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The risks of POTS after COVID-19 vaccination and SARS-CoV-2 infection: it's worth a shot

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Postural orthostatic tachycardia syndrome (POTS) can follow COVID-19 as part of the post-acute sequelae of SARS-CoV-2 infection, but it can also develop after COVID-19 vaccination. A new study shows that the rate of new-onset POTS diagnoses is slightly increased after COVID-19 vaccination, but is five times lower than the rate of POTS diagnoses after SARS-CoV-2 infection.

Vaccines represent one of the most groundbreaking scientific advances that substantially reduced the mortality and morbidity associated with various infectious pathogens. Since the introduction of COVID-19 vaccines in the USA in December 2020, vaccination against SARS-CoV-2 has remained the most effective and influential global public health strategy to mitigate the pandemic. However, reports of post-vaccination adverse events involving various cardiovascular and neurological manifestations, including POTS, have been mounting in the Vaccine Adverse Event Reporting System[1].

POTS, a common disorder of the autonomic nervous system, is characterized by an increase in heart rate of at least 30 beats per minute within 10 minutes of standing and symptoms of orthostatic intolerance, such as pre-syncope, palpitations, lightheadedness, generalized weakness, headache and nausea, with symptom duration exceeding three months[2]. In the USA, the pre-pandemic prevalence of POTS has been estimated to be in the range of 500,000–3,000,000 people, affecting predominantly women of reproductive age and roughly 1 in 100 teenagers[3]. However, current prevalence is likely significantly higher owing to post-COVID-19 POTS, which can develop as part of the post-acute sequelae of SARS-CoV-2 infection (PASC)[4,5].

New-onset POTS can also follow vaccination (Fig. 1) and was reported in the literature after immunization with Gardasil, a human papillomavirus (HPV) vaccine, in 2010 and, more recently, after the administration of COVID-19 vaccines[6–8]. However, a causative relationship between HPV vaccines and increased incidence of POTS has not been thoroughly investigated. This is despite several case series reported from different countries and two studies that demonstrated an increased signal for POTS and its associated symptom clusters following HPV vaccination, based on data from the World Health Organization's pharmacovigilance database and a meta-analysis of clinical study reports from 24 clinical trials[9–11].

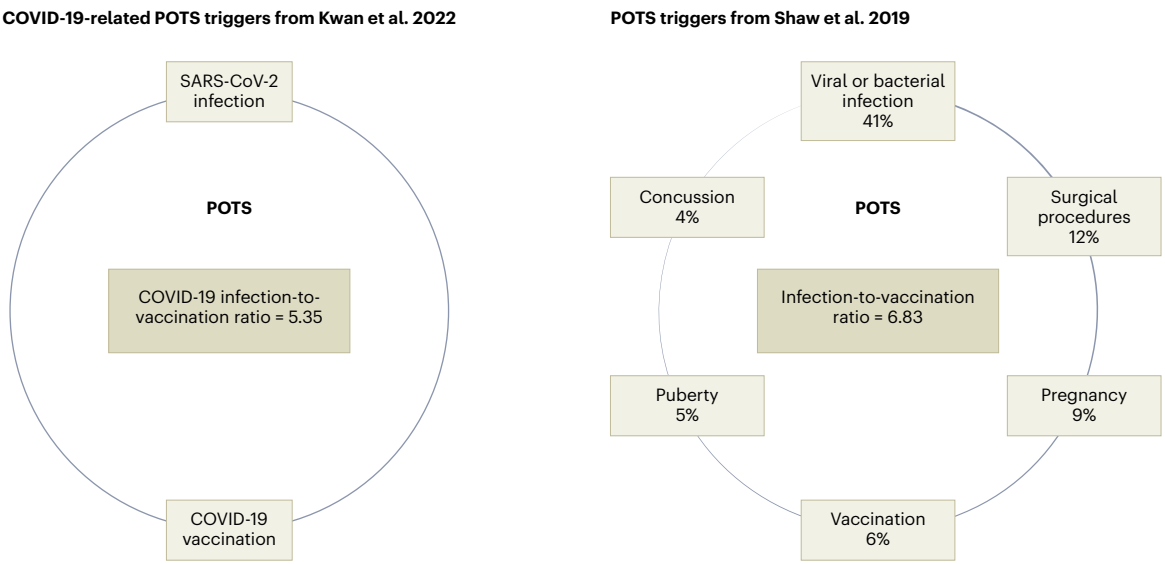

Fig. 1 | Known triggers of POTS and infection-to-vaccination ratios. Data taken from Kwan et al.[12] and Shaw et al.[6].

In a study published in this issue of *Nature Cardiovascular Research*, Kwan et al. examined the frequency of new POTS-associated diagnoses — POTS, dysautonomia, fatigue, mast cell disorders and Ehlers–Danlos syndrome — before and after COVID-19-vaccination[12]. They found that the odds of POTS and associated diagnoses were higher in the 90 days after vaccine exposure than the 90 days before exposure, with a relative risk increase of 33%[12]. Furthermore, the authors showed that the odds of new POTS-associated diagnoses following natural SARS-CoV-2 infection were more than five times higher compared to the post-vaccination period[12].

