ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Distinctive clinicopathological features and differential gene expression of cerebral venous thrombosis mimicking brain tumors

Longxiao Zhang[1,2†], Shixiong Lei[1,2†], Yan Hu[1,2†], Shengqi Zhao[1,2], Mingchu Zhang[1,2], Chengcheng Duan[1,2], Mingkun Wei[1,2], and Fuyou Guo[1,2*]

[1]Department of Neurosurgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, 450052, PR China

[2]International Joint Laboratory of Nervous System Malformations, Henan Province, 450052, PR China

Abstract

Cerebral venous thrombosis (CVT), a rare type of cerebrovascular disease, can mimic a brain tumor (CVT mimicking brain tumor [CVTMBT]), due to its space-occupying imaging features. We aimed to describe the clinicopathological features and identify the thrombophilia-related gene expression changes in the brain following CVT. We conducted a retrospective qualitative study of CVT patients who were misdiagnosed with brain tumors before surgery at our hospital from 2016 to 2021. We analyzed the clinicopathological characteristics of the cases from our hospital and previously published cases. Five subjects were retrospectively studied, but one refused to provide biological specimens. We performed messenger ribonucleic acid (mRNA) sequencing from eight specimens (four CVTMBT and four non-CVTMBT samples). Differentially expressed genes (DEGs) were screened using the "edge" package in R 3.6.1 software. Thrombophilia-related genes were obtained from the MalaCards human disease database and were cross-checked with DEGs. The intersection was considered to be the potential genes in the pathogenesis of CVTMBT. The medical histories of the five patients with CVTMBT included oral non-steroidal anti-inflammatory drug use, oral contraceptive use, cesarean section, and anemia. All patients underwent craniotomy and were pathologically diagnosed with CVT. The follow-up results revealed that all patients had favorable outcomes without any recurrence. DEG analysis revealed 813 upregulated and 253 downregulated DEGs between patients with CVTMBT and controls. Nine DEGs were associated with thrombophilia, including *SERPINE1*, *SELP*, *THBD*, *ITGB3*, *TFPI*, *F13A1*, *PROS1*, *PPBP*, and *PROCR*, which were considered potential key genes in CVTMBT. CVTMBT presents with enhancement and mass effect on magnetic resonance imaging, accompanied by various predisposing factors, shorter disease duration, and coagulation dysfunction. The nine key genes identified as potential key genes in the pathogenesis of CVTMBT may be potential biomarkers for accurate screening and appropriate treatment.

Keywords: Cerebral venous thrombosis; Brain tumor; Gene expression; Mimicking; mRNA sequencing

†These authors contributed equally to this work.

***Corresponding author:**
Fuyou Guo
(chyou666@hotmail.com)

Citation: Zhang L, Lei S, Hu Y, *et al*., 2023, Distinctive clinicopathological features and differential gene expression of cerebral venous thrombosis mimicking brain tumors. *Brain & Heart,* 1(1): 188. https://doi.org/10.36922/bh.v1i1.188

Received: September 6, 2022

Accepted: December 23, 2022

Published Online: January 27, 2023

1. Introduction

Cerebral venous thrombosis (CVT), a relatively rare type of cerebrovascular disease, is defined as thrombosis of the intracranial veins or sinuses. CVT accounts for 0.5% of strokes, with a bimodal age distribution: The first peak in neonates and the second in individuals in their 30 s[1,2]. It is a multifactorial disease with several etiologies, and thus requires extensive preliminary screening. Moreover, CVT can cause vascular and cytotoxic edema, of which the mechanism remains unclear[2,3]. Most patients with CVT have favorable prognoses, with a mortality rate of <10%, which is better than that of arterial stroke[2,4]. However, it is difficult to predict the individual prognosis of patients with CVT[1]. Existing studies have mostly focused on arterial cerebral infarction, without much attention to CVT. Large hemorrhagic cerebral infarction accompanied by prominent vascular edema and brain tissue displacement may result in life-threatening complications when patients experience deterioration, due to delayed diagnosis and treatment[5]. An epileptic state is considered a cause of acute death in CVT[2]. Altered consciousness can occur in 15 – 19% patients with extensive venous embolism or bilateral thalamic involvement[6]. Hence, early and accurate diagnosis and treatment are often associated with better prognosis[7].

Patients with CVT can be easily misdiagnosed with various nervous system diseases due to its rarity, limited neuroimaging findings, and varying initial clinical manifestations, including isolated headache, focal neurological dysfunction, and altered consciousness[1]. These manifestations may present separately or in combination with other signs and symptoms[2]. An early diagnosis of CVT is primarily established by magnetic resonance imaging (MRI) and magnetic resonance venography. Several studies have well-characterized the imaging findings of CVT, which predominantly presents with a space-occupying effect[8,9]. However, these studies have several limitations and technical flaws[1,5,10,11]. Cerebral venous infarction, which is observed in approximately 60% of patients with CVT, may present with malignant vasogenic edema with minor parenchymal hemorrhage and a space-occupying mass-like enhancement in primary MRI; thus, it is often misdiagnosed as brain tumor[3,5,12]. Fewer than 10 cases of CVT mimicking brain tumor (CVTMBT) have been reported in the previous studies[7,11,12-15]. Moreover, CVT can also manifest as subarachnoid hemorrhage or a metastatic tumor[7,16,17]. In cases where establishing a pre-operative diagnosis is difficult, biopsy is performed[7].

In fact, differentiating CVTMBT from neuroglioma earlier on is necessary because the treatments and prognoses for these two diseases are different. Conventional therapies, including maximum resection, radiotherapy, and chemotherapy, play a crucial role in the treatment of brain gliomas[18]. CVT is best treated with a comprehensive therapy, emphasizing the management of pathogenic factors, antithrombotic therapy, and symptomatic treatment[2,19]. Biopsy often is the last resort for cases with difficulty in pre-operative diagnosis[7]. Invasive surgery for CVT remains controversial. Although heparin, as a first-line anticoagulant therapy, can improve the prognosis of CVT, aggressive treatment should also be considered for patients who are deteriorating[1]. So far, given the equivocal evidence of efficacy for local thrombolysis, it has not yet been considered a first-line treatment for CVT[2]. This retrospective qualitative study aimed to analyze the distinctive and clinicopathological features of patients with CVTMBT. In particular, we performed messenger ribonucleic acid (mRNA) sequencing on human lesion peripheral tissues from four CVTMBT samples and four non-CVTMBT samples from our hospital to identify the gene expression signatures in this distinctive lesion.

