Review

Inherited prothrombotic risk factors in children with first ischemic stroke

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Abstract

Stroke in children is a heterogeneous disorder. Over 100 risk factors for stroke have been reported and genetic predisposition to stroke has been established. The most frequently reported risk factors are congenital heart malformations, hemolytic anemias, collagen vascular diseases, some rare inborn metabolic disorders, trauma, infection and thrombophilia. The aim of this article is to provide an overview of investigated inherited prothrombotic risk factors in children with first ischemic stroke. Various prothrombotic risk factors have been investigated in pediatric stroke including elevated homocysteine and lipoprotein (a), antithrombin, protein C and protein S deficiency, Factor V Leiden, Factor II G20210A and plasminogen activator inhibitor-1 4G/5G polymorphism. Despite similar criteria for inclusion of different studies in meta-analyses investigating first ischemic stroke in children, the obtained results were not consistent for all prothrombotic risk factors. The discrepancies found could be explained by methodological issues like different sample sizes, patient populations included and lack of controls. In order to provide the necessary power for randomized control trials, multi-center, multi-national approaches like International Pediatric Stroke Study have been initiated with the aim to describe risk factors for childhood stroke and explore their relationship with presentation, age, geography, and infarct characteristics. Although it is evident from numerous studies that the frequency of inherited prothrombotic factors is increased in pediatric stroke, single thrombophilia does not fully explain stroke in a child as it represents only a mild risk factor. Further studies are needed, as improved understanding of underlying mechanisms will improve primary and secondary prevention of childhood stroke.

Key words: prothrombotic risk factors; childhood arterial ischemic stroke; ischemic perinatal stroke; cerebral sinovenous thrombosis

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Introduction

Stroke is defined by the World Health Organization as rapidly developing signs of focal disturbance of cerebral function with symptoms lasting at least 24 hours or leading to death with no apparent cause other than of vascular origin (1). This definition is far from ideal for children, because children with symptoms compatible with transient ischemic attack can have brain infarction shown by brain imaging despite the transient nature of their symptoms. Consequently, pediatric stroke is defined as any neurological event including a seizure associated with an acute infarction shown by magnetic resonance imaging (2,3).

Pediatric stroke is divided into ischemic and hemorrhagic stroke with subdivision of ischemic stroke according to the time of onset to childhood ischemic stroke and ischemic perinatal stroke (IPS). Ischemic stroke is also divided into arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT). Classification of stroke is presented in Figure 1.

Childhood ischemic stroke is characterized by findings of the arterial- or venous- distribution ischemia in a child aged from the 29th day postpartum to 18 years.

IPS is defined as a group of heterogeneous conditions characterized by focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging or neuropathological studies (4). Because the timing of the vascular event leading to IPS is almost always unknown, it was suggested that classification of IPS should be based on gestational or postnatal age at diagnosis. Three subcategories have been suggested: (i)

