Combined Cerebral and Splanchnic Vein Thrombosis: A Retrospective Cohort Study

Background

Venous thrombosis in unusual sites, such as cerebral venous sinus thrombosis (CVT) and splanchnic vein thrombosis (SVT), share common pathophysiological mechanisms characterized by systemic prothrombotic states, endothelial activation, neutrophil extracellular trap (NET) formation, platelet hyper-reactivity, and the intrinsic vulnerability of low-flow venous territories[1–3]. Conditions such as myeloproliferative neoplasms (MPN), paroxysmal nocturnal haemoglobinuria (PNH), antiphospholipid syndrome (APS), severe inflammatory states, or immune-mediated events represent well-described models of diffuse thrombophilia capable of involving multiple venous districts.[4–8]

Despite this shared pathophysiological background, it remains unclear why some cases involve the cerebral district while others affect the splanchnic territory, and whether differences in timing of onset may be linked to distinct clinical or prognostic characteristics. Evidence from PNH, MPN, and APS suggests that multiple thrombotic events in unusual sites may reflect different stages of a single prothrombotic condition, modulated by the overall thrombophilic burden, by local triggering factors, and by the anatomical vulnerability of the various vascular territories.[4,9–11]

The available evidence on the coexistence of CVT and SVT comes from approximately 30 published cases, mostly isolated reports. This limited number of observations does not clarify whether individuals who develop thrombosis in both cerebral and splanchnic venous districts represent a particularly unstable or more severely thrombophilic phenotype. It also remains uncertain whether the temporal sequence of events carries prognostic implications or whether these patients require a different management strategy compared with those with isolated SVT. As a result, accurate risk stratification and individualized decisions regarding surveillance, anticoagulation, and thrombophilia screening remain difficult.[11]

Across the reported cases, 12 patients presented with Budd–Chiari syndrome (BCS), 5 with portal vein thrombosis (PVT), 8 with both BCS and PVT, and 5 with splanchnic vein thrombosis that was not further specified.[12-31]

The timing of events was heterogeneous: SVT occurred before CVT in 6 patients, after CVT in 15 patients, and concurrently in 9 patients.[12-31]

A broad range of risk factors was described, and in some cases they were concomitant. Paroxysmal nocturnal haemoglobinuria was the most recurrent condition, followed by combined estrogen–progestin contraceptive use, COVID-19 vaccination, chronic inflammatory bowel disease, and pregnancy. Additional factors, including antithrombin III deficiency, myeloproliferative neoplasms, cytomegalovirus infection, hyperhomocysteinemia, and congenital cardiac malformations, were each reported only once. Notably, none of the available cases mentioned congenital thrombophilias or antiphospholipid syndrome.[12-31]

Primary objective

The primary objective of this study is to describe the etiologic and clinical characteristics, treatment strategies, and outcomes (recanalization, thrombus progression, symptom resolution, liver transplantation, and death) in patients with combined CVT and SVT, and to compare them with those of patients with isolated SVT.

Methods

Study design

This retrospective observational study will be conducted by cross-referencing data from the ENVIE/VALDIG, Cohort360 and BNDMR databases to identify all patients diagnosed with CVT and SVT, regardless of the temporal sequence between the two events. For both, the date of diagnosis will be defined as the date of the first imaging examination confirming thrombosis. The index date will be defined as the date of the first imaging-confirmed diagnosis of SVT. The date of CVT will be used to describe and analyze the temporal sequence between CVT and SVT (CVT before, after, or concomitant with SVT).

Finally, our cohort, will be compared with a multicentre validation cohort from the VALDIG (Vascular Liver Disease Group), which represents the main European network for vascular liver diseases.

Disease group (cases)
The case group will include patients with SVT: Budd–Chiari syndrome (BCS), non-cirrhotic portal vein thrombosis (NC-PVT), who also have a confirmed diagnosis of CVT.

Control group
The control group will consist of patients with isolated SVT (BCS or NC-PVT) and no history of CVT. Controls will be selected among patients diagnosed within the same time interval as the cases and will be matched for age (±2) and sex to the case group.

Validation cohort
An external multicentre replication cohort from VALDIG will be used to assess the reproducibility of the main comparative findings between SVT+CVT and isolated SVT under the same inclusion/exclusion criteria and matching strategy.

Outcome definition

This study will be based on five outcomes: recanalization, progression, symptom resolution, liver transplantation, and death.

Complete recanalization is defined as the full restoration of venous patency of the affected splanchnic or hepatic veins, with no visible residual thrombus on imaging and re-establishment of normal antegrade flow on Doppler ultrasound, CT, or MRI.