2. Materials and methods

2.1. Study subjects

Patients with an initial diagnosis of intracranial occupying lesion and who underwent surgical treatment at our neurosurgical center between November 2016 and October 2021 were reviewed systematically. The inclusion criteria were as follows: Patients (1) initially diagnosed with brain tumor, with their post-operative pathological results revealing CVT; (2) with available pre-operative and post-operative neuroimaging examination results, which were evaluated by multiple experienced radiologists and neurosurgeons; and (3) with consecutive medical data and sufficient follow-up information. The exclusion criteria included the following: Patients (1) pathologically diagnosed with other space-occupying lesion; (2) with insufficient consecutive neuroimaging information; (3) with incomplete medical data and follow-up information, and (4) with CVT who did not present with brain tumor-like features. Five patients with CVTMBT were included as the study subjects, but one of these patients refused to provide biological specimens. The subjects' baseline characteristics, including demographics, pre-operative neurological dysfunction status, routine blood and coagulation function status, course of disease, seizure characteristics, detailed surgical records, and other vital records, were collected. Four subjects with CVTMBT had not received previous treatments before surgery and their specimens were obtained from the tissues surrounding the infarcts during surgery at the initial diagnosis. Another four normal brain tissues were obtained at the time of surgery from four non-CVTMBT patients, including

one tentorial meningioma, one meningioma in the base of the anterior cranial fossa, one intracranial lymphoma, and one glioblastoma, at our hospital; these patients were assigned as the control group. The selection criteria for the control group included the following: Patients (1) without a history of stroke; (2) without liver, kidney, hematopoietic system, and cardiovascular diseases or other serious primary diseases; and (3) without predisposing factors for CVT, such as oral non-steroidal anti-inflammatory drug (NSAID) use or oral contraceptive use and pregnancy. Written and verbal informed consents for the use of the specimens were obtained before surgery.

All biopsy-confirmed patients from our hospital received anticoagulation therapy based on the definitive diagnosis of CVTMBT. Patients who presented with seizures initially received antiepileptic drugs to prevent seizure recurrence.

All procedures performed were approved by the Ethics Committee for Human Experiments of the Zhengzhou University (approval number: 2021-KY-0156-002).

2.2. mRNA library construction and sequencing

RNA sequencing was performed by GeneFund Biotechnology Co., Ltd. (Shanghai, China). The RNA was extracted from tissues surrounding the infarcts in four subjects with CVTMBT and normal brain tissues in four subjects with non-CVTMBT. mRNA extraction was performed using KAPA Stranded mRNA-Seq Kits according to the manufacturer's instructions. The RNA fragments with polyA tail were captured by oligo(dT) beads. By heating, the captured mRNA fragments were interrupted to 200 – 300 base pairs (bp). Strand Synthesis Master Mix was added to the incubation and the mRNA was reverse transcribed to complementary deoxyribonucleic acid (cDNA). The DNA fragments were end-repaired, an adenine (A) base was added to the 3' end, and the sequencing adaptors were ligated. Real-time polymerase chain reaction was used to synthesize cDNA with a size of 300–400 bp. The library was sequenced using the Illumina HiSeq/NextSeq platform after qualifying. The connector sequences were removed using the cutadapt program. Clean data were retained and low-quality sequences were eliminated using the Trimmomatic program[20]. Clean data volume was calculated using FastQC software (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) with q20 and q30 proportions and was aligned to the reference genome using the HISAT program[20]. Reads were spliced into transcripts using StringTie[21]. Data volume was calculated and the data were compared. The results of the comparison were annotated and the known RNAs were selected for subsequent analysis. Differential expression analysis was performed using the HISAT2 tool (select default parameters), StringTie (select default parameters), and the process-recommended downstream differential expression analysis method edgeR[22]. The *P*-value, *Q*-value (the false positive rate [FDR] error control method was used to correct *P*-value by multiple hypothesis testing, and the corrected *P*-value was the *Q*-value), and FC (fold change) were calculated for each gene. The genes met the differential analysis criteria: *Q*-value ≤ 0.05 and FC ≥ 2 or FC ≤ 0.5 were taken as differentially expressed genes (DEGs).

2.3. Screening of DEGs associated with thrombophilia

Thrombophilia-associated genes were downloaded from the MalaCards human disease database (https://www.malacards.org/) and were cross-checked with all confirmed DEGs.

3. Results

3.1. Clinicopathological features and surgical findings

Five patients (four females and one male; age, 13 – 48 years) with distinct CVTMBT in different locations and with unique clinicopathological features were included in the study. The short course of disease, which ranged from 3 to 6 days, was one of the significant clinical characteristics, with symptoms of epileptic seizure (three patients) and headache (three patients). Other significant symptoms included numbness in the right arm (one patient) and altered consciousness (one patient). The common risk factors included medication history of oral NSAIDs or analgesics (two patients), Marvelon use for hypermenorrhea (one patient), long-term anemia (one patient), and a medical history of cesarean section (one patient). All patients had remarkable routine blood and coagulation dysfunctions. The lesion was observed at a specific location (two frontal lobe, one parietal lobe, one temporal lobe, and one temporal occipital lobe) linked to a large cerebral vein on MRI. Intraoperative findings revealed that three of the five lesions were involved in remarkable occlusion of a large drainage vein and four of the five lesions presented with secondary hemorrhage surrounding the vein. Histopathological findings revealed abundant small vascular obstruction, inflammatory cell infiltration, and regional hemorrhage. The detailed data of the five patients with CVTMBT are shown in Table 1.

