New insights into paediatric haemostasis: thrombosis and bleeding issues

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Substantial progress in the understanding of the coagulation and fibrinolytic systems in neonates and infants has been made over the past two decades. Paediatric haemostasis differs from that in adults, offering some protection against thrombotic manifestations in the healthy paediatric individual (1-3). Venous and arterial thromboses are rare diseases which are, however, being increasingly diagnosed and recognised also in infancy and childhood (2, 4, 5). Thrombus formation and thrombus growth are the result of local coagulation activation combined with a disturbance in the balance between pro- and anti-coagulant mechanisms, leading to a prothrombotic state in the affected paediatric patient. Numerous clinical and environmental factors have been reported to result in elevated thrombin generation with subsequent thrombus formation in infancy and childhood. In addition, in vivo and in vitro studies have demonstrated that components of the haemostatic system differ between neonates, infants and adults (1, 3).

In the newborn, plasma concentrations of the vitamin K-dependent coagulation factors, contact factors and high molecular weight kininogen are approximately 50% of adult values. These levels increase rapidly in the first weeks of life, and low range adult reference values for most coagulation proteins are reached by 6 months of age. However, during childhood (neonate to 18 years), levels of coagulation proteins are still 10-20% lower than the normal adult values. The vitamin K-dependent natural anticoagulant proteins C and S are low (as compared to normal adult range) in the neonatal period as well. Furthermore, the capacity of newborn plasma to generate thrombin, which is clearly dependent on plasma concentrations of antithrombin and protein C, is reduced to approximately 50% of that of adults (3). These relations, however, do not seem to increase the risk of bleeding complications, but may provide a mechanism for thrombosis protection during infancy and childhood: In risk patients presented with cardiac diseases, central venous lines, cancer, rheumatic diseases, metabolic disorders, infections or trauma, thrombotic manifestations occur in less than 5% of children compared with approximately 40% of adults. Besides age-specific underlying triggering factors, various genetic pro-thrombotic defects following a different distribution with respect to ethnic backgrounds studied have been established as risk factors for thromboembolism also in paediatric patients. Within the entire childhood population, neonates are at greatest risk of thromboembolic complications, which may also start early in utero, affecting the foetus. Thereafter the incidence of vascular complications decreases significantly within the first year of life, with a second peak of thrombotic risk during puberty and adolescence. In this issue of *Thrombosis and Haemostasis* a collection of articles related to the theme issue of “Paediatric Haemostasis” will provide more insight into thromboembolic as well as bleeding complications in newborn and infants, and possible strategies of therapeutic intervention (see pages 678-738).

As a potential basis for future collaborative studies, Brenner et al. summarise important information on obstetric complications induced by maternal thrombophilia (6), e.g. the possible involvement of foetal wastage, prematurity or intrauterine growth retardation (7). Further studies have also to take into account potential, yet hardly proven, interrelations between neonatal thromboembolism and maternal thrombophilia. The study presented by Rehak et al. highlights the interactions...
between von Willebrand factor and platelet function in the neonate (8), whereas Salonvaara and colleagues focus on age-dependent normal coagulation values and their interrelations mainly in preterm babies (9).

The most common causes/sites for thrombus formation in neonates are peripartal stroke (10), cerebral venous thrombosis, and renal venous thrombosis, respectively (11). The European view of paediatric ischaemic stroke in neonates and older children and possible directions towards future research strategies are given by Kirkham et al. (12). Duering and colleagues report on the evaluation of reference values of total tissue factor pathway inhibitor (TFPI) antigen in children and adolescents (under the age of eighteen years) and the independent role of low TFPI values for the risk of developing stroke or venous thrombosis during childhood (13). Kenet and colleagues discuss new data on incidence and outcome of cerebral venous thrombosis in Israel (14), Swarte et al. report on four cases with neonatal cerebral venous thrombosis associated with the prothrombin mutation (15), while Kuhle et al. add new clinical information from the “1-800-NO-CLOTS Consultation Service”, a phone-call based database obtained from children with venous and arterial thromboembolism, from the Canadian point of view (16). In addition, this working group separately report on a large series of neonatal renal venous thrombosis in North America (17). The latter, along with the German long-term follow-up data very recently published by Kosch et al. (11), give important information on this rare thrombotic entity in paediatric patients. This issue continues with a comparison of home treatment options for paediatric thromboembolic diseases reported by the Australian group (18), and the final contribution of this “Paediatric Theme Issue” summarises data available on the use of recombinant factor VIIa in various bleeding conditions in non-haemophilic children (19).

In summary, besides new insights into possible mechanisms of neonatal/paediatric thrombotic complications, contributions to this theme issue pointed out the need for large collaborative international studies based on similar ethnic backgrounds to clarify not only the role of congenital prothrombotic disorders in paediatric patients with arterial or venous thromboses, but also the need to focus on valid guidelines for prophylaxis and therapy. In addition, strong cooperation between international paediatric coagulation specialists and e.g. paediatric neurologists or nephrologists, or adult haematologists is essential of gaining deeper knowledge about causes of thrombotic and bleeding disorders in paediatric patients.

Acknowledgements
The authors thank Susan Griesbach for help in editing this manuscript.

References