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Antiphospholipid antibodies and cerebrovascular thrombosis in the pediatric population: Few answers to many questions

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(Article begins on next page)

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Title

Antiphospholipid antibodies and cerebrovascular thrombosis in the pediatric population: Few answers to many questions

Abstract

Most of the knowledge in pediatric antiphospholipid syndrome (APS) is derived from studies performed on the adult population. As in adults, antiphospholipid antibodies (aPL) can contribute to thrombosis, especially cerebrovascular thrombosis, in neonates and children. Since aPL have the potential to cross the placental barrier, and since the pediatric population is prone to infections, confirmation tests are required to specify a role for aPL in cerebrovascular thrombosis. In this review, we aimed at assessing the prevalence of aPL, criteria or non-criteria, in neonatal and childhood ischemic stroke and sinovenous thrombosis. Also, we looked into the effect of aPL and anticoagulants/antiplatelets on the long term neurological outcomes of affected neonates or children. While most questions remained un-answered because of the very limited evidence, the neurological outcomes seem to be affected by the titers of aPL at the time of the event and subsequent confirmatory tests. In the settings of pediatric population, anti-beta-2 glycoprotein I antibodies (anti-β2GPI) antibodies have been associated with unusual arterial locations. Long term administration of aspirin has been safe, even though neurological complications have been noted. Anticoagulation with low-molecular-weight heparin (LMWH) or vitamin K antagonists, especially in combination with aspirin, has shown favorable outcomes in few cases. However, the limited amount of data requires caution when interpreting the available evidence, especially when referring to the most optimal choice of anticoagulation.
Keywords: Antiphospholipid antibodies; pediatric population; cerebrovascular thrombosis; anticoagulation

1. Introduction

Antiphospholipid syndrome (APS), also known as Hughes syndrome, is characterized by hypercoagulability triggered by autoantibodies to phospholipids or phospholipid-binding proteins (1). APS can be primary or secondary to another autoimmune disorder, usually systemic lupus erythematosus (SLE). The 2006 revised Sapporo international classification for APS requires that the patient meets at least one clinical criterion and one laboratory criterion (2). The clinical criteria include pregnancy morbidity and vascular thrombosis in arteries, veins, or small vessels (2). Ischemic stroke is an example of a clinical criterion. The laboratory criteria consist of persistently positive circulating antiphospholipid autoantibodies (aPL) (2). The aPL included in the revised Sapporo criteria were lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and anti-β_2-glycoprotein-1 antibodies (aβ_2GPI) (2).

Pediatric APS includes patients below the age of 18 who fulfill the diagnostic criteria for APS (1). Since the updated Sapporo criteria were formulated based on studies performed on adults, pediatric APS may be underdiagnosed. According to an international registry, the most common clinical manifestation of pediatric APS is venous thrombosis (60%), typically deep vein thrombosis (DVT), followed by arterial (32%) and small vessel (6%) thrombosis (3). Pregnancy morbidity is rarely applicable to the pediatric population since pregnancy in this age group is uncommon and limited to the adolescents (4). In addition, pediatric APS often does not occur in the setting of acquired pro-thrombotic risk factors, such as hypertension and atherosclerosis, as in adult APS (5).

Regarding aPL, LAC occur more frequently in children than adults possibly related to infectious exposures (6). On the contrary, aCL and aβ_2GPI occur at similar frequency in both populations (3). Besides criteria, non-criteria aPL have been reported in the pediatric population (**Table 1**). Some of these antibodies have been associated with thrombotic events (3, 7, 8). As in adults, the presence of aPL can act as a risk factor for cerebral ischemia in children (9-13). For example, 25% of children with acute stroke and no previous head injury or CNS infection tested positive for aPL (14). In addition, it has been reported that aPL positive children have more than a 6-fold risk of stroke compared with healthy children (15). Interestingly, non-criteria aPL, particularly anti-phosphatidylcholine and anti-phosphatidylethanolamine antibodies, were associated with cerebral infarction in the pediatric population (7). Classified by age, pediatric vascular thrombosis has two main categories; perinatal ischemic stroke or neonatal sinovenous thrombosis occurring from week 28 of gestation to 28 postnatal days of life and childhood ischemic stroke or childhood sinovenous thrombosis occurring after 28 days to 18 years of age (16).

