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Impact of COVID-19 Vaccination on Varicella Zoster Virus Reactivation: A Case Control Study

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ABSTRACT

Background: *Herpes zoster (HZ) is a medical condition of a significant global impact, with millions of people affected and rising incidence. Some risk factors of this disease had been reported in previous literatures worldwide; however, studies that pool evidence to provide estimates of newly emerged risk have yet to be conducted, especially in the context of the current pandemic. Therefore, the purpose of this study is to examine the association between COVID-19 vaccination and the risk of developing HZ in Kuwait.*

Methods: *Clinically diagnosed 186 HZ patients were enrolled, along with 186 controls (1:1) with matched age (± 5 years), sex and nationality. Data from cases and controls was collected using a predesigned interview questionnaire. The data was analyzed using logistic regression.*

Results: *Most of cases and controls were non-Kuwaiti (61.8%) and male (69.4%). About one fifth (19.4%) of HZ cases developed HZ following vaccination against COVID-19 within the study period (two months). Cases were more likely than controls to have had COVID-19 vaccination history (adjusted matched odds ratio (OR) = 4.87; 95 percent confidence interval (CI): 2.40–9.89; P< 0.001). Vaccinated HZ cases experienced significantly more lateralization to the left side (χ^2 = 12.146, P = 0.000).*

Conclusions: *Vaccination with COVID-19 had significant statistical association with varicella zoster activation. Future studies may contemplate to verify the observed results.*

Keywords

Complications, COVID-19 vaccines, Herpes zoster, Reactivation.

Introduction

Varicella-zoster virus (VZV; human herpesvirus 3) is a human neurotropic alpha herpes virus. Primary VZV infection is a systemic infection that results in chickenpox. During primary infection, the virus gains access to neurons through retrograde transport from the site of cutaneous lesion [1]. Varicella-zoster reactivation from latency, which lies dormant in the spinal and cranial sensory ganglia after primary infection in childhood [2,3]. Herpes zoster (HZ) which is a vesicular skin eruption associated with pain that respect the dermatomal distribution occur after VZV reactivation. Through various mechanisms, VZV is reactivated to cause HZ. Numerous studies have identified risk factors associated with reactivation of VZV, many of which are related to a decrease in T-cell immunity, such as aging and immunosuppression, but some are related to family history or stress [4,5].

As of April 2021, 13 vaccines are authorized by at least one national regulatory authority for public use: five conventional inactivated vaccines (BBIBP-CorV, CoronaVac, Covaxin, WIBP-CorV and CoviVac), two RNA vaccines (the Pfizer–BioNTech vaccine and the Moderna vaccine), four viral vector vaccines (Sputnik V, the Oxford–AstraZeneca vaccine, Convidecia, and the Johnson & Johnson vaccine), and two protein subunit vaccines (EpiVacCorona and RBD-Dimer) [6].

Recognizing the urgent need for the COVID-19 vaccine, the analysis of the safety data of different COVID vaccines trials and its post marketing use is of prime importance. Most of the reactions reported resolved within days of receiving the vaccine and were mild to moderate whereas a few with severe intensity. The commonly reported local adverse events were pain at the site of injection, redness, and swelling. The systemic reactions included fever, headache, fatigue, and myalgia. Laboratory derangements were reported in some trials like decreased hemoglobin, increased bilirubin, altered SGOT and SGPT. None of these alterations were clinically manifested and were self-limiting. Few clinical trials reported serious adverse events, but they were reported as unrelated to vaccination. However, long-term post-marketing surveillance data, particularly in high-risk vulnerable populations (elderly and those with co-morbidities, pregnant women, and children) is warranted to ensure the safety of COVID-19 vaccines [7].

Although some researchers found that people with certain autoimmune diseases were likely to develop VZV reactivation after receiving BNT162b2 mRNA COVID-19 vaccination [8]. Earlier in this year a case of VZV in a 78-year-old man following vaccination with inactivated COVID-19 vaccine was reported [9]. To the best of our knowledge this is the first case control study studying the risk of developing VZV after receiving different types of COVID -19 vaccines, our study aimed to assess if there is an association between COVID-19 vaccination and VZV reactivation.

