

<https://helda.helsinki.fi>

Dural arteriovenous fistulas in cerebral venous thrombosis Data from the International Cerebral Venous Thrombosis Consortium

Int CVT Consortium

2022-03

Int CVT Consortium , Lindgren , E , Rentzos , A , Hiltunen , S , Putaala , J & Tatlisumak , T 2022 , ' Dural arteriovenous fistulas in cerebral venous thrombosis Data from the International Cerebral Venous Thrombosis Consortium ' , European Journal of Neurology , vol. 29 , no. 3 , pp. 761-770 . <https://doi.org/10.1111/ene.15192>

<http://hdl.handle.net/10138/353360>

<https://doi.org/10.1111/ene.15192>

cc_by_nc_nd

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.



This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

ORIGINAL ARTICLE

Dural arteriovenous fistulas in cerebral venous thrombosis

Data from the International Cerebral Venous Thrombosis Consortium

Erik Lindgren^{1,2}  | Alexandros Rentzos^{3,4} | Sini Hiltunen⁵ | Fabiola Serrano⁶ |
Mirjam R. Heldner⁷  | Susanna M. Zuurbier⁸ | Suzanne M. Silvis⁸ | Maryam Mansour⁹ |
William Allingham¹⁰ | Martin N. M. Punter^{11,12,13} | Blake F. Giarola¹⁴ | Jeremy Wells¹⁵ |
Mayte Sánchez van Kammen⁸ | Eike I. Piechowiak¹⁶ | Nicole Chiota-McCollum¹⁵ |
Carlos Garcia-Esperon¹⁷ | Christophe Cognard¹⁸ | Timothy Kleinig¹⁹ | Masoud Ghiasian⁹ |
Jonathan M. Coutinho⁸ | Marcel Arnold⁷ | Antonio Arauz⁶ | Jukka Putaala⁵ |
Katarina Jood^{1,2} | Turgut Tatlisumak^{1,2,5} | the International CVT Consortium

¹Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

²Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden

³Diagnostic and Interventional Neuroradiology, Sahlgrenska University Hospital, Gothenburg, Västra Götaland County, Sweden

⁴Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

⁵Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

⁶National Institute of Neurology, Neurosurgery Manuel Velasco Suarez, Mexico-City, Mexico

⁷Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

⁸Department of Neurology, Amsterdam University Medical Centers, AMC, Amsterdam, The Netherlands

⁹Department of Neurology, Sina Hospital, Hamadan University of Medical Science, Hamadan, Iran

¹⁰The Balfour Hospital, National Health Service Orkney, Kirkwall, Orkney, UK

¹¹Department of Neurology, Wellington Regional Hospital, Capital and Coast

Abstract

Background and purpose: To explore the prevalence, risk factors, time correlation, characteristics and clinical outcome of dural arteriovenous fistulas (dAVFs) in a cerebral venous thrombosis (CVT) population.

Methods: We included patients from the International CVT Consortium registries. Diagnosis of dAVF was confirmed centrally. We assessed the prevalence and risk factors for dAVF among consecutive CVT patients and investigated its impact on clinical outcome using logistic regression analysis. We defined poor outcome as modified Rankin Scale score 3–6 at last follow-up.

Results: dAVF was confirmed in 29/1218 (2.4%) consecutive CVT patients. The median (interquartile range [IQR]) follow-up time was 8 (5–23) months. Patients with dAVF were older (median [IQR] 53 [44–61] vs. 41 [29–53] years; $p < 0.001$), more frequently male (69% vs. 33%; $p < 0.001$), more often had chronic clinical CVT onset (>30 days: 39% vs. 7%; $p < 0.001$) and sigmoid sinus thrombosis (86% vs. 51%; $p < 0.001$), and less frequently had parenchymal lesions (31% vs. 55%; $p = 0.013$) at baseline imaging. Clinical outcome at last follow-up did not differ between patients with and without dAVF. Additionally, five patients were confirmed with dAVF from non-consecutive CVT cohorts. Among all patients with CVT and dAVF, 17/34 (50%) had multiple fistulas and 23/34 (68%) had cortical venous drainage. Of 34 patients with dAVF with 36 separate CVT events, 3/36 fistulas (8%) were diagnosed prior to, 20/36 (56%) simultaneously and 13/36 after (36%, median 115 [IQR 38–337] days) diagnosis of CVT.

Conclusions: Dural arteriovenous fistulas occur in at least 2% of CVT patients and are associated with chronic CVT onset, older age and male sex. Most CVT-related dAVFs are detected simultaneously or subsequently to diagnosis of CVT.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology

District Health Board, Wellington, New Zealand

¹²Department of Medicine, University of Otago, Dunedin, New Zealand

¹³Division of Neuroscience and Experimental Psychology, School of Biological Sciences, University of Manchester, Manchester, UK

¹⁴Department of Neurology, Royal Prince Alfred Hospital, University of Sydney, Sydney, New South Wales, Australia

¹⁵Department of Neurology, University of Virginia Health System, Charlottesville, Virginia, USA

¹⁶Inselspital, University Institute for Diagnostic and Interventional Neuroradiology, Bern, Switzerland

¹⁷John Hunter Hospital, University of Newcastle and Hunter Medical Research Institute, Newcastle, New South Wales, Australia

¹⁸Department of Diagnostic and Therapeutic Neuroradiology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

¹⁹Department of Neurology, South Australian Medical Research Institute, Royal Adelaide Hospital, University of Adelaide, Adelaide, Australia

Correspondence

Erik Lindgren, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska University Hospital, Sahlgrenska Academy at University of Gothenburg, Blå Stråket 7, 3rd floor, Gothenburg 413 45, Sweden. Email: erik.lindgren@neuro.gu.se