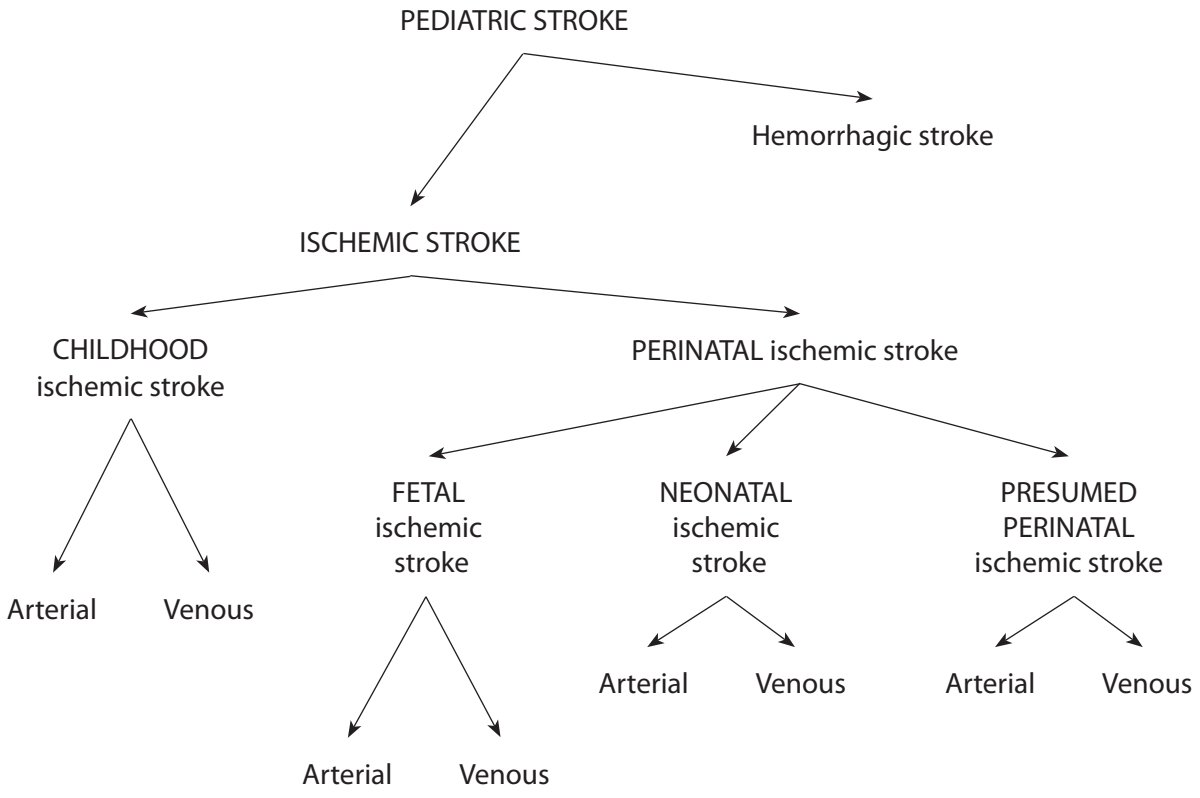

Figure 1. Classification of pediatric stroke.

fetal ischemic stroke diagnosed before birth by using fetal imaging methods; (ii) neonatal ischemic stroke diagnosed after birth and before 28th postnatal day including preterm; (iii) presumed perinatal ischemic stroke, diagnosed in infants after the 28th postnatal day in whom it is presumed that the event occurred between the 20th week of fetal life through the 28th postnatal day.

Although predominantly a disease occurring in adults, stroke is not uncommon in children and is increasingly recognized as an important cause of childhood disability and lifelong morbidity. There have been various population based studies of the incidence of pediatric stroke published over the last 30 years, with considerable variation in the reported incidence rates (rate *per* 100,000 children at risk *per* year). For overall ischemic and hemorrhagic stroke, reported incidence rate ranges from 1.3 to 13.0 (5,6), with about half of the cases due to ischemia. The estimated incidence rate for CSVT is 0.67 while the incidence rate of childhood AIS ranges from 0.2 to 7.9, with increased frequency in black children and in boys (7,8). The incidence of perinatal AIS ranges from 17 to 63 *per* 100,000 live births (9,10).

Stroke in children is a heterogeneous disorder. Over 100 risk factors for stroke have been reported (Table 1) and genetic predisposition to stroke has been confirmed in animal models and in humans (11,12). The most frequently reported risk factors are congenital heart malformations, hemolytic anemias, and collagen vascular diseases, as well as some rare inborn metabolic disorders, trauma, infection and thrombophilia (13-15). Despite the extensive investigation of potential risk factors, especially in last 10 years, no identifiable risk factor can be established in up to 30% of children (16).

Thrombophilia is an increased predisposition for the development of both arterial and venous thrombosis due to acquired or congenital abnormalities of the coagulation system (17,18). The well established inherited prothrombotic risk factors for venous thrombosis are deficiency of natural anticoagulants, protein C (PC), protein S (PS) and antithrombin (AT), Factor V (FV) Leiden and Factor II

Table 1. Risk factors for arterial ischemic stroke, cerebral sinovenous thrombosis and hemorrhagic stroke*

Arterial ischemic stroke	Cerebral sinovenous thrombosis	Hemorrhagic stroke
Cardiac • Congenital • Acquired • Iatrogenic	General • Dehydration • Infection • Fever • Hypoxic-ischemic injury • Post lumbar puncture	Genetic vasculopathy
Hematologic disorders • Hemoglobinopathies • Thrombophilia • Iron deficiency anemia • Thrombocytopenia	Hematologic disorders • Iron deficiency anemia • Sickle cell disease • Thalasemia • Autoimmune hemolytic anemia • Paroxysmal nocturnal hemoglobinuria • Thrombophilia	Hematologic disorders • Hemoglobinopathies • Platelet disorders • Coagulopathy • Hypofibrinogenemia
Infections • Meningitis	Head and neck disorders • Infections • Injury • Hydrocephalus • Post intracranial surgery	Trauma
Vasculitis • Primary • Secondary	Autoimmune disorders	Hypertension • Congenital • Acquired
Vasculopathies	Malignancy	
Other • Trauma • Toxin/Drugs • Metabolic conditions	Other • Cardiac disease • Renal disease • Drugs • Chromosomal disorders • Metabolic conditions	

* based on references 11 and 12

(PT) G20210A (19). A brief summary of the most important factors and their role in hemostasis is presented in Table 2. Although various prothrombotic risk factors have been investigated in pediatric stroke, including elevation in homocysteine and lipoprotein (a) [Lp(a)], AT, PC and PS deficiency, FV Leiden and PT G20210A, they still represent one of the most confusing areas in childhood stroke literature. In this review article, data collected from numerous studies and meta-analyses on prothrombotic markers in childhood stroke are discussed.

Childhood arterial ischemic stroke

Published frequencies of inherited prothrombotic risk factors and magnitude of association in childhood AIS are shown in detail in Table 3.

Several studies have demonstrated the increased frequency of FV Leiden in childhood AIS as compared to healthy controls (20-25,27,31,32,34,41). The most significant positive correlation between childhood AIS and FV Leiden (OR 6.0; 95% CI 3.0-12.1) has been found in a study with the largest number of AIS patients among case-control studies by German investigators (23), as well as in studies by Akar *et al*., Duran *et al*. and Herak *et al*. (27,32,34).

