Preterm Infant with a Catastrophic Hemorrhagic-Thromboembolic Incident

Adel E. Abdelhamid

Rosie Hospital, Cambridge University Hospitals, Cambridge, UK

Established Facts

- Neonates are at increased risk for thrombosis; in part, pregnancy is a prothrombotic condition, and plasma concentrations of factors involved in coagulation and fibrinolysis differ significantly compared to children and adults.
- Thrombophilic disorders, known to be multigenic, may be phenotypically expressed in different perinatal and neonatal thrombotic syndromes that may lead to lifelong disability.
- An association between thromboembolic/hemorrhagic brain diseases in the newborn and both factor V_{Leiden} and prothrombin G20210A mutations has been recognized.

Novel Insights

- Disseminated intravascular coagulopathy, representing the extreme stage of thrombohemorrhagic conditions, may be secondary to a prothrombotic disorder of combined heterozygosity.
- Neonatal thrombotic risk in response to a paternal or combined parental disorder may be underreported, with the focus being on mothers during pregnancy.
- Neonates with significant/widespread disseminated intravascular coagulopathy but no clear cause may be candidates for thrombophilia screening.

Key Words

Preterm infant • Neonate • Thrombosis • Embolism • Bleeding • Coagulopathy • Stroke

Abstract

Thrombotic disease of the newborn is uncommon but usually associated with serious morbidity and mortality. Although the operating mechanisms of coagulation and fibrinolysis are the same in all age groups, plasma concentrations

of the two systems' components are significantly different in neonates compared to children and adults. This places neonates at greater risk for thrombosis that may rise considerably if a predisposing factor is present or a genetic or medical condition predisposing to thrombosis coexists. While marginal, the possibility of abnormal bleeding secondary to congenital prothrombotic disorders has been described. A significant association between thromboembolic/hemorrhagic disease in newborns and each of factor V_{Leiden} and prothrombin G20210A mutations has been reported. Al-

though not a frequent occurrence in adults and children, congenital 'multigenic' thrombophilia is well known. However, the combined heterozygote state of both mutations is perhaps underreported in preterm infants. We present a severely intrauterine growth-restricted preterm baby born to consanguineous parents. He had stroke as part of a generalized bleeding-thromboembolic incident caused by combined heterozygote mutation of factor V_{Leiden} and prothrombin G20210A, each of which was then found in a heterozygote form in each of the 2 parents.

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Introduction

Both thrombin-stimulated fibrin clot formation and plasmin-induced clot lysis pathways are carefully linked and regulated [1]. As clot formation progresses, thrombin binds to thrombomodulin to activate protein C and stop platelet activation or fibrinogen cleavage [2]. Activated protein C and protein S inactivate prothrombinase and intrinsic X-ase, respectively [3].

Thrombophilia is the term used to describe a group of inherited conditions associated with increased, and often recurrent, tendency for venous and/or arterial thromboembolism [4].

Thrombophilia is a 'multigenic' disorder that represents an interaction between the collective effects of the genotype at one or multiple loci either to raise or to lower susceptibility to disease, combined with a variety of environmental exposures that may trigger, accelerate, exacerbate or protect against the disease process [5].

A crucial element for successful gestation is the healthy growth and development of the placental vasculature. The uteroplacental interface receives almost 20% of maternal cardiac output. This initiates a self-protective physiologic adaptation in the form of increased 'thrombogenicity' at the interface. If the mother has a thrombotic tendency, the placenta may develop an unduly thrombogenic microenvironment [6].

In addition to the higher risk of placental thrombotic vasculopathy resulting in such complications as pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and placental abruption, maternal thrombophilia is also associated with a higher risk of neonatal thrombosis [7].

Neonatal thrombophilia is rare and not usually promoted by heterozygosity at a single thrombophilia locus, but rather by rare homozygous and combined heterozygous mutations of multiple genes [8].

Although all thrombophilias have been associated with neonatal thrombosis, only homozygous or compound heterozygous protein C and/or protein S deficiencies are reported as adequate to induce neonatal thrombosis [9].