Anti-phospholipid antibody	Criteria	Anti-β_2-glycoprotein-1 IgG and IgM (3) Anticardiolipin IgG and IgM (3) Lupus anticoagulant (3)
	Non-criteria	Anticardiolipin IgA (17) Anti-β_2-glycoprotein-1 IgA (18) Anti-annexin A2 and A5 (19)

		Anti-phosphatidylethanolamine (7, 8) Anti-phosphatidylcholine (7, 8) Anti-phosphatidylinositol (8) Anti-phosphatidylserine/prothrombin (8)

Table 1. The occurrence of criteria and non-criteria anti-phospholipid antibodies in the pediatric population.

Because the data on pediatric APS and cerebrovascular thrombosis are still scarce, this review aims at highlighting the implication of aPL in triggering cerebrovascular events in the pediatric population. In addition, this review will discuss the neurological outcomes and management options of neonatal and childhood APS ischemic stroke and sinovenous thrombosis.

2. Antiphospholipid antibodies and cerebral thrombosis

2.1. Lupus anticoagulant

In neonates and children, LAC are sometimes found incidentally due to prolongation of activated partial thromboplastin time (20). As LAC can be transient and associated with infections and transplacental passage (21, 22), they are not usually associated with clinically relevant complications (23). Therefore, the differentiation between *de novo* and acquired LAC has important therapeutic implications and is crucial for prognosis (24).

2.1.1. Perinatal ischemic stroke

Before LAC had been isolated in neonates, the transplacental transport of LAC had been described in case reports to be associated with perinatal ischemic strokes (25). The reports on the existence of *de novo* LAC in neonates with perinatal stroke and no other prothrombotic risk factors denoted the role of LAC (**table 2**). Although limited, the data on the implication of LAC in perinatal stroke is contradictory. The confirmation test is important to specify whether LAC had a true contributory role to perinatal stroke. In the only case where LAC was confirmed positive, monoparesis persisted upon follow-up. Therefore, the persistence of LAC can be associated with worse outcomes after perinatal strokes, but this observation needs further studies to be tested.

Reference	Type	Scenario	Result	Confirmed	Management/Outcome
de Klerk et al. (26)	Case report	3-day-old Male Left MCA stroke	LAC 18.9 GPL units/mL Negative after 1 month	Y	Phenobarbital 12 months: No neurological complications
Sousa et al. (10)	Case report	8-hour-old Female Right caudate and lenticular nucleus, with extension to the cerebral peduncle	Positive LAC	Y	Aspirin 12 months: Monoparesis grade 3 of the left upper limb.
Berkun et al. (24)	Prospective cohort	5 patients with perinatal stroke	5/5 (100%) 1/5 (20%) after 3 years	Y	4 with no anticoagulation 1 with indefinite anticoagulant

Table 2. Literature data describing the prevalence of *de novo* lupus anticoagulant in perinatal ischemic stroke.
LAC: Lupus anticoagulant; MCA: Middle cerebral artery; GPL: 1 microgram of IgG antibody; Y: Yes; N: No

2.1.2. Neonatal sinovenous thrombosis

Few characteristics are known about neonatal sinovenous thrombosis, because it is a rare disease. One of these characteristics is its association with thrombophilia. Mutation in factor II G20210A is found in 11% of neonates with sinovenous thrombosis, while factor V G1691A mutation is present in 4.9% of patients (27). Although LAC has the ability to affect the blood flow in small cerebral blood vessels

leading to ischemic damage to brain tissue (28), there has been no evidence so far on its involvement in the pathogenesis of neonatal sinovenous thrombosis.

2.1.3. Pediatric ischemic stroke

Pediatric ischemic strokes have been linked to connective tissue diseases, such SLE (29). Compared to perinatal stroke, there are more studies that discussed the role of LAC in pediatric ischemic stroke (**table 3**). Despite that 4 of these studies reported a prevalence of more than 10%, the study which enrolled the greatest number of patients reported a prevalence of 3.5% (30). It is evident that the confirmatory test leads to a lower prevalence. Therefore, in the absence of other pro-coagulative factors, either durable positive LAC or other aPL could be contributing to arterial ischemic strokes in children.

