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Association of Physical Trauma with Risk of Herpes Zoster among Medicare Beneficiaries in United States

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Risk factors for herpes zoster (HZ) are poorly defined. An age-matched case-control study was conducted to assess the effect of physical trauma on HZ using Medicare data. HZ cases were 3.4 times as likely as controls to have experienced trauma in the week before HZ onset, but the magnitude of the association between trauma and HZ declined over time. Cases who had cranial HZ were >25 times more likely than controls to have had cranial trauma in the week before HZ onset. Therefore, recent trauma can be a trigger for HZ.

Herpes zoster (HZ) is responsible for a large burden of disease in the United States, with about one million cases occurring annually [1]. Known risk factors for HZ include advanced age [2], immunosuppression [3], race / ethnicity [4], sex [5], family history [6], exposure to varicella [7], and certain chronic diseases [8]. Most investigators speculate that these risk factors suppress systemic varicella zoster virus (VZV)-specific cell-mediated immunity (CMI). However, the recognized risk factors for HZ cannot distinguish the 30% of healthy persons who experience HZ during their lives from the 70% of persons who do not [9].

Trauma was associated with HZ in a small case-control study [10], though the findings were subject to recall bias. To examine the association between trauma and HZ, we conducted a case-control study using Medicare claims data in 2006-2007 and explored how the magnitude of the association varied over time.

METHODS

Study design and data source

This was an age-matched case-control study. Cases and controls were selected from data files consisting of a 5% random sample of Medicare beneficiaries in 2006 and 2007, obtained from the Centers for Medicare and Medicaid Services (CMS). These files include summary demographic information, data on the presence of any of 21 chronic disease conditions defined by CMS [11], and Medicare claims in inpatient and outpatient settings. Each claim record includes fields for up to 10 diagnoses with an accompanying claim date.

Selection of cases and controls

Cases were defined as beneficiaries aged ≥ 65 years who had HZ as the first or second diagnosis on a claim in 2007 and no HZ claim during the 52 weeks before this claim date. The

International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes for HZ, 053.xx, was used to select cases; cases of post herpetic trigeminal neuralgia (053.12) and post herpetic poly-neuropathy (053.13) were excluded. For each case, the index date was defined as the date on which the first claim for HZ was made. Controls were age-matched to cases: for each case, 10 controls were randomly selected from beneficiaries born within 365 days of the case's date of birth and who had no claim for HZ during the 52 weeks before the index date of the case.

Cases and controls were limited to beneficiaries who had continuous coverage for Medicare Parts A (Hospital Insurance) and B (Medical Insurance), but not C (Advantage Plan), during the 52 weeks before the index date, and who were living during that time. Beneficiaries were excluded from the study as cases or controls if their claims data contained ICD-9-CM codes, in any diagnosis field on any claim during the 52 weeks before the index date, for the following immunocompromising conditions that place persons at increased risk of HZ: leukemia or lymphoma (200.xx - 208.xx); human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) (042.xx); neoplasm of other lymphatic and hematopoietic tissues (238.7); disorders involving the immune mechanism (279.xx); aplastic anemia and other bone marrow failure syndromes (284.xx); diseases of white blood cells (288.xx); other diseases of blood and blood-forming organs (289.89, 289.9); other spinocerebellar diseases (334.8); chronic kidney disease (585.xx); renal failure (586.xx); and complications of transplanted bone marrow (996.85).

Independent variables

Trauma was identified as the presence of any of the following ICD-9-CM codes in the first or second diagnosis field during the 52 weeks before the index date: dislocations (830.xx –

839.xx); sprains and strains of joints and adjacent muscles (840.xx – 848.xx); intracranial injuries (850.xx – 854.xx), excluding those with skull fracture; internal injuries of the thorax, abdomen, and pelvis (860.xx – 869.xx); open wounds of the ocular adnexa (870.xx – 897.xx); injuries to blood vessels (900.xx – 904.xx); superficial injuries (910.xx – 919.xx); contusions with intact skin surface (920.xx-924.xx); crushing injuries (925.xx – 929.xx); burns (940.xx – 949.xx); and injuries to nerves and spinal cord (950.xx – 957.xx). We grouped trauma by site (cranium, trunk, limbs, and unspecified) and by type (sprain/strain, contusion, open wound, dislocation, and unspecified). Only those who had multiple claims in the same trauma site and type, or single trauma claim, or no trauma claim during the 52 weeks before the index date were included. The earliest of the multiple claims was used to calculate time from trauma to index date. This was done so that trauma sites and types were mutually exclusive.

