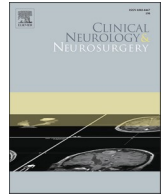




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Brain dural arteriovenous fistulas in the COVID-19 Era: A warning and rationale for association

Sergio Garcia-Garcia^{*}, Santiago Cepeda, Ignacio Arrese, Rosario Sarabia

Neurosurgery Department, Hospital Universitario Río Hortega, Valladolid, Spain

ARTICLE INFO

Keywords:

Brain dural arteriovenous fistula
COVID-19
Cerebral venous thrombosis
Vaccine
Neurovascular
Pathogenesis
Warning

ABSTRACT

Objectives: Brain dural arteriovenous fistulas (bDAVFs) are anomalous connections between dural arteries and cerebral veins or sinuses. Cerebral venous thrombosis (CVT) often precedes or coincides with bDAVFs and is considered a risk factor for these vascular malformations. Recently, vaccine-induced thrombotic thrombocytopenia causing CVTs has been associated with COVID-19 vaccines. Concurrently with the start of massive vaccination in our region, we have observed a fivefold increase in the average incidence of bDAVFs. Our objective is to raise awareness of the potential involvement of COVID-19 vaccines in the pathogenesis of bDAVF. **Methods:** A retrospective review of demographic, clinical, radiological, COVID-19 infection and vaccination data of patients diagnosed with bDAVFs between 2011 and 2021 was conducted. Patients were divided into two cohorts according to their belonging to pre- or post-COVID-19 vaccination times. Cohorts were compared for bDAVFs incidences and demographic and clinical features.

Results: Twenty-one bDAVFs were diagnosed between 2011 and 2021, 7 of which in 2021. The mean age was 57.7 years, and 62 % were males. All cases except one were treated; of them, 85 % exclusively managed with surgery. All treated cases were successfully occluded. The incidence in 2021 was significantly higher than that in the prevaccination period (1.72 vs 0.35/100,000/year; $p = 0.036$; 95 % Confidence Interval = 0.09–2.66). Cohorts were not different in age, sex, hemorrhagic presentation, dural sinus thrombosis or presence of pro-thrombotic or cardiovascular risk factors.

Conclusion: The significant increase in the incidence of bDAVF following general vaccination policies against COVID-19 observed in our region suggests a potential correlation between these two facts. Our findings need confirmation from larger cohorts and further pathogenic research.

1. Introduction

Brain dural arteriovenous fistulas (bDAVF) are anomalous shunts between dural arteries and venous sinuses or cortical veins. DAVFs are uncommon vascular malformations with a reported incidence in the general population of 0.15–0.29 per 100,000 persons per year [1]. Although originally considered benign congenital lesions, this statement was contested by Castaigne and Djindjian in the late 1970s [2]. Currently, most of them are considered acquired and potentially threatening. Some conditions are regarded as risk or enabling factors that may ultimately lead to the development of bDAVF (cranial surgeries, cranioccephalic trauma, hormonal alterations, sinusitis, meningiomas, endurance sports) [1,3].

Among all these factors, cerebral venous thrombosis (CVT) plays a

paramount role, whether as a direct consequence of DAVFs or as a hemodynamic condition that may not only stagnate blood and open pre-existing arteriovenous connections but also might stimulate neoangiogenesis and create de novo DAVFs [4]. CVT is an uncommon disease with a female predominance that mainly affects medium-aged adults, with an incidence of 1.3–1.6 per 100,000 persons per year. In a recent multicenter study, the prevalence of DAVFs in a cohort of more than 1000 patients diagnosed with CVT was 2.4 % [4]. In this subset of patients, only a small proportion of DAVFs could be explained by other conditions different from CVT.

Since the coronavirus disease (COVID-19) pandemic outbreak, many social, geopolitical and medical tenets have been turned upside down. Some well-established beliefs have been contested, and we have been driven into an era of uncertainty and bewilderment. This virus soon

^{*} Correspondence to: Calle Dulzaina n2. 47002, Valladolid, Spain.

E-mail addresses: iskender_brave@hotmail.com (S. Garcia-Garcia), cepeda_santiago@hotmail.com (S. Cepeda), iarreser@saludcastillayleon.es (I. Arrese), rsarabia@saludcastillayleon.es (R. Sarabia).

<https://doi.org/10.1016/j.clineneuro.2022.107367>

Received 4 May 2022; Received in revised form 24 June 2022; Accepted 12 July 2022

Available online 14 July 2022

0303-8467/© 2022 Elsevier B.V. All rights reserved.

proved to be much more than a respiratory infection with some systemic manifestations. Smell loss was one of the first neurological symptoms to be ascribed to COVID-19. Disgeusia, asthenia, encephalitis, myelitis, peripheral neuropathies, psychiatric disorders and cerebrovascular diseases followed [5–7]. In addition, immune-mediated vaccine-induced thrombotic thrombocytopenia (VITT) has been recently related to vaccination against COVID-19 [8,9]. This rare side effect was fundamentally associated with adenovirus vector-based vaccines; later on, a weaker association with mRNA-based vaccines was also suggested [10]. Remarkably, in addition to cerebral thrombotic events imputable to COVID-19, the main manifestation of VITT are CVTs [11].

