SYMPOSIUM

Cerebral venous thrombosis: pathogenesis, presentation and prognosis

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The advent of non-invasive brain imaging methods in the 1980s resulted in increased recognition of cerebral venous thrombosis. Before that time, only physicians with a high index of suspicion considered the diagnosis in patients with otherwise unexplained headache, focal deficits, seizures, impaired consciousness, or combinations of these features[1]. This paper and the three which follow it review the modern approaches to diagnosis and treatment.

PATHOGENESIS

Virchow's triad of causes of thrombosis is damage to vessel wall, disorders of coagulation and stagnant flow. In contrast to cases in which the precipitant is arterial thrombosis, damage to the vessel wall is a causal factor in only about 10% of patients with cerebral venous thrombosis[2]; in those cases the underlying disease consists of infection, infiltration, or trauma. Much more important are disorders of coagulation (70%; see Box 1)[2]. The most common inherited coagulation defect is factor V Leiden mutation, which is found in some 20% of patients without obvious other causes[3–5]. Stagnant flow contributes not more than a few per cent (episodes associated with dehydration or with dural puncture, sometimes in combination with hyperosmolar contrast agents). In 20% of patients no contributing factors can be identified and the cause remains a mystery.

Often there is not a single cause but a combination of contributing factors—for example, the postpartum period and protein S deficiency[6]; pregnancy and Behçet's disease[7]; oral contraceptive drugs and the factor V Leiden mutation[8,9], or the same combination with dural puncture as a third factor[10]. The risk of cerebral venous thrombosis in the postpartum period increases with maternal age[11] and with performance of caesarean section[12].

In neonates, cerebral venous thrombosis is usually associated with acute systemic illness such as shock or dehydration; in older children the most frequent underlying conditions are local infection (the leading cause until the antibiotic era), coagulopathy[13,14] and in Mediterranean countries Behçet's disease[15].

PRESENTATION

The clinical features of cerebral venous thrombosis consist essentially of headache, focal deficits, seizures, and impairment of consciousness, in various combinations and degrees of severity. The symptoms and signs depend to some extent on which sinus is affected, and to an important extent on whether the thrombotic process is limited to the dural sinus or extends to the cortical veins[2].

In the case of the superior sagittal sinus (which is most often affected), in 70–80% of the total[16,17], sinus thrombosis alone will lead to the syndrome of *intracranial hypertension*, i.e. headache and papilloedema. Up to 30% of patients with so-called 'benign intracranial hypertension' (BIH) may in fact have sinus thrombosis[18]. An anatomical obstruction within the superior sagittal sinus may exist in up to 50% of all patients with BIH[19,20], but the cause of the obstruction is not necessarily thrombosis. Those with underlying venous thrombosis are more often non-obese or male, but are otherwise indistinguishable from patients with idiopathic BIH[18]. Papilloedema can cause transient visual obscurations and sometimes irreversible constriction of visual fields, beginning in the inferonasal quadrants[1]. The increased pressure of the cerebrospinal fluid (CSF) may also give rise to VIth nerve palsies, and sometimes to other cranial nerve deficits. The onset of the headache is usually gradual, but in up to 15% of patients it is sudden and may initially suggest the diagnosis of a ruptured aneurysm[21].

Involvement of *cortical veins* causes one or more areas of venous infarction, with or without haemorrhagic transformation. If the affected veins drain into the sagittal sinus the venous infarcts are typically located near the midline in the Rolandic and parieto–occipital regions, often on both sides. In the case of the lateral sinus, the venous infarct is usually located in the posterior temporal area[22]. If the thrombotic process extends to the petrosal sinus the trigeminal nerve may be affected, and in the case of the jugular vein the cranial nerves IX–XI[2].