The incidence of PT G20210A in children with AIS has also been investigated and included in a number of cohort and case-control studies (21-23,25,30,31,34,40,41) with controversial results.

At least two meta-analyses have been published assessing the association between childhood AIS and FV Leiden and PT G20210A (40,41). While in a meta-analysis of Haywood *et al*. in 2005 (40), FV Leiden and PT G20210A were not associated with increased risk for chilhood AIS, Kenet *et al*. (41) revealed statistically significant association between

Table 2. Pathophysiological background of presumed prothrombotic risk factors for childhood first ischemic stroke*.

Prothrombotic factor	Pathophysiological relevance
Factor V Leiden	Single point mutation in FV gene causing resistance to proteolytic action of activated protein C, leading to increased thrombin generation.
Factor II G20210A	Mutation in 3' untranslated region of FII gene associated with slightly increased plasma FII levels resulting in hypercoagulable state.
Methylenetetra-hydrofolate reductase C677T	Mutation leading to mild decrease in enzymatic activity and increased homocysteine level which is prothrombotic.
Antithrombin deficiency	Multifunctional serpin that inhibits acivated clotting enzymes (IIa, IXa, Xa, XIa) of the coagulation pathway.
Protein C deficiency	Vitamin K-dependent protein with anticoagulant properties (proteolytic degradation of FVa and FVIIIa).
Protein S deficiency	Cofactor of activated protein C, vitamin K-dependent.
Lipoprotein (a) elevation	Due to structural homology with plasminogen, it reduces plasmin generation by competing with plasminogen binding to fibrin.
Plasminogen activator inhibitor-1 4G/5G polymorphism	Polymorphism associated with elevated PAI-1 levels and an increased risk of thromboembolic disease.
Factor XIII-A Val34Leu	Transglutaminase which mechanically stabilizes fibrin clot; in the presence of FXIII-A Leu34 the formed fibrin is more susceptible to fibrinolytic degradation.
Human platelet alloantigen-1 polymorphism	Leu33Pro polymorphism of the β_3 integrin gene which codes for the IIIa subunit of the GPIIb-IIIa platelet receptor involved in platelet adhesion and thrombus formation.

*based on reference 19.

AIS and FV Leiden and PT G20210A (OR 3.7; 95% CI 2.8-4.8 and OR 2.6; 95% CI 1.7-4.1, respectively).

In children with first-episode stroke, only homozygous (TT) methylenetetra-hydrofolate reductase (MTHFR) C677T polymorphism has been shown to independently increase the risk of stroke (23,37). The meta-analysis of Kenet *et al*. (41) demonstrated that the MTHFR C677T was found with higher frequency in childhood AIS than in healthy controls (OR 1.6; 95% CI 1.2-2.1). Although MTHFR C677T is generally considered to be relevant if serum homocysteine is elevated, homocysteine data were not available in the pediatric cohort examined in this meta-analysis.

Deficiencies of AT, PC and PS were also investigated in childhood AIS in a number of studies but only PC deficiency has been demonstrated as a risk factor for AIS in multiple case-control studies (23-25). The meta-analyses by Haywood *et al*. and Kenet *et al*. confirmed even stronger associations reported in the above studies (40,41). As natural anticoagulant deficiencies can be transient, the potential limitation of the previously cited studies is that the data provided demonstrate an association between acquired thrombophilias and AIS only.

Lp(a) is a complex of low-density lipoprotein and apolipoprotein (a). Due to structural homology with plasminogen, Lp(a) inhibits plasmin generation by competing with plasminogen binding to fibrin. Lp(a) may also promote thrombosis through its lipoprotein (a) moiety by binding and inactivating tissue factor pathway inhibitor (42). Elevated Lp(a) has been identified as a genetically determined risk factor for stroke in young adults. Regarding its role as a risk factor for AIS in children, Lp(a) data are limited to three studies (23,24,39) and one meta-analysis (41) that clearly showed association of elevated Lp(a) (> 0.3 mg/L) with presentation of AIS in white children.

The available data for other investigated prothrombotic risk factors [Plasminogen activator inhibitor-1 (PAI-1) 4G/5G, Factor XIII-A Val34Leu and Human platelet alloantigen-1 (HPA-1)] are not sufficient at the moment to make conclusions about their role as independent risk factors for childhood AIS (28,29,35) although Biswas *et al*. (35) found association of HPA-1 and AIS in children.

Table 3. Published frequencies of inherited prothrombotic risk factors and magnitude of association in childhood arterial ischemic stroke relative to healthy controls in different populations.