Covariates

We controlled for potential confounders including sex, race/ethnicity, diabetes, depression, rheumatoid arthritis / osteoarthritis, and health care utilization. Diabetes, depression, and rheumatoid arthritis / osteoarthritis were predefined in Medicare data [11]. The number of claims during the 52 weeks before the index date was used as a proxy for health care utilization.

Data analyses

We analyzed the temporal relationship of trauma, trauma site and type with HZ, calculating intervals in weeks before the index date. ICD-9-CM codes generally do not contain information about the site of HZ, with the exception of HZ in cranial distributions (codes 053.11; 053.2; 053.20; 053.21; 053.22; 053.29; 053.71). We used these codes to distinguish cranial HZ from non-cranial HZ and assessed the association of cranial HZ with cranial trauma.

Chi-square tests were used to examine the distribution of demographic characteristics and chronic diseases between cases and controls. Conditional logistic regressions were used to estimate the adjusted odds ratios (aOR) and 95% CIs for trauma, trauma site and type from week 1 through 52 before the index date, after controlling for age, sex, race/ethnicity, diabetes, depression, rheumatoid arthritis / osteoarthritis, and health care utilization. Since aORs for trauma, trauma site and type in weeks 4 - 52 before the index date were marginally or insignificantly different for cases versus controls, and there was no significant interaction between trauma site and type, we estimated aORs in the final model by pooling data for these weeks and using no interaction term between trauma site and type. Similar multivariate analyses were performed to assess the association of cranial trauma with cranial HZ. Analyses were carried out using SAS version 9.2 (SAS Institute).

RESULTS

A total of 16,771 incident cases of HZ were identified, and 167,702 age-matched controls without HZ were chosen randomly from a population of 1,196,410 Medicare beneficiaries eligible for this study. HZ was more likely to occur among females (69.8% of cases) and less likely to occur among African Americans (3.4% of cases and 6.9% of controls). The prevalence of diabetes among cases (22.0%) was lower than among controls (24.4%). The prevalence of depression and of rheumatoid arthritis / osteoarthritis among cases was higher than among controls (10.9% vs. 9.8% and 26.0% vs. 23.6%, respectively).

A higher proportion of HZ cases than controls had trauma during any of the 52 weeks before the index date (Table 1). HZ cases had a 3.4-times aOR (95% CI, 2.8 – 4.2) of having had trauma in the week preceding the index date compared to controls; aORs declined steadily

over time. A similar pattern existed for all 3 trauma sites and all trauma types except dislocation. We found the highest aORs for trauma involving the cranium or trunk in the week before the index date, and for sprains/strains and open wounds also in the week before the index date. After week 1, the aORs were not higher for trauma involving the limbs, or for open wounds, or for contusions. Cases with cranial HZ had a 27.5-fold aOR (95% CI 5.4-140.3) of having had cranial trauma in the week before the index date compared with controls (Table 2).

DISCUSSION

This study demonstrated an association between trauma and HZ. In addition to confirming the results of Thomas et al. [10], we show that the effect of trauma appeared to be at least partially local; the magnitude of the association between cranial HZ and cranial trauma was particularly large. Furthermore, the effect was rapid, peaking in the first week after trauma. These suggest that local factors play a role in the incidence of HZ.

Our results are analogous to the well-documented association between trauma and reactivation of herpes simplex virus (HSV). The causal role of trauma and other physical and chemical stimuli in reactivation of HSV1 and HSV2 and subsequent development of cold sores and genital herpes, respectively, has been demonstrated using human and animal models. The herpetic lesions develop within a matter of days following provocation [12, 13].