Reference	Type	Population	Result	Confirmed	Management/Outcome
Kenet et al. (15)	Case-control	58 children with stroke	6/58 (10.3%)	Y	NR
Bonduel et al. (30)	Prospective cohort	112 consecutive children with acute ischemic stroke	4/112 (3.5%)	Y	1 patient on acenocoumarol with no recurrence
Balasa et al. (31)	Case-control	22 children with ischemic cerebrovascular disease	3/10 (30%)	N	NR
Angelini et al. (32)	Case series	13 children with cerebral ischemia	2/13 (15.4%) 1/13 (7.7%) on second determination	Y	NR
Berkun et al. (33)	Prospective cohort	11 children with pediatric APS and cerebral vascular ischemic lesion	6/11 (54.5%) Decreased titers with time	Y	1 treated with prolonged LMWH and aspirin without complications
Gattorno et al. (34)	Prospective cohort	14 children with primary APS	5/14 (35.7%)	Y	NR

Table 3. Literature data describing the prevalence of lupus anticoagulant in pediatric ischemic stroke.
APS: Antiphospholipid syndrome; Y: Yes; N: No; LMWH: Low-molecular-weight heparin; NR: Not reported

2.1.4. Pediatric sinovenous thrombosis

While LAC have been associated with DVT and Budd-Chiari syndrome in children (35), a weak evidence exists on its association with pediatric sinovenous thrombosis. In the two studies that assessed the prevalence of LAC among pediatric patients with sinovenous thrombosis, other prothrombotic conditions were also assessed (**table 4**). In general, the association of prothrombotic disorders with childhood sinovenous thrombosis remains controversial. Some of the literature studies support the involvement of protein C deficiency (36), while others highlight the role of thrombophilia genetic mutations (37). Among LAC positive children, one study did not record positivity for thrombophilia genetic mutations such as factor V Leiden or prothrombin G20210A mutation (30). On the other hand, the other study found one positive patient that had co-existent protein C deficiency (38).

Reference	Type	Population	Result	Confirmed	Management/Outcome
Bonduel et al. (30)	Prospective cohort	38 consecutive children with cerebral venous thrombosis	2/38 (5.2%)	Y	NR
Unver et al. (38)	Case series	11 children with cerebral venous thrombosis	1/11 (9%)	N	Lifelong aspirin

Table 4. Literature data describing the prevalence of lupus anticoagulant in pediatric sinovenous thrombosis.
Y: Yes; N: No; NR: Not reported

2.2. Anticardiolipin antibody

Like LAC, aCL is characterized by a transient nature in neonates and children. Some of the causes that might trigger aCL positivity include upper airway infections and vaccinations (39). Neonates born to mothers with primary or secondary APS are also prone to aCL positivity (40). However, aCL can disappear completely by 12 months of age which indicates that aCL detection assay might represent a good assay for predicting the risk of thrombosis induced by transmitted aPL (41). The presence of IgG aCL in children has been associated with autoimmune cytopenia (42). Among cases of pediatric SLE, a weak association has been concluded between aCL and thrombosis in contrast to LAC (42).

2.2.1. Perinatal ischemic stroke

The evidence on the association of *de novo* aCL and perinatal ischemic stroke is still limited to few case reports and prospective cohort studies (**table 5**). All the case reports reported the occurrence of the IgG isotype of aCL. Since aCL was detected at high titers in a 3-day old infant with perinatal ischemic stroke (43), it is questionable whether aCL cause perinatal stroke at lower titers in older infants, and whether the titer of aCL at the time of stroke has any clinical significance. Most of the cases noted a positive confirmation test. In the only case where aCL disappeared upon confirmation (44), the infant developed long term neurological complications. However, this infant was also heterozygous for factor V Leiden mutation, which questions the role of the transient IgG aCL positivity. It is still unknown whether perinatal stroke induced exclusively by aCL leads to milder or to more severe long term clinical complications than perinatal stroke induced by other risk factors.

Reference	Type	Scenario	Result	Confirmed	Management/Outcome
Akanli et al. (45)	Case report	6-hour old male Left MCA stroke	IgG: borderline high	N	Phenobarbital Neurodevelopmental delay
Chow and Mellow (46)	Case report	48-hour old female Left MCA stroke	IgG 13.4 GPL U/mL	N	Anticonvulsants Neurologically normal
Paro-Panjan et al. (47)	Case report	13-hour old female Left MCA stroke	IgG >100 GPL	Y	Phenobarbitone Trunk hypotonia
Merlin et al. (43)	Case report	3-day old male Left MCA stroke	IgG 191 GPL/mL	Y	Aspirin At 3.5 years: No recurrence or neurological complication
Sousa et al. (10)	Case report	8-hour-old female Right caudate and lenticular nucleus, with extension to the cerebral peduncle	IgG 17.5 GPL/ml	Y	Aspirin At 12 months: Monoparesis grade 3 of the left upper limb.