Funding information

EL has received research grants from the Swedish Neurological Society, Elsa And Gustav Lindh's Foundation, Per Olof Ahl's Foundation and Rune And Ulla Amlöv's Foundation for research on CVT. JMC has received research funding for CVT from Boehringer and Bayer. All fees were paid to JMC's institute (no personal compensation). TT has received academic research funding from University of Gothenburg and Sahlgrenska University Hospital for cerebral venous thrombosis research. The funding sources had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, preparation, review or approval of the manuscript, or the decision to submit the manuscript for publication

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare disease with an incidence of 1.3–1.6 per 100,000 adults, mainly affecting working-aged individuals and predominantly females [1–3]. The occurrence of dural

KEYWORDS

cerebral venous thrombosis, dural arteriovenous fistula, follow-up, long-term outcome, stroke

arteriovenous fistulas (dAVFs) has been reported among 0.9%–13% of patients up to 6 months after diagnosis of CVT, but data are lacking from large cohorts [3–6]. It has been suggested that thrombi in the cerebral venous system may stagnate blood flow, increase venous pressure and thereby cause enlargement of preexisting physiological

arteriovenous shunts or stimulation of neoangiogenesis and development of a dAVF [7–11]. However, diagnosis of dAVF is challenging as low-grade fistulas may remain asymptomatic, and it is not known whether CVT cause dAVFs or vice versa [12]. In a cohort of 69 patients with dAVF, CVT was present in 39% [13]. In case reports, diagnosis of dAVF has been described prior to, simultaneously and subsequent to the diagnosis of CVT [7,14–17]. Hence, the frequency and time correlation of dAVF among CVT patients remains unclear.

Untreated high-grade fistulas (i.e., fistulas with retrograde cortical venous drainage) entail a 10% annual risk of mortality and a 15% annual risk of intracerebral hemorrhage or non-hemorrhagic neurological sequelae [12,18–20]. The impact of dAVF on clinical outcome has not been systematically investigated among CVT patients.

In the present study, we aimed to explore the prevalence and time correlation between CVT and dAVF as well as to describe the risk factors for and characteristics of dAVF in a large multicenter CVT patient cohort. Further, we aimed to investigate the impact of dAVF on clinical outcome.

METHODS

Study design and participants

Patients were recruited from eight hospital-based consecutive adult CVT registries within the International CVT Consortium [21]. Details of the consortium are described in Table S1 and Table S2 in the Supplemental Material. Start of recruitment varied by hospital, the earliest being August 1987. We included patients diagnosed with CVT until October 2018.

Due to the particularly rare combination of CVT and dAVF, we centrally reviewed all patients with suspected CVT and dAVF within the consortium and discovered five additional patients with suspected CVT and dAVF that did not originate from consecutive CVT registries; the University of Virginia Health System ($n = 4$, Charlottesville, VA, United States) and the John Hunter Hospital ($n = 1$, Newcastle, Australia). These patients were included for descriptive analyses exploring features of dAVF but were not included in the epidemiological or outcome analyses.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Each center received permission from the relevant national authorities and ethical committees for collecting observational data.

Data collection

Data including demographics, clinical features, symptoms of CVT and dAVF, risk factors, clinical features and neurological imaging

were obtained from medical records. CVT diagnosis was confirmed either by computed tomography (CT) venography, magnetic resonance imaging (MRI) combined with magnetic resonance venography, conventional angiography, or autopsy, in accordance with international guidelines [22].

Central imaging review of patients with suspected CVT and dAVF

Following local neuroradiologists' neuroimaging review, raw data on all routine care radiological examinations from patients with suspected CVT and dAVF were referred centrally for evaluation by an experienced specialist in interventional neuroradiology at Sahlgrenska University Hospital, Gothenburg, Sweden, in accordance with a preset study formula. The dAVF group comprised patients in whom both CVT and a dAVF could be confirmed, regardless of their respective occurrence in time, and for whom imaging from a digital subtraction angiography (DSA) was available at the central imaging review. The dAVFs were categorized in accordance with Cognard's Classification System for dAVF where grade IIb or higher represents fistulas with retrograde cortical venous drainage [19]. Number of individual dAVFs with independent feeders was assessed and patients with more than one dAVF were regarded as having multiple dAVFs. Ambiguous cases were discussed and validated by experienced experts within the field. The index date for CVT and dAVF was defined as the imaging date when the first radiological signs appeared for each condition, respectively. If indirect signs of dAVF were observed on MRI or CT that were later diagnosed as dAVF at the same location on a DSA, the conduct date of the first imaging was considered as the dAVF index date. Recurrent CVTs confirmed at different imaging studies and dates were considered as separate events. To determine the degree of relationship between the fistula and venous thrombus, all CVT events were categorized into three groups depending on location of the CVT versus location of the dAVF as follows: (i) "probable": CVT and dAVF located in the same sinus; (ii) "possible": CVT located directly downstream of dAVF, but not in the same sinus; and (iii) "unlikely": CVT located on the contralateral side or upstream of the dAVF without radiological evidence of hemodynamic influence at the location of the thrombus.

Clinical outcome

Clinical outcome was measured with the modified Rankin Scale (mRS) at last follow-up. We defined poor clinical outcome as mRS score 3–6.

Statistical analyses

We compared consecutive CVT patients with dAVF and without dAVF using Fisher's exact test for dichotomous data and the

Mann-Whitney *U*-test for continuous data. We considered a two-sided probability value below 0.05 as significant and calculated positive predictive values for all variables that fulfilled these criteria. We used logistic regression to investigate the association of dAVF with clinical outcome, adjusted for age and sex. In a subgroup analysis, we also evaluated clinical outcome of dAVF patients with retrograde cortical venous drainage. We performed sensitivity analyses with and without non-consecutively recruited cases. All data were analyzed using IBM SPSS Statistics version 23.0 (International Business Machines Corporation).