Representative case: A 13-year-old female patient presented with headache and epileptic seizure. The initial diagnosis was low-grade glioma, instead of vein infarction. Considering that the lesion showed atypical features on both computed tomography and MRI, the patient was misdiagnosed before surgery. T2 hyperintensity indicated

Table 1. Clinicopathological features of five cerebral venous thrombosis mimicking brain tumor cases from our hospital

Case	Age (year)	Sex	Symptoms	History	Laboratory tests	Location	Misdiagnosis	Treatment	Intraoperative finding
1	23	Female	Headache, vomiting	Caesarean birth	High platelet count and D-dimer	Left frontal lobe and corpus callosum	Glioma	Anticoagulation after biopsy	Left superior cerebral vein to superior sagittal sinus drainage was obstructed, focal hemorrhage
2	48	Female	Headache, epilepsy, numbness over right arm	Oral ibuprofen	Low APTT and high D-dimer	Left parietal lobe	Glioma	Anticoagulation after biopsy	Large branch of Labbé vein infarction, focal hemorrhage
3	13	Female	Headache, epileptic seizure	Excessive menstruation treated by Marvelon	High platelet count and TT; low APTT and Fib	Left temporal lobe	Glioma	Anticoagulation after biopsy	Labbé vein infarction, regional hemorrhage
4	31	Male	Epileptic seizure	Oral paracetamol	High D-dimer	Right frontal lobe	Glioma	Anticoagulation after biopsy	Right superior cerebral vein to superior sagittal sinus drainage was obstructed, regional hemorrhage
5	35	Female	Headache, dizziness incontinence (twice)	Long-term moderate to severe anemia	Hemoglobin<60 g/L	Left temporal-occipital lobe	Glioma	Anticoagulation after biopsy	The draining vein of the left temporal cortex was blue-black

APTT: Activated partial thromboplastin time; Fib: Fibrinogen; TT: Thrombin time

that the edema was induced by venous occlusion. The slightly increased choline (Cho) level and decreased N-acetylaspartate (NAA) level by magnetic resonance spectroscopy (MRS) analysis could have also misled the diagnosis. An infarcted inferior anastomotic vein (vein of Labbé) was confirmed during the surgery and its vascular structure was dark and swollen. The lesion was totally resected and the vein of Labbé was preserved well with sufficient decompression to relieve the symptoms of intracranial hypertension. Hematoxylin and eosin staining revealed thrombosed vein and excessive inflammatory cell infiltration (Figures 1-3).

Follow-up was continued from 1 month to 5 years. All the study subjects had favorable outcomes with intact neurological function and without symptom recurrence after surgery. Follow-up information was not available in previously published cases.

3.2. Identification of DEGs between CVT mimicking brain tumor (CVTMBT) and non-CVTMBT

In total, 1066 DGEs, including 813 upregulated and 253 downregulated genes, were identified based on the selection criteria. A heat map and a volcano plot of the 1066 DGEs are shown in Figure 4A and B, respectively.

3.3. Key genes in the pathogenesis of CVT mimicking brain tumor

In total, 38 genes were related to thrombophilia, as demonstrated by the MalaCards human disease database. According to the differential gene criteria Q-value ≤ 0.05 and FC ≥ 2 or FC ≤ 0.5, the following nine differential genes were screened: *SERPINE1*, *SELP*, *THBD*, *ITGB3*, *TFPI*, *F13A1*, *PROS1*, *PPBP*, and *PROCR*. The expression levels of nine DEGs are presented in Table 2 and in a heatmap in Figure 5. The roles of the nine DEGs are presented in Table 3.

4. Discussion

Glioma was the most common type of misdiagnosis in the present study, which is consistent with the results of the previous studies[7,15]. Misdiagnosis was observed in the present study due to non-specific primary imaging findings, including enhancement and mass effect, accompanied by intracranial hypertension and similar neurological deficits. The majority of patients had predisposing factors and coagulation dysfunction. Anticoagulation can effectively improve patients' prognosis. A flowchart for the diagnosis of CVTMBT is presented in Figure 6. In addition, we identified nine DEGs associated with thrombophilia,

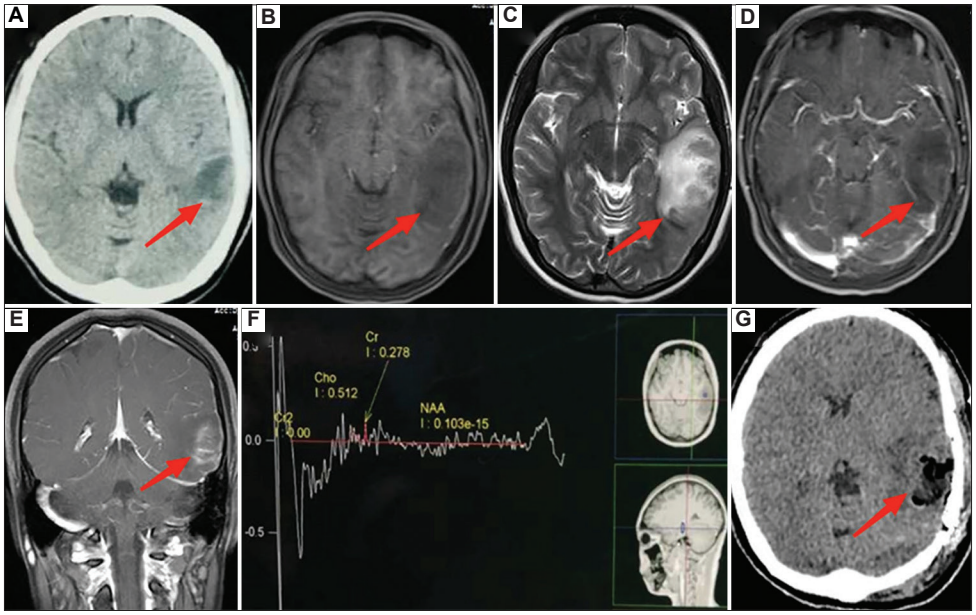

Figure 1. Typical pre-operative imaging images of a patient with CVTMBT from our hospital. (A) CT scan showing low-density lesion located in the left temporal lobe (red arrow). (B and C) Axial MRI demonstrating isointense on T1-weighted and hyperintense on T2-weighted lesion, respectively (red arrow). (D and E) Axial and coronal T1-weighted MRI showing no enhancement after gadolinium injection (red arrow). (F) Showing slightly increased Cho level and decreased NAA level by MRS analysis. (G) Post-operative CT showing lesion removed.
Cho: Choline; CT: Computed tomography; CVTMBT: Cerebral venous thrombosis mimicking brain tumor; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NAA: N-acetylaspartate