Partial recanalization is defined as the persistence of residual thrombus with partial restoration of lumen patency and detectable intraluminal flow, corresponding to <50% of the original vessel lumen being obstructed.

Progression is defined as an increase in thrombus size, extension to new venous segments not previously involved (e.g., mesenteric, splenic, portal, or hepatic veins), or an increase in the degree of luminal obstruction (>50%) compared with previous imaging.

Symptom resolution is defined as the absence of residual neurological deficits in cases with cerebral vein thrombosis, and the absence of ascites, variceal bleeding, or other portal hypertension–related complications in cases with splanchnic vein thrombosis.

Liver transplantation and death will be recorded as final clinical outcomes.

Explanatory variables

Explanatory variables included:

- Demographic data: sex, age, ethnicity
- Lifestyle data: BMI, alcohol, tobacco, physical activity
- Gynaecological data: hormonal therapy, PCOS, endometriosis, pregnancy, miscarriages.
- Data related to thrombosis: Family history of thrombosis, location/extent of thrombosis, other thrombosis, recanalization, thrombotic recurrence
- Date of CVT and SVT diagnosis
- Symptoms leading up to diagnosis of CVT and of splanchnic vein thrombosis
- Disease-related data: Presence of ascites, presence of varices (bleeding/non bleeding), intestinal ischemia
- Liver function-related data: Liver function tests, liver stiffness
- Spleen-related data: spleen size, spleen stiffness
- Biological data: platelet count, PCR, creatinine, TP/INR, FV, D-dimer
- Treatment-related data: steroids, anticoagulation, angioplasty, TIPS, etc.
- Thrombophilia work-up

Expected results

We hypothesize that patients with combined CVT and SVT represent a distinct clinical phenotype, probably characterized by a younger age, a higher prevalence of female sex and a high prevalence of systemic prothrombotic conditions.

We hypothesize that the temporal sequence of events (CVT→SVT, SVT→CVT or concomitant onset) is associated with different clinical and prognostic trajectories.

Finally, we hypothesize that, compared with patients with isolated SVT, those with combined CVT and SVT have a higher risk of adverse clinical outcomes, including failure of recanalization, recurrent thrombotic events, radiological extension of the initial thrombosis, development or worsening of portal hypertension and death.

Table Characteristics of splanchnic vein thrombosis and cerebral venous sinus thrombosis

Study	Case	BCS/PVT characteristics	CVT characteristics	Timing	Underlying diagnosis	Outcome
1992 Alfaro[12]	34F	BCS Presenting with pleural effusion, ascites. Treated with blood transfusion and portocaval shunt 1 year later	Presenting with headache and focal neurological. Treated with dexamethasone and coumadin	BCS 3 years before CVT	PNH	Complete recovery of CVT. No mention of BCS outcome.
1998 Kakar[13]	20M	BCS, then PVT Presenting with ascites, jaundice, progressing to HE, kidney dysfunction. IVC thrombosis, progressing to portal vein thrombosis. While on dalteparin	Presenting with headache, vomiting, visual symptoms. Treated dalteparin, ATB, steroids	BCS 2 years after CVT	Not identified (but oral ulcers and erythema nodosum)	Death 4 weeks after BCS diagnosis from ALF
2005 Sharma [14] (no full text)	26M	BCS NS Treated with TIPS	NS	BCS 9 months after CVT	PNH	NS
2007 Altunayoglu[15]	20F	BCS Presenting with RUQ pain and abnormal liver enzymes	Presenting with visual symptoms. Treated with IV heparin	BCS 1 week after CVT	Pregnancy 14th week	Death 15 days from CVT from coma and MOF
2009 Tufano[16]	27F	BCS Presenting with abdominal pain, ascites, fever. Treated with enoxaparin.	Presenting with headache, visual loss, seizures Treated with diuretics and steroids only.	BCS 2 years after CVT	PNH OCP	Death 6 months from BCS from liver failure
2012 Brodsky[17]	25M	BCS, then PVT Presenting with abdominal pain, ascites. Treated enoxaparin. Despite enoxaparin, progression, TIPS placed but thrombosed, developed PVT, recurrent HV thrombosis, 2x pulmonary embolism 4 years later treated with eculizumab, with improvement of liver function and ascites.	Presenting with headache, emesis Treated enoxaparin, steroids.	Concomitant	PNH	Recovery
2013 Jaqua[18]	22M	BCS Presenting with diarrhea/ hematochezia/ UC flare. Elevated transaminase, normal liver function. Treated lovenox, then warfarin x 6 months	Presenting with headache Treated lovenox. Steroids for concomitant ITP.	Concomitant	UC flare Acquired ATIII deficiency	Recovery
2015 Meppiel[19]	20F (#3)	BCS Treated LMWH	Presenting with headache, diplopia. Switch LMWH, switch to UH	BCS 1 year before to CVT	PNH	NS