RESULTS

In total, 1218 adult CVT patients were included from eight consecutive registries. The study recruitment flowchart appears in Figure 1.

From the consecutive CVT cohort, neurological imaging of 41 patients with suspected CVT and dAVF were reviewed centrally, and presence of CVT and dAVF was confirmed in 29 patients. The remaining 12 patients were disqualified because of insufficient imaging data ($n = 7$, suspected dAVF on CT and/or MRI, but no DSA available), inability to confirm either CVT or dAVF ($n = 4$), and concurrent meningioma situated at the same location as the suspected CVT ($n = 1$).

Five additional patients with high suspicion of CVT and dAVF were included separately from the University of Virginia Health System ($n = 4$) and the John Hunter Hospital, Newcastle, Australia, ($n = 1$). These cases were centrally reviewed and CVT and dAVF could be confirmed in all patients, but these patients were not included in the epidemiological or the outcome analysis. There was no difference in sex or age between the non-consecutive CVT and

dAVF patients as compared to consecutively recruited CVT and dAVF patients.

Prevalence of and risk factors for dAVF

Among consecutive adult CVT patients, the prevalence of dAVF was 29/1218 (2.4%) during a median (interquartile range [IQR]) follow-up of 8 (6–12) months. Baseline data comparing patients with dAVF versus patients without dAVF are shown in Table 1. The median (IQR) follow-up time from diagnosis of CVT did not differ between patients with and without dAVF (6 [5–12] vs. 8 [6–12] months; $p = 0.453$). In univariable analyses, patients with dAVF were older, more often male, more often had chronic CVT onset and sigmoid sinus thrombosis, and less often had a parenchymal lesion at baseline imaging as compared to CVT patients without dAVF. Treatment with oral anti-coagulation did not differ between patients with and without dAVF.

Risk for dAVF, as calculated by positive predictive value, was best predicted by chronic CVT onset (>30 days) in combination with either sigmoid sinus thrombosis, 10/37 (27%), male sex, 9/49 (18%), onset age >41 years, 8/52 (15%), or no parenchymal lesion at baseline imaging, 7/68 (10%).

Time correlation and degree of relationship

In total, 34 patients were diagnosed with CVT and dAVF centrally (29 patients from the consecutive CVT cohort and five patients from non-consecutive series). Two patients with CVT and dAVF had multiple episodes of CVT, therefore, we investigated each thrombus event separately with regard to time correlation and degree of

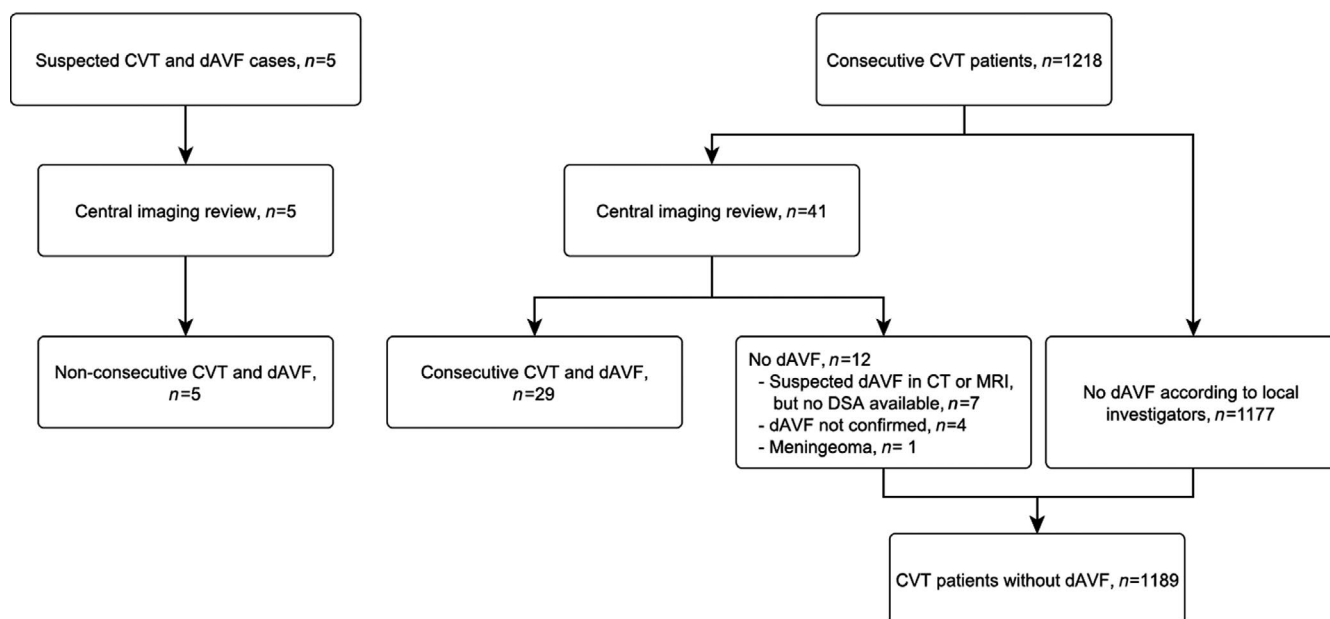


FIGURE 1 Flow chart displaying study participants. Abbreviations: CT, computed tomography; CVT, cerebral venous thrombosis; dAVF, dural arteriovenous fistula; DSA, digital subtraction angiography; MRI, magnetic resonance imaging