Inherited thrombophilia	Population	Cases	Controls	OR (95% CI)	Reference
Factor V Leiden	English	6/50	4/77	2.3 (0.6-8.6)[1]	Ganesan (20)
	Austrian	6/22	7/152	4.6 (1.2-17.2)	Zenz (21)
	Turkish	7/28	10/106	3.2 (1.1-9.3)	Akar (22)
	German	30/148	12/296	6.0 (3.0-12.1)	Nowak-Göttl (23)
	German	5/38	4/100	3.6 (0.9-14.9)[2]	Sträter (24)
	Israeli	10/58	4/118	4.8 (1.4-16.5)	Kenet (25)
	Turkish	12/46	3/68	6.4 (1.7-23.0)	Akar (27)
	Argentinean	1/44	2/102	1.2 (0.2-13.2)	Bonduel (30)
	Portuguese	3/21	4/115	4.6 (0.9-22.4)	Barreirinho (31)
	Turkish	7/30	1/33	9.7 (1.1-452.3)	Duran (32)
	Croatian	4/33	2/112	7.6 (1.3-43.5)	Herak (34)
	Asian-Indian	8/54	10/58	0.9 (0.3-2.3)[1,4]	Biswas (35)
	Serbian	1/26	2/50	1.0 (0.1-11.1)	Djordjevic (36)
	Meta-analysis	71/629	39/2004	1.2 (0.8-1.9)	Haywood (40)
	Meta-analysis	-/1014	-/2581	3.7 (2.8-4.8)[3]	Kenet (41)
Factor II G20210A	Austrian	1/17	1/98	3.9 (0.1-307.6)	Zenz (21)
	Turkish	5/28	3/106	7.4 (1.7-33.5)	Akar (22)
	German	9/148	4/296	4.7 (1.4-15.6)	Nowak-Göttl (23)
	Israeli	2/58	3/118	1.3 (0.2-8.2)	Kenet (25)
	Argentinean	0/44	1/102	/	Bonduel (30)
	Portuguese	2/21	1/115	11.8 (1.0-136.5)	Barreirinho (31)
	Croatian	1/33	4/112	1.0 (0.1-7.3)	Herak (34)
	Serbian	2/26	3/50	1.3 (0.2-8.4)	Djordjevic (36)
	Meta-analysis	35/550	15/1902	1.1 (0.5-2.3)	Haywood (40)
	Meta-analysis	-/1059	-/2278	2.6 (1.7-4.1)[3]	Kenet (41)
Methylenetetra-hydrofolate reductase C677T (only TT homozygotes)	Turkish	4/28	6/106	3.9 (0.7-12.1)	Akar (22)
	German	30/148	12/296	2.6 (1.5-4.5)	Nowak-Göttl (23)
	Israeli	8/58	18/118	1.1 (0.4-2.7)	Kenet (25)
	Spanish	6/21	4/28	2.0 (0.5-8.0)[1]	Cardo (26)
	Turkish	4/46	6/68	1.0 (0.3-3.7)[1]	Akar (27)
	Portuguese	1/21	13/115	0.4 (0.1-3.0)	Barreirinho (31)
	Croatian	5/33	10/112	1.8 (0.6-5.8)	Herak (34)
	Asian-Indian	2/58	0/58	/[4]	Biswas (35)
	Serbian	1/26	5/50	0.4 (0.04-3.3)	Djordjevic (36)
	Polish	9/64	2/59	5.8 (1.0-42.7)	Zak (37)
	USA	4/15	5/90	1.1 (0.2-4.0)	Morita (38)
	Meta-analysis	107/589	127/1678	1.7 (1.2-2.3)[5]	Haywood (40)
	Meta-analysis	-/777	-/1715	1.6 (1.2-2.1)[3]	Kenet (41)
Antithrombin deficiency	German	0/148	0/296	/	Nowak-Göttl (23)
	German	0/38	0/100	/	Sträter (24)
	Israeli	0/58	0/89	/	Kenet (25)
	Meta-analysis	1/435	0/952	1.0 (0.3-3.7)	Haywood (40)
	Meta-analysis	-/639	-/684	3.3 (0.8-15.5)[3]	Kenet (41)
Protein C deficiency	German	9/148	2/296	9.5 (2.0-44.6)	Nowak-Göttl (23)
	German	6/38	1/100	18.5 (2.1-16.0)[2]	Sträter (24)
	Israeli	4/58	1/89	7.0 (0.7-65.1)	Kenet (25)
	Meta-analysis	39/470	11/1081	6.5 (3.0-14.3)	Haywood (40)
	Meta-analysis	-/844	-/1207	11.0 (5.1-23.6)[3]	Kenet (41)
Protein S deficiency	German	0/148	0/296	/	Nowak-Göttl (23)
	German	0/38	0/100	/	Sträter (24)
	Israeli	0/58	0/89	/	Kenet (25)
	Meta-analysis	13/428	0/944	1.1 (0.3-3.8)	Haywood (40)
	Meta-analysis	-/574	-/572	1.5 (0.3-6.9)[3]	Kenet (41)

Table 3. (continued)