Over the course of 2021, we noticed a fivefold increase in the incidence of bDAVFs. Our neurovascular department belongs to the public health system and is not heavily influenced by demographic changes or variations in the population referred to our unit that could have easily explained this phenomenon. We consider that this unusual rise, along with the current epidemiological context and the abovementioned body of evidence, deserves judicious and further study. Herein, we present our series of bDAVFs collected during 2021 and compared it with our historic cohort (2011–2020) to illustrate the particularity of such a concentration of cases and to raise awareness regarding this potential association.

2. Methods

This report follows the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12].

Data including demographics, clinical features, prothrombotic risk factors, COVID-19 diagnosis and vaccination scheme were retrospectively collected from medical records of patients diagnosed with DAVFs between 2011 and 2021. COVID-19 diagnosis was considered confirmed in cases of positive PCR from nasal or pharyngeal swabs, blood antibodies or nasal or pharyngeal antigen tests. Date and test type were recorded to establish a potential temporal relation of causality. In a similar way, vaccine type (mRNA or vector-based), manufacturer, number of doses and date of administration were also considered. Neuroimaging (AngioCT, MRI and angiography) was examined and analyzed to define bDAVF location, feeders, grade according to Cognard's classification [13], sinus thrombosis and the existence of previous or acute bleeding. Treatment modality, related complications and

occlusion rates were also assessed. Platelet count, fibrinogen, Dimer-D and INR values were collected in those patients with available blood tests between COVID-19 infection or vaccine administration and DAVF diagnosis.

The population at risk of suffering a bDAVF and being diagnosed at our center was considered the population belonging to our reference area, which covers the province of Segovia and approximately half of the province of Valladolid [14]. Incidence was calculated as the number of patients diagnosed with a bDAVF in a given year divided by the total population of the reference area in that year and expressed as figures per 100,000 persons per year.

2.1. Statistics

Statistical analysis was performed using R version 4.0.2 (R Core Team, Vienna, Austria). Categorical variables were compared with the chi-square and Fisher exact tests. The incidence of bDAVFs was compared using the *fmsb* package for R, in which the null hypothesis is that the ratio of two incidence rates is equal to 1. Statistical significance was considered if the alpha error was less than 0.05.

3. Results

A total of 21 bDAVFs were diagnosed between 2011 and 2021 at our center (Fig. 1). The majority of patients were male (62 %), and the average age was 57.7 years. bDAVF presented as ruptured malformations in 6 cases, while the remaining bDAVF were diagnosed incidentally or by other reasons, such as headache or gait imbalance. The majority of bDAVFs were treated exclusively with surgery (85 %). Embolization was implemented as adjuvant therapy in one case and with curative intention in two patients. One bDAVF grade I spontaneously obliterated. All treated bDAVFs were angiographically obliterated at one month, with the exception of one transverse sinus bDAVF that required retreatment. Table 1 summarizes the main features of bDAVFs included in the present study.

By July first 41.4 % of the reference population had received two doses of the vaccine. This rate progressively increased to reach 82.6 % by December 29th [15].

The incidences of bDAVF before (0.329/100,000 persons/year) and after (1.107/100,000 persons/year) the COVID-19 pandemic outbreak were significantly different (difference=0.778, 95 % confidence

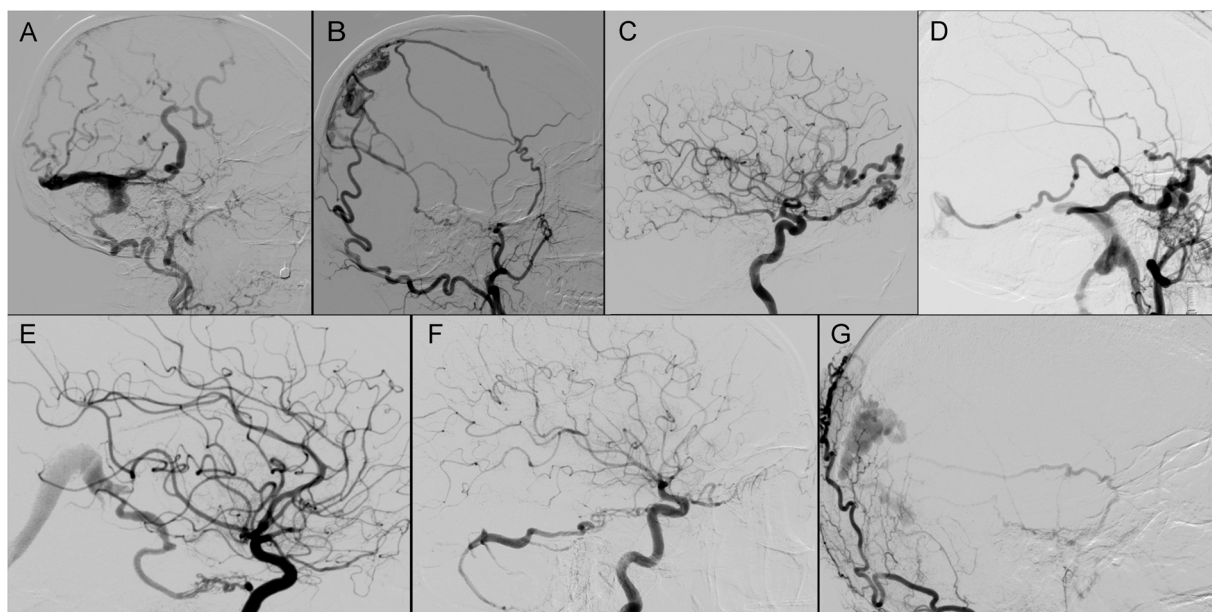


Fig. 1. Diagnostic angiographies of bDAVF diagnosed in 2021 corresponding to cases number 15–21 (A-G).

