Review Article

Sinus thrombosis—do animal models really cover the clinical syndrome?

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Abstract: Cerebral venous sinus thrombosis (CVST) is an important cause of stroke in young patients. CVST represents with 0.5-3% of stroke cases a relatively rare disease. CVST affects 3-4 cases per 1 million overall and 7 cases per 1 million children and neonates. Typical clinical symptoms include headache, visual deficits and seizures. Beside the main condition associated with CVST in women in pregnancy and puerperium, the most frequently identified risk factors are oral hormonal contraceptives in combination with coagulation disorders. The initial treatment contains heparin and its efficacy is based on two randomized placebo-controlled trials including 79 patients together. A lack of understanding of the pathophysiology of CSVT makes animal models of this disease indispensable. Previously developed animal models of sinus sagittalis superior contributes to further clarify the pathophysiologic mechanisms and surrounding circumstances in the topic of cerebral venous thrombosis.

Keywords: Cerebral venous thrombosis; animal model; pathophysiology; cerebral blood flow

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Cerebral venous thrombosis in humans

While cerebral venous sinus thrombosis (CVST) affects children and young adults in particular, it can potentially occur in all age groups. Due to specific predispositions, such as oral contraceptives, pregnancy and the postpartum period, CVST predominantly occur in women with a sex ratio of 3:1 (1,2).

Other common risk factors include hereditary and acquired thrombophilia. The list of known causes or predispositions is long and summarized in *Table 1*. On the whole, the aetiology of CVST is often multi-factorial and despite a large number of manifest causes, it remains unexplained in approx. 20-30% of cases. In contrast to typical arterial thrombosis, which can suddenly lead to vascular occlusion and often causes clearly defined clinical symptoms for the vessels in question, one third of venous thromboses start off chronically, one third subacutely and one third acutely due to an imbalance in simultaneously occurring prothrombotic and thrombolytic processes.

The "International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)", published in 2004, with a cohort size of 624 patients, revealed that the mortality of the disease is clearly below 10%; in most cases caused by brain edema. At the end of the 16-month observation period 79% of patients made a complete recovery. Only a small percentage of patients remained disabled. The unfavourable prognostic signs identified were age >37 years, male gender, neuropsychological deficits on admission, clinically severe impaired levels of consciousness on admission (GCS <9) and thrombosis of the internal cerebral veins. Total mortality for the age group >65 years lay at around 27%, and was clearly higher than for the age group <65 years (7%) (1). The recurrence rate is very low; at around 2% per annum, it is comparable to the recurrence rate for deep vein thrombosis (1,3).

The clinical symptoms of CVST are extremely variable and exhibit a chronic to hyperacute dynamics. The

Table 1 Risk factors observed for venous thrombosis

Inherited risk factors
Homocysteinemia
Factor V Leiden homozygous mutation
G20210A prothrombin gene
Methylene-tetra-hydro-folate-reductase 677 TT mutations
Protein C and S deficiency
Anti-thrombin III deficiency
Positive anti-cardiolipin or anti-phospholipid antibodies
Acquired risk factors
Brain tumors
Head trauma
Intracranial hypotension
Internal jugular vein abnormalities
Local head infection
Extracerebral neoplasia
Dural fistulas
Hematological conditions
Nephrotic syndrome
Systemic vasculitis
CNS infections (bacterial meningitis, cerebral malaria)
Parameningeal infections (ear, sinus, mouth, face and neck)
Mechanical precipitants (central *vs*. catheter)
Medicaments (cisplatin, methotrexate, steroids)
Neurological surgery
Lumbar puncture
Pregnancy
Puerperium

Table 2 Clinical syndrome/symptoms and signs

Isolated intracranial hypertension syndrome
Headache
Vomiting/nausea
Visual loss
Papilledema
Sixth nerve palsies
Retinal hemorrhages
Meningeal signs
Aphasia
Dysarthria
Hemiparesis
Sensory symptoms
Dizziness
Ataxia
Nystagmus
Focal seizure
Seizure with generalization
Encephalopathy
Mental status disorder
Stupor/coma

symptoms range from asymptomatic cases or isolated headaches up to severe neurological deficits or coma (*Table 2*). Headaches are the most common symptom of CVST, occurring in approx. 90% of cases (4). In addition to headaches, seizures and focal neurological deficits occur; in 20-40% of cases the syndrome manifests as an isolated increase in intracranial pressure (ICP) with headaches, nausea and vomiting, and bilateral papilloedema (5). Finally, also consistent with thrombosis of the inner cerebral veins with bilateral involvement of the thalamus, symptoms ranging from the initial clouding of consciousness to coma may arise.