Inherited thrombophilia	Population	Cases	Controls	OR (95% CI)	Reference
Lipoprotein (a) elevation (> 0.3 mg/L)	German	39/148	14/296	7.2 (3.8-13.8)	Nowak-Göttl (23)
	German	7/38	5/100	4.3 (1.3-14.4)	Sträter (24)
	Turkish	14/52	10/78	2.5 (1.0-6.2)	Teber (39)
	Meta-analysis	-/616	-/578	6.5 (4.5-9.6)[3]	Kenet (41)
Plasminogen activator inhibitor-1 4G/5G (only 4G4G homozygotes)	German	65/198	275/951	1.2 (0.9-1.7)	Nowak-Göttl (28)
	Turkish	13/43	28/113	1.3 (0.4-3.5)	Akar (29)
Factor XIII-A Val34Leu	Turkish	25/116	27/100	0.8 (0.4-1.5)[1]	Akar (33)
Human platelet alloantigen-1	Croatian	10/33	30/112	1.2 (0.5-2.8)	Herak (34)
	Asian-Indian	18/58	6/58	3.0 (1.1-8.1)[1,4]	Biswas (35)
≥ **2 Genetic traits**	Meta-analysis	-/701	-/1265	18.7 (6.5-54.1)[3]	Kenet (41)

OR – odds ratio; CI – confidence interval.
[1]OR and corresponding 95% CI calculated by the present authors based upon data provided in the original report, [2]only children with arterial ischemic stroke of cardiac origin; [3]pooled data of perinatal and childhood arterial ischemic stroke; [4]only children with non-cardioembolic arterial ischemic stroke; [5]pooled heterozygous and homozygous data.

Ischemic perinatal stroke

Ischemic stroke is 17 times more common in perinatal period than at any other time in childhood and adolescence. The pathogenesis of IPS is poorly understood but it may be due to a combination of changes in the maternal hemostasis system and thromboembolism from the placental side of the circulation. Besides the risk factors such as maternal health, pregnancy, delivery and family history for thrombotic events, congenital thrombophilic risk factors in the mother may aggravate the risk for thrombosis in the fetus (43).

In order to properly evaluate the importance of various prothrombotic factors in development of perinatal stroke, an extensive analysis was performed of the possible impact of prothrombotic factors in this disease entity. In Table 4, inherited prothrombotic risk factors associated with arterial IPS are summarized. In one prospective multicentre case control study (44), 62 out of 91 infants had at least one prothrombotic risk factor compared with 44 out of 182 controls (OR 6.7; 95% CI 3.8-11.6). The inherited prothrombotic abnormalities found were FV Leiden, PT G20210A, homozygous (TT) MTHFR and PC deficiency, and the most common abnormality was elevated Lp(a) observed in 22% of cases (OR 4.8; 95% CI 2.2-10.9). However, a cohort study of 35 neonates with stroke and 434 controls found a similar frequency of prothrombotic risk factors in both groups except for PT G20210A but statistical significance was not reached (47).

Although the role of infant thrombophilia is extensively investigated, the role of maternal thrombophilia in the etiology of IPS has not been studied until recently. Two studies evaluating the biological profile of mother-child pairs with arterial IPS reported a higher prevalence of trombophilia in mothers than in children (48,49). Mothers and children did not frequently (69%) share the same prothrombotic risk factor or factors, which implies a possible contribution of paternal thrombophilia to perinatal ischemic thrombosis (48). In the study by Simchen *et al*. (48), of 23 mother-infant pairs, 12 (52%) infants and 14 (61%) mothers had genetic thrombophilia markers. Compared to healthy nulliparous pregnant women, mothers carrying FV Leiden increased 8.5-fold the risk for IPS in their children (95% CI, 4.1-17.5). The data presented suggest that understanding contribution of inherited prothrombotic factors, in both the mother and the child, is important but that the exact role of maternal thrombophilia in pathogenesis of IPS needs to be further evaluated.

Cerebral sinovenous thrombosis

Specific inherited prothrombotic risk factors that have been explored in childhood CSVT include

Table 4. Published frequencies of inherited prothrombotic risk factors and magnitude of association in arterial perinatal ischemic stroke relative to healthy controls in different populations.