Table 1

Cases of bDAVF between 2011 and 2021.

	Date of Dx (mmm-yy)	Age	Sex	Symptom	Rupt	Location	Thrombosis	Cognard	Treatment	Prothrombotic Risk Factors	CVRF
1	Feb-12	55	M	Headache	N	TS	Y	2ab	Surgery	N	N
2	Feb-13	53	M	DC	Y	SPS	Y	4	Embolization Surgery	N	N
3	Jul-15	69	M	ICH	N	TS	Y	2ab	Surgery	N	HT, DLP
4	Oct-15	75	F	Seizure	N	TS	Y	2a	Surgery	N	DLP
5	Jul-16	30.2	M	DC	Y	PCA	N	3	Surgery	N	N
6	Oct-16	73.0	F	Tinnitus	N	TS	N	1	Embolization	N	HT,DLP
7	Nov-17	67.7	F	Ataxia	N	Occipital-SLS	Y	4	Surgery	TIA	N
8	Feb-18	39.3	M	Incidental	N	Ethmoidal	N	3	Surgery	Frontal Trauma	Sm
9	Aug-18	69.2	M	DC	Y	IPS	N	3	Surgery	No	HT,DLP
10	Feb-19	47.1	M	Headache	N	TS-SS	Y	2ab	Surgery	Pr.G20210A	HT
11	Aug-19	57.4	M	Gait disturbance	N	Tentorial	Y	2ab	Surgery	N	HT,DLP
12	Sep-19	70.6	M	DC	Y	Ethmoidal	N	4	Surgery	N	HT,DLP
13	Jun-20	68.3	M	Headache	N	Tentorial	Y	2ab	Surgery	N	N
14	Nov-20	43.8	F	Tinnitus	N	J	Y	1	No	OC	N
15	Feb-21	67.2	F	Vertigo	N	TS-SS	Y	2ab	Embolization	Pr.G20210A	DLP
16	Mar-21	49.2	M	Headache	Y	Occ-SLS	N	3	Surgery	N	Sm
17	Apr-21	52.9	M	Headache	N	Etmoidal	Y	3	Surgery	N	DLP
18	Aug-21	64.6	F	Headache	N	Sphenoidal	N	4	Surgery	N	HT,DLP
19	Aug-21	68	M	Incidental	N	Incisural	N	3	Surgery	N	HT,DLP
20	Oct-21	32	F	Vertigo	Y	SPS	N	3	Surgery	N	N
21	Dec-21	56	F	Hemianopsia	Y	Occ-SLS	N	2ab	Surgery	N	DLP

CVRF: Cardiovascular Risk Factors; DC: Decreased consciousness; DLP: Dyslipidemia; Dx: Diagnose; F: Female; HT: Hypertension; IPS: Inferior petrosal sinus; J: Jugular; M: Male; N: No; OC: Oral contraceptive; Occ: Occipital; PCA: posterior cerebral artery; Pr. G20210A: Prothrombin mutation G20210A; SLS: Superior longitudinal sinus; Sm: Smoker; SPS: Superior petrosal sinus; SS: Sigmoid sinus; TIA: Transient ischemic attack; TS: Transverse sinus; Y: Yes.

interval=0.031 – 1.524, $p = 0.041$). Similarly, the difference between the incidence of bDAVF before (0.345/100,000 persons/year) and after (1.722/100,000 persons/year) the outset of general vaccination was statistically significant (difference= 1.38, 95 % confidence interval= 0.088–2.66, $p = 0.036$) (Table 2) (Figs. 2 and 3).

Fisher's exact test demonstrated no significant differences in sex predominance between the pre- and post-COVID periods ($p = 0.166$) or between the pre- and postvaccination periods ($p = 0.213$). Likewise, the number of bDAVFs ruptured at diagnosis did not significantly vary between the pre- and post-COVID-19 eras ($p = 0.477$) or before and after the start of general vaccination ($p = 0.701$). A comparison between the historic cohort and the sample of patients with bDAVF diagnosed in 2021 is summarized in Table 3. Table 4 contains the vaccination and COVID-19 records of the patients diagnosed with bDAVF in 2021. Table 5 displays the results of coagulation tests of these same patients.

