# Cerebral venous thrombosis and Escherichia coli infection in neonates

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*Aim:* To present a possible association between cerebral venous thrombosis (CVT) and infection with *Escherichia coli. Methods:* Four neonates with deep CVT occurring during an *E. coli* infection are presented. *Results:* In these patients the thrombotic disease was found by Doppler ultrasonography. The thrombosis involved at least the sagittal sinus and the transverse sinus according to subsequent MRI scans. The *E. coli* strains did not produce verotoxin or haemolysin. Disseminated intravascular coagulation was not demonstrated. Three patients presented with seizures. At discharge, all of the patients had signs of neurological damage, but two of them have improved significantly since then. None of the patients has had recurrent (venous) thrombosis.

*Conclusion: E. coli* infections in neonates may predispose to CVT, a finding that has clinical implications.

**Key words:** Cerebral venous thrombosis, Doppler ultrasonography, Escherichia coli infection, MRI scans, neonates

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Cerebral venous thrombosis (CVT) in neonates is a rare disorder, but it is usually diagnosed after CT and MRI scanning (1, 2). Several risk factors have been identified, including infection, dehydration, perinatal hypoxia (1–5), and in recent years, prothrombotic disorders (1, 2, 5, 6). We describe four neonates with CVT, all occurring during an *Escherichia coli* infection. Two patients had septicaemia with meningitis and ventriculitis. The other two had urinary tract infections with suspected, but not verified urosepsis. None of the patients was known to have had recurrent thrombosis at follow-up. This prompted the question of a specific association between *E. coli* infection and the development of CVT.

### Patients and methods

MRI scans were performed with a Siemens Magnetom 1.5 Tesla, Erlangen, Germany, and colour Doppler ultrasonograms were performed with an Acuson XL 128 machine.

The *E. coli* isolates were found using routine microbiological methods in the local hospitals. Blood cultures were drawn and incubated using the BactAlert blood culture system (Organon Teknika). The isolates were tested for their ability to produce haemolysin on blood agar plates, and were checked for verotoxin or Shiga-like toxin by the vero cell assay (7). Serotyping

was done in the Escherichia and Klebsiella Centre (WHO) in Copenhagen, Denmark (8).

### Case reports:

### Patient 1

This boy, born at term by vaginal delivery, was transferred to the neonatal ward at the local hospital at 1 d of age because of tachypnoea and hypoglycaemia. Doppler ultrasonogram showed a partially obstructed left pulmonary artery, believed to be due to a thrombus. The patient was discharged at 12 d of age. Readmission followed 11 d later owing to weight loss, lethargy and dehydration. C-reactive protein (CRP) was 177 mg/L and E. coli (more than 100000 colonies/ml) was isolated from urine. Antibiotic treatment was started. Lumbar puncture was unsuccessful. After 3 d the child had convulsions. A Doppler ultrasonogram indicated absent flow in the superior sagittal sinus with a suspected CVT. An MRI at our hospital confirmed the occurrence of thrombi in several intracranial veins: the sagittal sinus, the sigmoid sinus, the transverse sinus and the galenic vein. Although structural changes were found in both hemispheres on MRI at discharge from our unit, the patient's development has been normal so far, 8 y later. However, he still receives anticonvulsive treatment. No urinary tract anomaly was found, and

	aPTT s	NT %	FDP +/-	Fibrinogen μmol/L	Platelet count 10 <sup>9</sup> /l
Patient 1	24	65/101	+	7.2	65/144/211
Patient 2	29	117	-	16/7.4	151/32/165
Patient 3	29	119	+	18	303/347
Patient 4	60/98/31	150	+	14.6/8.2	129/557

Table 1. Results of coagulation tests.

NT: prothrombin time; aPTT: activated partial thromboplastin time, normal activity 70–140%; FDP: fibrin degradation products.

coagulation tests were normal (Table 1). Testing for prothrombotic disorders included protein C, protein S and antithrombin III, with normal neonatal values, 58%, 67% and 80%, respectively.

