POTS association with COVID-19 vaccination and COVID-19 infection

Postural orthostatic tachycardia syndrome (POTS) has been observed following SARS-CoV-2 infection. In this study, we observed occurences of POTS following COVID-19 vaccination, albeit at a lower rate than following COVID-19 infection.

This is a summary of:
Kwan, A. C. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-CoV-2 COVID infection. *Nat. Cardiovasc. Res.* https://doi.org/10.1038/s44161-022-00177-8 (2022).

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The question

The COVID-19 pandemic has profoundly affected worldwide health through both acute illness and the long-term effects of infection. Vaccination efforts against COVID-19 have been instrumental in limiting transmission and preventing severe disease. However, anecdotal reports of postural orthostatic tachycardia syndrome (POTS) developing after COVID-19 vaccination have also emerged. POTS is a clinical syndrome that manifests with orthostatic intolerance and postural tachycardia[1]. Although POTS was previously recognized as a condition that can develop after SARS-CoV-2 infection[2], data on its potential development after vaccination have been scarce. As COVID-19 vaccines will continue to be necessary for the foreseeable future, pharmacovigilance regarding off-target effects will improve our ability to engage patients in a balanced discussion on the relative benefits versus the risks of vaccination. Thus, we examined the extent to which new diagnoses of POTS are increased following COVID-19 vaccination in our health system, a large quaternary care system in Los Angeles.

The observation

We set out to identify the incidence of new POTS-related diagnoses that occur after COVID-19 vaccination. This type of analysis is inherently difficult owing to the lack of ideal controls, multiple confounding factors related to the context of the pandemic and the effect of COVID-19 vaccination on patients' engagement with the healthcare system. We recognized that pharmaco-epidemiology studies had previously used self-controlled designs, wherein patients serve as their own control[3]. We also recognized that by comparing the incidence of POTS-related diagnoses against the incidence of common diagnoses that are not POTS-related (for example, urinary tract infections, gastroesophageal reflux disease and hypertension), we could provide a benchmark that can account for healthcare engagement.

Using a sequence-symmetry analysis in over 280,000 COVID-19 vaccination records, we compared the odds of POTS-related diagnosis after exposure to COVID-19 versus before exposure, and compared these results with those for 'common primary care' diagnoses that are not POTS-related. A similar analysis was performed in over 12,000 SARS-CoV-2 infection records. We found that most POTS-related diagnoses increased after COVID-19 vaccination to a greater degree than non-POTS-related diagnoses (Fig. 1a). The odds of developing POTS-related diagnoses after vaccination compared with before vaccination was 1.33 (1.25–1.41), and the odds ratio of post-vaccine POTS-related versus non-POTS-related diagnoses was 1.10 (1.03–1.17). In the SARS-CoV-2 population, for most conditions studied, post-infection rates were higher than post-vaccination rates (Fig. 1b). For POTS-related diagnoses, the post-infection rate was higher after exposure to SARS-CoV-2 infection (4.86%) than after exposure to vaccination (0.91%) in the analyzed populations. Although any comparison of post-exposure rates should be interpreted cautiously, given the baseline differences in POTS incidence in the two mutually exclusive populations, these results indicate that POTS might be occurring at a higher-than-expected frequency following COVID-19 vaccination, although at an overall rate lower than the frequency of POTS occurring following SARS-CoV-2 infection.

The interpretation

We hope that our results can offer an evidence-based context of understanding for patients who experience POTS-like symptoms after COVID-19 vaccination, as well as their healthcare providers. As POTS is a frequently underrecognized condition that can cause substantial debility in affected patients[4], greater understanding of POTS in general is required to improve overall awareness and rates of appropriate diagnosis and treatment.

These study results are not intended to discourage use of the COVID-19 vaccine, especially given the relatively higher risk of developing POTS after SARS-CoV-2 infection. Given the complex design of our study, which was intended to account for potentially important confounders, the estimated risks are reported in relative terms; that is, after exposure relative to before exposure or POTS-related diagnoses relative to non-POTS-related diagnoses. Therefore, deriving precise estimates of risk per exposure is difficult, and follow-up studies are needed to determine the absolute risk of POTS after vaccination. Further studies are also necessary to understand the pathophysiology underlying both POTS occurring after vaccine and POTS occurring after infection.