4. Discussion

The present article seeks to raise awareness of a potential correlation between the occurrence of DAVF and the current global epidemiological context, capitalized by COVID-19. We found a significant increase in the incidence of bDAVF during what we could define as the COVID-19 era (2020–2021) compared with a historic cohort collected from the previous 9 years. The features of these recently diagnosed bDAVFs were not significantly different from those of the precedent years. Neither the size and characteristics of the population nor the potential risk factors, which could eventually drive the development of bDAVFs, were uneven between the two considered periods. Establishing a relation of causality between COVID-19 or the new vaccines designed to prevent it and these vascular malformations would require further studies, longer periods of observation and the pooling of data from larger populations. However, we consider that our findings deserve to be reported and interpreted with caution. The following discussion will focus on the potential involvement of vaccines in the development of bDAVF since the rise in their incidence was remarkably superior after the kick off of massive vaccination, which in our region took place on January 4th 2021.

According to the classic paper “The environment and disease:

association or causation?” by A. Bradford Hill, there are nine main principles that must be considered to suggest causality between two facts: Strength, Temporality, Specificity, Analogy, Plausibility, Coherence, Biological Gradient, Experiment and Consistency [16]. Some of these criteria might not be possible to elucidate due to the nature of the involved elements or the lack of tools or experiments to build the required evidence. However, the presence of a majority of them would allow us to elaborate a coherent argumentation to suggest a possible or probable correlation between two facts.

The strength of the association was considered by A.B. Hill as the most important factor to demonstrate the association between a disease and an epidemiological fact [16]. In our case, this is given by the increase in the incidence, which was five times higher during 2021 than the average incidence of the previous nine years. This rise is even higher when compared to previous reports in which the incidence of bDAVF is estimated to be between 0.15 and 0.29 per 100,000 per year [1,4,17, 18]. In fact, the incidence of other vascular malformations did not experience such an increase during the same period. For instance, the incidence of arteriovenous malformations between 2011 and 2020 was not different to the rate during the COVID-19 vaccination period (1.33 per 100,000 per year vs 0.74 per 100,000 per year, 95 % confidence interval= –0.32–1.50, $p = 0.203$).

Temporality is demonstrated by the fact that the suspected cause precedes the consequence in a reasonable timeline. Except for two cases that suffered COVID-19 infection prior to the vaccine and to the diagnosis of bDAVF, the remaining cases received their first dose 90–200 days before the diagnosis. If a prothrombotic phenomenon is suspected as a potential mechanism for vaccines or COVID to lead to the occurrence of bDAVFs, it is important to note that it has been reported that the incidence of bDAVF significantly increases during the first 6 months following CVT [4,19]. For COVID-19 infections, the time frame in our cohort was 60–80 days. Indeed, the time from COVID symptoms to CVT reported by other authors is estimated to be between 1 and 2 weeks [20,21]. The occurrence of CVTs would precede the diagnosis of bDAVFs in up to 6 months, which agrees with our findings.

Plausibility, coherence and analogy are discussed together in an attempt to provide a credible explanation supported by, or at least,

Table 2
Population, cases of bDAVF and incidence variations between 2011 and 2021.

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2011/2020	2021
Population	402308	402631	404411	403274	403951	406052	406986	408047	407399	406538	405160	406538
bDAVF	0	1	1	0	2	2	1	2	3	2	1.4	7
Incidence (100,000 persons/year)	0	0.248	0.247	0	0.495	0.492	0.246	0.490	0.736	0.492	0.345	1.722

without conflicting the available evidence. Accordingly, our rationale is built on the evidence of vaccines causing immune-mediated VITT, which elevates the risk of CVT, and the fact that CVTs often precede or coexist with bDAVFs. VITT is a rare syndrome that belongs to a wider spectrum of disorders characterized by the activation of platelets via anti-PF4 antibodies induced by an immunizing stimulus, often heparin or heparin-like molecules [22]. VITT was first related to adenoviral vector-based vaccines against COVID (ChAdOx1 CoV-19 vaccine, AstraZeneca and Ad26. COV2. vaccine, Janssen) [8,22,23]. Later, other reports also described this syndrome in patients receiving mRNA-based vaccines (BNT162b2, Pfizer-BioNTech) [10]. VITT is characterized by mild to severe thrombocytopenia, a low to normal range of fibrinogen, elevated D-dimer and normal or mildly increased coagulation times [24]. Some authors prefer the term thrombosis with thrombocytopenia syndrome in the absence of laboratory-proven immunological mechanisms. Similarly, pre-VITT syndrome has been reserved for patients who present with clinical and laboratory findings of VITT without imaging of thrombosis following vaccination [25,26]. A remarkable feature of thrombosis in VITT is that, in addition to occurring in typical sites of venous thrombosis (lungs and lower limbs), it shows a predilection for unusual locations, such as cerebral and ophthalmic veins [24,27]. The reaction induced by anti-PF4 antibodies in VITT is not limited to platelets; instead, it spreads, provoking a pan-cellular activation that involves monocytes, neutrophils and endothelial cells, which express their respective cytokines [8,22,27]. Overall, this global activation magnifies the thrombosis risk and might act as a trigger of neo-angiogenic mechanisms leading to DAVFs, as suggested by the evidence derived from animal models [28–30]. The actual pathogenesis of bDAVF is unclear, but growing evidence suggests that neoangiogenesis induced by vascular endothelial growth factor (VEGF) release following venous hypertension might be a plausible mechanism [28–30]. The retrospective nature of this report and the wide range of time that may asymptotically elapse from VITT to the diagnosis of bDAVF hinder the active investigation of coagulation or hematologic abnormalities. In those cases, in which blood and coagulation tests had been performed somewhere between the vaccine or COVID diagnosis and bDAVF diagnosis, the data were compatible with VITT [9] (Table 5). However, compatibility is a vague concept, and confirmation of VITT requires further evidence, such as PF-4 antibody testing [22].