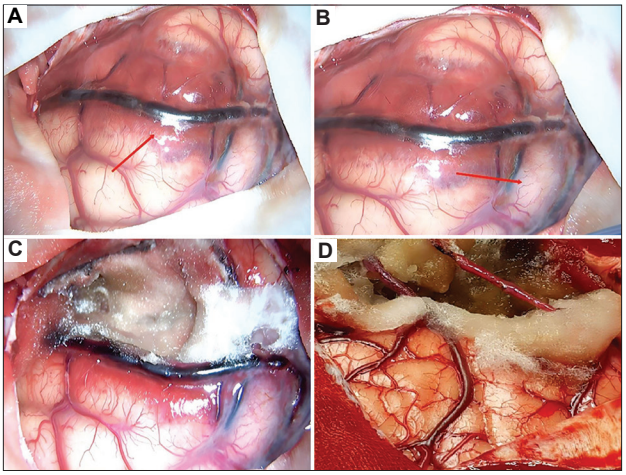

Figure 2. Representative intraoperative findings of a patient with cerebral venous thrombosis mimicking brain tumor from our hospital. (A) Intraoperative photo showing obvious Labbé vein infarct (red arrow indicates the Labbe vein), with dark and swollen vascular structure. (B) Red arrow indicates the occlusion involved in the main branch of the Labbé vein. (C) Lesion totally removed and the Labbé vein preserved well. (D) Normal structure and blood flow of drainage vein as control.

including *SERPINE1*, *SELP*, *THBD*, *ITGB3*, *TFPI*, *F13A1*, *PROS1*, *PPBP*, and *PROCR*, by mRNA sequencing between patients with CVTMBT and non-CVTMBT. The screening of key genes may provide valuable information for accurate diagnosis.

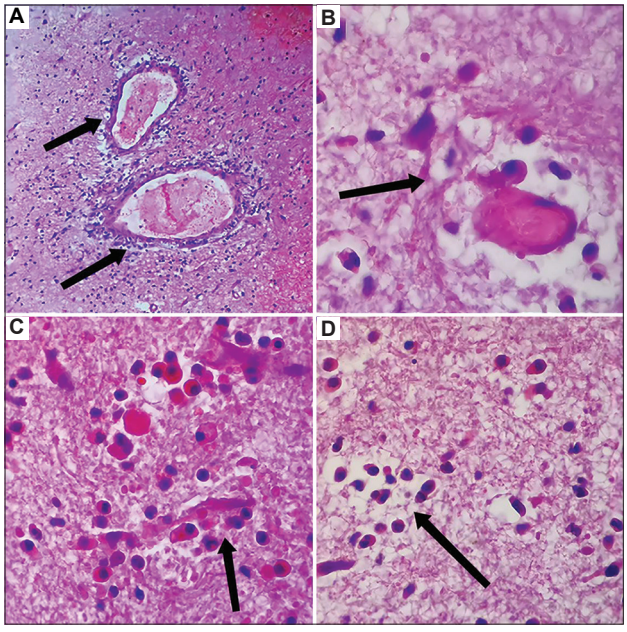

Figure 3. Hematoxylin and eosin (H and E) staining of post-operative pathology of a patient with cerebral venous thrombosis mimicking brain tumor from our hospital. (A) H and E staining showing two thrombosed vein and excessive inflammatory cell infiltration scattered in the surrounding of vein (original magnification ×10). (B) H and E staining showing thrombosed vein and excessive inflammatory cell infiltration (original magnification ×40). (C) H and E staining showing regional hemorrhage. (D) Vacuolar degeneration of nerve tissue enclosed by inflammatory cell.

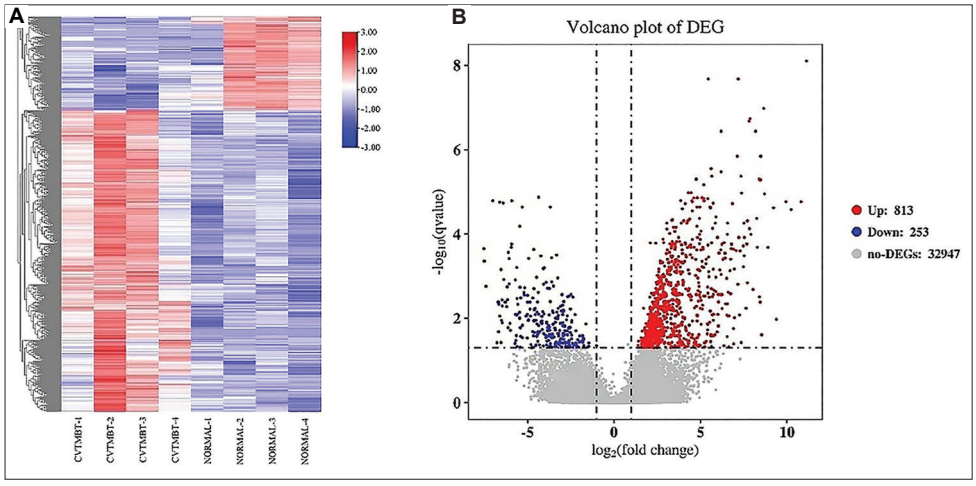

Figure 4. Heatmap and volcano plot of differentially expressed genes (DEGs) between cerebral venous thrombosis mimicking brain tumor (CVTMBT) and non-CVTMBT. (A) Heatmap of 1066 DEGs: Each row represents one specimen and each column represents one gene. Red represents upregulated genes and blue represents downregulated genes. (B) Volcano plot of DEGs: Red ones represent upregulated genes, blue ones represent downregulated genes, and grey ones represent the rest of DEGs.