	35M (#14)	BCS Treated with danaparoid	Presenting with headache. Treated with danaparoid	BCS 1 year before to CVT	PNH	NS
	23F (#6)	BCS and PVT HV and PV	Presenting with headache, aphasia Treated with cyclosporine UF switched to LMWH	Concomitant	PNH OCP	NS
	49F (#8)	BCS and PVT HV and PV	Presenting with headache, seizures Treated with danaparoid	Concomitant	PNH OCP	NS
	26F (#11)	BCS Also with DVT/PE	Presenting with headache. Treated with transfusion UF then switched to danaparoid	Concomitant	PNH	NS
	Five pts	BCS or PVT (not specified)	NS	BCS after CVT during median FU 6 years (range 1.3-18 years)	PNH	3 died of BCS
2016 De-la-Iglesia[20]	46M	BCS and PVT Presenting with "portal hypertension" Later recurrent variceal bleeding, surgical portocaval shunt placed	Treated with acenocoumarol Treated with eculizumab 8 years after initial CVT	BCS 2 years after CVT	PNH	Recovery
2018 Gashgarey[21]	27M	BCS Presented with ascites and liver dysfunction Treated with angioplasty of IVC and RHV Treated with IV heparin, then warfarin+ASA (Also developed DVT)	Presenting with headache and vomiting Treated with heparin, then warfarin	BCS 2 years after CVT	Ebstein's anomaly	Recovery
2018 Mestrovic[22]	37M	BCS and PVT Presented with ascites, abdominal pain HV, PV, SMV, splenic vein. Progression of liver failure Development of renal vein thrombosis	Presented with seizures and focal neurological symptoms	BCS just before CVT ("a short period of time")	UC flare	Death 1 month from BCS diagnosis with MOF
2020 Alashkar[23]	NS (#3)	BCS with cholecystitis Treatment with ATB and ACO	NS Treatment with eculizumab	BCS at least 4 years after CVT	PNH Pregnancy	Successful pregnancy and delivery
2020 Teng[24]	54M	PVT Presented with abdominal pain Splenic, PVT, SMV Treated with warfarin, switched to dabigatran	NS	PVT 5 months after CVT	Inherited ATIII deficiency (novel Serpinc1 mutation)	NS
2021 Graf[25]	29M	PVT Presented with hematemesis PVT and mesenteric Treated with IVIg and argatroban	Presented with headache Treated with IVIg and argatroban	Concomitant	COVID19 vaccine – thrombotic thrombocytopenia	Residual slight aphasia Recanalization of PVT and CVT

2021 Sorensen[26]	30F	PVT Treated with tinzaparin, switched to fondaparinux due to HITT suspicion, switched to rivaroxaban at discharge	Presented with headache	Concomitant (PVT 2 days prior to CVT, after tinzaparin started)	COVID19 vaccine – thrombotic thrombocytopenia OCP Heterozygosity for the prothrombin G20210A mutation	Recovery and regression of CVST and PVT, with residual dizziness
2022 Asif[27]	28M	BCS Asymptomatic RHV, also PE	Presented with headache, visual symptoms Treated with argatroban, IVIg Switched to apixaban	Concomitant	COVID19 vaccine – thrombotic thrombocytopenia	Recovery
2022 Silva Cruz[28]	60F	PVT Presented with abdominal pain, fever PV, splenic, SMV Treated with ATB and lMWH Switched to AVK	Treated with anticoagulation for 1 year, with ASA	PVT 5 years after CVT	MTHFR mutation Hyperhomocysteinemia	Recovery
2023 Rubio Nazabal[29]	28F	PVT Elevated liver enzymes Partial RPV and LPV	Presented with seizure, fever, aphasia Treated IV heparin and ganciclovir	Concomitant	OCP CMV infection	Recovery
2023 Chatzileontiadou [30]	(#2)	BCS and PVT Mesenteric vein thrombosis + BCS Treated with eculizumab	With concomitant PVT	BCS 1 year after CVT	PNH	NS
	(#3)	BCS with “multiple visceral thrombosis of liver, spleen, kidney” Treatment with eculizumab	“numerous cerebral vascular thromboses”	BCS 2 years before CVT	Polycythemia vera PNH	NS
2024 Umurungi[31]	25F (#1)	BCS with liver transplant	Presented with cervicalgia Treated with LMWH, switch AVK	BCS before to CVT	JAK2 + ET	Partial recanalization of CVT at 1 year

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