Systemic anticoagulation with unfractioned heparin is recommended in American and European Guidelines as first line treatment (6,7), based on a single randomized trial. Low-molecular-weight heparin (LMWH) was not superior to placebo in a Dutch trial (8), however, ISCVT data indicate that LMWH may be safer than unfractioned heparins. In spite of an optimum oral anticoagulation the rate of morbidity and mortality in patients suffered from CVST counts about 13.4% (1). Due to the high morbidity and mortality rate alternative aggressive treatment strategies such as endovascular thrombolysis or catheter-based mechanical thrombectomy become the further focus of clinical trials. Due to expected poor outcomes and increased ICP in patients with severe CVST such as multiple sinus occlusions including the jugular veins without associated hemorrhage endovascular thrombolysis may be an alternative primary treatment (9-11).

In small case series, mechanical thrombectomy serves as potential alternative or supplement to endovascular thrombolysis (11).

In case of impending risk of transtentorial herniation or brainstem compression secondary to massively increased ICP decompressive craniectomy may be life-saving measure (12). Studies on decompressive craniotomy in CVST showed fairly good outcomes with more than 50% of patients remaining functionally independent.

Objectives of animal models in the CVST

The contribution of experimental research for a better knowledge of physiological and pathophysiological changes in cerebral vascular system is of high importance. Animal models are of great value for further investigation of cerebral venous thrombosis and for the experimental evaluation of treatment strategies.

The pathophysiological processes in the context of cerebral vein and sinus thrombosis are complex and they are not yet fully known. The severity of the clinical symptoms does not appear to be correlated with the severity of the CVST. As Röttger *et al*. successfully demonstrated in 2005, over half of patients with venous infarctions go into full remission or experience clear reduction in the volume of the lesion (13). While this recovery is faster in patients who exhibit a rapid recanalisation of the affected sinuses using MRI criteria, ultimately, it does not depend on recanalisation or on a persistent occlusion. Nor is there a clinical difference regarding outcome depending on recanalisation or persistent occlusion (14). This allows for the conclusion that obviously, collateral vessels are adapted during the process or angiogenesis takes place or both. The vessels or newly formed vessels studied here are of a magnitude that cannot be depicted by the usual imaging procedures in humans. Autopsies on patients who died from sinus thrombosis are performed far too seldom to provide systematic insights. Besides, the localisation and the stage of the venous thrombosis need to be standardised, in order to assess the changes to the vascular system caused by them in a scientific manner.

Pathophysiology

During the initial stage the intravascular thrombus exhibits a laminated structure, with layers of aggregated and degranulated thrombocytes, with infiltration of leukocytes and layers of fibrin. After 5-10 days the thrombus takes on a homogeneous, hyaline structure.

At a later stage (8-20 days) the thrombus will be organised with the growth of fibroblasts and capillaries and endothelium-coated gap junctions. The thrombus undergoes conversion into a vascularised, fibrous mass which may lead to partial recanalisation due to clot retraction (15,16). In symptomatic patients the superior sagittal sinus (SSS), transverse sinuses and the sigmoid sinuses are the most commonly affected structures, while thrombosis of the cortical veins and the inner cerebral veins occur less frequently (4). The formation of venous thrombi, especially if they spread into bridging veins and cortical veins, causes a drop in cerebral perfusion pressure, with a simultaneous increase in ICP (17). In deed venous infarcts have only been observed when either two or more cortical veins or the inner cerebral venous system have been affected (18). As a result, the local cerebral blood flow decreases, which lead to the formation of a cytotoxic oedema and also lead to consecutive venous infarction. After the blood-brain barrier has been disrupted and capillary filtration increases, a vasogenic oedema will arise, resulting in congestive bleeding.