Methods

At the outpatient department of infection disease hospital (IDH), which is the tertiary level health care facility that deal with HZ cases in Kuwait, a matched case control study was performed. Suspected HZ cases seen in other Kuwaiti clinics/ hospitals were referred to IDH for confirmation of diagnosis and care. All participants provided informed consent to participate in the study after MOH ethics committee approved it. To collect data from each case and its matched control, a structured interview questionnaire was used. Cases and controls were enrolled over a two-month period (February and March 2021). The questionnaire addressed demographic, social, and physical factors.

Cases of HZ was defined by presence of painful, blistering skin eruption in a unilateral dermatomal distribution (Figures 1 - 3). The diagnosis was made by the attending infectious disease specialist with the presence of at least one clinical claim linked to HZ (ICD-10 codes B02, B02.2, B02.3, B02.7, B02.8, and B02.9) consistent with an antiviral drug prescription (as acyclovir or valaciclovir). Controls were selected from patients and their relatives attended IDH hospital for reasons other than HZ (etc. animal bite, brucella, UTI). They were matched to each case based on age (5 years), gender and nationality. Individuals with known allergic reaction of any severity to vaccines or drugs, pregnant and lactating women, children, and adolescents below age of 18 years and those with history of recent COVID-19 infection (within the last 3 months) were excluded from the study.

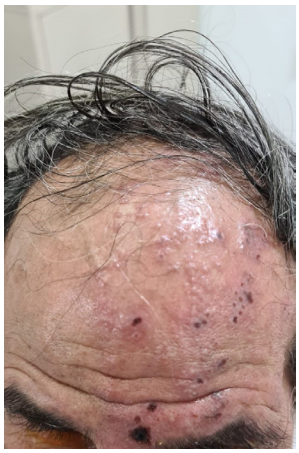

Figure 1: 58 years old man with HZ following dermatomal distribution of ophthalmic branch of left trigeminal nerve 7 days after mRNA vaccine.

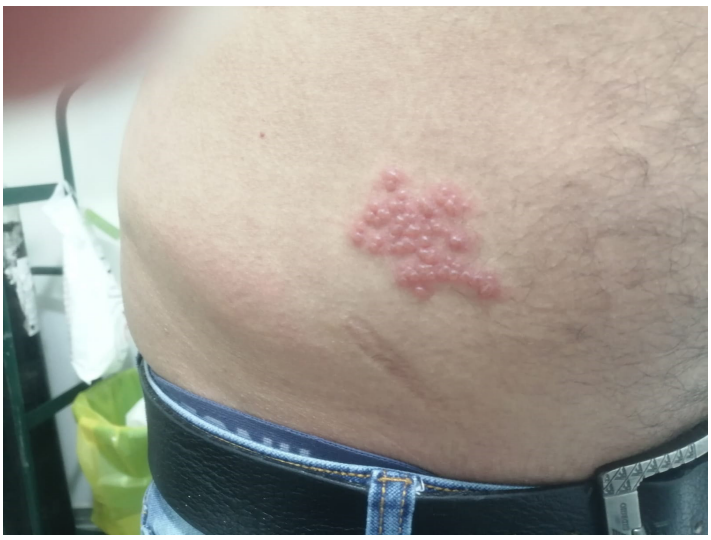

Figure 2: 43 years old man with HZ following the dermatomal distribution of Rt. T_{11} 10 days after viral vector vaccine.

The means and standard deviations (SD) of quantitative variables as well as the frequencies of qualitative variables were computed using descriptive analysis. For comparison between categorical variables, Fisher exact test was used. Using multinomial logistic regression model, risk factors for HZ were analyzed. The adjusted OR (mORadj) and their 95% confidence intervals (CI) were determined using the final model's parameter estimates. The 2-tailed test was used to measure all of the probability values (P- value),

with a value of less than 0.05 indicating statistical significance. Independent variables tested were immunosuppressive diseases or drugs, smoking, family history of HZ, comorbidities, stress (subjective description), and history of COVID-19 vaccination. Statistical analyses were conducted using SPSS 20.

Results

In the current study, a total of 190 HZ cases were asked to participate and 186 (97.9%) accepted. In total, 362 subjects were enrolled in the study: 186 HZ cases along with 186 controls (1:1) with matched age (± 5 years), sex and nationality. The mean age (± SD) was 46.31 (± 15.40) and 45.89 (± 15.17) for cases and controls, respectively. Most of cases and controls were non-Kuwaiti (61.8%) and male (69.4%). Among cases (table 1), stress (39.8%) was the most prevalent risk factor followed by family history of HZ (34.9%), comorbidities (34.4%), smoking (23.1%), and immunosuppression (2.7%). Statistically significant differences were shown between cases and controls regarding the prevalence of family history of HZ (χ^2 = 20.853, P < 0.000) and stress (χ^2 = 82.556, P < 0.000). About one fifth (19.4%) of cases had previous history of COVID-19 vaccination vs. 8.6% of controls with statistically significant difference between both groups (χ^2 = 8.942, P = 0.003).