Factor V_{Leiden} (FVL), attributable to a specific autosomal dominant gene mutation, is an abnormal version of factor V that is not susceptible to cleavage by activated protein C and is inactivated more slowly, resulting in a hypercoagulable state [3].

Prothrombin G20210A mutation (PGM) is another autosomal dominant mutation marked by enhanced thrombin generation leading to increased activation of thrombin-activatable fibrinolysis inhibitor, resulting in inhibition of fibrinolysis and increased thrombotic risk [8].

Each mutation predisposes patients with a heterozygous or homozygous state to a considerable risk of thromboembolism. The combined heterozygote state of both mutations in an individual may further increase this risk than each mutation alone [10].

We report on a case of an IUGR preterm infant presenting with a disseminated intravascular coagulopathy (DIC) picture of mixed thrombosis and bleeding secondary to a prothrombotic disorder of combined heterozygosity of 2 'thrombophilic' genes in accordance with history elements, supported by autopsy findings of multi-organ involvement. The parents' thrombophilia screens confirmed the heterozygote state of each, pointing to the importance of thrombophilia screening in such a context of abnormal obstetric, perinatal and neonatal history.

Case Report

An IUGR preterm male infant with a birth weight of 0.620 kg (<3rd centile), an occipitofrontal circumference of 22 cm (<3rd centile) and no dysmorphic features was born at 28 weeks' gestation to a 33-year-old, G4P₀₊₂₊₁ Asian, rubella-immune housewife with negative hepatitis B virus and HIV serology who presented with severe preeclampsia.

Apart from 2 stillbirths at 28 and 29 weeks' gestation and an intrauterine fetal death at 33 weeks' gestation, all in rural India, no past medical or obstetric history of note was reported. Her husband is her first cousin.

On admission, she was severely hypertensive and significantly albuminuric. Following obstetric review, she was commenced on antihypertensives, moved to theatre and had an emergency cesarean section.

Fig. 3. a Postmortem examination of the brain. A large infarct surrounded by hemorrhage occupied part of the right occipital, temporal and parietal lobes and affected the basal ganglia in particular. Left-side IVH with ventricular dilatation. **b** Postmortem examination of solid organs. (A) Lungs. Mottled external surface. Congested cut surfaces with evolving bronchopulmonary dysplasia, wide inter-alveolar septa and fibrosis, intra-alveolar macrophages, prominent arterioles and numerous thrombi. (B) Liver. Variegated with extensive hemorrhage, extramedullary hemopoiesis and ductular proliferation. (C, D) Adrenals and spleen. Widespread congestion, hemorrhage and thrombosis. (E) Kidney. Focal interstitial hemorrhage, extramedullary hemopoiesis and eosinophilic casts in some tubules. **c** Placenta examination. Superficial implantation and many small infarcts consistent with maternal vascular underperfusion.

Discussion

In support to the hypothesis that thrombophilia is a 'multigenic' disorder, with varied phenotypic expressions, we present this case of an IUGR preterm infant,

possibly as a consequence of maternal FVL-related pregnancy complications, born to an Asian couple that had no identifiable risk factors. The baby presented with a widespread mixed thrombohemorrhagic picture secondary to a prothrombotic disorder of combined heterozygosity of

Table 1. Blood results and transfusion incidents in the infant

	Day of life												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Hb, g %	14.2/14.1	13.8/13.9	14/11.4	15.9/12.9	13	13.4/14.9/13.8	17.1/13.5	14.1	14.4/13.9	11.5	15.9	15/11.5	15.7
PRBC Tn				*	*	*			*	*		*	*
Platelet count, $\times 10^9/l$	140/148	191/ 163	143/153	107/71	25	19/110/121	167/126	39	67/48	249	114	52/19	52
Platelet Tn					*	*	*		*			*	
PT, s	13	12.4/12.1	12.7	18.5	22	24.8	24.6	18.3	18.3	14.1		19.4	20.9
APTT, s	32.3	29.2/29.7	26.9	77.2		>180	74.7	63.6	64.7	42.3		79.1	55.5
INR	1.4	1.5/1.6	1.4	1.7	2.2	2.4	2.4	1.7	1.7	1.3		1.8	2
Fibrinogen, s	2	2.3/2.1	2.2	1	1.1	1	1.1	1.1	0.9	1.5		0.9	1.3
FFP Tn					*	*	*		*			**	*