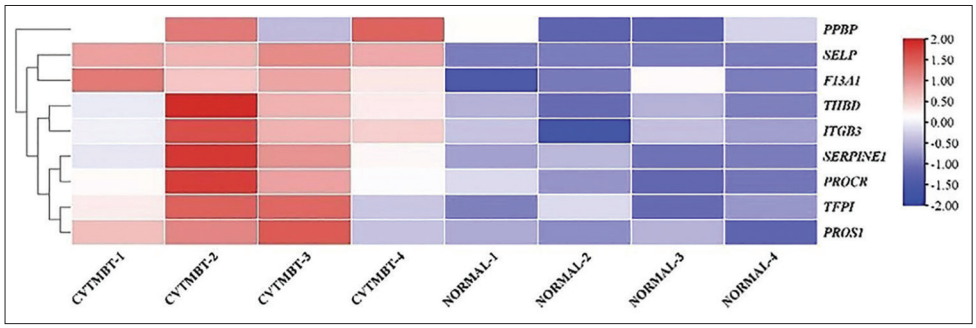

Figure 5. Heatmap of thrombophilia-related differentially expressed genes between cerebral venous thrombosis mimicking brain tumor (CVTMBT) and non-CVTMBT patients from our hospital. Each column represents one specimen and each row represents one gene.

A previous study has demonstrated that elevated venous pressure and abnormal venous reflux as a result of venous thromboembolism could lead to brain edema and intracranial hypertension, which may present as T2 hyperintensity on MRI. Eventually, brain tissues experience anoxia when the blood-brain barrier is disrupted, which could present as tumor-like enhancement[23]. Although CVT may not be clearly observed on MRI, an indication to its location would still be helpful in explaining symptoms or preparing for biopsy. Moreover, a significant decrease in NAA levels may be observed in acute cerebral infarction by MRS[24,25], unlike in glioma.

Similar with the previous studies[7,11,13-15], the common thrombophilia-related risk factors of the five patients from our hospital included a medication history of oral NSAIDs or analgesics (two patients), Marvelon use for hypermenorrhea (one patient), long-term anemia (one patient), and a medical history of cesarean section (one patient). The average duration that our patients were symptomatic was <1 week. A relatively rapid progression of symptoms usually points to vascular disease, rather than invasive glioma. Our patients initially presented with generalized seizures, whereas the previous studies have reported that the most common clinical manifestation is acute hemiparesis[7,11,13-15]. Therefore, we conclude that the various sizes, locations, and degrees of cerebral venous occlusion are the causes of the varying initial symptoms. Our patients who presented with seizures received antiepileptics to prevent seizure recurrence. In addition to seizures, headache and vomiting caused by hypertension were also the common symptoms; a prompt depression could block the progression of cerebral infarction[23]. Benefited from the sensitivity to molecular diffusion of water, diffusion-weighted MRI (DW-MRI) can distinguish either the type of edema or the change of injury accompanied by the history of seizure[3]. Therefore, DWI can be an alternative modality to explore the pathophysiology of CVT and prospectively predict its prognosis in the future.

Table 2. Expression levels of differentially expressed genes related to thrombophilia

Gene ID	Gene name	C-1	C-2	C-3	C-4	N-1	N-2	N-3	N-4	FC	*P*-value	Q-value
ENSG00000106366	*SERPINE1*	2.25126	479.993	56.1023	5.22394	0.413546	0.76462	0.14045	0.181902	352.8751368	2.58404E-09	5.17005E-06
ENSG00000174175	*SELP*	0.270996	0.197471	0.369313	0.239218	0	0	0	0	27.92495	3.07748E-08	2.27553E-05
ENSG00000178726	*THBD*	1.81339	57.5268	7.93675	3.36236	0.772478	0.259109	0.77242	0.375565	31.84366175	3.41029E-07	0.000133801
ENSG00000259207	*ITGB3*	1.14117	36.6532	6.2385	3.65576	0.540819	0.027796	0.514465	0.27465	34.14724589	2.2115E-06	0.000442469
ENSG00000003436	*TFPI*	4.07518	18.1522	17.1041	1.78063	0.831571	2.21498	0.644038	1.05931	8.591435853	7.35482E-05	0.005510118
ENSG00000124491	*F13A1*	38.3088	10.5174	18.4394	6.11608	0.161204	0.482464	4.75645	0.512676	12.33398636	9.76149E-05	0.006748326
ENSG00000184500	*PROS1*	7.44899	11.377	15.6811	3.01435	2.52432	2.04695	2.69163	1.44264	4.294925185	0.000455682	0.020902556
ENSG00000163736	*PPBP*	0.577429	17.5531	0.097438	30.4097	0.62949	0	0	0.184277	57.01516573	0.000570659	0.024538326
ENSG00000101000	*PROCR*	4.15475	17.7491	8.25014	3.7969	2.94748	1.72016	1.16286	1.3534	4.705337837	0.001501439	0.048398952

Table 3. Role of nine differentially expressed genes in cerebral venous thrombosis mimicking brain tumor

Gene name	Description	Function
SERPINE1	Serpin family E member 1	Procoagulant[36]
SELP	Selectin P	Procoagulant[32,37]
THBD	Thrombomodulin	Anticoagulant[38]
ITGB3	Integrin subunit beta 3	Procoagulant[39]
TFPI	Tissue factor pathway inhibitor	Anticoagulant[40,41]
F13A1	Coagulation factor XIII A chain	Procoagulant[35]
PROS1	Protein S	Anticoagulant[42]
PPBP	Pro-platelet basic protein	Procoagulant[43,44]
PROCR	Protein C receptor	Procoagulant[45,46]

All our patients had remarkable routine blood and coagulation dysfunctions. D-dimer is considered a highly sensitive and specific laboratory screening indicator, but its normal value is not an obviating standard[15,26]. Five of nine patients from the previous studies have shown normal routine blood and coagulation function[7,11,13-15]. However, the combination of D-dimer value and risk factors can still be helpful to predict thrombosis[26]. Studies are now focusing on biomarkers associated with cerebral venous infarction. Serum high-sensitivity C-reactive protein level is considered an essential indicator associated with the severity of CVT in acute/subacute phase[27].

