

## Theme Issue Case Report

# Factor II gene (prothrombin G20210A) mutation and neonatal cerebrovenous thrombosis

The incidence of stroke is reported to be 28 in 100.000 live births. All age groups show an unexplained male predominance. Of the two types of cerebral stroke, arterial ischaemic stroke and (sino-)venous thrombosis, the arterial one is most frequent (1, 2). Non-invasive methods such as ultrasound, computerized-tomography (CT) or magnetic resonance imaging (MRI) can detect these thrombotic events in the brain (3, 4).

Etiologic (genetic or acquired) factors predisposing to thrombosis may shift the haemostatic balance towards elevated procoagulant activity resulting in a hypercoagulable state that predisposes to venous or arterial thrombosis. Lower concentrations of antithrombin, protein S and C, along with reduced fibrinolytic capacity, put neonates at greater risk of thromboembolic complications than older children (5).

Several studies have reported associations with congenital thrombotic risk factors such as the factor V Leiden mutation and protein C and S deficiency (2, 6). Also the prothrombin G20210A mutation (heterozygous/homozygous), either *de novo* or hereditary is a known risk factor for venous thrombosis outside the brain, and was recently reported in adults and children with (sino-)venous thrombosis (7). Due to the elevation of plasma prothrombin levels, this situation increases the risk of hypercoagulability (8). The mutation occurs in more than 2% of the general population and was shown to be a common, but mild, risk factor for thrombosis in children and adults (9). Here, we report four neonates with cerebrovenous thrombosis and prothrombin G20210A mutation.

All four neonates showed cerebrovenous thrombosis on cerebral ultrasound scan, and were therefore analysed by standard protocol. This comprised medical history and blood tests,

such as prothrombin time, activated partial thromboplastin time, thrombin-clotting time, fibrinogen, antithrombin (Berichrom<sup>®</sup>, Dade Behring, Germany), plasminogen, protein S and C (Asserachrom<sup>®</sup>, Diagnostica Stago, Roche, Germany), resistance to activated protein C, lupus anticoagulans, anticardiolipin and antiphospholipid antibodies, specific factor analysis (including prothrombin), lipoprotein (a), amino acids and organic acids including homocystinic acid. Furthermore, prothrombin G20210A and factor V Leiden mutations were assessed twice by DNA-analysis (ThromboType<sup>®</sup>, Hain Lifescience, Germany) (10). For all patients parental informed consent was obtained for genetic testing.

### Patient 1

This boy was born at term with a birth weight of 3640g, and delivery was uncomplicated. Apgar scores were 6 and 8 at 1 and 5 min, respectively. Four days after birth he showed opisthotonus and grunting. CT and ultrasound revealed bleeding in the left thalamus and frontal white matter, left intraventricular haemorrhage, superior sagittal sinus thrombosis and left internal cerebral vein thrombosis (Fig. 1A). Clinical follow-up was not available yet. DNA-analysis showed heterozygous prothrombin G20210A mutation. The parents did not test positively for prothrombotic defects, and the family histories were negative for thrombosis.

### Patient 2

This girl was born at term with a birth weight of 2840g. An emergency caesarean section was performed because of meconium-stained liquor, reduced foetal movements and heart rate variability. Apgar scores were 3 at 1 and 5 at 5 min, respectively. Seizures were noted 2 hrs after birth, and EEG documented bilateral epileptic periods. Ultrasound and MRI documented bilateral haemorrhage in the parietal subcortex resulting from superior sagittal sinus thrombosis (Fig. 1B). Clinical follow-up was normal at the age of 18 months. DNA-analysis revealed a heterozygous prothrombin G20210A mutation in both the girl and her mother. The girl's prothrombin level was 1.42 IU/ml. The mother and her siblings had no clinical history of thrombosis.