After adjusting for age, sex and nationality, the final multinomial logistic regression test revealed that cases were more likely than controls to have had immunosuppression (mOR_{adj} = 6.34; 95% CI: 1.08–37.09; p <0.05), comorbidities (mOR_{adj} = 1.79; 95% CI: 1.03–3.08; p <0.05), family history of HZ (mOR_{adj} = 82.59; 95% CI: 24.30–280.66; p <0.001), and stress (mOR_{adj} = 4.46; 95% CI: 2.47–8.06; p <0.001). Cases were more likely to have had COVID-19 vaccination history compared to controls (mOR_{adj} = 4.87; 95% CI: 2.40–9.89; p <0.001).

About one fifth of HZ cases had history of COVID 19 vaccination (36 person, 19.4% of cases). More than three quarters of them, (77.8%) had onset of HZ following mRNA COVID-19 vaccination and 22.2% had HZ following viral vector vaccine? About 72% of vaccinated cases had onset of HZ after receiving 1st dose of vaccine compared to 28% who showed onset of HZ after 2nd dose. Less than two thirds of vaccinated cases (63.9%) had onset of HZ within seven days of receiving the vaccine with mean duration of 8.5 ± 4.802 days. Among vaccinated cases, HZ is significantly more prevalent among older age group (63.9% vs. 38% in non-vaccinated cases), Kuwaiti citizens (72.2% vs. 30% in non-vaccinated cases), those with positive family history of HZ (61.1% vs. 90.7% in non-vaccinated cases), (χ^2 = 7.938, P < 0.005), (χ^2 = 21.930, P < 0.000), (χ^2 = 19.832, P < 0.000) respectively. Herpes zoster tended to significantly affect left side dermatomes in vaccinated cases in comparison to non-vaccinated cases (75% vs. 42.7%, χ^2 = 12.146, P = 0.000) (Table 3).

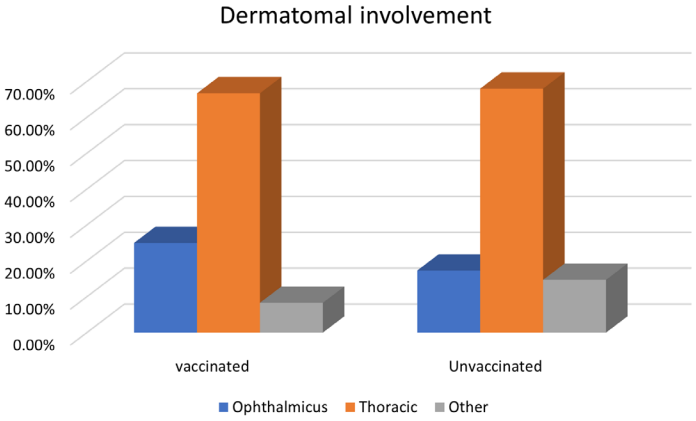

Figure 4: Dermatomal involvement in both vaccinated and non-vaccinated HZ cases.

Table 1: Distribution of potential risk factors in cases and controls enrolled in a case-control study of risk factors for HZ in Kuwait (February-March 2021).

Potential risk factors of HZ	Cases n = 186		Controls n = 186		OR {CI}	Test of significance
	No.	%	No.	%		
Immunosuppression						
No	181	97.3	184	98.9	2.541	
Yes	5	2.7	2	1.1	**{0.487-13.268}**	P = 0.449#
Comorbidities						
No	122	65.6	134	72.0	1.352	
Yes	64	34.4	52	28.0	**{0.870-2.100**	χ^2 = 1.804 P = 0.1799
Family history of HZ						
No	121	58.9	159	85.5	3.163	
Yes	65	34.9	27	14.5	**{1.905-5.254}**	χ^2 = 20.853 P< 0.001*
Smoking						
No	143	76.9	153	82.3	1.394	
Yes	43	23.1	33	17.7	**{0.839-2.316}**	χ^2 = 1.654 P = 0.198
Stress						
No	112	60.2	183	58.3	40.304	
Yes	74	39.8	3	13.3	**{12.409-130.901}**	χ^2 = 82.556 P< 0.001*
COVID-19 vaccine						
No	150	80.6	170	91.4	2.550	
Yes	36	19.4	16	8.6	**{1.360-4.781}**	χ^2 = 8.942 P = 0.003*

