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Clinical short communication

Ischemic stroke shortly after vaccination against SARS-CoV-2: A case-control study

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ABSTRACT

Background and purpose: Vaccination against SARS-CoV-2 has been associated with rare occurrences of severe venous thromboses. Very little data exist about arterial ischemic strokes. We have assessed the features of ischemic strokes occurring shortly after vaccination against SARS-CoV-2 in the Cremona area, Italy.

Methods: From February 1, to July 31, 2021, all patients with ischemic stroke within four weeks of vaccination against COVID-19 admitted to our stroke unit were consecutively collected, and their main features were compared with those of all other patients with ischemic strokes admitted during the same period.

Results: Sixteen strokes after vaccination were collected. They represented 10.5% of all ischemic strokes. Median interval from vaccination was 12 days (range 1–24). Fifteen (93.8%) had received the BNT162b2 (Pfizer–BioNTech) vaccine and 1 (6.2%) the ChAdOx1 nCoV-19 (AstraZeneca). Two patients (12.5%) had a mild thrombocytopenia on admission (128,000 and 142,000/ml), without any evidence of bleeding or venous thrombosis. Thrombolysis and/or thrombectomy were carried out in 4 cases (25.0%). When compared with 137 strokes without recent vaccination, none of the demographic, clinical, and laboratory features of post-vaccination strokes were significantly different.

Conclusions: Ischemic strokes occurring shortly after COVID-19 vaccination at our center were similar to those of non-vaccinated patients. Therefore, the relatively high percentage of such patients probably relates to the very high fraction of elderly people vaccinated against SARS-CoV-2 in the Cremona area, rather than to a consequence of vaccination.

1. Introduction

Vaccination against the SARS-CoV-2 virus has brought about the problem of adverse events due to the vaccines. The most widely publicized adverse event has been the syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) [1,2], due to the development of antibodies against platelet factor 4 [3]. The syndrome has been associated with adenovirus-based vaccines [1,4]. While VITT is rare, with the progress of mass vaccination, a patient with acute ischemic stroke shortly after vaccination has become a much more common occurrence. Although this could be just a coincidence, a causal relationship between vaccination and arterial stroke cannot be discarded. This has several consequences, such as reporting in the national drug adverse event registry, appropriate diagnostic investigations, choice of antithrombotic medication, and counselling about administration of the second dose of the vaccine. In order to clarify the pattern of ischemic stroke associated with recent vaccination against SARS-CoV-2 (ISARVAS), we collected a consecutive series of ischemic strokes within 4 weeks after vaccination, and compared them with all other ischemic strokes admitted to our hospital during the same period.

2. Patients and methods

2.1. Study design and study population

From February 1, 2021, to July 31, 2021, we prospectively collected all cases of ischemic stroke occurring within 28 days after vaccination against the SARS-CoV-2 virus. Stroke was defined as an acute ischemic...
lesion at brain computed tomography (CT) or magnetic resonance imaging (MRI). The following features were recorded: age, sex, cerebrovascular risk factors (current smoking, hypertension [systolic pressure greater than 140 mm or diastolic pressure > 90 mm, or ongoing antihypertensive treatment], diabetes [fasting blood glucose greater than 126 mg%, or ongoing antidiabetic treatment], hypercholesterolemia [fasting plasma cholesterol >240 mg% or ongoing statin treatment], ischemic heart disease, atrial fibrillation, vaccine type (BNT162b2 Pfizer-BioNTech, ChAdOx nCoV-19 AstraZeneca, mRNA-1273 Moderna), dose number (first or second), days since vaccination, platelet number at entry, venous thrombosis, stroke mechanism according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [5], ischemic lesion territory, number and side, thrombectomy, National Institutes of Health Stroke Scale (NIHSS) score at entry, and modified Rankin Score at discharge. These features were compared with those of all patients with ischemic stroke who had not been vaccinated in the previous month, admitted to our hospital during the same period.

2.2. Statistical methods

The Chi square test with Fisher’s correction was used to compare categorical variables. The Mann Whitney U test was used for continuous non parametric variables. The SPSS software was used for statistical analysis (SPSS 21.0; Armonk, NY).

2.3. Ethical issues

The study was approved by the institutional review board of the ASST Cremona. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. The need for written informed consent was waived because all data are anonymized and are part of the routine management of the patients.

3. Results

3.1. ISARVAS and other strokes

We admitted 153 patients with ischemic stroke during the study period, 16 of whom (10.5%) had received an anti-SARS-CoV-2 vaccine within 4 weeks of their stroke. They were 11 men (68.8%) and 5 women (31.2%), of Caucasian race, with a median age of 80 yrs. (interquartile range 77–87 yrs) (Table 1). Fifteen had received the BNT162b2 Pfizer-BioNTech vaccine (93.8%), and 1 the ChAdOx nCoV-19 AstraZeneca vaccine (6.2%) (Table 2). The median interval from vaccination was 12 days (range 1–24 days). Stroke occurred after the first dose in 12 patients (75.0%), and after the second dose in 4 (25.0%). Stroke pathomechanisms were atherothrombotic in 2 cases (12.5%), cardioembolic in 6 (37.5%), lacunar in 6 (37.5%), and undetermined in 2 (12.5%). Median NIHSS score on admission was 4 (interquartile range 4–10). Intravenous thrombolysis and/or thrombectomy were carried out in 4 patients (25.0%). Three patients (18.8%) had multiple acute ischemic lesions at CT or MRI, in the same arterial territory. Two Pfizer-BioNTech patients (12.5%) had a mild thrombocytopenia on admission (128,000 and 142,000/ml), that remained stable. One of them had advanced cholangiocarcinoma and the other had a lacunar stroke. The single ChAdOx patient had a mild stroke of undetermined origin, that received thrombolysis. No patient had any venous thrombosis. The control group included 137 consecutive patients, whose main features are shown in Table 1.

