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Review Article

Management and investigation of neonatal thromboembolic events: Genetic and acquired risk factors

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ABSTRACT

Newborns comprise the largest group of children developing thromoboembolic events (TE_S), due to the peculiarities of their developmental hemostatic system. Moreover, in the sick newborn, especially preterm, numerous acquired perinatal and iatrogenic conditions might result in a disturbance between coagulation and fibrinolysis, leading to thrombus formation.
Nevertheless, the contribution of acquired prothrombotic disorders in the pathogenesis of thromboembolic disease in newborns remains poorly defined. Few data are currently available regarding the influence of maternal or fetal genes on thrombotic risk in the fetus and neonate. Ongoing National and International registries are partially answering these questions.
The purpose of this review is to evaluate the current knowledge about the role of inherited, acquired perinatal and maternal prothrombotic risk factors in neonatal cerebral nervous system (CNS) thrombotic events and non-CNS thrombotic events.

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Introduction

Thromboembolic events (TE_S) are uncommon during childhood. The incidence of symptomatic TEs is 0.07/10.000 in children [1], compared to 2.5-5% in adults. Nevertheless, TEs are increasingly recognised problems in the pediatric age, occurring in children surviving previously life-threatening primary disease. Due to the unique peculiarities of their developmental coagulation system, newborns are at highest risk of developing TEs among pediatric patients [2].

Recently, several studies based on national and international registries [1,3–5] have evaluated the role of risk factors for thrombosis both in children and newborns, emphasizing the differences between different paediatric age and adult age.

Nevertheless, few data are currently available regarding the influence of inherited thrombophilia, maternal thrombophilia and prenatal gestational risks on development of thrombosis in the fetus and neonate. Moreover, at present there is no consensus about recommendations on screening for thrombophilia in newborns with TEs.

Aim of the present study was to provide an overview of the current knowledge about the role of risk factors in neonatal cerebral nervous system (CNS) thrombotic events and non-CNS thrombotic events.

In preparation for this manuscript, search for the published English language literature was performed via the MEDLINE database and was supplemeted with additional cross-references through bibliographies.

The neonatal hemostatic system

The hemostatic system is a dynamic evolving system and during infancy and early childhood it profoundly differs from adults. Plasmatic levels of several clotting factors are low at birth, reaching adult ranges only after weeks or months. In normal neonates, the levels of FII, FVII, FIX, FX, FXI, Prekallikrein, High-Molecular-Weight Kininogen, Protein S, Protein C, Antithrombin (AT), Heparin Cofactor II, and Plasminogen are all approximately 50% of adult levels, while levels of FV, FVIII, FXIII, and fibrinogen are closer to adult values. The endothelium and platelets generally appear to be less reactive in neonates than in adults though high levels of von Willebrand Factor are usually present. Despite increased tissue plasminogen activator (t-PA), newborns have lower plasma levels and activity of plasminogen and increased concentration of plasminogen activator inhibitor (PAI) [6–8].

Some characteristics (i.e. the delayed and reduced capacity to generate thrombin) provide protection against thrombosis, other (i.e. decreased levels of natural anticoagulants) provide protection against hemorragic events. Therefore the hemostatic system of the healthy neonate, although immature, is generally in balance; on the other hand, in the sick newborn, especially preterm, numerous acquired perinatal and iatrogenic conditions might result in a disturbance between coagulation and fibrinolysis, leading to TEs. Indeed, the incidence of neonatal thromboembolism is likely to increase as care advancements are made in neonatology.

The physiological reduction of some coagulation factors and anticoagulant proteins may lead to a difficult interpretation of laboratory investigations and therefore deficiencies need to be confirmed by repeat testing later in infancy (i.e. beyond 6 months or afterward in premature infants) [9].

Inherited thrombophilia

The term thrombophilia is used to describe an extensive range of inherited defects in the coagulation system, in the fibrinolytic system, in the endothelial cells and in platelets which are likely to predispose to thrombosis. Over the last decade the number of identified prothrombotic abnormalities has increased dramatically.

Genetic prothrombotic polimorphisms FV G1691A (R506Q, FV Leiden mutation), Factor II G20210A and the homozygous TT genotype of the methylentetrahydrofolate reductase (MTHFR) C677T polymorphism, are estabilished inherited thrombophilic conditions [10].

Normal levels of natural anticoagulants Protein C, Protein S and AT are significantly lower in newborns than in older children and adults, mean values being 35%, 36% and 63% of adult means, respectively [8]. Whether these transient physiologically reduced levels may be implicated in the pathogenesis of neonatal thromboembolism remains to be determined. On the contrary, despite the low prevalence, congenital deficiencies in naturally occurring inhibitors of coagulation are recognized inherited thrombophilic conditions.

More recently, some studies indicated that increased Lp(a) concentrations play an important role in childhood and neonatal thrombosis, too [11–13].

Other very rare disorders, such as dysfibrinogenaemia, dys/hypoplasminogenemia, homozygous homocystinuria are associated with increased risk of thrombosis but their role in favouring thrombotic events in newborns is not completely clear yet.

Maternal thrombophilia and gestational risk factors

Few data are currently available regarding the influence of maternal thrombophilia (prothrombotic polymorphisms, dislipidemia, antiphospholipid antibodies) and prenatal gestational risks (gestational diabetes, pregnancy-induced hypertension-preeclampsia, intrauterine growth restriction) on thrombotic risk in the fetus and neonate.

During gestation, the maternal and fetal circulation systems coexist and interact with the placenta. Association between thrombosis and infarction in the placenta and peri- and neonatal infarction, the most commonly presumed mechanism being embolization to the fetus, has been reported in literature [14–16]. Pregnancy itself is a prothrombotic state as shift toward prothrombotic reactions is seen in women as gestation progresses through the second and third trimesters and just after gestation [17] (increased levels of vitamin K-dependent factors II, VII, and X; increased levels of thrombin-antithrombin complexes, increased endothelial activation with elevated levels of circulating von Willebrand factor and soluble thrombomodulin; increased triglyceride and lipoprotein(a) levels; reduced levels of free and total Protein S and reduced activated Protein C sensitivity ratio). However, maternal thrombosis during and just after pregnancy often occurs in the presence of additional risk factors (i.e advanced maternal age, cesarean section, hypertension, gestational diabetes, infections, pre-eclampsia/eclampsia, antiphospholipid syndrome -APLS, and inherited thrombophilia). Some of these maternal factors may also predispose to placental infarction with subsequent cerebral infarction in the fetus.

Pre-eclampsia may lead to endothelial activation of coagulation. Gestational diabetes leads to maternal vascular damage which can predispose to placental thrombosis and infarction. In case of chorioamnionitis, inflamed vessels of the placenta lead to localized thrombosis, vasospasm and infarction and maternal sepsis during gestation may lead to disseminated intravascular coagulation resulting in placental thrombosis and infarction, too. Maternal smoking may lead to vasospasm and/or endothelial activation with resulting placental injury and growth retardation and maternal cocaine use may predispose to vasoconstriction with resulting placental infarction. Moreover, thrombocytosis has been observed in neonates of mothers with history of polydrug use. At the time of delivery, placental-fetal transfusion may lead to polycythemia [18].