*OR: Odd's ratio (crude), CI: Confidence Interval, HZ: Herpes zoster, * Significant (p<0.05), χ^2: Chi squared test, # Fisher exact 2-tailed P-value.*

Table 2: Multivariable conditional logistic regression model of risk factors associated with HZ in Kuwait (February-March 2021).

Potential risk factors of HZ	Adjusted matched OR	95 % CI	P value
Immunosuppression (yes vs. no)	6.34	1.08-37.09	P = 0.041*
Comorbidities (yes vs. no)	1.79	1.03-3.08	P = 0.040*
Family history of HZ (yes vs. no)	82.59	24.30-280.66	P< 0.001*
Smoking (yes vs. no)	0.78	0.39-1.59	P = 0.509
Stress (yes vs. no)	4.46	2.47-8.06	P< 0.001*
COVID-19 vaccine (yes vs. no)	4.87	2.40-9.89	P< 0.001*

*OR: Odd's ratio, CI: Confidence Interval, HZ: Herpes zoster, * Significant (p<0.05).*

Table 3: Distribution of HZ cases enrolled in a case-control study of risk factors for HZ in Kuwait (February-March 2021) according to some variables.

Variable	Not vaccinated n = 150		Vaccinated n = 36		Test of significance
	No.	%	No.	%	
Age					
<50 years	93	62.0	13	36.1	$\chi^2 = 7.938$
≥ 50 years	57	38.0	23	63.9	P = 0.005*
Sex					
Male	102	68.0	27	75.0	$\chi^2 = 0.669$
Female	48	32.0	9	25.0	P = 0.413
Nationality					
Kuwaiti	45	30.0	26	72.2	$\chi^2 = 21.930$
Non-Kuwaiti	105	70.0	10	27.8	P< 0.001*
Family History of HZ					
No	14	9.3	14	38.9	$\chi^2 = 19.832$
Yes	136	90.7	22	61.1	P< 0.001*
HZ required hospital admission.					
No	113	75.3	26	72.2	$\chi^2 = 0.149$
Yes	37	24.7	10	27.8	P = 0.700
Lateralization of HZ					
Right	86	57.3	9	25.0	$\chi^2 = 12.146$
Left	64	42.7	27	75.0	P< 0.001*
Complication					
No	131	87.3	34	94.4	P = 0.377
Yes	19	12.7	2	2.56	

** Significant (p<0.05), χ^2 Chi squared test, HZ: Herpes zoster, # Fisher exact 2-tailed P-value.*

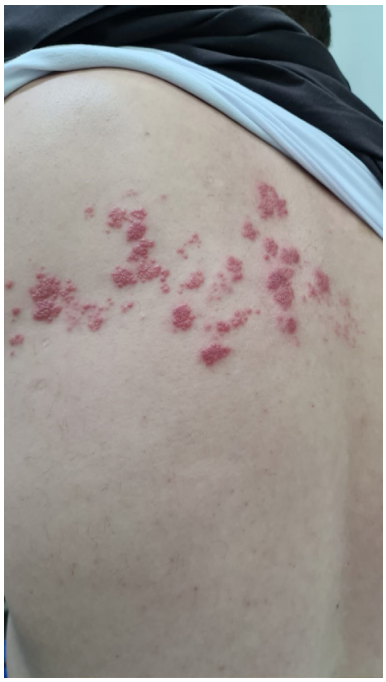

Figure 3: 33 years old man with HZ following the dermatomal distribution of Lt. T_7 5 days after viral mRNA vaccine..

Figure 4 compared the dermatomal involvement in both vaccinated and non-vaccinated HZ cases with no statistical significance among those with ophthalmic (χ^2 = 1.117, P = 0.291), thoracic involvement (χ^2 = 0.024, P = 0.878), and other dermatomal involvement (χ^2 = 1.001, P = 0.317).