3.2. Statistical analysis

None of the analyzed features was significantly different between the two groups (Table 1). In particular, age, platelet number below 150,000 at entry, stroke mechanism, stroke severity at entry, use of recanalization therapies, single vs multiple ischemic lesions, disability at discharge, and death during hospitalization were similar in the 2 groups.

4. Discussion

The consequences of vaccination against the SARS-CoV-2 virus are still incompletely understood, because of the relatively short observation period. We found that about 10% of all ischemic strokes occurring during 6 consecutive months in the Cremona area fell within 4 weeks after vaccination against the SARS-CoV-2 virus. We have concentrated on the first month after vaccination because a potential relationship between stroke and vaccination may be more apparent in this early period. Furthermore, this interval has also been used to characterize VITT [6]. Such strokes may raise the question of a vaccine-related complication, with all its epidemiological, diagnostic, therapeutic, and medico-legal implications. Severe venous thrombotic complications have occurred with adenovirus-based vaccines [1,4]. A few cases of ischemic stroke after vaccination have also been described [7,8], but such reports are sparse, and mostly focused on the relationship with thrombocytopenia and the ChAdOx vaccine [7,8], while a systematic description of these strokes is still lacking. More than 70% of the

| Table 1 | Demographic and clinical cases of features and controls. |
| ISARVAS | Controls | p |
| n = 16 | n = 137 |
| Age (median; IQ range) | 80 (77–87) | 76 (70–85) | ns |
| Men | 11 (68.8%) | 78 (56.5%) | ns |
| Hypertension | 12 (75.0%) | 115 (83.9%) | ns |
| Diabetes | 2 (12.5%) | 34 (24.8%) | ns |
| Current smoking | 0 | 12 (8.8%) | ns |
| Hypercholesterolemia | 12 (75.0%) | 86 (62.8%) | ns |
| Ischemic heart disease | 4 (25.0%) | 2 (16.1%) | ns |
| Atrial fibrillation | 6 (37.5%) | 59 (43.1%) | ns |
| TOAST classification | | |
| Atherothrombotic | 2 (12.5%) | 17 (12.4%) | ns |
| Cardioembolic | 6 (37.5%) | 56 (40.9%) | ns |
| Undetermined | 2 (12.5%) | 36 (26.3%) | ns |
| Lacunar | 6 (37.5%) | 22 (16.1%) | ns |
| Other | 0 | 6 (4.4%) | ns |
| NIHSS at entry (median, IQ range) | 5 (4–10) | 4 (2–14) | ns |
| 0–7 | 11 | 88 |
| 8–14 | 3 | 20 |
| ≥ 15 | 2 | 29 |
| mRS at discharge (median, IQ range) | 2 (1–4) | 3 (1–4) | ns |
| Death at discharge | 0 | 13 (9.5%) | ns |
| Platelets at entry x 10^3 | 201 (189–267) | 218 (162–258) | ns |
| Platelet <150,000/ml at entry | 2 (12.5%) | 6 (4.4%) | ns |
| Ischemic lesion | | |
| Carotid territory | 10 (62.5%) | 98 (71.5%) | ns |
| Posterior territory | 6 (37.5%) | 35 (25.6%) | ns |
| Both | 0 | 4 (2.9%) | ns |
| Single | 13 (81.2%) | 107 (78.1%) | ns |
| Bilateral/carotid-posterior | 0 | 29 (21.2%) | ns |
| Thrombolyis | 4 (25.0%) | 18 (13.1%) | ns |
| Thrombectomy | 2 (11.8%) | 21 (15.3%) | ns |

 ISARVAS = Ischemic stroke after recent vaccination against SARS-CoV-2; IQ = Interquartile.

| Table 2 | Vaccination features. |
| Vaccine type | n = 16 |
| BNT162b2 (Pfizer–BioNTech) | 15 (93.8%) |
| mRNA-1273 (Moderna) | 0 |
| ChAdOx1 nCoV-19 (AstraZeneca) | 1 (6.2%) |
| Stroke after first dose | 12 (75.0%) |
| Stroke after second dose | 4 (25.0%) |
| Stroke-vaccination interval (median, days, range) | 12 (1–24) |
residents of the Cremona area older than 60 have received at least one dose of the authorized vaccines during the period of our study, and none of the features of the ISARVAS group was significantly different from those of all the other ischemic strokes admitted during the same period. Furthermore, no ISARVAS patient had severe thrombocytopenia or venous thrombosis. Finally, only one stroke occurred after the ChAdOx vaccine, which has been directly implicated in VITT [8]. These observations suggest that the strokes were probably not triggered by vaccination, but occurred because of the same set of risk factors that lead to ischemic stroke in the general population of our area. The recent vaccination did not decrease use of acute recanalization therapies, and was not associated with a higher initial severity of stroke or an increased death rate in the short term. The main limitation of our study is the relatively small size of the ISARVAS group, which does not allow for very robust comparisons with the overall stroke population, and cannot be assumed to represent all the possible stroke types that may follow COVID-19 vaccination. Therefore, our results require confirmation in larger studies. However, although single instances of ischemic stroke directly related to SARS-CoV-2 vaccination may certainly happen [7], our data seem reassuring, and may be used for subjects who fear the complications of vaccination, and to plan diagnostic and therapeutic strategies by treating physicians.

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Declaration of Competing Interest

None.

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