Inherited thrombophilia	Population	Cases	Controls	OR (95% CI)	Reference
Factor V Leiden	German	17/91	10/182	3.9 (1.7-9.0)	Günther (44)
	German	32/215	10/182	2.7 (1.3-5.7)[1]	Kurnik (45)
	German	19/76	4/76	5.8 (1.7-20.1)	Debus (46)
	USA	1/35	14/433	0.9 (0.1-6.9)[1]	Miller (47)
	Croatian	3/26	2/112	7.2 (1.1-45.4)	Herak (34)
	Israeli	10/47	7/112	3.4 (1.2-9.5)[1]	Simchen (48)
	Estonian	1/49	12/400	0.7 (0.1-5.3)	Laugesaar (50)
	Meta-analysis	n.a.	n.a.	3.6(2.3-5.5)	Kenet (41)
	Meta-analysis	217/1328	100/1863	3.0 (2.4-3.9)[1,2]	Renaud (51)
Factor II G20210A	German	4/91	4/182	2.0 (0.4-8.3)	Günther (44)
	German	8/215	4/182	1.7 (0.5-5.7)[1]	Kurnik (45)
	German	4/76	2/76	2.3 (0.3-17.2)	Debus (46)
	USA	2/35	8/420	3.0 (0.6-14.7)[1]	Miller (47)
	Croatian	0/26	4/112	0.5 (0.1-8.7)	Herak (34)
	Israelian	3/47	4/112	1.8 (0.4-8.3)[1]	Simchen (48)
	Estonian	1/49	13/400	0.6 (0.1-4.8)	Laugesaar (50)
	Meta-analysis	n.a.	n.a.	2.0 (1.0-4.0)	Kenet (41)
	Meta-analysis	61/1157	35/1442	2.2 (1.4-3.3)[1,2]	Renaud (51)
Methylenetetra-hydro-folate reductase C677T (only TT homozygotes)	German	15/91	20/182	1.6 (0.8-3.3)	Günther (44)
	German	9/76	10/76	0.6 (0.2-2.4)	Debus (46)
	USA	4/35	52/434	1.0 (0.3-2.8)[1]	Miller (47)
	Croatian	4/26	10/112	1.9 (0.5-6.5)	Herak (34)
	Israeli	9/47	17/112	1.3 (0.5-3.0)[1]	Simchen (48)
	Meta-analysis	-/777	-/1715	1.6 (1.2-2.1)[2]	Kenet (41)
Antithrombin deficiency	German	0/91	0/182	/	Günther (44)
	German	1/76	0/76	/	Debus (46)
	Israeli	0/47	0/112	/	Simchen (48)
	Meta-analysis	-/639	-/684	3.3 (0.8-15.5)[2]	Kenet (41)
Protein C deficiency	German	6/91	0/182	/	Günther (44)
	German	3/76	0/76	/	Debus (46)
	Israeli	9/47	2/112	10.7 (2.2-51.5)[1]	Simchen (48)
	Meta-analysis	-/844	-/1207	11.0 (5.1-23.6)[2]	Kenet (41)
Protein S deficiency	German	0/91	0/182	/	Günther (44)
	German	0/76	0/76	/	Debus (46)
	Israeli	6/47	0/112	/	Simchen (48)
	Meta-analysis	-/574	-/572	1.5 (0.3-6.9)[2]	Kenet (41)
Lipoprotein (a) elevation (> 0.3 mg/L)	German	20/91	10/182	4.8 (2.2-10.9)	Günther (44)
	German	10/76	6/76	2.1 (0.6-7.1)	Debus (46)
	Meta-analysis	-/616	-/578	6.5 (4.5-9.6)[2]	Kenet (41)
Plasminogen activator inhibitor-1 4G/5G (only 4G4G homozygotes)	USA	7/35	98/433	0.6 (0.3-1.3)[1]	Miller (47)
Human platelet alloantigen-1	USA	4/35	102/434	0.5 (0.2-1.4)[1]	Miller (47)
	Croatian	5/26	30/112	0.6 (0.2-1.9)	Herak (34)
≥ 2 Genetic traits	Meta-analysis	-/701	-/1265	18.7 (6.5-54.1)[2]	Kenet (41)

OR – odds ratio; CI – confidence interval; n.a. – not available.
[1]OR and corresponding 95% CI calculated by the present authors based upon data provided in the original report; [2]pooled data of perinatal and childhood arterial ischemic stroke.

FV Leiden and PT G20210A, MTHFR C677T, AT, PC and PS deficiencies, Lp(a), PAI-1 4G/5G and HPA-1 polymorphism (Table 5). Two small pediatric case-control studies have examined the role of prothrombotic disorders in CSVT. Kenet *et al*. found prothrombotic condition in 19/46 children with CSVT, which was similar to the prevalence among 112 healthy controls (9). Heller *et al*. compared prothrombotic risk factors in 149 pediatric patients with CSVT to 149 matched controls and found a significant association of CSVT with FV Leiden and Lp(a), PC and PS deficiencies (53). Strong association of FV Leiden (OR 12.9; 95%CI 2.3-73.0) and PT G20210A (OR 11.9; 95%CI 2.1-67.2) with CSVT was found in a study of Laugessar *et al*. (50). The meta-analysis that Laugessar *et al*. performed suggests that the risk for childhood CSVT is 3.1-fold increased both among FV Leiden and

Table 5. Published frequencies of inherited prothrombotic risk factors and magnitude of association in childhood cerebral sinovenous thrombosis relative to healthy controls in different populations.