Animal models

An animal model of spontaneously occurring CVST does not exist. Also, there are no animal strains which are CVST-prone. To study CVST in a standardized animal model precludes more or less invasive induction of sinus or cortical vein thrombosis with chances of collateral damage due to operation or intervention the smaller the animal model chosen.

With only a few exemptions, most models did not study long-term effects of CVST, but animals were euthanised after a short investigation period of only a few hours.

In contrast to ischemic cerebral infarction, there are only a few animal experiment studies into CVST (*Table 3*). Those few studies were carried out on rats, pigs, cats, gerbils and rabbits (17,20,22,39-46). For the most part, these methods were invasive interventions and they often led to iatrogenic parenchymal defects in the brain. Furthermore, the transfer of results to the clinical situation of these studies was limited, because it was not possible to influence the duration of the thrombosis or the recanalisation. The efficacy of therapeutic options and their assessment could only be investigated to a limited degree. The purpose of the studies was the modification of local cerebral perfusion due to CVST, using laser Doppler flowmetry or the hydrogen clearance method, oximetric measurements of local oxygen saturation, measuring ICP using parenchymal and ventricular probes and fluorescein angiography to identify disruptions of the blood-brain barrier.

All of these studies used the option of histopathological regeneration. Angiogenesis was studied in animal models of arteriovenous fistula which were, for example, created by operative anastomosis of the carotid artery and the jugular vein, partly with the induction of a sinus thrombosis. Various forms of thrombosis induction were used (47,48).

Table 3 Reported animal models

Animal	Method of thrombosis induction
Pig	• Operative SSS exposure, balloon occlusion and fibrin injection (19)
Rat	• Operative SSS exposure, thrombosis induction with ferric chloride (13,20,21);
	• Operative SSS exposure, sinus ligation with prolene suture and injection of kaolin/cephalin suspension (22);
	• Operative cortex exposure, photochemical cortical vein thrombosis induction (17,23);
	• Operative exposure, bipolar electrocoagulation of the anterior and posterior anastomotic veins (24,25);
	• Cannulation of the external jugular vein and retrograde embolization of blood clots (26);
	• Insertion of a self-made plastic graft in the superior sagittal sinus (27)
Cat	• Operative SSS exposure and coagulation or injection of cyanoacrylate monomer (28);
	• Operative SSS exposure and ligature (29);
	• Operative SSS exposure, ligature and lard oil injection (30);
	• Operative SSS exposure, occlusion with polyethylene catheter (31);
	• Operative exposure of bridging veins, occlusion by ligature (32);
	• Operative exposure of bridging veins, occlusion by electrocoagulation (33)
Gerbil	Operative SSS exposure, sinus ligation with a monofilament nylon suture (18)
Mouse	• Operative SSS exposure, thrombosis induction with iron chloride (34)
Rabbit	• Operative SSS exposure, occlusion by metal clip (35);
	• Operative SSS exposure, occlusion by metal clip and thrombin injection (35)
Dog	• Operative exposure of cortical veins, sodium morrhuate injection (36);
	• Operative exposure of SSS, balloon occlusion and/or thrombin injection (37)
Rhesus monkey	• Operative sinus exposure, ligation and/or injection of paraffin or muscle tissue (38)

Wang *et al*. produced sinus thrombosis in pigs using thrombin injections and balloon dilatation of SSS (45), Stracke *et al*. used human blood clots injected into the SSS of pigs and studied them using MR imaging (49), Schaller *et al*. induced sinus thrombosis by way of a ligature on the posterior section of the SSS in cats (29), Röttger *et al*. using a topical application of Iron (III) chloride in rats (20). Furthermore, other models with occlusion of the SSS or cortical veins by local injections of thrombogenic materials such as cyanoacrylate (21) or kaolin cephalin (40,42) were used. All of the above-mentioned models are reversible models which revealed that the clinic, diagnostics and use of therapeutic options could only be assessed to a limited extent.

A major drawback of the above mentioned models is that the thrombus does not spontaneously propagate into the cortical veins causing larger venous infarcts. Nakase *et al*. (17) induced cortical vein thrombosis by direct illumination in a photothrombotic dye model with Bengal rose. However, concerns exist that direct illumination of the cortical surface may cause cortical damage by simply activating the dye in arterioles rather than by pure venous circulation compromise.