Giani et al. (44)	Case report	10-day old child Left MCA stroke	IgG 45 U/ml Negative at confirmation	Y	Aspirin for 9 months At 9 months: Hypotonia, right hemiplegia, and global delay in psychomotor development.
Berkun et al. (24)	Prospective cohort	5 patients with perinatal stroke	IgM 2/5 (40%) IgG 1/5 (20%) Persistence in 1 patient after 18 years	Y	1 with indefinite anticoagulant
Kurnik et al. (48)	Prospective cohort	215 neonates with acute ischemic stroke	19/215 (8.8%)	N	No recurrence in aCL positive infants

Table 5. Literature data describing the prevalence of *de novo* anticardiolipin antibodies in perinatal ischemic stroke.
aCL: Anticardiolipin antibodies; MCA: Middle cerebral artery; GPL: 1 microgram of IgG antibody; Y: Yes; N: No;

2.2.2. Neonatal sinovenous thrombosis

The discussion of the association between neonatal sinovenous thrombosis and *de novo* aCL is insufficient because it is limited to only one case report (49). The interesting finding in this report is the normal neurological development of the patient. It is still to be deciphered whether the long-term outcome of neonatal cerebral sinovenous thrombosis induced exclusively by *de novo* aCL is more benign than when triggered by other causes, although neonates in general develop severe complications, such as cognitive impairments and epilepsy (50).

2.2.3. Pediatric ischemic stroke

In adults, the data on the association of aCL with arterial or venous thrombosis is contradictory. While certain studies find no association with arterial or venous thrombotic events including ischemic stroke (51), others show that high titers of aCL are closely related to APS clinical severity (52). In children, few case reports, prospective and retrospective cohort studies, and cross-sectional studies discussed the association of aCL with ischemic stroke (**table 6**). The results obtained by these studies are also contradictory. Few case reports illustrated low titers of aCL, while only one case reported high aCL titer which eventually disappeared with time (44). The prevalence of aCL among the studies is variable. When both IgG and IgM were assessed, IgG were more prevalent, even after confirmation which is similar to adult ischemic stroke (53). Interestingly, very few patients developed long-term neurological complications. However, one patient with low positive titer of aCL developed infarcts in multiple brain areas and suffered long-term neurological and non-neurological complications (54).

Reference	Type	Population	Result	Confirmed	Management/Outcome

Alshekaili et al. (55)	Case report	6-months old male Left MCA stroke	IgG 26 GPL	Y	NR No further recurrence or neurological deficit
Cabral et al. (54)	Case report	6-months old male Multiple de novo acute ischemic infarcts in the frontal, right temporal, and parietal lobes	aCL unspecified 5.4 U/mL	Y	LMWH After 5 years: developmental delay, systemic hypertension, and mild renal insufficiency.
Giani et al. (44)	Case report	6-months old female Right MCA stroke	IgG 20 U/mL Negative after 3 months	Y	Regular rehabilitation/ Satisfactory functional recovery
Strater et al. (56)	Prospective cohort	38 newly diagnosed children with ischaemic stroke	4/38 (10.5%) total aCL	N	NR
Duran et al. (57)	Retrospective cohort	30 children with ischemic stroke	5/30 (16.67%)	N	NR
Bonduel et al. (30)	Prospective cohort	112 consecutive children with acute ischemic stroke	5/112 (4.5%) total aCL	Y	NR
Balasa et al. (31)	Case-control	22 children with ischemic cerebrovascular disease	8/10 (80%) total aCL	N	NR
Angelini et al. (32)	Case series	13 children with cerebral ischemia	IgG 8/13 (61.5%) IgG 11/13 (84.6%) on confirmation IgM 2/13 (15.4%) IgM 3/13 (23%) on confirmation	Y	Two had multiple recurrencies
Berkun et al. (33)	Prospective cohort	11 children with pediatric APS and cerebral vascular ischemic lesion	IgG 5/11 (45.5%) IgM 3/11 (27.2%) Decreased titers with time	Y	1 treated with prolonged LMWH and aspirin without complications
Krelza et al. (58)	Cross-control	77 children with transient ischemic attack	IgG aCL 1/77 (1.3%)	N	NA
Gattorno et al. (34)	Case report	14 children with APS	3/5 (60%)	Y	Multiple CNS ischemic lesions in one patient

