**Research Article**

### Intracerebral Hemorrhage in Neonates and Hereditary Thrombophilia

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**Abstract**

**Background:** Hemorrhage of the central nervous system in neonates is mostly associated with risk factors like early prematurity, way of delivery, birth trauma, vitamin K deficiency, hereditary hemophilia or acquired coagulopathy. However, in some patients the pathogenesis of ICH remains unclear.

**Patients and Methods:** Cohort study of 27 term and near to term neonates with Intracerebral Hemorrhage (ICH). In the subgroup of patients without obvious risk factors for ICH (n=20), thrombophilic diagnostic workup was performed.

**Results:** 15 terms and 12 preterms (> 32 weeks GA) were examined. Way of delivery was cesarean section (n=12), assisted vaginal delivery (ventouse delivery; n=1, forceps delivery; n=3) or spontaneous (n=11). First clinical symptoms for ICH were isolated persistent abnormal body temperature (n=5) or seizures (n=14), or the combination of fever with seizures and/or paleness, muscular weakness and arterial hypotension.

In this cohort study, known risk factors like birth asphyxia (n=4), vitamin K deficiency (n=1), hereditary haemophilia A (n=1) and traumatic brain injury (n=1) were identified. In 2 patients chromosomal anomalies (Prader Willi Syndrome resp. Noonan Syndrome) were diagnosed. For the remaining 18 patients; 7 cases with single or double hereditary thrombophilia (homozygous Protein S deficiency (n=1), Factor XII deficiency (n=2), Mutation in MTHFR Gene (C677T, A1298C) (n=3), Factor V Leiden Mutation (G1691A) (n=3), Prothrombin-Mutation (n=1) and Hyperhomocysteinaemia (n=1) were found.

**Conclusion:** Herein, an association between hereditary thrombophilia and neonatal ICH was found. Further investigations are necessary to reveal the role of hereditary thrombophilia in the pathogenesis of neonatal ICH.

**Keywords:** Neonates, ICH, Hereditary Thrombophilia, Fever, Sinuous Thrombosis, Prader Willi Syndrome, Noonan Syndrome

### Introduction

Neonatal intracerebral hemorrhage is a rare disease, however, its true incidence and prevalence remains unknown [7]. The occurrence of Intraventricular Hemorrhage (IVH) is described in premature infants with an incidence up to 25 % in preterm below 32 weeks Gestational Age (GA) [15]. Low birth weight and early gestational age represent the main risk factors for IVH in preterm. Additionally, hypoxia, alterations of physiological arterial carbon dioxide partial pressure (pCO2) and instability of the arterial blood pressure are associated with IVH in preterm and reflect the lacking autoregulation mechanisms to ensure a constant cerebral pressure and blood flow in the premature organism [1].

However, these pathomechanisms of Intracerebral Hemorrhage (ICH) might not be transferrable to the group of near to term or term neonates. The phenotype of bleeding of the central nervous system in full-term neonate is different. Subarachnoid Hemorrhage (SAH), Intraventricular Hemorrhage (IVH) and cerebellar hemorrhage occur more often in preterm infants whereas Subdural Hemorrhage (SDH) and Intraparenchymal Hemorrhage are mostly observed in neonates with higher gestational age [3].

Well known causes of cerebral hemorrhage in term neonates are birth trauma, asphyxia and vitamin K deficiency respectively Hemorrhagic Disease of the Newborn (HDN). HDN is caused by a low postnatal plasma level of vitamin
diagnosis intracranial bleeding (n = 31; gestational age 33 – 41 weeks) admitted between January 2005 and 2013 to the Neonatal Intensive Care Unit (NICU) at the department of pediatrics at the University Hospital Frankfurt/Main, Germany were included.

Patient data were obtained from the chart report either from the Neonatal Intensive Care Unit (NICU) or the out-patient clinic. Patients with missing / inconsistent data or lacking parental informed consent were excluded (n=4).

The approval from the Ethics committee of the JW Goethe University Hospital was obtained (No. 251/13).