### of age the child has mild visual, hearing and psychomotor impairment. Coagulation tests were normal (Table 1).

### Patient 4

This boy was born at term after a vaginal delivery. The infant was breastfed. At 3 wk of age he had convulsions.



# *Fig. 1.* MRI scans. a. From patient 2: T1-weighted axial view showing thrombosis in the superior sagittal sinus (arrows). b. From patient 3: T1-weighted sagittal view demonstrating thrombosis in the sagittal and straight sini (arrows). c. Also from patient 3: T1-weighted coronal view showing thrombosis in the sagittal sinus and the straight sinus (black arrows) and hydrocephalus development (white arrow). d. From patient 4: T1-weighted view demonstrating the thalamic bleeding (black arrow) and thrombosis in the distal superior sagittal sinus (white arrow).

### Patient 2

This boy, vaginally delivered at term, was admitted to the local hospital at 10 d of age after suffering fever, lethargy and anorexia for two days. CRP was 247 mg/L. E. coli was cultured from urine and blood, and antibiotic treatment was started. After five days the patient became irritable and had convulsions. A Doppler ultrasonogram showed absent flow in the superior sagittal sinus. The patient was then transferred to our hospital. A ventricular puncture revealed an opaque fluid with 2500 cells per ml and growth of *E. coli*. The subsequent six punctures revealed sterile fluid, with a cell count decreasing to 46 per ml after three weeks. An MRI scan showed thrombosis in deep cerebral veins, the sagittal sinus and the transverse sinus (see Fig.). Owing to increasing hydrocephalus, a ventriculoperitoneal shunt was inserted. Neurological sequelae with hypotonia and uncertain visual contact had developed at discharge. After seven years of follow-up, the boy has delayed motor development and needs a hearing aid. Image studies of the urinary tract were normal, as were coagulation tests (Table 1).

## Patient 3

This boy, delivered vaginally at term, was admitted to the local hospital at 8 d of age with fever, irritability and poor feeding ability. Antibiotic treatment for septicaemia was commenced. E. coli was cultured from blood while the urine was sterile. A lumbar puncture after one day of treatment revealed an opaque fluid so dense with cells and cell aggregates that counting was impossible. However, no pathogen was isolated. A Doppler ultrasonogram showed absent flow in the superior sagittal sinus, and a CVT was suspected. After admission to our department, an MRI scan confirmed this diagnosis. Thrombi were found in the transverse sinus, the sagittal sinus and the straight sinus (see Fig.). There were no convulsions, and EEG was normal. Neurosurgical evacuation of subdural empyema containing E. coli was performed 13 d after antibiotics had been started. Later, a ventriculoperitoneal shunt was inserted. At 7 y

When he was admitted to the local hospital, it became apparent that the infant had lost 25% of his birthweight and was dehydrated. A lumbar puncture revealed blood in the cerebrospinal fluid (CSF) and a cell count of 220 per ml. The CSF was sterile. A CT scan showed an intracerebral haematoma located in the thalamus region. E. coli was cultured from urine, and antibiotic treatment was commenced. Image studies of the urinary tract were normal. Coagulation tests (see Table 1 for details) showed a possible bleeding tendency with a prolonged activated partial thromboplastin time (aPTT) of 60 s, increasing to 98 s the next day. Haemophilia was suspected, and the patient was referred to our hospital. Here an MRI scan showed thrombi in the sagittal sinus, the transverse sinus, the straight sinus and the internal cerebral vein (see Fig.). The haematoma was believed to be secondary to the thrombus (9), and therefore no anticoagulant treatment was administered. The aPPT was normal a week later (31 s). Assessment of coagulation factors VIII and IX and von Willebrand factor showed normal activity. Six years later, the child's neurological development is normal.

# Microbiology results

*E. coli* grew in blood cultures from two patients, in urine from three patients, and in CSF from two patients (Table 2). The saved blood culture and CSF isolates from patients 2 and 3 were further characterized. They were negative for verotoxin and haemolysin production. The blood culture isolate from patient 2 was the serotype O78:K-:H-, an extra-intestinal strain. CSF drawn six days later yielded the same type of *E. coli*. An *E. coli* of the serotype O18ac:K1:H7 was found in the blood of patient 3, and the same bacterium was cultured from subdural empyema 13 d later.