		5 children with cerebral thrombosis			
Giani et al. (44)	Case report	5-months old female Cortico-subcortical, fronto-temporal-parietal, left malacia extending to the ipsilateral capsular regions	IgG 101 U/mL Disappeared after 20 months	Y	Baby aspirin Mild neurological outcome

Table 6. Literature data describing the prevalence of anticardiolipin antibodies in pediatric ischemic stroke.
MCA: Middle cerebral artery; APS: Antiphospholipid syndrome; aCL: Anticardiolipin; GPL: 1 microgram of IgG antibody; Y: Yes; N: No; LMWH: Low-molecular-weight heparin; CNS: Central nervous system; NR: Not reported

2.2.4. Pediatric sinovenous thrombosis

In children with cerebral sinovenous thrombosis, the presence of aCL is considered a major acquired risk factor (59) (30). A prospective cohort study assessed aCL among children with sinovenous thrombosis to find that 6.25% of study individuals were positive for IgG aCL (60). However, no confirmation test was performed and no long-term follow-up was done. A better picture of outcome and management could be taken from a case report of an 11-year-old male which did not have any long-term complications while placed on anticoagulation (61). However, no confirmatory test was performed as well. The estimated prevalence of aCL among pediatric sinovenous thrombosis patients is still to be determined.

2.3. Anti- β2-glycoprotein I antibody

In healthy individuals, there are naturally low concentrations of the IgG isotype of anti-β2GPI antibodies, and these normally increase with age (62). In children, the prevalence of anti-β2GPI antibodies in healthy children was estimated at 6.6%, which has been referred to the high frequency of infections in children (63).

2.3.1 Perinatal ischemic stroke

So far, the association between *de novo* anti-β2GPI and perinatal ischemic stroke is mostly based on case reports and prospective cohort studies (**table 7**). Many of the case reports noted a very high titer of anti-β2GPI antibodies. The titer seem to inversely proportion to the age of the neonate, although more studies are required to confirm the hypothesis. The long term follow-up in many cases did not indicate any recurrence or further neurological complications, while on anti-platelets. Further large studies are needed to test whether perinatal strokes triggered by anti-β2GPI antibodies have a better outcome than if induced by other aPL.

Reference	Type	Population	Result	Confirmed	Management/Outcome
Merlin et al. (43)	Case report	3-day old male Left MCA stroke	IgG 258 GPL/mL	Y	Aspirin At 3.5 years: No recurrence or neurological complication
Sousa et al. (10)	Case report	8-hour-old female Right caudate and lenticular nucleus, with extension to the cerebral peduncle	IgG 133 U/ml	Y	Aspirin At 12 months: Monoparesis grade 3 of the left upper limb.
Giani et al. (44)	Case report	10-day old child Left MCA stroke	IgG 60 U/ml Negative at confirmation	Y	Aspirin for 9 months At 9 months: Hypotonia, right hemiplegia, and global delay in psychomotor development.
Giani et al. (44)	Case report	6-months old female Right MCA stroke	IgG 20 U/mL Positive after 3 months Negative after 16 months	Y	Regular rehabilitation/ Satisfactory functional recovery
Giani et al. (44)	Case report	5-months old female Cortico-subcortical, fronto-temporal-parietal, left malacia extending to	IgG >100 U/mL Disappeared after 20 months	Y	Baby aspirin Mild neurological outcome

		the ipsilateral capsular regions			
Berkun et al. (24)	Prospective cohort	5 patients with perinatal stroke	2/5 (40%)	N	No anticoagulation
Ebeling et al. (64)	Case report	8-day old male Left internal capsule	IgG 29 SGU	Y	Normal neurological development
Ebeling et al. (64)	Case report	2-day old male Right temporoparietal and left parietal region infarct	IgG 39 SGU	Y	Normal mental development

Table 7. Literature data describing the prevalence of *de novo* anti-β2 glycoprotein I antibodies in perinatal ischemic stroke.
MCA: Middle cerebral artery; GPL: 1 microgram of IgG antibody; Y: Yes; N: No;

2.3.2. Neonatal sinovenous thrombosis

Although no association between *de novo* anti-β2GPI antibodies and neonatal sinovenous thrombosis has been found in the literature, some data suggest that this association could exist. Antibodies against myelin oligodendrocyte glycoprotein have been linked to neonatal sinovenous thrombosis (65). In addition, anti-β2GPI antibodies can lead to sinovenous thrombosis in adults (66).