The study is based on a large series of approximately 300,000 vaccinated individuals from one geographic territory in the USA (Los Angeles County), with 0.27% new post-vaccination POTS diagnoses compared with 0.18% in the pre-vaccination period, giving an odds ratio of 1.52 for post-vaccination POTS diagnoses[12]. Accumulating all POTS-associated diagnoses in one group gave slightly lower odds. Interestingly, among 12,460 individuals with confirmed SARS-CoV-2 infection, the pre-infection incidence of POTS was 1.73%, compared with 3.42% after infection. This suggests that those with symptomatic COVID-19 infection were more likely to develop POTS in general, and that the risk of post-infection POTS is much higher than post-vaccination POTS in this cohort[12].

The study has some limitations. First, the accuracy of POTS and POTS-associated diagnoses is crucial for study validity. Second, the general awareness and diagnostic vigilance of POTS and access to adequate diagnostic modalities are decisive for POTS incidence reliability. Third, the generalizability of this report is limited to a specific population. Moreover, the traditional POTS diagnostic criteria require symptoms to occur over a duration of at least 3 months — that is, at least 90 days — which is the assessed period. As such, some of the affected individuals may have recovered later. We therefore cannot exclude the possibility that the incidence of POTS and POTS-associated diagnoses was overestimated.

Despite these limitations, the study by Kwan et al.[12] is of major importance to POTS research and patient care for several reasons. First, it undeniably establishes POTS and dysautonomia in general as adverse events after vaccination that should be recognized and investigated as other well-accepted post-vaccination syndromes, such as Guillain–Barre syndrome and acute disseminated encephalomyelitis. Second, it clearly demonstrates that POTS and POTS-associated comorbidities occur more frequently after COVID vaccination than before, and much more frequently than myocarditis, which, despite increasing at a higher rate after vaccination, remains a rare post-vaccination complication. Consequently, POTS and POTS-associated conditions may be among the most common adverse events after COVID-19 vaccination. Third, it reaffirms that POTS occurs at a high rate after SARS-CoV-2 infection and is likely one of the major phenotypes of PASC. Fourth, the rate of new-onset POTS diagnoses is more than five times higher following natural SARS-CoV-2 infection than after COVID-19 vaccination. The last point is particularly poignant and clinically relevant, as it provides compelling evidence that can be referenced during physician–patient encounters in support of vaccination and against vaccine hesitancy.

We hope that large prospective studies utilizing the new ICD-10 diagnostic code specific for POTS, which has been implemented by the US Center for Disease Control and Prevention committee as of October 1, 2022, can be conducted in the future. Similarly, mechanistic studies investigating POTS following SARS-CoV-2 infection and COVID-19 vaccination are needed to determine causation and delineate the underlying immune-mediated mechanism, possibly involving the spike protein and/or formation of autoantibodies to G-protein-coupled receptors and other targets in the cardiovascular system and beyond[13]. Furthermore, developing a screening pathway with genetic testing to identify at-risk individuals with a genetic predisposition toward post-vaccination adverse events is necessary, and would lead to a reduction in serious post-vaccination adverse events and promote public trust and vaccination compliance.

As we continue to navigate and mitigate the SARS-CoV-2 pandemic and long-term post-COVID-19 complications with the help of COVID-19 vaccines, the need to invest in POTS research to advance our understanding, diagnosis and management of POTS — a common sequela of both SARS-CoV-2 infection and COVID-19 vaccination — has never been more pressing.

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References

1. Chen, G. et al. *Front Immunol.* **12**, 669010 (2021).
2. Fedorowski, A. *J. Intern. Med.* **285**, 352–366 (2019).
3. Mar, P. L. & Raj, S. R. *Annu Rev Med.* **71**, 235–248 (2020).
4. Blitshteyn, S. & Whitelaw, S. *Immunol. Res.* **69**, 205–211 (2021).
5. Bisaccia, G. et al. *J. Cardiovasc. Dev. Dis.* **8**, 156 (2021).
6. Shaw, B. H. et al. *J. Intern. Med.* **286**, 438–448 (2019).
7. Blitshteyn, S. *Eur. J. Neurol.* **17**, e52 (2010).
8. Eldokla, A. M. & Numan, M. T. *Clin Auton. Res.* **32**, 307–311 (2022).
9. Blitshteyn, S. et al. *Immunol Res.* **66**, 744–754 (2018).
10. Chanlder, R. E. et al. *Drug Saf.* **40**, 81–90 (2017).
11. Jorgensen, L. et al. *System. Rev.* **9**, 43 (2020).
12. Kwon, A. et al. *Nat. Cardiovasc. Res.* https://doi.org/10.1038/s44161-022-00177-8 (2022).
13. Fedorowski, A. et al. *Europace* **19**, 1211–1219 (2017).

Competing interests

The authors declare no competing interests.