**Diagnostic Workup/Hemostasiological Workup**

The initial diagnosis of ICH was made by cerebral ultrasound and confirmed by CT or MRI in most cases. In all patients, immediate analysis of Red Blood Cells (RBC), White Blood Cells (WBC), platelets, hematocrit and plasmatic coagulation parameters was done including Prothrombin Time (PT), Partial Thromboplastin Time (PTT), fibrinogen and Antithrombin (AT). Additionally, cerebral ultrasound was done. Administration of either oral or intramuscular application of Vitamin K was checked. As a positive family history of bleeding or thrombosis is a stronger indicator of inherited diseases of the coagulation system rather than standard coagulation parameters, parents were interviewed on this item [11]. Retrospectively, symptoms, time course and type of bleeding as well as neurosurgical interventions and analysis of risk factors known to be associated with ICH like perinatal asphyxia was performed after parental consent was obtained. Herein, perinatal asphyxia was defined
as fetal stress and umbilical arterial cord pH < 7, 0 and/or 5
min APGAR < 6 and/or base excess >-16 mmol/l. In most cases
after the initial stabilization period, a MRI or emergency CT
scan were performed to document the extend of bleeding and
to detect potential sinus thrombosis. In those patients without
obvious risk factors for ICH, thrombophilic workup was
initiated (Figure 1).

Vitamin K policy
All newborns received 1 mg Vitamin K orally directly
postpartum. In case of directly postpartum admission to NICU,
all patients received 1 mg Vitamin K intramuscular. Outborn
patients received 1 mg vitamin K intramuscular after admission
regardless the hemostatic treatment in the delivering hospital.

Results
31 term or near term neonates (34-41 weeks gestational age;
15 inborns 16 outborns) with the diagnoses of ICH were
identified. Of those, 27 patients with complete data set and
parental informed consent were elected for the study. 15
patients were full-term neonates and 12 were preterm > 33
weeks GA. 21 of the neonates were male and 6 female. Mean
birth weight was 2725 g with 10 patients being small for
gestational age (SGA). Except for the patients with Noonan
and Prader Willi Syndrom (PWS), SGA was explained as the
result from primary placental insufficiency.

Analysis of risk factors for ICH
In four patients, all born either by ventouse delivery, forceps
or emergency C-section, asphyxia with a 5/10 min APGAR
score of 5 (mean) and the need for extended cardiopulmonary
resuscitation in two cases after birth could be identified.

Regarding the way of delivery of the residual non asphyxiated
group of patients we found 12 patients born vaginally (1 with
assisted vaginal delivery; forceps) and 11 patients born via
primary or secondary Cesarean section.

HDN respectively Vitamin K deficiency was diagnosed in
one case, where parental consent for vitamin K administraton
could not be obtained. One case with traumatic brain injury
after maternal maltreatment directly after birth was identified.

Moreover, in two patients chromosomal anomalies in which
an association with intracerebral bleeding is described in
the literature (Prader Willi Syndrome resp. Noonan
Syndrome) were found. The patient with PWS showed
unilateral intraventricular bleeding with posthaemorrhagic
hydrocephalus without the need of liquor drainage. Extended
infratentorial bleeding with consecutive hydrocephalus and
the need for temporary external liquor drainage was diagnosed
in the patient with Noonan Syndrome.

Hereditary F VIII deficiency (severe hemophilia A, residual
Factor VIII activity < 3%) was overt in one case. The patient
experienced subdural bleeding after ventouse delivery.
Neurosurgical intervention with drainage of the subdural
space was performed.

Of the remaining patients without risk factors as described
above (n=18); in 7 cases single or double hereditary
thrombophilia (homozygous Protein S deficiency (n=1), Factor
XII deficiency (n=2), Mutation in MTHFR Gene (C677T,
A1298C) (n=3), Factor V Leiden Mutation (G1691A) (n=3),
Prothrombin-Mutation (n=1) and Hyperhomocysteinaemia
(n=1) was diagnosed.

Symptoms
Most of the newborns expressed typical signs for ICH:
seizures (n=14) muscular hypotension with or without
reduced consciousness (n=10) and arterial hypotension
(n=4). However, cumulative 9 patients were observed with
isolated pathologic body temperature: 4 neonates had fever
(> 35° and 5 showed body temperature disturbances with rapid
changes between hypothermia and hyperthermia (none of the
asphyxiated patients underwent therapeutic hypothermia).

Hemostatic treatment
8 patients received Fresh- Frozen- Plasma (FFP), 9 newborns
obtained transfusion of RBC was necessary in 9 cases. 4 patients
received Platelet Concentrates (PltC). Prothrombin complex
concentrate was administered in the patient without Vitamin K
prophylaxis and later confirmed Vitamin K deficiency.