Inherited thrombophilia	Population	Cases	Controls	OR (95% CI)	Reference
Factor V Leiden	USA	0/9	2/65	/	Hagstrom (52)
	German	22/149	8/149	3.4 (1.3-9.3)[1]	Heller (53)
	Argentina	1/23	2/102	2.3 (0.2-6.2)	Bonduel (30)
	Israelian	6/46	7/112	2.1 (0.7-6.5)[2]	Kenet (9)
	USA	2/24	14/433	2.6 (0.5-12.0)[2]	Miller (47)
	Estonian	2/7	12/400	12.9 (2.3-73.0)	Laugesaar (50)
	Meta-analysis	-/1625	-/2842	2.7 (1.7-4.3)	Kenet (41)
	Meta-analysis	33/258	45/1261	3.1 (1.8-5.5)	Laugesaar (50)
Factor II G20210A	German	7/149	3/149	3.8 (0.8-17.3)[1]	Heller (53)
	Argentina	1/23	1/102	4.6 (0.3-76.3)	Bonduel (30)
	Israelian	2/46	4/112	1.2 (0.2-6.9)[2]	Kenet (9)
	USA	1/24	8/420	2.2 (0.3-18.2)[2]	Miller (47)
	Estonian	2/7	13/400	11.9 (2.1-67.2)	Laugesaar (50)
	Meta-analysis	-/1409	-/2613	1.9 (0.9-4.1)	Kenet (41)
	Meta-analysis	13/249	29/1183	3.1 (1.4-6.6)	Laugesaar (50)
Methylenetetra-hydrofolate reductase C677T (only TT homozygotes)	Israeli	2/46	4/112	1.2 (0.2-6.9)[2]	Kenet (9)
	USA	3/24	52/434	1.0 (0.3-3.6)[2]	Miller (47)
	USA	0/8	5/90	/	Morita (38)
Antithrombin deficiency	German	5/149	0/149	/	Heller (53)
	Israelian	0/46	0/112	/	Kenet (9)
	Meta-analysis	-/167	-/469	18.4 /3.2-104.3)	Kenet (41)
Protein C deficiency	German	6/149	1/149	14.2 (1.6-129.3)[1]	Heller (53)
	Israelian	3/46	2/112 /1468	3.7 (0.6-22.6)[2]	Kenet (9)
	Meta-analysis	-/1031		6.3 (1.6-25.4)	Kenet (41)
Protein S deficiency	German	8/149	1/149	17.0 (1.9-151.2)[1]	Heller (53)
	Israelian	1/46	0/112	/	Kenet (9)
	Meta-analysis	- /187	- /369	5.3 (1.5-18.2)	Kenet (41)
Lipoprotein (a) elevation (>0.3 mg/L)	German	44/106	17/149	7.2 (3.7-14.2)[1]	Heller (53)
Plasminogen activator inhibitor-1 4G/5G (only 4G4G homozygotes)	USA	5/24	98/433	0.9 (0.3-2.5)[2]	Miller (47)
Human platelet alloantigen-1	USA	8/24	102/434	1.4 (0.6-3.2)[2]	Miller (47)
≥ 2 Genetic traits	Meta-analysis	-/926	-/1720	6.1 (0.9-43.1)	Kenet (41)

OR – odds ratio; CI – confidence interval.
[1]univariate analysis; [2]OR and corresponding 95% CI calculated by the present authors based upon data provided in the original report.

PT G20210A carriers (50). In contrast, in meta-analysis by Kenet *et al*. (41), that included up to 1625 CSVT patients and 2842 healthy controls, the association was demonstrated for FV Leiden only. In the same study Kenet *et al*. reported about the role of multiple thrombophilias as risk factors for CSVT that together with PT G20210A did not show a statistically significant association with first CSVT.

Overview and limitations of published studies

It is well known that the reliability of meta-analyses is dependent on inclusion of high-quality, methodologically similar studies. Numerous factors, e.g., sample sizes, patient populations included, proper selection of adequate controls, etc., have direct influence on reliability of results (40,54). Despite similar criteria for the inclusion of different studies of childhood AIS in meta-analyses by Haywood *et al*. (40) and Kenet *et al*. (41), the obtained results were not consistent for all prothrombotic risk factors investigated. Both meta-analyses gave concordant results for majority of examined prothrombotic risk factors (AT, PC and PS deficiencies, MTHFR C677T). Discrepancies obtained for FV Leiden and PT G20210A results could be explained by the number of studies included in each meta-analysis (9 *vs*.17 and 7 *vs*.13, respectively), as well as by the number of patients and controls. In the above meta-analyses, a large amount of published data could not be included because of lack of controls; while in meta-analysis by Haywood *et al*. case-control studies were restricted to 4 countries (Germany, United Kingdom, Turkey and Israel), meta-analysis by Kenet *et al*. included additional countries (Austria, Portugal, Spain, North and South America). Moreover, the majority of studies were retrospective and not all inherited prothrombotic risk factors were tested in all patients. The same explanation can be applied for PT G20210A in CSVT patients in meta-analyses by Laugessar *et al*. (50) and Kenet *et al*. (41). Although a similar number of studies were included in both meta-analyses (6 and 5, respectively), the number of patients and controls was different. Furthermore, 3 case-control studies included in both meta-analyses originated from Argentina, Germany and Israel. Additional case-controls in the meta-analysis by Laugessar *et al*. (50), including their own, were from the United States (California and Philadelphia) while Kenet *et al*. (41) included 2 studies from Turkey.

For IPS, despite the fact that only 6 studies were available for the meta-analysis by Kenet *et al*. (41), summary ORs for FV Leiden (OR 3.6; 95% CI 2.3-5.5) and PT G20210A (OR 2.0; 95% CI 1.0-4.0) were similar to ORs obtained when pooled data of perinatal and childhood arterial ischemic stroke in the same meta-analysis were evaluated (OR 3.7; 95% CI 2.8-4.8 and OR 2.6; 95% CI 1.7-4.1, respectively). Furthermore, the obtained data are in concordance with results obtained in a meta-analysis by Renaud *et al*. (FV Leiden OR 3.0; 95% CI 2.4-3.9 and PT G20210A OR 2.2; 95% CI 1.4-3.3) (51). Although it is obvious that children with IPS are underrepresented in comparison with older children in the literature, the published results evaluating IPS only suggest that thrombophilia is still a risk factor.

