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Prothrombotic Risk Factors in the Evaluation and Management of Perinatal Stroke

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The ischemia in children affected by perinatal stroke has long been thought to be driven by nonhematologic maternal and perinatal events. New information from clinical studies, however, tells us that plasma-phase risk factors, such as factor V Leiden, elevated lipoprotein (a), and mutations in MTHFR, may be important in the pathogenesis of perinatal stroke, if not always in the risk of recurrence. With regard to stroke recurrence, this risk is only about 2% according to the largest follow-up study to date, and certainly less than 5%. Nonetheless, when strokes do recur, they tend to be associated with the presence of plasma-phase risk factors in the affected child, suggesting that a small percentage of children with a first perinatal stroke may benefit from anticoagulation therapy, both to prevent stroke recurrence as well as occurence of a second, non-CNS thrombotic event. Counselling of parents with regard to subsequent pregnancies should always include medical management of systemic maternal disorders, such as diabetes, persistently elevated antiphospholipid antibodies, and inherited maternal hypercoagulability states.

KEYWORDS perinatal stroke, prothrombotic risk factors, thrombophilia, maternal preeclampsia, placental pathology, diagnostic imaging, anticoagulation

Ischemic cerebrovascular accidents in children overall are uncommon, with an estimated incidence of about 7 per 100,000 children per year, but they are potentially devastating to those affected.[1] In newborns, the incidence of arterial ischemic stroke (AIS) has been estimated to be higher, at 18[2] to 93 per 100,000 live births.[3] Causes or potential risk factors for such stroke include infection, preeclampsia, diabetes, and drug use in the mother; and infection, dehydration, traumatic delivery, complex congenital heart disease, and catheter placement in the newborn.[2] However, inherited or acquired defects of coagulation are receiving increasing attention. These defects can shift the balance between coagulation and anticoagulation toward thrombosis. Although the specific risk posed by prothrombotic states for stroke in newborns remains controversial, there is growing evidence that certain plasma-phase risk factors (1) contribute to the pathogenesis of newborn stroke, (2) are associated with recurrent stroke in the fewer than 5% of neonates who suffer recurrence, (3) may be predictive of non-central nervous system (CNS) thromboembolic events during the first year of life, and (4) may be predictive of subtle cognitive impairment within the first 2 years of life.

In the following review, we outline (1) some of the important risk factors, including plasma-phase risk factors, important to consider in evaluating acute AIS in neonates; and (2) our current recommendations for diagnostic assessment and management of AIS in the newborn, including those relatively uncommon situations warranting use of anticoagulation. It is important to note that many of the plasma-phase risk factors are thought to contribute to venous—and even arterial—thromboembolism in all age groups. With the notable exception of polymorphisms in methylenetetrahydrofolate reductase (MTHFR), all plasma-phase risk factors cited below are assumed to be the heterozygous state; homozygous states of inherited plasma-phase risk factors exist as well, but these are beyond the scope of the present article.

Causes of Perinatal Stroke

For most cases of perinatal stroke, the etiology remains presently unknown. Nonetheless, as new knowledge is gained

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about its pathophysiology, it is important to retain a distinction between strokes which occur in utero and those more acute strokes which occur just before or at the time of birth. The latter often present with seizures and encephalopathy, as many of these are due to thromboembolism from an intracranial or extracranial vessel, the heart, or the placenta, or result from vasoconstriction or direct compression of intracranial vessels. Associated conditions include congenital heart disease, patent foramen ovale, infection, shock, maternal antiphospholipid antibodies, maternal diabetes, umbilical artery and vein catheters, and birth trauma. Prognosis is considered favorable for children with acute strokes insofar as what may appear initially as significant tissue loss on brain MR, in follow up, often shows tissue regeneration and/or repair from re-perfusion of the infarcted region. In utero strokes can be undiagnosed at birth and may go unnoticed until months or even years later, when a child is brought to his pediatrician or a pediatric neurologist with hemiparesis or unexplained developmental delay.