TABLE 1 Baseline data on 1218 consecutive patients with cerebral venous thrombosis

	CVT and dAVF, <i>n</i> = 29	CVT only, <i>n</i> = 1189	<i>p</i> -value
Clinical characteristics			
Women, <i>n/N</i> (%)	9/29 (31)	798/1189 (67)	<0.001
Age in years, median (IQR) ^a	53 (44–61)	41 (29–53)	<0.001
Headache, <i>n/N</i> (%)	22/29 (76)	982/1172 (84)	0.305
Focal neurological deficits, <i>n/N</i> (%)	11/29 (38)	666/1180 (56)	0.058
Coma (GCS < 9), <i>n/N</i> (%)	2/29 (7)	77/1170 (7)	0.716
Seizure(s), <i>n/N</i> (%)	6/27 (22)	383/1171 (33)	0.303
Symptom onset, <i>n/N</i> (%)			
Acute (<48 h)	7/28 (25)	443/1172 (38)	<0.001
Subacute (48 h–30 days)	10/28 (36)	643/1172 (55)	
Chronic (>30 days)	11/28 (39)	86/1172 (7)	
Risk factors, <i>n/N</i> (%)			
Cancer	2/29 (7)	135/1172 (12)	0.765
Previous venous thrombosis	4/29 (14)	110/1163 (9)	0.351
Hereditary thrombophilia	4/25 (16)	152/1038 (15)	0.777
Local trauma	0/25 (0)	48/996 (5)	0.626
Surgery	2/25 (8)	31/992 (3)	0.193
Local infection	3/25 (12)	128/1156 (11)	0.752
Oral contraceptive use ^b	1/9 (11)	335/776 (43)	0.086
Hormone replacement therapy ^b	2/9 (22)	34/602 (6)	0.094
Pregnancy, puerperium ^b	1/9 (11)	92/792 (12)	1.000
Any female-specific risk factor ^b	4/9 (44)	451/727 (62)	0.314
Imaging characteristics, <i>n/N</i> (%)			
Any parenchymal lesion	9/29 (31)	599/1085 (55)	0.013
Intracerebral hemorrhage	5/29 (17)	389/1086 (36)	0.048
Cerebral edema/infarct	6/29 (21)	368/1066 (35)	0.164
Sulcal subarachnoid hemorrhage	1/29 (3)	108/1059 (10)	0.351
Cerebral venous thrombus location, <i>n/N</i> (%)			
Superior sagittal sinus	12/29 (41)	626/1185 (53)	0.261
Sigmoid sinus	25/29 (86)	487/948 (51)	<0.001
Sigmoid sinus, right	12/29 (41)	240/948 (25)	0.081
Sigmoid sinus, left	14/28 (50)	287/947 (30)	0.036
Transverse sinus	20/29 (69)	825/1184 (70)	1.000
Transverse sinus, right	11/29 (38)	481/1184 (41)	0.850
Transverse sinus, left	14/29 (48)	498/1183 (42)	0.570
Cortical vein	0/29 (0)	152/913 (17)	0.009
Straight sinus	2/29 (7)	198/1184 (17)	0.208
Cavernous sinus	0/29 (0)	13/766 (2)	1.000
Treatment, <i>n/N</i> (%)			
Oral anticoagulation	23/29 (79)	1069/1184 (90)	0.061
Decompressive craniectomy	3/29 (10)	50/949 (5)	0.204

Groups compared using Fisher's exact test for categorical data and Mann Whitney U test for continuous data.

Abbreviations: CVT, cerebral venous thrombosis; dAVF, dural arteriovenous fistula; GCS, Glasgow Coma Scale; IQR, interquartile range; *n/N*, number of cases/number of observations.

^aNo missing data.

^bAmong female patients.

relationship between CVT and dAVF. In total, 36 CVT events in 34 patients were recognized at central imaging review.

Comparison of the first date of radiologically confirmed CVT or dAVF showed that dAVF was diagnosed prior to the CVT in 3/36 cases (8%; median 569 [IQR 375–574] days), simultaneously to CVT in 20/36 cases (56%), and subsequently to the CVT in 13/36 cases (36%; median 115 [IQR 38–337] days).

Among 32/36 (89%) CVT events, at least one of the thromboses was situated either at the same sinus or in direct venous downstream in relation to the fistulas, and their relationship was categorized as probable. The remaining 4/36 (11%) CVT events were located directly downstream of the dAVF but not in the same sinus, hence, their relationship was considered as possible. No cases were assigned to the unlikely group.

Characteristics of dAVF

Radiological characteristics including classification of dAVF are presented in Table 2. Among patients with CVT and dAVF, 17/34 (50%) had multiple dAVFs, most commonly two or three. Neuroimaging from a representative patient with CVT and multiple dAVFs is presented in Figure 2. Fistulas most frequently involved the sigmoid sinus or the transverse sinus, with a preference for the left side. Nineteen patients (56%) had a dAVF engaging the sigmoid transverse junction and 23/34 (68%) had at least one fistula with retrograde cortical venous drainage. Most patients with dAVF, 25/34 (74%), were treated with endovascular intervention, 9/34 patients (26%) were treated conservatively and 3/34 patients (9%) underwent a neurosurgical procedure.

Clinical symptoms were reported by treating physicians as related to dAVF in 31 patients, including: tinnitus, bruit or pulsatile tinnitus in 15/31 (48%), headache in 14/31 (45%), visual impairment in 7/31 (23%), aphasia in 6/31 (19%), seizures in 5/31 (16%), decreased consciousness or cognitive decline in 5/31 (16%), paresis in 4/31 (13%), nausea in 4/31 (13%), ataxia in 2/31 (6%) and disturbance of gait in 2/31 patients (6%).