Reactivating latent VZV by local factors such as trauma suggests an entirely different molecular mechanism from that by suppressing CMI, which has been well documented to play a pivotal role in controlling the reactivation of the virus and progression to manifested HZ. Our observations would be consistent with the possibility that trauma reactivates the latent virus by stimulating local sensory nerves, or by disrupting local cutaneous immunity. That is, some level

of neuronal VZV reactivation and antegrade transport to cutaneous sites could occur commonly but be clinically silent if the reactivation is controlled by local cutaneous immunity; thus, if this immune process is disrupted by trauma, HZ could result. Both of these explanations, which are not mutually exclusive, are consistent with the rapid development of HZ following trauma we observed. Finally, we cannot exclude the possibility that any effect of trauma might be mediated partially by a non-local mechanism, which evidenced by some level of association between HZ and trauma to the limbs.

Our study has the limitations of administrative data. Diagnoses in the Medicare claims data cannot be validated through medical record review. However, other studies have, through medical record review, demonstrated the validity of administrative data in accurately identifying various acute diagnoses and procedures, including HZ [14, 15]. Trauma severity is not reflected in Medicare claims data. However, this study likely reflected a range of severity because we used a random sample of individuals in different settings. Also, timing of trauma in claims data may be differentially precise. Persons experiencing open wounds likely sought care immediately, whereas delays of several days may have occurred before persons with other trauma types, such as sprains/strains, sought care. Finally, our exclusion criteria were incomplete, as not all individuals with immunocompromising conditions have been excluded from our study.

Confirmation of a role for local factors (whether local stimulation of sensory nerves or local disruption of cutaneous immunity) in the development of HZ would have potentially important implications. Unrecognized cutaneous factors might contribute to the risk of HZ and help explain what distinguishes the almost one third of immunocompetent persons who experience HZ during their lifetime from the two thirds who do not. Similarly, cutaneous

senescence might increase the risk of HZ with aging. Also, perhaps the zoster vaccine partially exerts its protective effects through cutaneous immunity, in conjunction with its effects through CMI, which would have implications for identifying correlates of protection.

Clinicians should be aware of the association between HZ and trauma, since the development of HZ at a trauma site might otherwise lead to confusion regarding the healing of the injury or the need for timely HZ treatment. Regardless of the various mechanisms through which VZV reactivation may occur, HZ vaccine remains an important tool for HZ prevention among adults aged 60 years and older.

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Table 1. Trauma, overall and by site and type, among herpes zoster (HZ) cases and age-matched controls during the 52 weeks before the index date.

Trauma and trauma site/type week before index date	HZ cases (n=16,771)	Controls (n=167,702)	aOR [a] (95%CI)
	No. (%)		
Any trauma			
1	117 (0.70)	354 (0.21)	3.40 (2.75-4.21)
2	77 (0.46)	419 (0.25)	1.76 (1.37-2.25)
3	61 (0.36)	411 (0.25)	1.49 (1.13-1.95)
4-52	2,493 (14.86)	21,983 (13.10)	1.09 (1.04-1.15)
Trauma site:			
Cranium			
1	28 (0.17)	49 (0.03)	6.18 (3.77-10.14)
2	8 (0.05)	64 (0.04)	1.18 (0.56-2.50)
3	11 (0.07)	52 (0.03)	2.04 (1.04-3.97)

4-52	308 (1.84)	2,644 (1.58)	1.13 (1.00-1.28)
Trunk			
1	44 (0.26)	106 (0.06)	4.08 (2.83-5.87)
2	31 (0.18)	122 (0.07)	2.45 (1.63-3.67)
3	23 (0.14)	95 (0.06)	2.29 (1.44-3.65)
4-52	803 (4.79)	6,848 (4.08)	1.13 (1.04-1.22)
Limbs			
1	26 (0.16)	165 (0.10)	1.60 (1.05-2.43)
2	28 (0.17)	203 (0.12)	1.25 (0.84-1.87)
3	23 (0.14)	221 (0.13)	1.02 (0.66-1.58)
4-52	1,139 (6.79)	10,568 (6.30)	1.04 (0.98-1.11)
Unspecified site			
1	19 (0.11)	33 (0.02)	6.53 (3.56-11.98)