The specificity of the association might be the most controversial item of the current argumentation. The specificity of the suggested association lies in the evidence of a proven ability of vaccines, and ultimately SARS-CoV-2, to provoke thrombosis through an immune-mediated pathophysiology. However, this fact alone might not be enough to state that vaccines or COVID elevate the risk of developing bDAVFs. Many other factors that coexist with COVID or vaccines could surreptitiously cause CVTs or bDAVFs by other unknown mechanisms in this specific period of time. For instance, a more sedentary lifestyle due to lockdown regimes or the increment of teleworking could lead to a higher risk of thrombotic phenomena.

Biological Gradient and Experiment do not apply for the present case since there is no evidence of a dose-dependent effect and the phases of experimentation for commercialized vaccines are over.

Consistency would require the repeated observation of this association by various researchers in other centers. Indeed, the purpose of this warning is precisely to raise awareness in this field to prompt other physicians to report their findings to contest or validate our observations. Undoubtedly, vaccines are the best available therapy to prevent the disease and tackle the pandemic. The incidence of bDAVFs in the vaccinated population is still very low. If confirmed, our results would only result in the communication of a very rare complication of vaccination that would not probably change at all current policies. In this sense, we have tried to temper our assertions and insist on the need for further studies.

The present report harbors several limitations. First, it is a retrospective series of patients from a single center in which the risk of

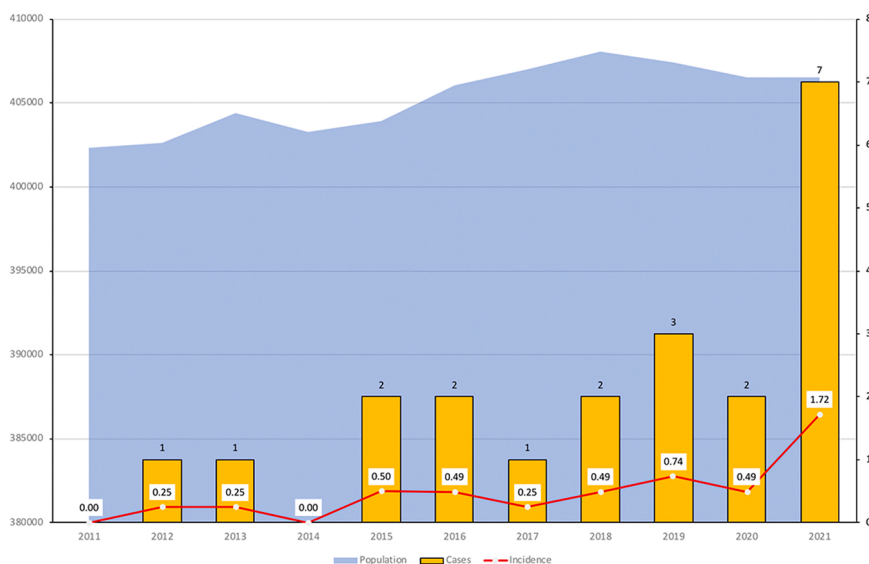


Fig. 2. Incidence of bDAVF. The graphic depicts the evolution of the population of reference (blue background), the number of patients diagnosed with DAVF (yellow bars) and the incidence per 100,000 persons per year (white boxes and red line).

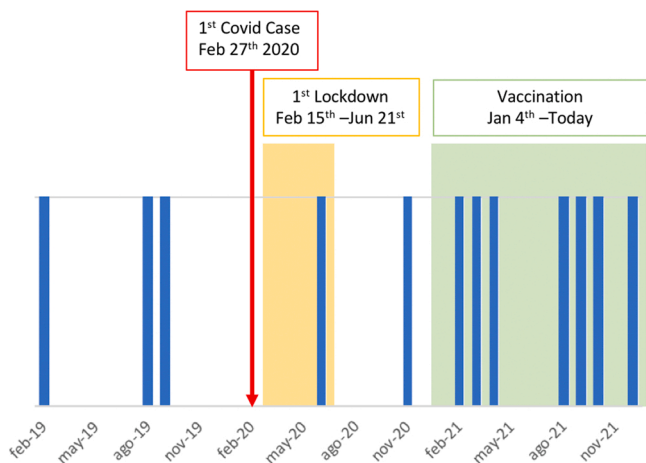


Fig. 3. Cases and COVID-19 pandemic events. The image illustrates the main events related to the COVID-19 pandemic over a timeline from February 2019 to December 2021, where each case of DAVF is represented on its corresponding date.

Table 3
Comparison of demographic and clinical data between the historic cohort and patients diagnosed with DAVF in 2021.