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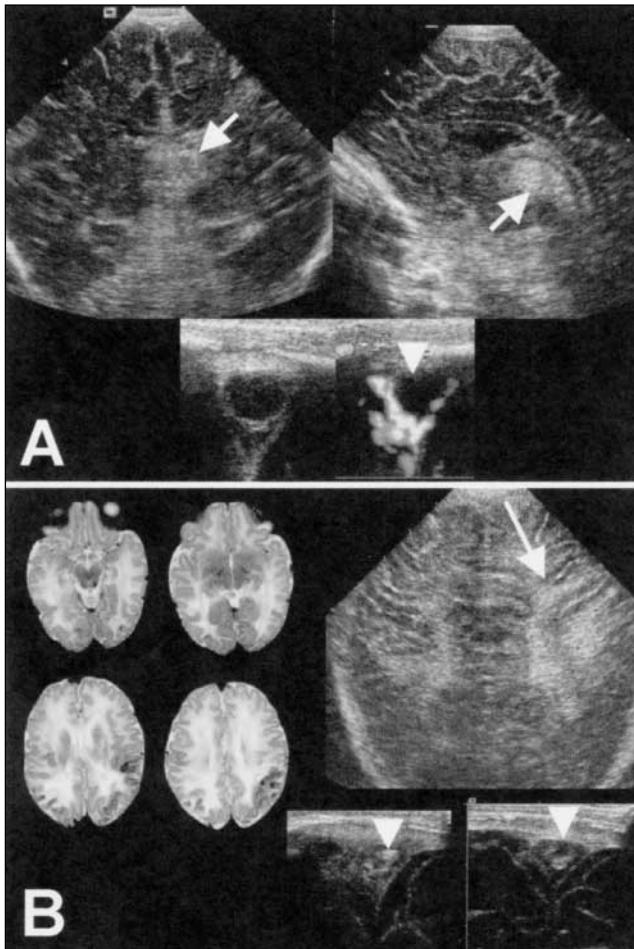
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**Figure 1: Cerebral ultrasound analysis.** (A) Top panels: deep venous thrombosis with bleeding in the left thalamus (arrows). Bottom panel: doppler flow (colour) with absence of flow in the superior sagittal (arrowhead). (B) Left panels: Cerebral MRI; top right panel: Cerebral ultrasound showing subcortical white matter damage (arrow); bottom right panels: sagittal sinus thrombosis (arrowheads).

### Patient 3

This boy was born at term with a birth weight of 3380g. A vacuum extraction was performed because of foetal distress and meconium-stained liquor. Apgar scores were 7 and 8 at 1 and 5 min, respectively. The boy had seizures 15 days after birth, which responded well to phenobarbitone. EEG showed epileptic activity over the left hemisphere. Ultrasound and MRI documented bleeding in the left thalamus, caudate nucleus and posterior limb of the internal capsule, and intraventricular haemorrhage resulting from thrombosis of the left internal cerebral vein. Clinical follow-up at four years of age showed right hemiplegia, refractory epilepsy and delayed language development. DNA-analysis revealed a heterozygous prothrombin G20210A mutation in both the boy and his father. The father and his siblings had no clinical history of thrombosis.

### Patient 4

This boy was born at a gestational age of 35 weeks with a birth weight of 1975g. Pregnancy was complicated by maternal hypertension (pre-eclampsia) and intrauterine growth retardation. Because of severe foetal distress an emergency caesarean section was performed. As Apgar scores were 8 and 4 at 5 and 10 min, respectively, respiratory and circulatory support were initiated. Because of neurological depression, ultrasound and CT scans of the brain were performed. The scans showed bleeding in the right thalamus, right caudate nucleus and white matter, and an intraventricular haemorrhage resulting from thrombosis of the right internal cerebral vein. The boy died on the second day. DNA-analysis showed a heterozygous prothrombin G20210A as well as a heterozygous factor V Leiden mutation in both the boy and his father as well as the father's brother. The father and his siblings had no clinical history of thrombosis.

### Discussion

We found prothrombin G20210A mutations in four neonates presenting with cerebrovenous thrombosis, and in one in combination with factor V Leiden mutation. The latter is a well-described association (10%) related to a greater risk of (cerebral) venous thrombosis in adults and children (11). One neonate had a *de novo* mutation. In the others, neither of the parents was a carrier. Patient 2 showed elevated prothrombin levels. Dysfunctional variants of prothrombin may be responsible for the fact that there is no correlation between prothrombin activity and protein concentration (12). Based on literature data, children presenting with venous (cerebral) thrombosis have at least one or two clinical risk factors or prothrombotic disorders (13). In our patients, risk factors other than prothrombin G20210A mutation were asphyxia and instrumental delivery (14, 15). An association with pre-eclampsia in the mother has been described (1). There is no reported evidence relating cerebrovenous thrombosis to caesarean section. Other risk factors, such as infection, dehydration, congenital heart disease, polycythemia or an indwelling catheter, were not present (16). This suggests that additional risk factors are required for manifestation of cerebral venous thrombosis. Only one of the neonates had no other risk factor than prothrombin G20210A mutation. Since a prothrombotic factor had already been detected in this patient and no material was left, lipoprotein (a), a well-known prothrombotic risk factor, was not tested secondarily (17, 18). There are no randomised trials of cerebral venous thrombosis treatment in neonates. In our patients treatment was not considered (13, 19).

Neonatal deep cerebrovenous thrombosis may be primary or secondary due to propagation from a thrombosed superior sagittal sinus (20). An interval of several days from birth to presentation does, therefore, not exclude trauma in which super-

ior sagittal sinus occurs first, followed later by deep venous thrombosis. Our report suggests that additional risk factors play a role in the manifestation of cerebrovenous thrombosis in newborns with prothrombin G20210A mutation.

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