2	10 (0.06)	30 (0.02)	3.59 (1.67-7.69)
3	4 (0.02)	43 (0.03)	1.01 (0.36-2.85)
4-52	243 (1.45)	1,923 (1.15)	1.24 (1.08-1.42)
Trauma type:			
Sprain and strain			
1	48 (0.29)	115 (0.07)	4.19 (2.96-5.95)
2	26 (0.16)	126 (0.08)	2.07 (1.34-3.19)
3	26 (0.16)	137 (0.08)	1.89 (1.23-2.91)
4-52	963 (5.74)	7,932 (4.73)	1.17 (1.09-1.25)
Open wound			
1	46 (0.27)	102 (0.06)	4.74 (3.29-6.82)
2	19 (0.11)	143 (0.09)	1.24 (0.76-2.01)
3	17 (0.10)	109 (0.06)	1.49 (0.89-2.50)
4-52	707 (4.22)	6,384 (3.81)	1.08 (1.00-1.18)

Contusion			
1	16 (0.10)	84 (0.05)	1.89 (1.09-3.27)
2	17 (0.10)	99 (0.06)	1.50 (0.89-2.54)
3	11 (0.07)	117 (0.07)	0.92 (0.49-1.73)
4-52	481 (2.87)	4,529 (2.70)	1.01 (0.92-1.12)
Dislocation			
1	2 (0.01)	29 (0.02)	0.67 (0.16-2.83)
2	7 (0.04)	30 (0.02)	2.13 (0.91-4.98)
3	3 (0.02)	27 (0.02)	0.94 (0.28-3.11)
4-52	229 (1.37)	2,096 (1.25)	1.02 (0.89-1.18)
Unspecified type			
1	5 (0.03)	24 (0.01)	1.88 (0.70-5.09)
2	8 (0.05)	21 (0.01)	2.89 (1.26-6.65)

3	4 (0.02)	21 (0.01)	2.55 (0.82-7.93)
4-52	113 (0.67)	1,042 (0.62)	1.07 (0.88-1.31)
No trauma in 52 weeks	12,969 (77.33)	136,257 (81.25)	Reference

[a] Odds ratios after adjusting for age, sex, race/ethnicity, diabetes, depression, rheumatoid arthritis / osteoarthritis, and health care utilization.

Table 2. Trauma, overall and by site and type, among the subset of cases with herpes zoster (HZ) that occurred on the cranium [a] and age-matched controls

Trauma and trauma site/type week before index date	HZ cases (n=1,246)	Controls (n=12,460)	aOR [b] (95%CI)
	No. (%)		
Trauma in week:			
1	15 (1.20)	24 (0.19)	6.10 (3.17-11.73)
2	3 (0.24)	33 (0.26)	0.89 (0.27-2.93)
3	1 (0.08)	30 (0.24)	0.31 (0.04-2.30)
Trauma site in week 1:			
Cranium	6 (0.48)	3 (0.02)	27.51 (5.40-140.29)
Trunk	4 (0.32)	6 (0.05)	5.51 (1.53-19.83)
Limbs	3 (0.24)	15 (0.12)	2.00 (0.56-7.10)
Trauma type in week 1:			

Sprain and strain	3 (0.24)	8 (0.06)	3.16 (0.83-12.01)
Open wound	8 (0.64)	7 (0.06)	16.83 (5.36-52.85)
Contusion	3 (0.24)	7 (0.06)	4.62 (1.13-18.84)
No trauma in 52 weeks	955 (76.65)	10,115 (81.18)	Reference

[a] Cases with cranial HZ identified by ICD-9-CM codes (053.11; 053.2; 053.20; 053.21; 053.22; 053.29; 053.71).

[b] Odds ratios after adjusting for age, sex, race/ethnicity, diabetes, depression, rheumatoid arthritis / osteoarthritis, and health care utilization.