Variable	2011–2020	2021	p	95 % CI
Number of DAVF	14	7		
Incidence	0.345	1.722	0.036	0.088–2.66
Age	58.6	55.9	0.661	-10.3 – 15.7
Sex (Male)	10 (71.4 %)	3(42.9 %)	0.346	
Prothombotic RF (n/ %)	4 (28.6 %)	0 (0 %)	0.255	
Ruptured (n/ %)	4 (28.6 %)	2 (28.6 %)	1.000	
Sinus Thrombosis (n/ %)	9 (64.3 %)	2 (28.6 %)	0.183	
Cardiovascular RF (n/ %)				
• Hypertension	6(42.9 %)	2(28.6 %)	0.656	
• Dyslipidemia	4(28.6 %)	5(71.4 %)	0.159	
• Smoking	1(7.1 %)	1(14.3 %)	1.000	

RF: Risk factors.

selection bias is not negligible. Indeed, the epidemiological context, where a majority of the population has been vaccinated or exposed to the virus, precludes comparing the cohort of 2021 with a control group of patients who have not been exposed to any of the suspected risk factors. The retrospective design of the current report prevented us from actively looking for inflammatory biomarkers, immune-mediated prothrombotic factors or coagulation disorders. Second, it remains unclear whether CVT precedes bDAVF or is a consequence of venous hypertension caused by fistulous flow. Evidence suggests that CVT and cerebral venous sinus abnormalities are associated with dural and cerebral arteriovenous malformations [31]. However, the actual frequency of bDAVF after CVT is unknown. So far, CVT have not prospectively and systematically been followed up with angiographic studies to calculate the risk of provoking bDAVF [19]. In addition, the size, location and treatment of CVT would probably modify this risk. Experiments in animal models have demonstrated that the occlusion of a cerebral venous sinus significantly increases the blood levels of VEGF and that VEGF is involved in the subsequent angiogenic response that might eventually develop into pathological arteriovenous communication [29,30]. However, the rate of CVTs was not higher in the vaccinated cohort than in the historical cohort. Nonetheless, as previously said, CVT could act as a trigger for neoangiogenic cascades leading to bDAVF and would not necessarily require coexisting with them. Indeed, it has been reported that the rate of diagnosed venous thrombosis in VITT is highly exceeded by the number of undiagnosed ones. Finally, other confounding or coexisting factors that might contribute to explaining the observed rise in the incidence of bDAVF could not be ruled out. Larger cohorts are needed to confirm the validity of our findings and answer all potential questions that may arise regarding this topic.

5. Conclusion

Our findings suggest the existence of a potential correlation between COVID-19 vaccines and bDAVFs. A pathogenic mechanism involving VITT, CVT and activation of angiogenic cytokines is proposed based on the current body of evidence. However, our results need to be confirmed in larger cohorts and prospectively observed to determine the actual underlying mechanisms that may explain this association. Therefore, a warning should be raised to encourage physicians worldwide to report if their experience concurs with our results.

Table 4
COVID-19 and vaccination records.

N	Date of Dx	Age	COVID infection			Vaccine						
			Test	Date	DTD	First Dose			Second Dose			
						Date	Type	DTD	Date	Type	DTD	
15	Feb-22 21	67	Yes	PCR	Jan-19 21	34	Apr-22 21	Pfizer-BioNTech (mRNA)	-59	May-13 21	Pfizer-BioNTech (mRNA)	-80
16	Mar-29 21	49	Yes	PCR	Nov-29 20	120	Jun-17 21	Pfizer-BioNTech (mRNA)	-80	Jul-8 21	Pfizer-BioNTech (mRNA)	-101
17	Apr-19 21	52	No				Jan-18 21	Pfizer-BioNTech (mRNA)	91	Feb-11 21	Pfizer-BioNTech (mRNA)	67
18	Aug-7 21	64	No				Mar-26 21	Vaxzevria AZ (vector)	134	Jun-10 21	Vaxzevria AZ (vector)	58
19	Aug-23 21	68	No				Apr-16 21	Pfizer-BioNTech (mRNA)	129	May-7 21	Pfizer-BioNTech (mRNA)	108
20	Oct-10 21	32	No				May-31 21	Pfizer-BioNTech (mRNA)	207	Jul-7 21	Pfizer-BioNTech (mRNA)	170
21	Dec-24 21	56	No				Jul-16 21	Pfizer-BioNTech (mRNA)	97	Ago-6 21	Pfizer-BioNTech (mRNA)	76

AZ: AstraZeneca; DTD: Days to bDAVF diagnosis; Dx: Diagnosis.

Table 5
Blood tests for patients 15–21.