Clinically the infarcts manifest themselves through *epileptic seizures*, or through *focal deficits* such as hemiparesis or dysphasia. If unilateral weakness develops

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Box 1 **Causal factors in the pathogenesis of cerebral venous thrombosis in adults (adapted from Ref. 2)**

Prothrombotic states
- Pregnancy; puerperium[23]

Hereditary coagulopathies
- Protein S deficiency[33]
- Antithrombin III deficiency[34]
- Factor II (prothrombin) gene mutations (20210 G→A)[35–38]
- Factor IV gene mutations (factor V Leiden)[3–5]
- Von Willebrand's disease
- 5,10 methylene tetrahydrofolate reductase mutation (677C→T)[39]
- Homocystinuria[40,41]
- Familial thrombophilia of unknown nature[42]

Coagulopathies secondary to blood dyscrasia
- Thrombocythaemia[43]
- Primary polycythaemia[43,43]
- Paroxysmal nocturnal haemoglobinuria[45–47]
- Iron deficiency anaemia[48]
- Sickle cell disease[49]
- Disseminated intravascular coagulation[2]
- After bone marrow transplantation[50]

Coagulopathies secondary to systemic disease
- Behçet's disease[51,52]
- Carcinoma (breast, prostate)[53,54]
- Lymphoma[1,55]
- Systemic lupus erythematosus[56]
- Nephrotic syndrome[1]
- Vasculitis
- Ulcerative colitis[57], Crohn's disease[58]
- Antiphospholipid antibodies[59]

Coagulopathies caused by drugs
- Oral contraceptives (3rd generation > 2nd)[9,60]
- Corticosteroids
- Dihydroergotamine[61]
- Androgens[62]
- Ecstasy[63]

Coagulopathies secondary to local infection or infiltration
- Otitis[64]
- Sinusitis[65]
- Dental abscess
- Tonsillitis
- Obstruction by tumour[66]

Coagulopathies secondary to general infection or infiltration
- Uveomeningitis
- Sarcoidosis[67]
- Chronic meningitis
- Subdural empyema
- Carcinomatous meningitis

Dural puncture
- Epidural anaesthesia
- Metrizamide myelography
- Diagnostic tap

Trauma[68]
Unknown (20%)

(with thrombosis originating in the superior sagittal sinus), it tends to predominate in the leg, in keeping with the parasagittal location of most venous infarcts. Obstruction of cortical veins draining into the posterior part of the superior sagittal sinus or into the lateral sinus will commonly lead to hemianopia, dysphasia, or a confusional state. *Impairment of consciousness* may result from multiple lesions in the cerebral hemispheres, or from transtentorial herniation and compression of the brain stem. Either epilepsy or a focal deficit is a presenting feature in 10–15% of patients[23]; in the course of the illness seizures occur in 10–60% of reported series and focal deficits in 30–80%[16,17,23,24].

Involvement of the *cortical veins alone*, without sinus thrombosis and its associated signs of increased CSF pressure, is an extremely rare occurrence[16,23]; recently four such cases have been published together, from different centres[25]. Thrombosis of the *deep venous system*, including the great vein of Galen, may lead to bilateral haemorrhagic infarctions of corpus striatum, thalamus, hypothalamus, the ventral corpus callosum, the medial occipital lobe and the upper part of the cerebellum[26]. Needless to say, in those instances the clinical picture is dominated by deep coma and disturbance of eye movements and pupillary reflexes. Partial syndromes exist and can be survived, sometimes with surprisingly few sequelae[16,27,28]. Thrombosis of *cerebellar veins* leads to clinical features resembling those with arterial-territory infarcts in the cerebellum (dominated by headache, vertigo, vomiting and ataxia, sometimes followed by impaired consciousness), but with a more gradual onset[1,29,30].

PROGNOSIS

Death rates in different series range between 5% and 30%, and probably depend more on case mix than on treatment[16,17,23,24]. Causes of death can be the underlying condition, the brain lesion, secondary complications, or a combination of these[2]. The same variation is found in reported proportions of patients with complete recovery (50–80%). Residual deficits consist mostly of hemispheral deficits or visual impairment from optic atrophy.

The risk of recurrence has seldom been addressed systematically. In a single longitudinal study spanning an average period of 6½ years, 9 of 77 patients (12%) experienced a second episode; 3 of them had Behçet's disease[31]. In young women with a peripartum episode of cerebral venous thrombosis a difficult question is whether a subsequent pregnancy ought to be discouraged. The sparse evidence available does not warrant such advice[2,32], although in patients with the factor V Leiden mutation the risk of a recurrent episode is probably higher than average[5].

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