Hb = Hemoglobin; PRBC = packed red blood cell; Tn = transfusion; PT = prothrombin time; APTT = activated partial thromboplastin time; INR = international normalized ratio; FFP = fresh frozen plasma.

* Transfusion given.

2 ‘thrombophilic’ genes, each subsequently found in one of the parents.

Although it is not the first reported case of neonatal thrombophilia associated with combined heterozygosity, it highlights areas in practice that may be overlooked in the management of familial, maternal and neonatal thromboembolic and hemorrhagic diseases in relation to prematurity.

Moreover, a relatively early-onset, possibly antenatal, extensive bleed associated with a big hemorrhagic parenchymal infarct in a 28-week preterm infant, in the context of DIC, would arguably need more than routine investigation.

This case indicates a higher risk of thrombosis/bleeding in preterm patients with a combined heterozygous defect, who are more prone to ‘atypical’ thrombosis/bleeding, especially intracranial.

As thrombosis/bleeding plus two thrombophilic mutations is perhaps a rare incident, the different presentations and risks need to be defined and addressed as more cases are identified.

Neonatal thrombophilia presents in different ways and involves different organ systems, especially the brain, resulting in neonatal stroke, central venous thrombosis and porencephaly, alongside such manifestations as purpura fulminans and renal vein thrombosis [9].

In addition to these common thromboembolic manifestations, fibrinolytic system disorders can also present with abnormal bleeding [11], which might have been responsible for, or at least contributory to, the DIC picture in our case.

Although underestimated, being masked by other pathologies known to present in preterm newborns, and not

fully addressed in some ethnicities, the incidence of pediatric thrombosis is the highest among neonates [8]. However, preterm babies represent a unique group in that the relatively frequent occurrence of intraventricular hemorrhage (IVH) usually masks the incidence of large venous thrombi or arterial stroke.

The mixed thrombotic-hemorrhagic state of DIC and IVH is not a rare incident in sick preterm neonates. The multifactorial etiology of the two conditions may involve coagulation/fibrinolysis disturbances and venous infarction, and many fibrinolytic system disorders, including FVL and PGM, have been found more commonly in preterm infants with IVH than in the general population. However, they are usually attributed to other pathologies. This may reflect not only the complexity of the disease processes and the multiplicity of risk factors involved, but also the subtle nature of clinical signs, lack of awareness or difficulties obtaining the necessary diagnostic tests.

Neonatal thrombophilia seems to be associated with multiple risk factors [12]. In the present case, apart from umbilical lines and perhaps cesarean section, risk factors such as infection, dehydration, congenital heart disease or polycythemia were systematically ruled out.

Evidence has pointed to maternal thrombophilic disorders as a cause of antenatal/neonatal thromboembolic manifestations [13]. However, neonatal thrombotic risk in response to a paternal or combined parental disorder is underreported.

The extent of the contribution of the father’s PGM and other risk factors to our baby’s DIC remains questionable. Data on the relation between maternal PGM and obstetric complications are very controversial. Few reports have

Table 2. Blood count, clotting and thrombophilia screening results in the infant's parents