N	Date of Dx	Age	COVID infection			Vaccine				Blood test			
			Date	Date	DTD	First Dose		Second Dose		Date	Determination		
						Date	DTD	Date	DTD		D-Dimer mg/L	Platelet/microL	Fibrinogen g/L
15	Feb-22 21	67	Yes	Jan-19 21	Apr-22 21	-59	May-13 21	-80	Feb-19 21	5.7	158,000		
16	Mar-29 21	49	Yes	Nov-29 20	Jun-17 21	-80	Jul-8 21	-101	Mar-1 21	N.A	116,000	4.3	0.98
17	Apr-19 21	52	No		Jan-18 21	91	Feb-11 21	67	Apr-4 21	7.9	119,000	3.3	1.26
18	Aug-7 21	64	No		Mar-26 21	134	Jun-10 21	58	N.A	N.A	N.A	N.A	N.A
19	Aug-23 21	68	No		Apr-16 21	129	May-7 21	108	Jul-10 21	30.9	201000	6.9	1.19
20	Oct-10 21	32	No		May-31 21	207	Jul-7 21	170	N.A 21	N.A	N.A	N.A	N.A
21	Dec-24 21	56	No		Jul-16 21	97	Ago-6 21	76	Dec-10 21	N.A	128,000	4.3	1.12

Values of reference compatible with VITT diagnosis(9): D-dimer= 1.7–35; mg/L; platelets= 17,000-116,000/microL; fibrinogen= 1.75–4.49 g/L. INR normal or slightly elevated.

Dx: Diagnosis; N.A.: Not available.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRedit authorship contribution statement

Sergio García: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Project administration. Address reviewer’s suggestions. Writing final draft.**Santiago Cepeda:** Methodology, Formal Analysis, Data curation, Review and editing. Approving final draft.**Iñaki Arrese:** Conceptualization, Investigation, Review and editing. Approving final draft.**Rosario Sarabia:** Conceptualization, Resources, Review and editing, supervision. Approving final draft.

Declaration of Competing Interest

There is no conflict of interests.

Acknowledgements

We would like to express our sincere gratitude to the patients and their relatives, which, through their altruist contribution, made this project possible.

Publication history

This manuscript was previously posted to Research Square (DOI: 10.21203/rs.3.rs-1323425/v1).

Disclosure

Patients signed an informed consent authorizing the use of their

anonymized clinical information and images with scientific purposes.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.clineuro.2022.107367](https://doi.org/10.1016/j.clineuro.2022.107367).

References

- [1] K.L. Chaichana, A.L. Coon, R.J. Tamargo, J. Huang, Dural arteriovenous fistulas: epidemiology and clinical presentation, *Neurosurg. Clin. N. Am.* 23 (1) (2012) 7–13, <https://doi.org/10.1016/j.nec.2011.09.001>.
- [2] P. Castaigne, Rene Djindjian, 1918-1977, *Rev. Neurol. (Paris)*. 133 (12) (1977) 736–738. Rene Djindjian 1918-1977.
- [3] A. Rodriguez-Hernandez, R. Torne, A. Blanco Ibanez de Opacua, et al., Amateur endurance athletes: at higher risk of suffering dural arteriovenous fistulas? Report of 3 cases, *World Neurosurg.* 140 (2020) 32–36, <https://doi.org/10.1016/j.wneu.2020.05.035>.
- [4] E. Lindgren, A. Rentzos, S. Hiltunen, et al., Dural arteriovenous fistulas in cerebral venous thrombosis: data from the International Cerebral Venous Thrombosis Consortium, *Eur. J. Neurol.* (2021), <https://doi.org/10.1111/ene.15192>.
- [5] M.A. Ellul, L. Benjamin, B. Singh, et al., Neurological associations of COVID-19, *Lancet Neurol.* 19 (9) (2020) 767–783, [https://doi.org/10.1016/S1474-4422\(20\)30221-0](https://doi.org/10.1016/S1474-4422(20)30221-0).
- [6] S. Garcia-Garcia, S. Cepeda, I. Arrese, R. Sarabia, Letter: hemorrhagic conditions affecting the central nervous system in COVID-19 patients, *Neurosurgery* 87 (3) (2020) E394–E396, <https://doi.org/10.1093/neuros/nyaa253>.
- [7] A. Varatharaj, N. Thomas, M.A. Ellul, et al., Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study, *Lancet Psychiatry* 7 (10) (2020) 875–882, [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X).
- [8] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, *N. Engl. J. Med.* 384 (22) (2021) 2092–2101, <https://doi.org/10.1056/NEJMoa2104840>.
- [9] F. Salih, L. Schonborn, S. Kohler, et al., Vaccine-induced thrombocytopenia with severe headache, *N. Engl. J. Med.* 385 (22) (2021) 2103–2105, <https://doi.org/10.1056/NEJM2112974>.
- [10] I. See, A. Lale, P. Marquez, et al., Case series of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination-United States, December 2020 to August 2021, *Ann. Intern. Med.* (2022), <https://doi.org/10.7326/M21-4502>.
- [11] R.J. Perry, A. Tamborska, B. Singh, et al., Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study, *Lancet* 398 (10306) (2021) 1147–1156, [https://doi.org/10.1016/S0140-6736\(21\)01608-1](https://doi.org/10.1016/S0140-6736(21)01608-1).