There was no major difference between consecutively recruited dAVF patients and non-consecutively recruited dAVF patients with regard to dAVF characteristics, clinical symptoms related to dAVF or time correlation between diagnosis of CVT and dAVF.

Clinical outcome

After adjustment for age and sex, presence of dAVF was not associated with poor clinical outcome at follow-up (mRS score 3–6, adjusted odds ratio [aOR] 1.0, 95% confidence interval [CI] 0.4–2.5, median [IQR] follow-up time 8 [6–12] months), compared to the consecutive CVT cohort. In a subgroup analysis, we examined the influence of cortical venous drainage on clinical outcome, but found no association (aOR 1.4, 95% CI 0.5–4.1).

TABLE 2 Characteristics and location of dural arteriovenous fistulas among patients diagnosed with cerebral venous thrombosis

	CVT and dAVF (n = 34)
Radiological characteristics, n/N (%)	
Multiple dAVFs	17/34 (50)
Dural venous sinus stenosis	7/34 (21)
Recanalization of CVT at time of dAVF diagnosis ^a	
No recanalization	17/31 (55)
Partial recanalization	10/31 (32)
Complete recanalization	4/31 (13)
Location of dAVF, n/N (%)	
Superior sagittal sinus	3/34 (9)
Sigmoid sinus	25/34 (74)
Sigmoid sinus, right	10/34 (29)
Sigmoid sinus, left	18/34 (53)
Transverse sinus	24/34 (71)
Transverse sinus, right	12/34 (35)
Transverse sinus, left	16/34 (47)
Involves both transverse and ipsilateral sigmoid sinus	19/34 (56)
Confluence sinus	12/34 (35)
Straight sinus	1/34 (3)
Cavernous sinus	0/34 (0)
Cognard's classification of dAVFs: n/N (%)	
I – normal antegrade dural sinus drainage	8/34 (24)
II – drainage into sinuses with insufficient antegrade venous drainage and reflux	
IIa – reflux into sinus(es) only	9/34 (26)
IIb – reflux into cortical vein(s) only	4/34 (12)
IIc – reflux into sinus(es) and cortical veins	16/34 (47)
III – drainage directly into cortical vein without venous ectasia	9/34 (26)
IV – drainage directly into cortical vein, with venous ectasia	3/34 (9)
V – drainage into spinal perimedullary veins	0/34 (0)

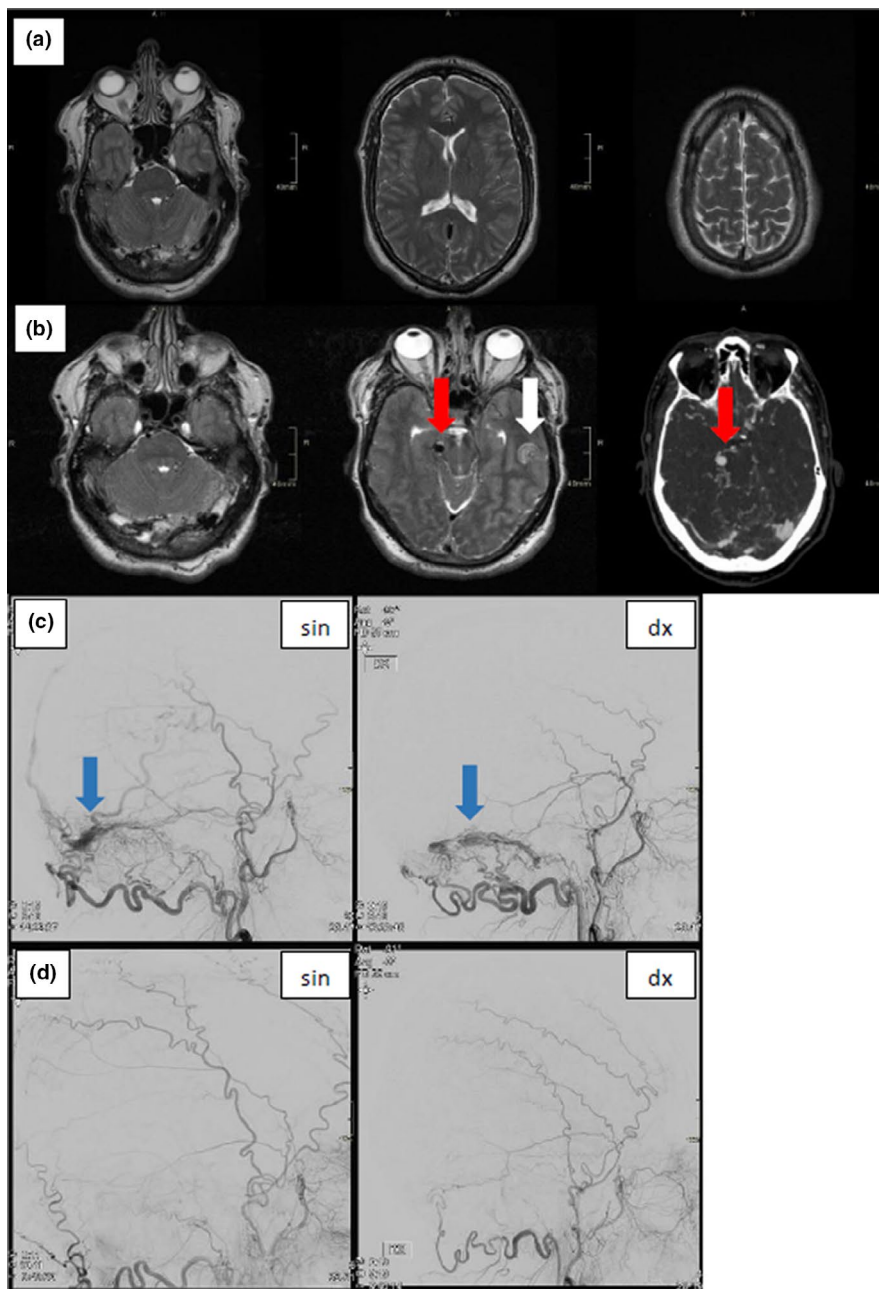
Abbreviations: CVT, cerebral venous thrombosis; dAVF, dural arteriovenous fistula.