# Discussion

We describe four boys born at term, with CVT during *E. coli* infection. None of the children had a urinary tract anomaly despite the fact that three had *E. coli* in urine cultures. The first three patients came from the same hospital. However, the isolated *E. coli* strains in patients 2 and 3 showed different serotypes.

There are several possible mechanisms by which *E. coli* can modulate the coagulation system. Toxins such as verotoxin and haemolysin, which are produced by certain strains of *E. coli*, may affect this system. However, our isolates were not toxin producing. Furthermore, *E. coli* releases lipopolysaccharide (LPS) that may cause a systemic reaction, with life-threatening shock and disseminated intravascular coagulation (DIC) (10). None of our patients had measurable DIC, while CRP, as a parameter of acute phase response, was highly elevated during the first days of the *E. coli* infection. Abnormal coagulation tests strongly support

Table 2. Isolation sites of E. coli in the four patients.

	Urine	Blood	CSF
Patient 1	+	_	*
Patient 2	+	O78:K-:H-	O78:K-:H-
Patient 3	_	O18ac:K1:H7	O18ac:K1:H7**
Patient 4	+	—	-

CSF: cerebrospinal fluid.

\* No CSF obtained owing to failed attempts at a lumbar puncture.

\*\* Fluid from a subdural empyema.

the diagnosis of DIC, while normal tests do not exclude it (11). Recently, Herwald et al. (12) identified surface proteins on Gram-negative bacteria including *E. coli* that specifically interact with proteins of the fibrinolytic and coagulation cascades.

Gram-negative meningitis, in neonates often caused by *E. coli*, generally gives a poorer outcome than Grampositive meningitis. It is known that the presence of K1antigen, found on one of our *E. coli* isolates, further increases the mortality and morbidity of the meningitis (13). However, in large series of neonatal meningitis (14–17) CVT is not listed among the complications, and DiNubile et al. (18) documented cortical vein thrombosis in only 1% of adult patients with meningitis.

Our patient no. 4 developed CVT without meningitis, but with urinary tract infection (UTI). Sterile CSF pleocytosis during UTI has been reported in neonates and children (19). Syrogiannopoulos et al. (19) assume that this is due to meningeal inflammation mediated by inflammation-inducing molecules derived from bacteria such as LPS.

The classic approach to the pathogenesis of thrombus formation by Virchow in 1856 includes endothelial damage, hypercoagulability and disturbances of blood flow. Moulding and overlapping of sutures during normal birth can damage underlying sinuses and induce thrombus formation (5). Catheters primarily cause arterial thromboembolism and hepatic and splenic vein occlusions, and are not a major contributory factor in cerebral venous thrombosis (5) Thrombophilia as a contributory factor has been well established (1, 2, 5). Dehydration (and in neonates, often the resulting hyperviscosity) causes altered blood flow and was a co-factor in our patient 4. Sepsis can cause hypotension and thereby reduced blood flow, and damage the vessel wall, as can meningeal inflammation (13). All our patients had one or more of these risk factors.

The pathogenesis of neonatal cerebral venous thrombosis is not well elucidated (1-6). Even after thorough investigation of known risk factors, such as infection, dehydration and asphyxia, and prothrombotic disorders, some cases with CVT remain idiopathic (1-6).

Wu et al. (6) found right-sided jugular vein thrombosis or sigmoid sinus thrombosis in 5% of infants on extracorporeal membrane oxygenation treatment, possibly caused by the iatrogenic occlusion of the right internal jugular vein. In the literature (1–6) there is very little information about microbes as cofactors in inducing CVT. The observation of coexisting *E. coli*- infection in all our cases may reflect an increased risk. This possible association between CVT and *E. coli* infection has one important clinical implication: the lethargy and convulsions often observed in neonatal *E. coli* infections warrant imaging studies such as colour Doppler ultrasonography of the head. The results obtained can be supplemented with an MRI scan, which is the gold standard of the CVT diagnosis since detailed information about all cerebral veins is obtained.

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