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Association between de Quervain syndrome and herpes zoster: a population-based cohort study

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ABSTRACT

Objective Both physical diseases such as infection and chronic pain and psychological disorders such as depression have been associated with herpes zoster (HZ) reactivation. However, the relationship between de Quervain syndrome (DQS), a painful tenosynovitis and HZ remains unclear. We investigated whether DQS increases the risk of HZ reactivation.

Design A retrospective population-based cohort study.

Setting Taiwan.

Participants We used a subset of Taiwan's National Health Insurance Research Database, the Longitudinal Health Insurance Database which contains the registration files and original claims data of 1 million randomly selected individuals from the National Health Insurance programme. The case group in this study comprised patients newly diagnosed with DQS between 2000 and 2012. Individuals without DQS comprised the control group. Cases and controls were 1:1 matched by age, sex and index year (defined as the year of DQS diagnosis).

Results Approximately 55% of the participants were ≤49 years. Most participants were women (77%). The incidence rate of HZ in the DQS group was 8.39 per 1000 person years. After adjustments for age, sex and comorbidities, patients with DQS had a 1.30 times higher risk of HZ reactivation than the control group. Stratification analysis revealed taht DQS increases the HZ risk in individuals ≤64 years, women, and patients without comorbidities.

Conclusion DQS is associated with an increased risk of HZ. Clinicians should be aware of this risk when dealing with patients with DQS, particularly in young adults.

Strengths and limitations of this study

- This population-based study was conducted using the National Health Insurance Research Database (NHIRD), which is a highly representative sample of the Taiwanese because it has a large sample size and thus the findings are highly generalisable.
- The patients were selected from the NHIRD based on diagnostic codes, which may have specialist-associated bias.
- Data on DQS and HZ severity are not available in the NHIRD and could therefore not be used in this study.
- Self-payment treatments for DQS or HZ are also not recorded in the NHIRD.

INTRODUCTION

De Quervain syndrome (DQS), also termed tenosynovitis, is a painful inflammation of the tendons on the radial side of the wrist.[1] The prevalence of DQS is higher in women (approximately 1.3%) than in men (0.5%).[2] Typically, it affects individuals in their forties and fifties.[3] Wolf *et al* analysed a military database and revealed that the incidence of DQS in a young, active population was 2.8 and 0.6 per 1000 person years for women and men, respectively. They also reported that female sex was a risk factor for DQS.[4] A single-dose steroid injection could alleviate symptoms in 82% of patients with DQS within 6 weeks.[5]

In Taiwan, the incidence of herpes zoster (HZ) increased from 5.04 cases per 1000 person years in 2004 to 5.65 in 2008. Moreover, HZ incidence increases with age, being 3.59 cases per 1000 person years in patients ≤49 years, and 12.81 cases per 1000 person years in patients aged 65–74 years in 2008.[6] In Italy and Germany, the incidence rate of HZ in adults aged ≥50 years was 6.46 and 6.7 per 1000 person years.[7 8] The highest incidence rate was 9.4 per 1000 person years in German adults aged ≥80 years.[8] Recently, Tseng *et al* observed that the incidence rate of HZ was as high as 9.92 per 1000 person years in immunocompetent, unvaccinated adults aged ≥50 years.[9] Postherpetic neuralgia is a problematic complication of HZ, it is found in 10%–15% of patients with HZ,[7] and the pain can last from months to years.

Stress, including physical stress in the form of diseases, is associated with the development of HZ. Infection,[10 11] chronic pain-associated diseases (such as chronic interstitial cystitis,[12] adhesive capsulitis of the shoulder,[13] lateral epicondylitis,[14] sciatica[15] and varicocele[16]) and psychological disorders (such as depression[17 18]) have all been associated with HZ reactivation. DQS and the associated pain may be stressful for affected individuals. Furthermore, pain is highly correlated with

depression.[19] Thus, a correlation may exist between DQS and HZ. Here, we investigated whether DQS increases the risk of HZ reactivation.