An early use of heparin may exert better effect, but its spontaneous agreeable change cannot be ignored[28]. Harada *et al.* have reported a case of a patient with venous infarction mimicking low-grade glioma resolving spontaneously without invasive operation[29]. In the previous reports, most patients were suspected with glioma and underwent excisional biopsy. All our patients underwent excisional biopsy and their histopathological results revealed abundant small vascular obstruction, inflammatory cell infiltration, and regional hemorrhage. We observed focal hemorrhage surrounding the vein in four of the five lesions, which is consistent with the findings of previous studies. Juxtacortical hemorrhage can thus be an important diagnostic indication[5,28].

Due to the rarity of CVT, few studies have focused on the gene expression changes in patients with CVTMBT. To identify the key genes associated with the pathogenesis of CVTMBT, mRNA sequencing was performed on specimens between patients with CVTMBT and non-CVTMBT at our hospital. Nine filtered genes were considered to be significantly related to CVT. Unexplained thrombosis is closely related to protein S deficiency induced through a new mutation *Gly222Arg* in *PROS1*[30]. The *SERPINE1* gene has shown an increased risk of arterial and venous thromboses[31]. In general, *SELP*, *SERPINE1*, *PROCR*,

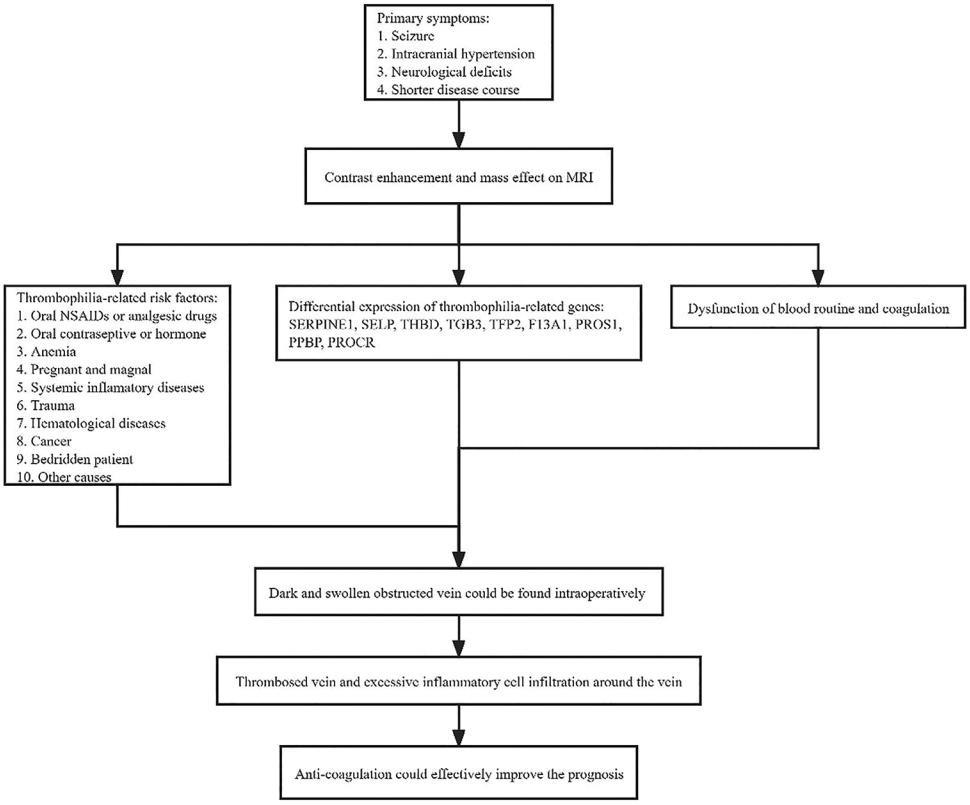

Figure 6. A flowchart for diagnosing CVTMBT. Non-specific primary imaging findings, including enhancement and mass effect, accompanied by intracranial hypertension and similar neurological deficits, were the main reasons for clinical misdiagnosis. However, various predisposing factors of CVT, shorter disease course, and coagulation dysfunction observed in patients may aid in differentiating CVTMBT from brain tumors. In cases where establishing the initial diagnosis is difficult, biopsy is performed. The effectiveness of anticoagulation therapy confirms the diagnosis of CVTMBT.
MRI: Magnetic resonance imaging; NSAIDs: Non-steroidal anti-inflammatory drugs; CVT: Cerebral venous thrombosis; CVTMBT: Cerebral venous thrombosis mimicking brain tumor

PPBP, and *F13A1* play a critical role in thrombosis[32-35], whereas a deficiency of *PROS1*, *THBD*, and *TFPI* increases the risk of thrombosis[36-38]. The potential mechanism of coagulation and anti-coagulation following CVTMBT remains unclear. The role of these thrombophilia-related DEGs in CVTMBT requires further studies.

There are several limitations to the present study. First, the study sample was small; hence, studies with larger sample sizes with long-term clinical observations for further statistical analyses are required in the future. Second, the potential interaction mechanism among the filtered genes was not fully elucidated in the present study and thus warrants further investigation.

5. Conclusions

CVTMBT presents with enhancement and mass effect on MRI, accompanied by various predisposing factors, shorter disease duration, and coagulation dysfunction. Obstructed vein can be found intraoperatively and thrombosed vein infiltrated by excessive inflammatory cells is the most pathogenic finding. Anticoagulation therapy is effective in treating CVTMBT. Furthermore, the nine key genes identified in the pathogenesis of CVTMBT may be potential biomarkers for accurate screening and appropriate treatment for CVT.

Acknowledgments

None.

Funding

This work was supported by the National Key Research and Development Program of China (2021YFE0204700) and Provincial and ministerial co-construction project of Henan Medical Science and Technology Research Plan (SB201901007).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization: Fuyou Guo
Formal analysis: Mingchu Zhang
Investigation: Longxiao Zhang, Chengcheng Duan, and Mingkun Wei
Resources: Shengqi Zhao
Supervision: Fuyou Guo
Writing – Original draft: Longxiao Zhang
Writing – Review & editing: Shixiong Lei and Yan Hu.