Discussion

The need for safe and effective vaccination against COVID-19 was urgent, thus multiple vaccines were developed and licensed under emergency use. However, these vaccines are still in the fourth phase and further side effects, other than those reported in the earlier phases, may be reported [10]. The current study revealed a rare side effect, HZ following vaccination against COVID-19.

The current study revealed that immunosuppression, associated comorbidities, positive family history of HZ, and stress were significantly more likely encountered among HZ cases than their matched controls. Age, sex and nationality could not be studied as these factors were matched. What is really important is that receiving COVID-19 vaccination was also more significantly encountered among cases with HZ than their controls. Several risk factors were recorded to predispose to HZ. Progress in age is the most important factor [11]. In addition to diseases with impaired cell mediate immunity (CMI) such as diabetes mellitus, systemic lupus erythematosus, and rheumatoid arthritis in addition to organ transplant and psychological stress [12].

Few case series studies reported individual cases suffering from different forms of HZ reactivation in the thoracic or cranial sensory ganglia [13-20]. The main involved mechanisms included lymphopenia and functional impairment of CD4 + T cells [21,22]. Reviewing the current available literature revealed that just only two studies have reported reactivation of VZV after vaccination against COVID-19. One study involved only six cases in a case series study, while the other one involved just only one case reported in a letter to the editor [8,9]. The current study revealed 36 HZ cases following vaccination against COVID-19 within the study period (two months). Herpes Zoster cases appeared within a short period following vaccination. The majority of HZ cases (63.9%) developed the disease within one week following receiving the vaccine with a mean duration of 8.5 + 4.8 days. A case series of six females developing reactivation of VZV after receiving mRNA vaccine against COVID-19 had a median duration of 5 days for appearance of HZ [8]. Another case series involving just only one HZ patient following inactivated vaccine against COVID-19 developed the disease after 5 days [9].

This study also showed that 72% of cases developed HZ after receiving the first dose. This similar to other reports that revealed 5/6 cases developed after receiving the first dose. Although the majority of cases (77.8%) received mRNA while the rest received non replicating viral vector vaccine yet, this difference could be attributed to the differences in the mechanism of action of the two vaccines or the availability of the vaccine. In Kuwait, mRNA was the first vaccine introduced into the country. Several theories can be forwarded to explain the relationship between VZV reactivation and vaccination against COVID-19. Vaccines can occasionally induce an acute autoimmune disease [23]. Vaccine enhanced disease was suggested to be caused by a cellular response to the vaccine involving T cells and eosinophils as well as inflammatory mediators [24-26].

Stimulation of innate immunity through toll-Like receptors (TLR) might be the link between vaccination against COVID-19 and reactivation of VZV.[27] These receptors stimulation has been linked with reactivation of VZV so that the dormant virus can stay dormant in the affected individuals [28]. The vaccination process against COVID-19 may stimulate secretion of type I INFs and other inflammatory cytokines which activates T and B cell immunity and may negatively affect antigen expression leading to HZ reactivation [9,29-30].

Comparing characteristics of COVID-19 vaccinated and unvaccinated HZ cases revealed several findings. The vaccinated cases were significantly more likely encountered among those aged more than 50 years (63.9% compared with 38.0%) and were also more commonly encountered among the Kuwaitis (72.2% compared with 30.0%). These findings can be attributed to priorities of vaccination process adopted in Kuwait. On contrast family history of HZ was more likely encountered among the non-vaccinated (90.7% compared with 61.1%). This may add evidence to the co-existence relationship between vaccination against COVID-19 and reactivation of VZV. No significant difference could be revealed between the vaccinated and non-vaccinated HZ cases with regard to severity of HZ infection as measured by hospitalization and occurrence of complications and the dermatomal distribution. However, lateralization to the left side was significantly more encountered among the vaccinated. The preferred site of vaccination (left arm) may be related to this lateralization however, the exact mechanism still needs more research and explanation.

The current study has some limitations due to the design adopted. In hospital based studies; mild cases of the disease may be missed and not presented to the clinical setting. Diagnosis of HZ was not based on molecular or histological investigation but mainly depended on the clinical diagnosis. Confirmation of a cause-effect relationship can not depend on a single research study but need multiple ones with large number of cases (this study dealt with only 36 cases). However, large scale epidemiological, clinical and immunological studies are highly recommended to establish such cause-effect relationship. The wide population vaccination could provide a unique opportunity for such studies.

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