosed malignancy.[2] In addition, several studies have noted VZV-specific cellular immunity to decline with ageing[3,4] which is reflected by the steep increase in HZ incidence with age.[5] Moreover, acquisition of chickenpox <1 year of age has been identified as a risk factor for HZ in childhood,[6] likely due to the limited development of VZV-specific cellular immunity at that young age.[7] VZV vaccine-induced boosting of primarily cellular immunity has been shown to be effective against the occurrence of HZ.[8] Interestingly, re-exposure to chickenpox has been shown to cause a temporary rise in VZV-specific cellular immunity[4,9–11] and was hypothesized and shown to protect against HZ.[12–14]

Epidemiological studies have identified several risk factors associated with HZ such as being female[15] or Caucasian,[16] recent mechanical trauma,[17] chemical exposure,[18] negative life events[19] and depression.[20] Irwin et al. presented in several studies an association between depression and lower VZV-specific cellular immunity.[21,22] Various clinical co-morbidities, thought to have an effect on cellular immunity either directly or via immunosuppressive medication, were also shown to be associated with HZ: diabetes mellitus,[23] systemic lupus erythematosus,[24] asthma (in children),[25] inflammatory bowel diseases[26] and rheumatoid arthritis.[27] Medications implicated in the occurrence of HZ are "disease modifying anti-rheumatic drugs",[27] oral corticosteroids,[28] TNF-alpha inhibitors[29] and recently statins.[30] A reduced intake of fruit, vegetables and micronutrients was found in HZ[31] and post-herpetic neuralgia[32] patients, respectively.

Although some studies found a peak in HZ incidence during the late spring – early summer months, many other studies did not (see review by Thomas and Hall[33]). Interestingly, Zak-Prelich et al. found support for an association between UV radiation intensity and HZ on exposed body regions,[34] a finding which is reminiscent of the inductive effect of UV radiation on cold sores caused by herpes simplex virus (HSV).[35] A host genetic susceptibility for HZ has been established by both epidemiological[36] and genetic association studies.[37] The host defence against the related HSV type 1 and 2 was also associated with host genetic variants for genes responsible for Toll-like receptors[38] and HLA molecules.[39] Recently, CMV seropositivity was found to be associated with both HSV-1[40] and VZV reactivation.[41]

In view of the above, VZV and HSV reactivation possibly share common elements such as the sensitivity for UV radiation, host genetic susceptibility and susceptibility for the effects of CMV infection. The present case–control study set out to investigate whether HZ occurrence was associated with herpes simplex in patients younger than 60 years seen in general practice, whilst controlling for known risk factors. In addition, we hypothesized that herpes zoster patients could be more prone to infections.

Materials and methods

Population

Data was obtained from a representative Flemish (Belgian region) general practitioner (GP) registration network (Intego) with more than 90 GPs and over 1.5 million patient-years (for more details see[2]). Diagnoses were classified according to ICPC-2 (International Classification of Primary Care)[42] and medications were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.[43] For the present study, diagnoses and prescribed medications registered from 1/1/1994 until 31/12/2011 were analysed.

Patients younger than 60 years and diagnosed with HZ were retained (n = 3736, 53% Female). The age limit was set in order to minimize the existence of co-morbidities and the effect of immunosenescence. Per HZ patient up to four age-gender-practice matched patients without a diagnosis of HZ during the registration period were included (n = 14,076).

Prior to sending the data to the central database, patient identification information was encrypted in each