^aAmong patients with dAVF after diagnosis of CVT.

DISCUSSION

In our multicenter cohort of 1218 consecutive adult CVT patients, the prevalence of dAVF was 2.4%. Most dAVFs (92%) were diagnosed simultaneously or subsequently to CVT. In univariable analyses, patients with CVT and dAVF were older, more often male, and more often had chronic CVT onset and sigmoid sinus thrombosis, but less frequently had parenchymal lesions at baseline imaging, compared to CVT patients without dAVF. Presence of dAVF in CVT

FIGURE 2 Radiological imaging of a representative patient with cerebral venous thrombosis and multiple dural arteriovenous fistulas. (a) Magnetic Resonance Imaging (MRI) showing bilateral transverse sinus thrombosis and partial sigmoid sinus thrombosis on admission. (b) 6 months later, the patient is readmitted with symptoms of severe headache. MRI and computed tomography (CT) angiography (on the right) reveal persistent bilateral transverse sinus thrombosis, partial sigmoid sinus thrombosis, a venous hemorrhage in the left temporal lobe (white arrow) and a venous aneurysm (red arrow). (c) Digital subtraction angiography (DSA) images 6 months after first admission, revealing bilateral dural arteriovenous fistulas (dAVF, blue arrows) where arterial contrast from the external carotid artery fills the transverse sinuses through the middle meningeal artery and the occipital artery on the left and right side respectively. (d) Follow-up DSA images after endovascular embolization of the left dAVF and neurosurgical treatment of the right dAVF, 16 months after first admission. Arterial contrast applied in the external carotid artery no longer reaches the transverse sinuses



patients was not associated with poor clinical outcome at last follow-up as compared to CVT patients without dAVF.

The prevalence of dAVF in the present cohort was higher than most previous reports among CVT patients [3–5]. One recent exploratory study investigated 30 CVT patients with four-dimensional magnetic resonance venography and detected dAVF in four patients within 6 months, but the investigated number of patients was low [6]. Within the International CVT Consortium, most patients routinely undergo follow-up imaging of their CVT with MRI or CT, thus increasing the likelihood of incidental suspicion and diagnosis of dAVF. Nevertheless, the prevalence of dAVF in the present study may still be an underestimation because: (i) the frequency, timing and modality of follow-up imaging was not standardized; (ii) not all CVT patients routinely undergo DSA; (iii) despite occasional high

suspicion, uncertain cases were excluded from the dAVF group on central imaging review; (iv) detection of dAVF was limited to the follow-up period of the study; and (v) radiological methods for detecting dAVF have improved over time and the study inclusion period ranges back to 1987.

Proposed risk factors for dAVF found in our CVT cohort are in line with risk factors for dAVF in general [18]. Most frequently, dAVF affects patients aged 50–60 years with no sex preference, in contrast to CVT which affects patients with a median age of ~40 years and predominantly female patients [3,18]. Overall, most dAVFs appear without clear cause, and apart from CVT, only small subsets can be explained by previous head trauma, local infection, craniotomy or intracranial tumors [23–25]. Due to a limited number of events, we were unable to perform multivariable analyses.

The vast majority of dAVF cases in our cohort were diagnosed simultaneously or subsequently to the diagnosis of CVT. As such, our data support the concept of cerebral venous obstruction increasing the risk of subsequent dAVF development. Patients with dAVF had a more insidious CVT symptom onset, suggesting that chronic CVT entails higher risk for the development of dAVF. Nevertheless, one-quarter of patients with dAVF had acute CVT onset and the possibility of development of dAVF within just a few days after CVT onset cannot be ruled out. However, in patients in whom the dAVFs and CVT were detected simultaneously, their mutual influence and time association remains unclear.

Our findings indicate an association between CVT and dAVF. The prevalence and incidence of dAVF among CVT patients is higher than that in the general population. Although no studies have investigated the incidence of dAVF in a healthy population, detection rates of 0.15–0.29 per 100,000 per year have been reported in population-based patient cohorts with previous intracranial arteriovenous malformations [26–29]. Further, nearly all fistulas were connected to or situated at the same location as the CVT. The fact that there was not a single patient in the cohort in whom CVT and dAVF locations were completely unrelated also brings indirect support that CVT and dAVF were related to each other in a cause-consequence order.

Sigmoid sinus thrombosis in particular was strongly associated with dAVF and, interestingly, fistulas were predominantly located to the left transverse or sigmoid sinuses. This left side tendency has also been described in previous reports [30], and coincides with left side tendency of hypoplastic transverse sinus which is present in 21%–31% of asymptomatic adults on magnetic resonance venography [31–34]. Venous stenosis was diagnosed in seven patients with dAVF. Acquired venous stenosis potentially increases risk of dAVF by partial venous occlusion, but it is not known whether congenital hypoplasia also increases risk of developing a dAVF. We did not discover a single case of dAVF involving any of the cavernous sinuses although cavernous sinus involvement has been reported in 6%–15% of patients with dAVF and cortical venous drainage [12,20].