In 3 patients with double thrombophilic mutations,
subcutaneous Low Molecular Weight Heparin (LMWH) was
given as secondary thromboembolic prophylaxis during their
hospital stay.

Outcome
All patients underwent intensive care treatment, 8 needed
ventilation for at least 24 hours. For 6 children, neurosurgical
intervention (2 x Rickham-Reservoir, 3 x drainage of subdural
hematoma, 1 x external liquor drainage) was necessary.

2 patients died on day of life (DOL) 10 respectively 10 months
after birth. All other patients could be discharged at home and
had long term survival. All surviving 6 patients with hereditary
thrombophilia were observed after discharge at the outpatient
clinic for pediatric hemostaseology for an observational period
of at least 3 months.

Discussion
Clinical presentation
In most of our patients, typical symptoms indicating for ICH
were recognized. The majority of our patients presented with
seizures or apneic convulsions as described in the literature [3].
Surprisingly, we found isolated abnormal body temperature
in 9 out of 27 patients (24% of cases, 4 presented with fever;
5 with dysregulation of body temperature) as single symptom indicating that 'something is wrong with the baby'. This is in concordance with the findings of Fang et al, who described hyperthermia as early sign for ICH in term neonates [5]. Our observation is pointed out in the group with confirmed thrombophilia and sinus thrombosis (Table 1), where in 3 out of 7 cases isolated temperature instability was observed as first symptom. Speculative, whether cases with slightly pathologic body temperature could have been included in the group of 9, 4% of patients, who were described to have no clinical signs directly related to ICH in the Brouwer study [3]. However, we suggest to perform cerebral ultrasound in any newborn with unexplained temperature instability even if apparently healthy.

An association between hereditary thrombophilia and the phenotype of bleeding could not be found in our study. Kersbergen described arterial thrombosis of the middle cerebral artery and sinus thrombosis followed by intracerebral bleeding as most common manifestation of a (hereditary) prothrombotic disease during the neonatal phase, affecting nearly 50% of those patients [9]. We did not see cerebral arterial cerebral infarction in our collective; however, we identified sinus thrombosis in 4 out of 7 patients with single or double hereditary thrombophilia. Diagnosis of sinus thrombosis was always made or at least confirmed via CT-scan or MRI. Sinus thrombosis can be missed by ultrasound based diagnostic and might have been misdiagnosed as reason for congestive bleeding in the historical collective of unexplained cases with ICH [10]. For the diagnosis of sinus thrombosis and the subsequent evaluation of the potential thrombolytic and anticoagulatoric treatment options of neonatal sinus thrombosis we would suggest performing early CT or MRI scan in neonates with unexplained ICH.

**Factors associated with ICH**

In our collective, we identified patients with known causes of cerebral hemorrhage like HDN resp. Vitamin K deficiency, trauma and asphyxia. Although the mode of delivery is also described as potential risk factor for bleeding of the central nervous system in neonates [12], we were not able to present statistically significant data on this, probably due to the small study collective.

Thrombocytopenia because of sepsis, asphyxia or fetal neonatal alloimmunithrombocytopenia (FNIAIT) are also known risk factor associated with the development of ICH in nearly 10 % of those cases [2]. However, we did not identify qualitative or quantitative platelet disorders as reason for ICH in any of the herein described cases except for the patient with Noonan Syndrome.

**Hereditary thrombophilic conditions**

In those patient without obvious explanations for ICH, we analyzed patients’ blood for Protein C/ Protein S deficiency (plasma activity levels and consecutive genetic confirmation), Factor XII deficiency (plasma activity levels), and a mutation in MTHFR Gene (C677T, A1298C), Prothrombin-Mutation (n=1) and Hyperhomocysteinaemia. Although the role of these mutations in the pathogenesis of ICH in term neonates are unclear, an association between a mutation in the MTHFR Gene (C677T, A1298C) and intraventricular hemorrhage in preterm neonates below 32 weeks of gestational age was found [16].