Currently, Li *et al*. (46) developed a new model of SSS using a combination of Ligation, injection of thrombin into the SSS and temporary carotid artery occlusion. Li *et al*. demonstrated, beside SSS thrombosis, affected cortical venous thrombosis and intraparenchymal hemorrhage. The main point of this model is a more accurately demonstration of the pathophysiologic circumstances in CVST than previous studies. Similar to human subjects this model creates cortical vein thrombosis, reveals thrombus, inflammatory cells, infarction and intraparenchymal haemorrhage. The limitation of this model is that the study of therapeutic treatment is in case of permanent ligation of the SSS is difficult. The permanent occlusion by ligation of the SSS leading to permanent alteration of blood flow is not physiologic. Furthermore temporary carotid artery ligation leads to cerebral hypoperfusion and changes in the regional CBF.

Conclusions

Animal models contributed significantly to our understanding

of the pathophysiology of CVST.

There are currently a number of established animal models for studying the pathophysiological processes involved in CVST (*Table 3*). In contrast to ischemic cerebral infarction, there are only a few animal experiment studies into cerebral veins and sinus thrombosis. Various forms of thrombosis induction were used. Wang *et al*. induced the sinus thrombosis with invasive, catheter-based thrombin injections and balloon dilatation in pigs and observed the effects of these thrombi over seven days, during which time one animal died and 4 exhibited occlusion of the SSS (45). Complications in the sense of a cerebral oedema, haemorrhage infarction could be depicted using MRT. Stracke *et al*. used human blood clots in pigs and studied then using MR imaging (49), Schaller *et al*. induced sinus thrombosis by way of a ligature on the posterior section of SSS in cats (29), Röttger *et al*. with topical application of Iron (III) chloride in rats (20). Iron (III) chloride was first used by Kurz *et al*. and described in connection with models of arterial thrombosis formation (21). All of the above-mentioned models are reversible models which revealed that the clinic, diagnostics and use of therapeutic options could only be assessed to a limited extent.

In these models the changes in the regional cerebral blood flow (rCBF) were determined using laser Doppler flowmetry or the hydrogen clearance method. Other techniques used in these models include oximetric measurement of local oxygen saturation, measurement of ICP using parenchymal and ventricular probes and fluorescein angiography to identify disruptions of the blood-brain barrier. All previous studies used the option of histopathological regeneration.

For the most part, these methods were invasive interventions and they often led to iatrogenic parenchymal defects in the brain. Furthermore, the transferability of these methods was very limited, as it was not possible to influence the duration of the thrombosis or the recanalisation. None of these models could account for permanent occlusion under clinical observation or changes to vascular structure beyond seven days. In a further development of the animal model of Röttger *et al*. (20), it was possible to demonstrate a sustained occlusion of the SSS occlusion for a period of 6 weeks in the living animal and allows for the study of pathophysiological conditions following permanent occlusion over longer periods of time (19). In this study we were able to demonstrate neoangiogenesis 6 weeks after thrombus induction within the lumen of the thrombosed SSS as a network of small venules which connect to cortical veins. These newly formed vessels coincide with the locally strong VEGF expression in the organized thrombus consistent with neoangiogenesis. The most important finding was an increase of the cortical venous volume fraction above control levels after 6 weeks, although only traces of VEGF expression could be found in the parasagittal region. This study examines angiogenesis in a standardized, non-lethal rat model of persistent SSS thrombosis. This model allows for standardization of the time of onset and control of physiological variables not possible in human case series. Micro- and nano-CT was used to study the venous vascular changes and demonstrated Neoangiogenesis as the main reason for the good clinical outcome and the reduced final infarct volume (19).

All of the animal models encountered complications such as venous infarctions and cerebral oedema. The efficacy of therapeutic options and their assessment could only be investigated to a limited degree.

All animal models with above mentioned Limitations do not carry the morbidity and mortality associated with cortical vein thrombosis seen in human patients.

The creation of an ideal and reliable model comprises simultaneously inducted cortical venous thrombosis, infarct and hemorrhage with consecutive clinical symptoms illustrating the pathophysiologic changings in CVST in humans allowing options for the study of therapeutic strategies.

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