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EXPERT OPINION

"Kwan and colleagues observed, from a large health organization clinical database, a potential increase in the incidence of POTS following COVID-19 vaccination. Because POTS can be disabling for patients, increased awareness of the existence and increased risks of this complication can help physicians and patients in recognizing this syndrome early, allowing appropriate natural history studies, developing risk prediction tools and potentially evaluating different interventions for future mitigation." **Peter Liu, University of Ottawa Heart Institute, Ottawa, Canada.**

FIGURE

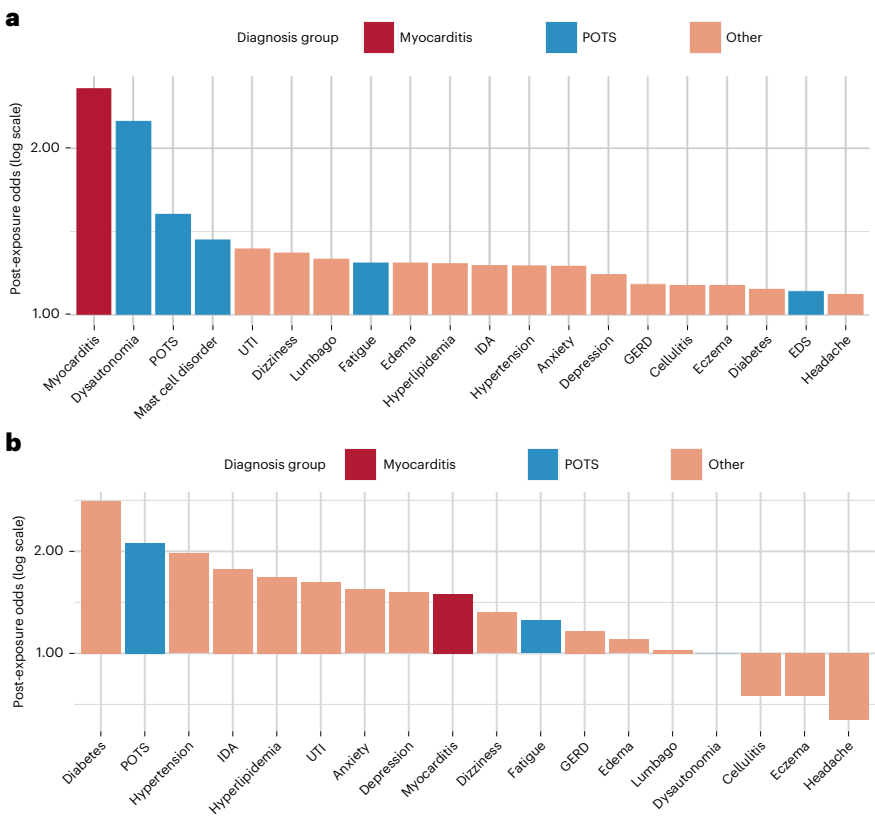

Fig. 1 | Odds of diagnoses post-vaccination and post-infection. a, Post-vaccination odds by diagnosis in all patients. **b**, Post-infection odds by diagnosis in all patients. EDS, Ehlers-Danlos syndrome; GERD, gastroesophageal reflux disease; IDA, iron deficiency anemia; UTI, urinary tract infection. © 2022, Kwan, A. C.

BEHIND THE PAPER

Our hospital played a substantial role in both care for patients and vaccination efforts in Los Angeles during the initial phases of the COVID-19 pandemic. Through this work, and institutional support for research efforts, we have been able to establish a large number of studies on COVID-19 infection and related therapies. A number of physicians and patient groups subsequently reached out to us with their experiences and observations, which included increased patient presentations with POTS-like symptoms after COVID-19 vaccination. Following up on this information, we developed the initial question about POTS after COVID-19 vaccination. We hope that our results feed back to the community in a positive way and spur further research to solve the issues presented to the medical community as a whole by the COVID-19 pandemic. **A.C.K. & S.C.**

REFERENCES

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   This paper describes the patient experience of POTS, with 75% of participants reporting misdiagnosis and a median diagnostic delay of 2 years.

FROM THE EDITOR

"The study by Kwan et al. shows that anti-SARS-CoV-2 vaccination can increase the incidence of POTS, although at a much lower frequency than the viral infection itself, and indicates the need to study the link between this dysfunction of the autonomic nervous system and the SARS-CoV-2 spike protein." **Elvira Forte, Associate Editor, *Nature Cardiovascular Research*.**