- [12] J.P. Vandenbroucke, E. von Elm, D.G. Altman, et al., Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration, *Epidemiology* 18 (6) (2007) 805–835, <https://doi.org/10.1097/EDE.0b013e3181577511>.
- [13] C. Cognard, Y.P. Gobin, L. Pierot, et al., Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage, *Radiology* 194 (3) (1995) 671–680, <https://doi.org/10.1148/radiology.194.3.7862961>.
- [14] Sanidad. Poblacion tarjeta sanitaria. Junta de Castilla y Leon. (<https://www.saludcastillayleon.es/transparencia/es/transparencia/sanidad-cifras/informes-estadisticos/ordenacion-alfabetica/poblacion-tarjeta-sanitaria.ficheros/1834571-PoblacionC3%B3n%20de%20Tarjeta%20Sanitaria%20de%20Castilla%20y%20Le%C3%B3n.%20Diciembre%202020.pdf>).
- [15] Sanidad. Situación epidemiológica del Coronavirus en Castilla y León. Junta de Castilla y León. (<https://analisis.datosabiertos.jcyl.es/pages/coronavirus/?seccion=vacunaciones-suministros>).
- [16] A.B. Hill, The environment and disease: association or causation? *Proc. R. Soc. Med.* 58 (1965) 295–300.
- [17] J. Satomi, K. Satoh, [Epidemiology and etiology of dural arteriovenous fistula], *Brain Nerve* 60 (8) (2008) 883–886.
- [18] R.D. Brown Jr., D.O. Wiebers, D.A. Nichols, Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients, *J. Neurosurg.* 81 (4) (1994) 531–538, <https://doi.org/10.3171/jns.1994.81.4.0531>.
- [19] J.M. Ferro, J.M. Coutinho, O. Jansen, et al., Dural arteriovenous fistulae after cerebral venous thrombosis, *Stroke* 51 (11) (2020) 3344–3347, <https://doi.org/10.1161/STROKEAHA.120.031235>.
- [20] D.D. Cavalcanti, E. Raz, M. Shapiro, et al., Cerebral venous thrombosis associated with COVID-19, *AJNR Am. J. Neuroradiol.* 41 (8) (2020) 1370–1376, <https://doi.org/10.3174/ajnr.A6644>.
- [21] R. Ghosh, D. Roy, A. Mandal, et al., Cerebral venous thrombosis in COVID-19, *Diabetes Metab. Syndr.* 15 (3) (2021) 1039–1045, <https://doi.org/10.1016/j.dsx.2021.04.026>.
- [22] I.H. Sorvoll, K.D. Horvei, S.L. Ernsten, et al., An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination, *J. Thromb. Haemost.* 19 (7) (2021) 1813–1818, <https://doi.org/10.1111/jth.15352>.
- [23] N. Gabarin, S. Patterson, M. Pai, et al., Venous thromboembolism and mild thrombocytopenia after ChAdOx1 nCoV-19 Vaccination, *Thromb. Haemost.* 121 (12) (2021) 1677–1680, <https://doi.org/10.1055/a-1585-6182>.
- [24] S. Pavord, M. Scully, B.J. Hunt, et al., Clinical features of vaccine-induced immune thrombocytopenia and thrombosis, *N. Engl. J. Med.* 385 (18) (2021) 1680–1689, <https://doi.org/10.1056/NEJMoa2109908>.
- [25] T.E. Warkentin, A. Greinacher, Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia, *Thromb. Res.* 204 (2021) 40–51, <https://doi.org/10.1016/j.thromres.2021.05.018>.
- [26] T.E. Warkentin, M. Makris, R.M. Jay, J.G. Kelton, A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia, *Am. J. Med.* 121 (7) (2008) 632–636, <https://doi.org/10.1016/j.amjmed.2008.03.012>.
- [27] C. Pomara, F. Sessa, M. Ciaccio, et al., Post-mortem findings in vaccine-induced thrombotic thrombocytopenia, *Haematologica* 106 (8) (2021) 2291–2293, <https://doi.org/10.3324/haematol.2021.279075>.
- [28] S.T. Yang, A. Rodriguez-Hernandez, E.J. Walker, W.L. Young, H. Su, M.T. Lawton, Adult mouse venous hypertension model: common carotid artery to external jugular vein anastomosis, *J. Vis. Exp.* 95 (2015) 50472, <https://doi.org/10.3791/50472>.
- [29] Q. Li, Q. Zhang, Q.H. Huang, et al., A pivotal role of the vascular endothelial growth factor signaling pathway in the formation of venous hypertension-induced dural arteriovenous fistulas, *Mol. Med Rep.* 9 (5) (2014) 1551–1558, <https://doi.org/10.3892/mmr.2014.2037>.
- [30] Y. Shin, H. Nakase, M. Nakamura, K. Shimada, N. Konishi, T. Sakaki, Expression of angiogenic growth factor in the rat DAVF model, *Neurol. Res.* 29 (7) (2007) 727–733, <https://doi.org/10.1179/016164107x208077>.
- [31] R. Torne, L. Reyes, A. Rodriguez-Hernandez, X. Urra, L. Sanroman, J. Ensenat, Anatomical variations of brain venous sinuses in patients with arteriovenous malformations: incidental finding or causative factor, *World Neurosurg.* 113 (2018) e465–e470, <https://doi.org/10.1016/j.wneu.2018.02.057>.