Due to the low rates of dAVF, our results do not support routinely screening all CVT patients for dAVF at follow-up. Nevertheless, in certain subsets of CVT patients, dAVFs were diagnosed in more than every fourth patient. We believe these findings are clinically important and can easily be implemented in clinical practice by increasing awareness of dAVF symptoms and asking high-risk CVT patients for symptoms of dAVF at admission and follow-up (i.e., tinnitus, pulsatile tinnitus). High-risk patients include those with chronic CVT symptom onset in combination with either sigmoid sinus thrombosis, male sex, age at CVT diagnosis >41 years or no parenchymal lesion at baseline imaging. Dynamic non-invasive angiographic imaging techniques (i.e., dynamic magnetic resonance venography) may play a future role in screening of selected patients with suspected dAVFs after CVT but require evaluation regarding accuracy for detection of dAVF in large cohorts prior to implementation in routine care [6].

We found no association between dAVF and worse clinical outcome. However, these findings are highly influenced by the fact that most patients with dAVF received endovascular treatment. Previous studies report increased risk of intracerebral hemorrhage or non-hemorrhagic neurological deficit of 15% and a mortality rate of 10% annually, in patients with high-grade dAVF who refused treatment or received insufficient therapy that did not eliminate the cortical venous drainage [20]. Further, parenchymal lesions, which are a strong predictor for poor clinical outcome among CVT patients, were less frequent in the dAVF group.

Strengths of the present study are our large cohort of CVT patients and our international, multi-center design with high data quality. Central imaging review increases consistency and accuracy in image interpretation. Our study cohort, including baseline data and clinical presentation, essentially matches previously reported cohorts [3]. Several limitations warrant comment. First, central imaging review was limited to patients with suspected CVT and dAVF. Second, clinical data were partly retrospective and on enrollment of these patients, study outcome measures were not defined and variables were not prespecified. Third, five out of 34 dAVF patients originated from non-consecutive series. These patients were therefore excluded from epidemiological aspects of the study. Further, in sensitivity analyses, baseline demographics, dAVF characteristics and time correlation between diagnosis of CVT and dAVF did not differ between consecutive and non-consecutively enrolled patients. Fourth, detection of dAVF was limited to the follow-up period, and a longer follow-up period might have yielded a higher prevalence.

To conclude, the prevalence of dAVF among adult CVT patients is at least 2.4%. The vast majority of CVT-related dAVFs are diagnosed simultaneously or subsequently to diagnosis of CVT. Male sex, higher age, chronic clinical CVT onset and sigmoid sinus thrombosis were all associated with dAVF among CVT patients, in univariable analyses. We found no association between presence of dAVF and poor clinical outcome.

ACKNOWLEDGMENTS

The authors are grateful for Monica Argus' excellent logistic support and for the English-language review performed by Judith Klecki.

CONFLICT OF INTERESTS

EL, AR, SH, FS, MRH, SMZ, SMS, MM, WA, MNMP, BFG, JW, MSK, EIP, NCM, CGE, CC, TK, MG, JMC, MA, AA, JP, KJ and TT report no disclosures that are directly or indirectly related to the work submitted for publication.

AUTHOR CONTRIBUTIONS

Erik Lindgren: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Validation (lead); Visualization (lead); Writing – original draft (lead); Writing – review and editing (lead). **Alexandros Rentzos:** Conceptualization (lead); Data

curation (lead); Formal analysis (lead); Investigation (lead); Visualization (equal); Writing – review and editing (equal). **Sini Hiltunen**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Fabiola Serrano**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Mirjam R. Heldner**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Susanna M. Zuurbier**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Suzanne M. Silvis**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Maryam Mansour**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **William Allingham**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Martin N. M. Punter**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Blake F. Giarola**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Jeremy Wells**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Mayte Sánchez van Kammen**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Eike I. Piechowiak**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Nicole Chiot-McCollum**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Carlos Garcia-Esperon**: Data curation (equal); Investigation (equal); Writing – review and editing (equal). **Christophe Cognard**: Data curation (equal); Investigation (equal); Validation (equal); Writing – review and editing (equal). **Timothy Kleinig**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Masoud Ghiasian**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Jonathan M. Coutinho**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Marcel Arnold**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Antonio Arauz**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Jukka Putaala**: Data curation (equal); Investigation (equal); Supervision (supporting); Writing – review and editing (equal). **Katarina Jood**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing – original draft (supporting); Writing – review and editing (lead). **Turgut Tatlisumak**: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing – original draft (supporting); Writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

All study data are available upon reasonable request.