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee for Human Experiments of the Zhengzhou University (approval number: 2021-KY-0156-002). Written and verbal informed consents for the use of specimens were obtained before surgery.

Consent for publication

Written and verbal informed consents for the use of the specimens were obtained before surgery.

Availability of data

Data can be obtained from the corresponding author following request.

References

1. Masuhr F, Mehraein S, Einhäupl K, 2004, Cerebral venous and sinus thrombosis. *J Neurol*, 251: 11–23.

   https://doi.org/10.1007/s00415-004-0321-7

2. Bousser MG, Ferro JM, 2007, Cerebral venous thrombosis: An update. *Lancet Neurol*, 6: 162–170.

   https://doi.org/10.1016/s1474-4422(07)70029-7

3. Mullins ME, Grant PE, Wang B, *et al.*, 2004, Parenchymal abnormalities associated with cerebral venous sinus thrombosis: Assessment with diffusion-weighted MR imaging. *AJNR Am J Neuroradiol*, 25: 1666–1675.

4. Bousser MG, Chiras J, Bories J, *et al.*, 1985, Cerebral venous thrombosis-a review of 38 cases. *Stroke*, 16: 199–213.

   https://doi.org/10.1161/01.str.16.2.199

5. Coutinho JM, van den Berg R, Zuurbier SM, *et al.*, 2014, Small juxtacortical hemorrhages in cerebral venous thrombosis. *Ann Neurol*, 75: 908–916.

   https://doi.org/10.1002/ana.24180

6. Mehraein S, Schmidtke K, Villringer A, *et al.*, 2003, Heparin treatment in cerebral sinus and venous thrombosis: Patients at risk of fatal outcome. *Cerebrovasc Dis*, 15: 17–21.

   https://doi.org/10.1159/000067117

7. Yu Y, Ren M, Yao S, *et al.*, 2016, Pathological confirmation of 4 cases with isolated cortical vein thrombosis previously misdiagnosed as brain tumor. *Oncol Lett*, 11: 649–653.

   https://doi.org/10.3892/ol.2015.3931

8. Tsai FY, Wang AM, Matovich VB, *et al.*, 1995, MR staging of acute dural sinus thrombosis: Correlation with venous pressure measurements and implications for treatment and prognosis. *AJNR Am J Neuroradiol*, 16: 1021–1029.

9. Bianchi D, Maeder P, Bogousslavsky J, *et al.*, 1998, Diagnosis of cerebral venous thrombosis with routine magnetic resonance: An update. *Eur Neurol*, 40: 179–190.

   https://doi.org/10.1159/000007978

10. Bousser MG, 2000, Cerebral venous thrombosis: Diagnosis and management. *J Neurol*, 247: 252–258.

    https://doi.org/10.1007/s004150050579

11. Masuoka J, Wakamiya T, Mineta T, *et al.*, 2009, Thrombosis of the superior petrosal vein mimicking brain tumor. Case report. *Neurol Med Chir (Tokyo)*, 49: 359–361.

    https://doi.org/10.2176/nmc.49.359

12. Lövblad KO, Bassetti C, Schneider J, *et al.*, 2001, Diffusion-weighted MR in cerebral venous thrombosis. *Cerebrovasc Dis*, 11: 169–176.

    https://doi.org/10.1159/000047634

13. Gradinscak DJ, Fulham MJ, Besser M, *et al.*, 2004, Post-traumatic cerebral venous infarct mimicking an infiltrative glioma. *Clin Nucl Med*, 29: 68–69.

    https://doi.org/10.1097/01.rlu.0000103233.31619.d1

14. Bakshi R, Lindsay BD, Bates VE, *et al.*, 1998, Cerebral venous infarctions presenting as enhancing space-occupying lesions: MRI findings. *J Neuroimaging*, 8: 210–215.

    https://doi.org/10.1111/jon199884210

15. Xu T, Liang R, 2019, Cerebral venous thrombosis with tumor-like features: A case report and review of the literature. *World Neurosurg*, S1878-8750(18)32932-2.

    https://doi.org/10.1016/j.wneu.2018.12.109

16. Chang R, Friedman DP, 2004, Isolated cortical venous thrombosis presenting as subarachnoid hemorrhage: A report of three cases. *AJNR Am J Neuroradiol*, 25: 1676–1679.

17. Benabu Y, Mark L, Daniel S, *et al.*, 2009, Cerebral venous thrombosis presenting with subarachnoid hemorrhage. Case report and review. *Am J Emerg Med*, 27: 96–106.

    https://doi.org/10.1016/j.ajem.2008.01.021

18. Xu S, Tang L, Li X, *et al.*, 2020, Immunotherapy for glioma: Current management and future application. *Cancer Lett*, 476: 1–12.

    https://doi.org/10.1016/j.canlet.2020.02.002

19. Einhäupl K, Bousser MG, De Bruijn SF, *et al.*, 2006, EFNS

guideline on the treatment of cerebral venous and sinus thrombosis. *Eur J Neurol*, 13: 553–559.

https://doi.org/10.1111/j.1468-1331.2006.01398.x

20. Bolger AM, Lohse M, Usadel B, 2014, Trimmomatic: A flexible trimmer for Illumina sequence data. *Bioinformatics*, 30: 2114–2120.

https://doi.org/10.1093/bioinformatics/btu170

21. Pertea M, Pertea GM, Antonescu CM, *et al.*, 2015, StringTie enables improved reconstruction of a transcriptome from RNA-seq reads. *Nat Biotechnol*, 33: 290–295.

https://doi.org/10.1038/nbt.3122

22. Robinson MD, Mccarthy DJ, Smyth GK, 2010, edgeR: A Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics*, 26: 139–140.

https://doi.org/10.1093/bioinformatics/btp616

23. Wang W, Lin C, Hong J, *et al.*, 2018, Effects of increased intracranial pressure gradient on cerebral venous infarction in rabbits. *World Neurosurg*, 120: e161–e168.