Taking into consideration all the published studies, the study of Kenet *et al*. (41) is so far the most comprehensive meta-analysis of the effect of thrombophilia on pediatric stroke. It clearly shows persistent, strong association of FV Leiden and all types of stroke studied (OR 3.7; 95% CI 2.8-4.8 for first AIS onset and OR 2.7; 95% CI 1.7-4.3 for first CSVT onset) resulting in summary OR of 3.3 (95% CI 2.6-4.1) for first AIS/CSVT onset. The association of PT G20210A and pediatric stroke (OR 2.6; 95% CI 1.7-4.1 for first AIS onset and OR 1.9; 95% CI 0.9-4.1 for first CSVT onset) resulted in significant summary OR of 2.4 (95% CI 1.7-3.5) for first AIS/CSVT onset. In contrast to weak association of MTHFR TT homozygosity with first AIS onset, such association was not demonstrated for CSVT. Meta-analysis by Kenet *et al*. (41) demonstrated the highest OR for combined genetic traits in first AIS and AIS/CSVT onset (OR 18.7; 95% CI 6.5-54.1 and OR 11.9; 95% CI 5.9-23.7, respectively). However, an unexpected finding was that ≥ 2 genetic thrombophilia traits are less associated with CSVT than AT deficiency alone (OR 6.1; 95% CI 0.9-43.1 and OR 18.4; 95% CI

3.2-104.3, respectively). The results of Kenet *et al*. highlight the fact that the ORs for AIS and CSVT differ with each thrombophilia, indicating distinct AIS and CSVT pathophysiologies. However, there are insufficient data in the article by Kenet *et al*. (41) or elsewhere in the literature to assess the possibly differing role of thrombophilia in these two subgroups.

Perspectives

Although a population-based cohort study is the superior study design for analyzing risk factors for a first stroke, ethnicity has a strong influence on prevalence of genetic thrombophilia and it is questionable whether the obtained results are applicable to other populations. Due to relative rarity of pediatric stroke, sufficient number of patients can only be achieved with multicenter, multi-national approaches in order to provide the necessary power for randomized control trials.

One prospective pediatric stroke registry is the International Pediatric Stroke Study (IPSS), the first international multi-center network of childhood stroke researchers from 30 centers in 10 countries. IPSS offers the advantage of rapid enrollment of patients through its web-based data entry where clinical presentations, risk factors, investigations, treatments and early outcomes are collected. IPSS was established in 2003 primarily to address the critical need to develop a set of standardized protocols to allow uniform collection of comprehensive data on the diagnosis (including laboratory testing), investigation, treatment and outcome assessment for all children with stroke. Until today 10 manuscripts have been published dealing with classification, risk factors and therapy of childhood AIS and neonatal AIS and CSVT (55-64).

One of the aims of IPSS is to describe the prevalence and spectrum of risk factors identified in children with AIS, to investigate:

a) whether the prevalence of risk factors varies by age and geographical region;

b) the association between a particular risk factor and mode of presentation; and

c) the association between risk factors and infarct characteristics.

In the IPSS study by Kirton *et al*. (62), results of prothrombotic testing were inconsistent in 248 neonates with AIS. The presence of possible thrombophilia was reported in 47 (19%) cases, including elevated Lp(a), homozygous (TT) MTHFR, FV Leiden, PT G20210A, PAI-1 4G/4G, AT and PS deficiency. Six children had multiple prothrombotic abnormalities. The authors conclude that their results do not contribute to the understanding of the role of thrombophilia in the etiology of neonatal AIS.

In the study by Mackay *et al*., 676 children with AIS across 30 centers were enrolled (63). Among 674 children tested, prothrombotic states were identified in 87 children (13%), which was less frequent than in previous studies (65). Single prothrombotic risk factor was reported in 67 children and more than 1 prothrombotic risk factor in 20 children. After excluding acquired and not specified thrombophilia, 75 inherited prothrombotic risk factors were detected. There was a higher prevalence of prothrombotic risk factors in Europe compared to Asia, Australia and America. There was no statistical difference in prevalence of prothrombotic risk factors regarding age, mode of presentation and infarct characteristics. According to accumulated results so far IPSS has decided, as a next step, to continue research activities by dividing into working groups in order to collect an expanded data-set on selected stroke subtypes.

In conclusion, despite the proven evidence that the frequency of inherited prothrombotic factors is increased in children with stroke, a single thrombophilia does not fully explain a stroke in a child as it represents only a mild risk factor (ORs 4-10). Additional risk factors, especially arteriopathy, multiple thrombophilias or congenital heart disease are associated with increased ORs. Further studies are needed, as improved understanding of underlying mechanisms will improve the prospects for primary and secondary prevention of childhood stroke.

Potential conflict of interest

None declared.

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