Thrombophilia and Arterial Ischemic Stroke

Although causes of both types of perinatal stroke are likely multifactorial, prothrombotic plasma-phase risk factors are very frequent, occurring in 127 of 215 (61%) neonates studied by Kurnik and coworkers.[4] Yet stroke recurrence is uncommon, being observed in only 4 of these same 215 children (2%) versus 7% to 22% in older children.[5] This suggests that such risk factors may contribute to the pathophysiology of perinatal stroke, but are not usually sufficient conditions for stroke. In the following section, we review the most widely examined plasma-phase risk factors that have been considered in the pathophysiology of AIS in children, including older children as well as newborns. We also wish to point out that there are very few studies focused specifically on newborns, these including those of Gunther and coworkers,[6] Mercuri and coworkers,[7] Curry and coworkers,[8] Simchen and coworkers,[9] and Kenet and coworkers.[10] The larger studies of Gunther and coworkers[6] (91 patients) and Mercuri and coworkers[7] (24 patients) deserve special weight.

Factor V Leiden

Factor V Leiden is a recently identified mutant form of factor V where there has been a G->A transition at nucleotide 1691 in exon 10 of the factor V gene. This results in the replacement of an arginine at position 506 by a glutamine, and the subsequent resistance of the factor to inactivation by activated protein C. It accounts for approximately 95% of activated protein C resistance, although other mutant forms of factor V have been described (Cambridge, Toronto). A significant number of case reports and case series have demonstrated an association between factor V Leiden and ischemic stroke in neonates,[5,6] older children, and young adults.[10-14] Factor V Leiden, however, was not found to be a risk factor for pediatric or neonatal stroke in two studies.[15,16]

Prothrombin 20210A

The prothrombin 20210 (PTG20210A) mutation involves a G->A transition at nucleotide position 20210 in the 3′ untranslated region of the prothrombin gene and is associated with increased levels of prothrombin activity. Although three small (33 to 63 patients) retrospective studies of PTG20210A failed to identify a risk of stroke in childhood patients,[10,16,17] a much larger (148 patients) prospective study by Nowak-Göttl and coworkers[11] and a study by Akar and coworkers[14] did show this mutation to be significantly associated with childhood stroke. Although Gunther and coworkers[6] found prothrombin 20210 not to be a risk factor, a definitive study of this gene mutation in newborn stroke is lacking.

Lipoprotein (a)

Elevated lipoprotein (a) is a newly identified genetically determined risk factor for atherosclerosis and cardiovascular disease. Several studies have suggested its importance in ischemic stroke in neonates[6] and older children.[11,18,19] Lipoprotein (a) is essentially a low-density lipoprotein with an additional covalently linked glycoprotein called apolipoprotein (a) as a distinguishing characteristic. Serum concentrations of lipoprotein (a) are minimally influenced by environmental factors, including diet. Apolipoprotein (a) is a member of a family of "kringle"-containing proteins and shares a high degree of sequence identity with plasminogen. The homology of segments of apolipoprotein (a) to the fibrin binding sites (kringles) of plasminogen is thought to be responsible for the antifibrinolytic activities of lipoprotein (a). In vitro studies show that lipoprotein (a) competes with plasminogen for binding sites on a specific endothelial cell receptor and may interfere with endogenous endothelial cell-mediated fibrinolysis. Lipoprotein (a) also binds and inactivates tissue factor pathway inhibitor.[20]

Antithrombin III, Protein C, and Protein S

The role of the hereditary deficiencies of the naturally occurring coagulation inhibitors, namely antithrombin III, protein C, and protein S, in the development of ischemic pediatric stroke remains debatable. Antithrombin III inhibits serine esterase activity, and this inhibition accounts for its effects not only on thrombin but also on activated forms of factors XII, XI, IX, and X. Protein C, a glycoprotein, is activated by the thrombomodulin–thrombin complex on the endothelial cell surface, thereby becoming a serine protease with both anticoagulant and profibrinolytic activities. In the presence of protein S, activated protein C degrades the thrombin-activated forms of factor V and VIII. In addition, activated protein C forms complexes with plasminogen activator inhibitor-1 (PAI-1), which process serves to decrease free PAI-1 and thereby diminish inhibition of tissue-plasminogen activator. Tissue-plasminogen activator, in turn, converts plasminogen into the enzyme plasmin. Case reports and case-