https://doi.org/10.1016/j.wneu.2018.07.264

24. Duijn JH, Matson GB, Maudsley AA, *et al.*, 1992, Human brain infarction: Proton MR spectroscopy. *Radiology*, 183: 711–718.

https://doi.org/10.1148/radiology.183.3.1584925

25. Gideon P, Henriksen O, Sperling B, *et al.*, 1992, Early time course of N-acetylaspartate, creatine and phosphocreatine, and compounds containing choline in the brain after acute stroke. A proton magnetic resonance spectroscopy study. *Stroke*, 23: 1566–1572.

https://doi.org/10.1161/01.str.23.11.1566

26. Smith E, Kumar V, 2018, BET 1: Does a normal D-dimer rule out cerebral venous sinus thrombosis (CVST)? *Emerg Med J*, 35: 396–397.

https://doi.org/10.1136/emermed-2018-207777.1

27. Duan J, Leng X, Han Z, *et al.*, 2021, Identifying biomarkers associated with venous infarction in acute/subacute cerebral venous thrombosis. *Aging Dis*, 12: 93–101.

https://doi.org/10.14336/ad.2020.0405

28. Jacobs K, Moulin T, Bogousslavsky J, *et al.*, 1996, The stroke syndrome of cortical vein thrombosis. *Neurology*, 47: 376–382.

https://doi.org/10.1212/wnl.47.2.376

29. Harada Y, Hirata K, Kobayashi H, *et al.*, 2012, A pitfall of C-11 methionine PET: Cerebral venous infarction mimicked a glioma. *Clin Nucl Med*, 37: 110–111.

https://doi.org/10.1097/rlu.0b013e3182336433

30. Xu J, Peng G, Ouyang Y, 2019, A novel mutation Gly222Arg in PROS1 causing protein S deficiency in a patient with pulmonary embolism. *J Clin Lab Anal,* 34: e23111.

https://doi.org/10.1002/jcla.23111

31. Seheult JN, Chibisov I, 2016, A case of unexplained cerebral sinus thrombosis in a 22-year-old obese Caucasian woman. *Lab Med*, 47: 233–240.

https://doi.org/10.1093/labmed/lmw023

32. Merten M, Thiagarajan P, 2004, P-selectin in arterial thrombosis. *Z Kardiol*, 93: 855–863.

https://doi.org/10.1007/s00392-004-0146-5

33. Gandrille S, 2008, Endothelial cell protein C receptor and the risk of venous thrombosis. *Haematologica*, 93: 812–816.

https://doi.org/10.3324/haematol.13243

34. Wenger RH, Hameister H, Clemetson KJ, 1991, Human platelet basic protein/connective tissue activating peptide-III maps in a gene cluster on chromosome 4q12-q13 along with other genes of the beta-thromboglobulin superfamily. *Hum Genet,* 87: 367–368.

https://doi.org/10.1007/bf00200921

35. Gemmati D, Vigliano M, Burini F, *et al.*, 2016, Coagulation factor XIIIA (F13A1): Novel perspectives in treatment and pharmacogenetics. *Curr Pharm Des*, 22: 1449–1459.

https://doi.org/10.2174/1381612822666151210122954

36. Spiroski I, Kedev S, Antov S, *et al.*, 2009, Investigation of SERPINE1 genetic polymorphism in Macedonian patients with occlusive artery disease and deep vein thrombosis. *Kardiol Pol*, 67: 1088–1094.

37. Blann AD, Nadar SK, Lip GY, 2003, The adhesion molecule P-selectin and cardiovascular disease. *Eur Heart J*, 24: 2166–2179.

https://doi.org/10.1016/j.ehj.2003.08.021

38. Quintero-Ronderos P, Mercier E, Gris JC, *et al.*, 2017, THBD sequence variants potentially related to recurrent pregnancy loss. *Reprod Biol Endocrinol*, 15: 92.

https://doi.org/10.1186/s12958-017-0311-0

39. Komsa-Penkova R, Golemanov G, Tsankov B, *et al.*, 2017, Rs5918ITGB3 polymorphism, smoking, and BMI as risk factors for early onset and recurrence of DVT in young women. *Clin Appl Thromb Hemost*, 23: 585–595.

https://doi.org/10.1177/1076029615624778

40. Gierula M, Ahnström J, 2020, Anticoagulant protein S-New insights on interactions and functions. *J Thromb Haemost,* 18: 2801–2811.

https://doi.org/10.1111/jth.15025

41. Dennis J, Kassam I, Morange PE, *et al.*, 2015, Genetic determinants of tissue factor pathway inhibitor plasma levels. *Thromb Haemost*, 114: 245–257.

https://doi.org/10.1160/th14-12-1043

42. Wang ZH, Zhao ZJ, Xu K, *et al.*, 2015, Hereditary protein S deficiency leads to ischemic stroke. *Mol Med Rep*, 12: 3279–3284.

https://doi.org/10.3892/mmr.2015.3793

43. Wismans LV, Lopuhaä B, De Koning W, *et al.*, 2022, Increase of mast cells in COVID-19 pneumonia may contribute to pulmonary fibrosis and thrombosis. *Histopathology*. Epub ahead of print.

https://doi.org/10.1111/his.14838

44. Horioka K, Tanaka H, Isozaki S, *et al.*, 2019, Hypothermia-induced activation of the splenic platelet pool as a risk factor for thrombotic disease in a mouse model. *J Thromb Haemost*, 17: 1762–1771.

https://doi.org/10.1111/jth.14555

45. Reiner AP, Carty CL, Jenny NS, *et al.*, 2008, PROC, PROCR and PROS1 polymorphisms, plasma anticoagulant phenotypes, and risk of cardiovascular disease and mortality in older adults: The Cardiovascular Health Study. *J Thromb Haemost*, 6: 1625–1632.

https://doi.org/10.1111/j.1538-7836.2008.03118.x

46. Stacey D, Chen L, Stanczyk PJ, *et al.*, 2022, Elucidating mechanisms of genetic cross-disease associations at the PROCR vascular disease locus. *Nat Commun*, 13: 1222.

https://doi.org/10.1038/s41467-022-28729-3