MATERIALS AND METHODS

Patient and public involvement

The single-payer National Health Insurance (NHI) programme in Taiwan was initiated on 1 March 1995. Over 99% of Taiwan's population is now covered by the programme. The medical records of enrollees are registered in the National Health Insurance Research Database (NHIRD). In this study, we used the Longitudinal Health Insurance Database, a subset of the NHIRD, which contains data of 1 million randomly selected enrollees from the NHI programme. The identification information was encrypted before use for research. The disease codes were identified according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-*CM*).

Study population

The case group comprised patients newly diagnosed with DQS (*ICD-9-CM* code: 727.04) from 2000 to 2012, and the control group comprised patients without DQS. We excluded patients with a history of HZ reactivation and patients younger than 20 years. Cases and controls were 1:1 matched by age, sex and index year (defined as the year of DQS diagnosis). All study participants were followed up until they were diagnosed with HZ occurrence, were lost to follow-up, died or until 31 December 2013.

Main outcome and comorbidities

HZ occurrence (*ICD-9-CM* code: 053) was the primary outcome of the present study. We considered the presence of the following comorbidities as potential confounders: chronic kidney disease (CKD; *ICD-9-CM* code: 585, 586), obesity (*ICD-9-CM* code: 278), diabetes (*ICD-9-CM* code: 250), coronary artery disease (CAD; *ICD-9-CM* code: 410–414) and depression (*ICD-9-CM* code: 296.2, 296.3, 300.4 and 311).

Statistical analysis

The baseline demographic characteristics and comorbidities of the case and control groups were compared using the χ^2 test and t-test. We calculated the incidence rate as per 1000 person years. The Cox proportional hazards regression model was applied to estimate HRs after adjustment for the following variables as appropriate: age, sex and the comorbidities of CKD, diabetes, CAD and depression. Stratified analysis of age group, sex and comorbidities was also performed. We obtained the cumulative incidence of HZ by using the Kaplan-Meier method and examined intergroup differences using a log-rank test; p≤0.05 was set as statistically significant.

RESULTS

This study recruited 8390 participants (4195 cases and 4195 controls). The mean follow-up time was 6.68 (±3.63) years for the case group and 6.60 (±3.62) years for the control group. Table 1 compares the baseline characteristics between the two groups. Almost 55% of the participants were younger than 49 years. Mean age for the two groups was approximately 47 years. Most participants were women (77%). The distributions of CKD, diabetes and cancer were similar between the two groups. The percentages of patients with obesity, CAD and depression were higher in the DQS cohort than in the DQS-free cohort.

Table 1 Demographic characteristics and comorbidities in cohorts with and without de Quervain syndrome

	de Quervain syndrome		
	No	Yes	
Variable	N=4195	N=4195	P value
Age, year			0.99
≤49	2299 (54.8)	2299 (54.8)	
50–64	1552 (37.0)	1552 (37.0)	
65+	344 (8.20)	344 (8.20)	
Mean±SD*	46.9±13.9	46.8±13.5	
Sex			0.99
Female	3229 (77.0)	3229 (77.0)	
Male	966 (23.0)	966 (23.0)	
Comorbidity			
Diabetes	222 (5.29)	209 (4.98)	0.52
CAD	414 (9.87)	499 (11.9)	0.003
Depression	227 (5.41)	281 (6.70)	0.01
Chronic kidney disease	43 (1.03)	28 (0.67)	0.07
Obesity	78 (1.86)	105 (2.50)	0.04
Cancer	101 (2.41)	106 (2.53)	0.72

Chi-Square Test
*T-Test
CAD, coronary artery disease.