ORCID

Erik Lindgren  <https://orcid.org/0000-0002-7628-5044>

Mirjam R. Heldner  <https://orcid.org/0000-0002-3594-2159>

REFERENCES

- Devasagayam S, Wyatt B, Leyden J, Kleinig T. Cerebral venous sinus thrombosis incidence is higher than previously thought: a retrospective population-based study. *Stroke*. 2016;47(9):2180-2182.
- Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. *Stroke*. 2012;43(12):3375-3377.
- Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670.
- Ferro JM, Coutinho JM, Jansen O, et al. Dural arteriovenous fistulae after cerebral venous thrombosis. *Stroke*. 2020;51(11):3344-3347.
- Preter M, Tzourio C, Ameri A, Bousser MG. Long-term prognosis in cerebral venous thrombosis: follow-up of 77 patients. *Stroke*. 1996;27(2):243-246.
- Schuchardt FF, Demerath T, Elsheikh S, et al. Dural arteriovenous fistula formation secondary to cerebral venous thrombosis: longitudinal magnetic resonance imaging assessment using 4D-Combo-MR-venography. *Thromb Haemost*. 2021;121(10):1345-1352.
- Cognard C, Casasco A, Toevi M, Houdart E, Chiras J, Merland JJ. Dural arteriovenous fistulas as a cause of intracranial hypertension due to impairment of cranial venous outflow. *J Neurol Neurosurg Psychiatry*. 1998;65(3):308-316.
- Kerber CW, Newton TH. The macro and microvasculature of the dura mater. *Neuroradiology*. 1973;6(4):175-179.
- Lawton MT, Jacobowitz R, Spetzler RF. Redefined role of angiogenesis in the pathogenesis of dural arteriovenous malformations. *J Neurosurg*. 1997;87(2):267-274.
- Terada T, Tsuura M, Komai N, et al. The role of angiogenic factor bFGF in the development of dural AVFs. *Acta Neurochir*. 1996;138(7):877-883.
- Terada T, Higashida RT, Halbach VV, et al. Development of acquired arteriovenous fistulas in rats due to venous hypertension. *J Neurosurg*. 1994;80(5):884-889.
- Soderman M, Pavic L, Edner G, Holmin S, Andersson T. Natural history of dural arteriovenous shunts. *Stroke*. 2008;39(6):1735-1739.
- Tsai LK, Jeng JS, Liu HM, Wang HJ, Yip PK. Intracranial dural arteriovenous fistulas with or without cerebral sinus thrombosis: analysis of 69 patients. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1639-1641.
- Conforto AB, Nader SN, Puglia Junior P, et al. Dural arteriovenous fistula and cerebral venous thrombosis. *Arq Neuropsiquiatr*. 2015;73(6):548.
- Mirza FA, Fraser JF. Multiple dural and pial arteriovenous fistulae in a twenty-four-year-old woman in the setting of superior sagittal sinus thrombosis: case report and review of literature. *J Stroke Cerebrovasc Dis*. 2016;25(10):e192-e199.
- Pasi M, Nappini S, Salvadori E, Mangiafico S, Limbucci N, Pantoni L. Rapidly progressive cognitive impairment in a patient with high flow dural arteriovenous fistulas, cerebral sinus thrombosis and protein S deficiency. *J Clin Neurosci*. 2014;21(9):1654-1656.
- Miki Y, Tomiyama M, Arai A, et al. Cerebral venous thrombosis with dural arteriovenous fistulas and antiphospholipid syndrome: a case report. *Neurol Sci*. 2010;31(2):237-238.
- Brown RD Jr, Wiebers DO, Nichols DA. Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients. *J Neurosurg*. 1994;81(4):531-538.

19. Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arteriovenous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. *Radiology*. 1995;194(3):671-680.
20. van Dijk JM, terBrugge KG, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. *Stroke*. 2002;33(5):1233-1236.
21. Lindgren E, Silvis SM, Hiltunen S, et al. Acute symptomatic seizures in cerebral venous thrombosis. *Neurology*. 2020;95(12):e1706-e1715.
22. Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192.
23. Bulters DO, Mathad N, Culliford D, Millar J, Sparrow OC. The natural history of cranial dural arteriovenous fistulae with cortical venous reflux—the significance of venous ectasia. *Neurosurgery*. 2012;70(2):312-318; discussion 8–9.
24. Vellimana AK, Daniels DJ, Shah MN, Zipfel GJ, Lanzino G. Dural arteriovenous fistulas associated with benign meningeal tumors. *Acta Neurochir (Wien)*. 2014;156(3):535-544.
25. Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML. Natural history, evaluation, and management of intracranial vascular malformations. *Mayo Clin Proc*. 2005;80(2):269-281.
26. Newton TH, Cronqvist S. Involvement of dural arteries in intracranial arteriovenous malformations. *Radiology*. 1969;93(5):1071-1078.
27. Brown RD Jr, Wiebers DO, Torner JC, O'Fallon WM. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. *Neurology*. 1996;46(4):949-952.
28. Satomi J, Satoh K. Epidemiology and etiology of dural arteriovenous fistula. *Brain Nerve*. 2008;60(8):883-886.
29. Al-Shahi R, Bhattacharya JJ, Currie DG, et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke*. 2003;34(5):1163-1169.
30. Elhammady MS, Ambekar S, Chapter HRC. 9 - Epidemiology, clinical presentation, diagnostic evaluation, and prognosis of cerebral dural arteriovenous fistulas. In: Spetzler RF, Moon K, Almefty RO, eds. *Handbook of Clinical Neurology*. 143: Elsevier; 2017:99-105.
31. Mas JL, Meder JF, Meary E, Bousser MG. Magnetic resonance imaging in lateral sinus hypoplasia and thrombosis. *Stroke*. 1990;21(9):1350-1356.
32. Ayanzen RH, Bird CR, Keller PJ, McCully FJ, Theobald MR, Heiserman JE. Cerebral MR venography: normal anatomy and potential diagnostic pitfalls. *Am J Neuroradiol*. 2000;21(1):74-78.
33. Alper F, Kantarci M, Dane S, Gumustekin K, Onbas O, Durur I. Importance of anatomical asymmetries of transverse sinuses: an MR venographic study. *Cerebrovasc Dis*. 2004;18(3):236-239.
34. Goyal G, Singh R, Bansal N, Paliwal VK. Anatomical variations of cerebral MR venography: is gender matter? *Neurointervention*. 2016;11(2):92-98.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lindgren E, Rentzos A, Hiltunen S, et al; the International CVT Consortium. Dural arteriovenous fistulas in cerebral venous thrombosis. *Eur J Neurol*. 2022;29:761-770. doi:[10.1111/ene.15192](https://doi.org/10.1111/ene.15192)