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COMMENTARY

Cerebral venous sinus thrombosis associated with COVID-19 vaccine-induced thrombocytopenia: Improvement in mortality rate over time

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The clinical picture of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites occurring within 4–28 days of vaccination with the SARS-CoV-2 vaccines ChAdOx1 nCov-19 (Oxford/AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson) has been named vaccine-induced immune thrombotic thrombocytopenia (VITT), and several publications have followed the first case reports on 28 March 2021 [1–5]. The pathophysiology of VITT is not yet clearly understood. However, there are similarities with the heparin-induced thrombocytopenia syndrome (HIT), and researchers have identified circulating platelet-activating platelet factor 4 antibodies in these patients.

Cerebral venous sinus thrombosis (CVST) is a rare and serious thrombotic complication, reported in about 70% of patients with VITT diagnosis [5,6]. More than 90% of reported patients with CVST were younger than 60 years, with more women being affected than men (2.5:1 ratio) and no other specific identified risk factors [7]. The clinical profile of CVST in patients with VITT is severe, with about 70% of patients suffering intracerebral hemorrhages, 30% with coma at presentation, high rates of concomitant thromboembolism, and in-hospital death due to brain herniation occurring in approximately half of all patients [5]. Very early on, the international community took a multidisciplinary approach. Treatment of CVST with VITT has been empirical, and mainly based on our experience in the treatment of HIT. Prevention of thrombosis progression has relied on the use of nonheparin products such as argatroban, bivalirudin, danaparoid, fondaparinux, or direct oral anticoagulants at therapeutic anticoagulant dose, even in the presence of intracranial hemorrhages [7]. Besides anticoagulation, intravenous immunoglobulins 1 g/kg body weight daily for 2 days were recommended, and platelet transfusion was contraindicated. Some expert recommendations also suggested the administration of steroids [7]. However, published data on the efficacy of this therapeutic strategy in patients with VITT are not yet available.

In this issue of *European Journal of Neurology*, Dr Van De Munckof and colleagues compare acute mortality rates for CVST before versus after the first scientific publication on VITT, on 28 March, to evaluate whether outcome of patients with CVST-VITT improved over time [8]. They used the EudraVigilance database of the European Medicines Agency to identify cases of CVST with concomitant thrombocytopenia occurring within 28 days of SARS-CoV-2 vaccination and grouped the adenovirus vector-based vaccines together, as the mRNA vaccines for the analysis. Among 270 cases, 266 cases occurred after an adenoviral vector-based vaccine ($n = 243$ for ChAdOx1 nCov-19 and $n = 23$ after Ad26.COV2.S); the authors found significantly reduced mortality rates in cases declared after 28 March (47%, 95% confidence interval [CI] = 37%–58% vs. 22%, 95% CI = 16–29%, $p < 0.001$). Of note, no fatalities were reported in the mRNA vaccine group ($n = 4$).

The present study has important strengths. First, it is the first study analyzing the shift in patients' outcome over time. The centralized EudraVigilance database included several hundreds of notified cases irrespective of vaccine type, with wide geographical coverage, screened with exhaustive criteria, and a central review of each case by a senior vascular neurologist. Nevertheless, the EudraVigilance database being a passive pharmacovigilance system, it has potential reporting bias, missing data, and lack of accuracy control on data collection. Importantly, demographic and clinical features with strong impact on patients' prognosis are not available and could have been differently distributed in the two time periods, especially because the population that received vaccination shifted over time. Because recognition of VITT occurred only in mid-March, when the vaccine

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rollout reached the younger age groups, it is also possible that before this time, older patients, or patients with severe comorbidities, presenting with thrombosis, sudden death, or both, may have had VITT and may have been missed or misclassified, underestimating the reported mortality rates in the first period of analysis. Previous exposure to SARS-CoV-2 infection could also have had an impact on CVST-VITT severity. Moreover, awareness of this entity might have led to declaration and collection of less serious cases, and the stratification of the analysis according to clinical severity is not possible given the missing data. Another important issue is that European health care systems are heterogeneous, and changes of clinical management were likely not immediately integrated everywhere.

Data from the work of Dr Van De Munckof highlight a decrease in mortality rate over time, without demonstrating causation by a better pathophysiological knowledge of this entity, early patient identification, or improved clinical management. Despite improvement, this syndrome remains very severe, with >20% in-hospital mortality in a disease that is usually associated with <5% mortality [5]. Nonetheless, this paper brings good news for the neurological community and beyond; it highlights the importance of international, multidisciplinary, coordinated efforts when facing a new and severe clinical entity.

AUTHOR CONTRIBUTIONS

Barbara Casolla: Conceptualization (lead), writing–original draft (lead), writing–review & editing (equal). **Charlotte Cordonnier:** Conceptualization (equal), writing–review & editing (equal).

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Not applicable.

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