The incidence rate of HZ in the case group was 8.39 per 1000 person years. Cases were 1.30 times (95% CI 1.16 to 1.47) more likely than the controls to have HZ (table 2). The adjusted HR of HZ occurrence in the subgroup aged 50–64 years was 2.65 (95% CI 2.31 to 3.04) and that in the subgroup aged ≥65 years was 2.79 (95% CI 2.27 to 3.43), with patients ≤49 years old considered the reference group. Patients with CKD, diabetes, CAD and depression also had significantly higher risks of developing HZ.

Stratified analysis (table 3) revealed that DQS increased HZ risk in individuals ≤64 years, women and patients without comorbidities. The cumulative incidence curve for the patients with DQS was higher than that for the controls. The difference between the two curves was significant (log-rank test: p=0.007; figure 1).

DISCUSSION

This is the first retrospective population-based study to demonstrate the association between DQS and HZ

Table 2 The incidence and risk factors for herpes zoster

Variable	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR (95% CI)
de Quervain					
No	154	24 442	6.30	1.00	1.00
Yes	206	24 558	8.39	1.33 (1.18 to 1.50)***	1.30 (1.16 to 1.47)***
Age, year					
≤49	113	28 427	3.98	1.00	1.00
50–64	199	17 152	11.6	2.92 (2.56 to 3.33)***	2.65 (2.31 to 3.04)***
65+	48	3421	14.0	3.53 (2.91 to 4.28)***	2.79 (2.27 to 3.43)***
Sex					
Female	294	37 761	7.79	1.33 (1.13 to 1.55)***	1.07 (0.92 to 1.25)
Male	66	11 238	5.87	1.00	1.00
Comorbidity					
Diabetes					
No	324	46 675	6.94	1.00	1.00
Yes	36	2325	15.5	2.23 (1.83 to 2.72)***	1.33 (1.08 to 1.64)***
CAD					
No	285	44 009	6.48	1.00	1.00
Yes	75	4991	15.0	2.32 (2.00 to 2.69)***	1.42 (1.21 to 1.66)***
Depression					
No	330	46 482	7.10	1.00	1.00
Yes	30	2518	11.9	1.68 (1.35 to 2.09)***	1.35 (1.09 to 1.68)***
Chronic kidney disease					
No	355	48 690	7.29	1.00	1.00
Yes	5	310	16.1	2.21 (1.32 to 3.70)***	1.34 (1.09 to 1.68)***
Obesity					
No	353	48 112	7.34	1.00	1.00
Yes	7	888	7.88	1.07 (0.69 to 1.66)	
Cancer					
No	353	48 054	7.35	1.00	1.00
Yes	7	945	7.41	1.01 (0.65 to 1.56)	

Rate#, incidence rate, per 1000 person years; Crude HR *, relative HR; Adjusted HR†: multivariable analysis including age, sex, and comorbidities of diabetes, CAD, depression, and chronic kidney disease;
*p<0.05, **p<0.01, ***p<0.001

reactivation. We observed that patients with DQS had a higher risk of HZ than those without DQS. After adjustments for age, sex and comorbidities, patients with DQS were found to be 1.3 times more likely to develop HZ.

Petit Le Manac'h *et al* found the prevalence of DQS among the working population to be 1.2%, with the prevalence for women and men being 2.1% and 0.6%, respectively. They also reported that the most significant factors related to work were twisting or driving screws.[20] These tasks involve bending and twisting of the wrist. Because DQS is more common in women, oestrogen involvement in the pathogenesis of DQS should be considered. Shen *et al* concluded that patients with relatively high oestrogen receptor (ER)-β expression exhibited more severe DQS and that ER-β may be a useful target for DQS treatment.[21] However, only a limited number of patients were enrolled in that study. In our cohort, most patients with DQS were women, consistent with previous studies.