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**Table 1: Hereditary thrombophilia.**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>GA</th>
<th>APGAR UA-pH</th>
<th>1 symptom</th>
<th>Type of bleeding</th>
<th>SVT y/n</th>
<th>Intervention</th>
<th>Mutation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>10/10/10</td>
<td>Seizures</td>
<td>Intracerebral mass bleeding</td>
<td>n</td>
<td>Homozygous Protein S deficiency</td>
<td>+ DOL 10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>8/9/9</td>
<td>fever</td>
<td>Unilateral IVH Grade II Thrombosis Sinus. sag.</td>
<td>y</td>
<td>Lumbal punctue</td>
<td>Heterozygous FV Leyden Mutation and MTHFR Mutation</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>8/10/10</td>
<td>Temp dysbalance</td>
<td>Unilateral IVH Grade III Thrombosis Sinus transversus</td>
<td>y</td>
<td>Homozygous FV Leyden Mutation and Heterozygous Prothrombin-Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>9/10/10</td>
<td>Temp dysbalance</td>
<td>Unilateral IVH Grade II Plexus chooroideus bleeding Thrombosis Sinus sag.</td>
<td>y</td>
<td>F II Deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>37</td>
<td>10/10/10</td>
<td>Seizurs Fever</td>
<td>Thalamusbleeding Thrombosis Sinus. sag and Sinus transversus</td>
<td>y</td>
<td>Hyperhomocystein-aemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>36</td>
<td>10/10/10</td>
<td>Intrauterin Hydrocephalus</td>
<td>Bilateral Plexus chooroideus bleeding</td>
<td>n</td>
<td>Homozygous MTHFR-Mutation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>8/8/9</td>
<td>none</td>
<td>SAB Plexus chooroideus bleeding Hydrocephalus</td>
<td>n</td>
<td>F XII deficiency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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FXII (Hageman Factor) has a key role in activation of intrinsic coagulation. Surprisingly FXII deficiency, which mostly occurs in a heterozygous condition, is not known to cause bleeding complication. Rather it is associated with thromboembolic complications [14]. However, FXII deficiency has not been examined in the context of either sinus thrombosis of any age nor neonatal thrombosis or intracerebral hemorrhage.

The key message we learned was that the first cerebral manifestation of a hereditary thrombophilic disease might be hemorrhage and not as expected, arterial infarction or thrombosis. This is pointed out in the one herein included case with homozygous Protein S deficiency. The patient was admitted with hemorrhagic shock due to intracerebral mass bleeding and not with purpura fulminans or deep venous thrombosis, which is described as typical manifestation of homozygous protein S deficiency [6].

 Syndromal disease
In two patients with indicative morphological features, genetic testing was performed. PWS resp. Noonan Syndrome, an autosomal dominant disorder with mutations in the PTPN11 gene in 50 % of cases was diagnosed. In both patients thrombophilic screening, performed as described above, was unremarkable. Moreover, von Willebrand disease and FXII deficiency were excluded, platelet morphology and platelet count remained normal. We confirmed the diagnosis of PWS in one child with mild perinatal asphyxia due to muscular hypotension and a unilateral intraparenchymatous bleeding. Perinatal intracerebral bleeding in PWS patients is only reported in single case reports [9] and pathogenesis of bleeding in the coexistence of PWS remains unclear. As our patient had no other associated risk factors for ICH including hereditary hemophilic conditions or platelet associated diseases, we are able to add a further case of PWS associated ICH unfortunately without elucidating the pathogenesis of ICH in this patient.

Noonan syndrome is described with the concordance of bleeding disorders either FIX deficiencies or others [11]. In our patient with Noonan syndrome we observed intratentorial bleeding and consecutive hydrocephalus. FIX was within normal range. The gene product of the mutated PTPN11 Gen is SHP-2-Protein, a protein which has multiple functions and plays for example an important role in the suppression of cell adhesion of different cells like platelets. Impairment of platelet aggregation that correlates with pathologic closure times is known in those patients [13] and a potential reason for the cerebral hemorrhage in this case.

Conclusion
In our study, we were able to confirm that severe asphyxia and birth-associated trauma serve as risk factor for ICH in mature newborns. In addition, we found an association of hereditary thrombophilia with neonatal ICH. Hereditary thrombophilic conditions with consecutive cerebral infarction or (sinus-) thrombosis should be considered in the differential diagnosis and therapy. Further studies are necessary to reveal the impact of hereditary thrombophilia in the genesis of neonatal ICH.

References