	Father	Mother	Adult reference range
Complete blood count			
Hb, g %	13.3	10.6	13–17
Platelet count × 10 ⁹ /l	338	549	150–450
Clotting			
PT, s	10.5	11	12–14
APTT, s	22	27	23–38
TT, s	10.3	11.1	
Fibrinogen, g/l	3.5	3.4	2–4
FVL mutation	negative	heterozygote	negative
PGM	heterozygote	negative	negative
Protein C activity, %	78	71	70–140
Activated protein C resistance ratio	<2	2	<2
Protein S			
Total, g/l	73	66	65–85
Activity, %	76	72	70–140
Antithrombin			
Activity, %	81	103	80–120
Antigen, g/l	2.4	3	2–4
Fasting plasma homo- cysteine, μmol/l	8	7	<18
Lipoprotein(a), mg/dl	10	13	<30
Factor VIII, %	115	142	70–150
Anticardiolipin			0–25
IgG, U/ml	11	9	
Anticardiolipin			
IgM, U/ml	12	14	0–25
Lupus anticoagulant	negative	negative	negative
Anti-β ₂ glycoprotein-I			
IgG, U/ml	1	3	<10
Anti-β ₂ glycoprotein-I			
IgM, U/ml	1	2	<10

Hb = Hemoglobin; PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time.

related PGM to cerebrovenous thrombosis in newborns [14, 15].

Consanguinity may indicate a homozygous disorder; however, in our case, the combined heterozygote state is perhaps unusual unless the family has both defects or one or both of the mutations are de novo.

Cases of thromboembolism associated with homozygous FVL or PGM in children and newborns are quite rare and even rarer for the combined heterozygote mutations. In adults and children, however, congenital 'multi-

genic' thrombophilia is well reported, but not as a frequent occurrence [16].

Although the clinical implications of such an occurrence are not fully established, the risk for spontaneous and recurrent venous thromboembolism with FVL and PGM is significantly higher compared to that with either gene alone. This association was even more noticeable in females, indicating that the combined mutation defect may be more serious, perhaps requiring a different preventive and therapeutic approach, especially in pregnant women [17].

While more common thrombophilias, including FVL and PGM, are associated with a lower thrombosis risk than the less common ones (antithrombin III, protein C, protein S deficiency), the risk is 5–10 times higher in FVL heterozygotes than in normal individuals and 50–100 times higher in homozygotes than in normal individuals [9].

The incidence of thrombosis in pregnancy among patients with FVL is estimated to be around 17%. The prothrombotic effect of the FVL mutation may be further compounded by the 'physiological' progressive decrease in activated protein C during pregnancy [18].

Moreover, pregnant women with the FVL mutation can develop placental thrombosis and, in turn, complications associated with placental hypoxia such as pre-eclampsia, placental abruption, IUGR, stillbirth and miscarriage which necessitate anticoagulant therapy [19].

Both FVL and PGM are autosomal dominant traits. It is difficult to estimate the risk of clinical thrombosis in a given individual with one or both mutations, especially if heterozygote. This may be attributed to the variable penetrance, polymorphism and/or degree of exposure to other risk factors [16]. In the present case, each of the parents was heterozygote for one mutation, but neither had a clear family or personal history of thromboembolism. However, the mother presented a full-blown picture of thrombophilia-associated complications of pregnancy, with a bad obstetric history that may be explained by the high risk of recurrence.

Possible explanations of this phenomenon could be 'gene/gene interaction', i.e. when two or more different genes influence the outcome of a single trait, a 'double hit' mechanism, i.e. where the phenotype results from the accumulating influence of different mutations, with one priming the cell for the effect of the other(s), or polymorphism maintained by selection favoring the heterozygote [20].

Conclusion

Given the frequency of the 2 mutations FVL and PGM, a pregnant woman who presents with either a family, personal or obstetric history suggestive of thrombophilia should undergo testing to ensure proper risk stratification and therapeutic management.

A complete laboratory evaluation for these disorders, for both the mother and baby, is indicated in cases of neonatal stroke, central venous thrombosis and late fetal loss.

Congenital thrombophilia should be considered in patients with spontaneous or extensive thrombosis, ischemic skin lesions or purpura fulminans or a family history of purpura fulminans.

However, IVH, especially if atypical, is another candidate for the list of disease states that may be triggered by thrombophilic coagulation abnormalities including FVL, especially in such a context of a complicated obstetric history.

Disclosure Statement

The author has no conflicts of interest or financial disclosures to report.

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