Our study found that patients with CAD or CKD had a higher risk of HZ. In 1989, the Framingham Heart Study did not identify a strong association between herpes occurrence and CAD incidence among elderly people.[22 23] Subsequently, Esteban-Hernández *et al* reported a high association between herpes and ischaemic heart disease (OR: 4.5) after adjustment for comorbidities, without hypercholesterolaemia.[24] A meta-analysis study assessed the relationship between cardiac risk and HZ development

Table 3 Incidence of herpes zoster by age, sex and comorbidity and Cox model measured HR for patients with de Quervain syndrome compared those without de Quervain syndrome

	de Quervain							
	No			Yes			Crude HR*	Adjusted HR&
Variables	Event	PY	Rate#	Event	PY	Rate#	(95% CI)	(95% CI)
Age, years								
≤49	43	14211	3.03	70	14216	4.92	1.63 (1.36 to 1.94)***	1.57 (1.32 to 1.87)***
50–64	88	88	10.2	111	8551	13.0	1.27 (1.05 to 1.53)***	1.25 (1.03 to 1.51)***
65+	23	23	14.1	25	1791	14.0	0.99 (0.67 to 1.47)	0.95 (0.64 to 1.40)
Sex								
Female	120	18899	6.35	174	18863	9.22	1.45 (1.27 to 1.67)***	1.43 (1.25 to 1.64)***
Male	34	5543	6.13	32	5695	5.62	0.92 (0.70 to 1.19)	0.87 (0.68 to 1.13)
Comorbidity								
No	105	20150	5.21	137	19320	7.09	1.36 (1.18 to 1.56)***	1.36 (1.19 to 1.56)***
Yes	49	4292	11.4	69	5239	13.2	1.15 (0.90 to 1.48)	1.17 (0.92 to 1.50)

Rate#, incidence rate, per 1,000 person-years; Crude HR *, relative hazard ratio; Adjusted HR† : multivariable analysis including age, sex, and comorbidities of diabetes, CAD, depression, and chronic kidney disease.
§ Individuals with any comorbidity of diabetes, CAD, depression, and chronic kidney disease, obesity, and cancer were classified into the comorbidity group.
*p<0.05, **p<0.01, ***p<0.001.

and found that cardiac events were significantly increased after HZ onset; the ORs were 1.31 at 3 months, 1.19 up to 1 year and 1.12 more than 1 year after HZ occurrence.[25] Increased cardiovascular risks after HZ development have been identified, but HZ risk following cardiovascular events remains unclear. However, in the present study, patients with CAD had a 1.42-fold increased risk of HZ.

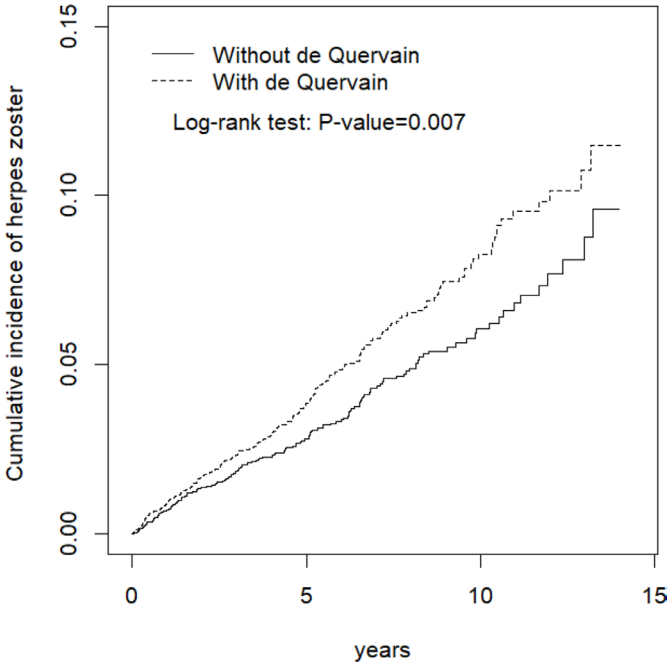

Figure 1 Cummulative incidence comparison of herpes zoster for patients with (dashed line) or without (solid line) de Quervain syndrome.

Several researchers have attempted to identify HZ risk among patients with CKD. Sato *et al* found that the incidence of HZ was only 8.2 per 1000 person years in patients with stage 1, 2 or 3 CKD, but increased to as high as 84.8 per 1000 person years in patients under haemodialysis or peritoneal dialysis.[26] Lin *et al* analysed HZ risk based on sustained kidney damage and therapy received, reporting that the HR of HZ occurrence was 8.46 for the renal transplantation group, 3.61 for the peritoneal dialysis group, 1.35 for the haemodialysis group and 1.21 for the CKD group compared with the control group.[27]

Mortality is high after HZ reactivation in patients with end-stage renal disease (ESRD). Ahn *et al* reported that half of patients with ESRD died within 2 years following HZ (mean time to death: 8.1 months). They also found that mortality increased as age and Charlson Comorbidity Index Score increased.[28] Comparing the incidence of HZ occurrence in ESRD patients with and without HZ vaccination, Tseng *et al* reported that the incidence of HZ was 11.7 per 1000 person years for the vaccinated group and 22.3 per 1000 person years for the unvaccinated group; thus, HZ vaccination reduced the risk by half. The authors concluded that HZ vaccination may provide a better protection soon after the initiation of dialysis.[29] In our study, patients with CKD were 1.34 times more likely to develop HZ.

CAD and CKD are considered risk factors for HZ reactivation. Our findings demonstrated that among participants with any comorbidities, individuals with DQS had a slightly higher risk of HZ than those without DQS. However, among patients without any comorbidities, HZ risk in patients with DQS was 1.36 times higher than in

those without DQS (table 3). This means that DQS must be a serious stressor for affected persons. In general, HZ incidence increases with age. Our results revealed that the risk of HZ among DQS patients was the highest in the age group of <50 years (table 3). Therefore, in our view, the disease burden of DQS should not be ignored, particularly among younger adults.

This was a population-based study conducted using NHIRD records. The NHIRD contains a highly representative sample of the Taiwanese population because it has a large sample size and the findings are highly generalisable. However, this study has several limitations. First, the data were selected from the NHIRD records based on diagnostic codes. The diagnosis of DQS and HZ might be made by neurologists, orthopedists, general practitioners or dermatologists who employ differing methods or criteria; thus, bias may exist related to the diagnostic codes of medical specialists. However, the NHI Administration audits the claims and enforces a punishment system. All claims are sent to the NHI Administration and checked by reimbursement experts. Therefore, the diagnostic codes are highly reliable. Second, NHIRD does not have data on DQS and HZ severity. The severity of diseases may influence treatment decision-making and affect prognosis. Third, self-payment treatments for DQS or HZ are not recorded in the NHIRD. Some patients might have used traditional Chinese medicine methods such as acupuncture or medicinal herb, to relieve pain at their own expense, resulting in an underestimation of the prevalence of DQS or HZ. Fourth, self-paid HZ vaccines might not be recorded in the NHIRD. The HZ vaccine has been available in Taiwan since 2013, but it is expensive and not covered by the NHI. Therefore, HZ vaccination is not common in Taiwan. This study followed enrollees until the end of 2013, and hence, the influence of the HZ vaccine can be ignored. Regardless of the limitations, our study reflects real-world circumstances with numerous samples and highly generalisability. Our data strongly indicate that patients with DQS have a higher HZ risk than those without. These findings may serve as reference for future research.

CONCLUSION

DQS is associated with an increased risk of HZ. Clinicians should be aware of this risk when dealing with patients with DQS, particularly in young adults.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The NHIRD encrypts patients' personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR4); the IRB also waived the consent requirement.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The NHIRD is maintained by the Taiwan Ministry of Health and Welfare (MOHW). The application to access the data for this study was approved by the MOHW. Any researcher interested in the data from the NHIRD can submit an application form to the MOHW or contact the staff of the MOHW (Email: stcarolwu@mohw.gov.tw) for assistance.

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