2.3.3. Pediatric ischemic arterial stroke

Most of the data present for the association of anti-β2GPI antibodies and pediatric ischemic stroke discussed the role of the IgG isotype (**table 8**). Other than the typical location of the stroke in the MCA, one of the cases reported the involvement of the corona radiata (64). Therefore, the association of anti-β2GPI antibodies with atypical stroke location in children is still to be deciphered. Another observation is the decrease in titers of anti-β2GPI antibodies with time, which needs further studies with long follow-up period to be tested.

Reference	Type	Population	Result	Confirmed	Management/Outcome
Alshekaili et al. (55)	Case report	6-months old male Left MCA stroke	75 U/l	Y	NR No further recurrence or neurological deficit
Cabral et al. (54)	Case report	6-months old male Multiple de novo acute ischemic infarcts in the frontal, right temporal, and parietal lobes	IgG 25.1 U/mL	Y	LMWH After 5 years: developmental delay, systemic hypertension, and mild renal insufficiency.
Giani et al. (44)	Case report	3-months old female	IgG 70 U/mL IgM 35 U/mL	Y	Observation

		Right parietal lobe and occipital lobe	Negative after 26 months		
Berkun et al. (33)	Prospective cohort	11 children with pediatric APS and cerebral vascular ischemic lesion	IgG 6/11 (54.5%) IgM 1/11 (9.1%) Decreased titers with time	Y	1 treated with prolonged LMWH and aspirin without complications
Ebeling et al. (64)	Case report	6-month old male Left MCA	IgG 26 SGU	Y	Decreased right hand activity
Ebeling et al. (64)	Case report	4-month old female Left MCA	IgG 101 SGU	Y	Partial right-sided spastic hemiparesis
Ebeling et al. (64)	Case report	11.5-month old male Left corona radiata-nucleus lentiformis	IgG 109 SGU	Y	Neurological improvement
Ebeling et al. (64)	Case report	11-month old male Left MCA	IgG 129 SGU	Y	Mild hemiparesis

Table 8. Literature data describing the prevalence of anti-β2 glycoprotein I antibodies in perinatal ischemic stroke.
MCA: Middle cerebral artery; APS: Antiphospholipid syndrome; GPL: 1 microgram of IgG antibody; Y: Yes; N: No; SGU: Standard IgG anti-beta-2 GPI units; NR: Not reported; LMWH: Low-molecular-weight heparin

2.3.4. Pediatric sinovenous thrombosis

In children, anti-B2GPI antibodies have not been found necessary for the development of sinovenous thrombosis in children with LAC (67). As in neonates, there are no studies that associate anti-B2GPI with pediatric sinovenous thrombosis. Therefore, it is still to be tested whether anti-B2GPI can independently contribute to the mechanism of sinovenous thrombosis in children.

2.4. Non-criteria antiphospholipid antibodies

Non-criteria antiphospholipid antibodies, including antiphosphatidylserine and antiphosphatidylinositol, were found in sera of pediatric SLE patients with renal complications (68). However, the true prevalence among neonates and children is still to be determined.

2.4.1. Neonatal cerebral thrombosis

The data on the role of *de novo* non-criteria aPL in neonates is still limited. Despite that phospholipids can play a major role in neonates (69), there are no data that antibodies can arise against these phospholipids leading to thrombotic complication.

2.4.2. Pediatric cerebral ischemic thrombosis

In children, the binding of antibodies to the phospholipids of vascular endothelial cells causes activation of the complement system and inflammatory cytokines leading to increased coagulation (70). In the literature, few case reports have described the clinical manifestations of non-criteria aPL. Cerebral ischemic stroke is one of these clinical manifestations. Interestingly, the cases that described the contribution of anti-phosphatidylcholine, anti-phosphatidylserine, and anti-phosphatidylinisitol reported no recurrence while on anti-coagulation (**table 9**). Further studies are required to elaborate whether no recurrence occurred because of the pathophysiology or because of the anticoagulation. It is evident as well that the titers of non-criteria aPL are inversely related to age. More studies are needed to test this hypothesis and to propose answers.

Non-criteria aPL	Reference	Type	Population	Result	Confirmed	Management/Outcome
Anti-phosphatidylcholine	Korematsu et al. (7)	Case report	1-year and 1-month old female Right vertebral and right PICA	Anti-phosphatidylcholine IgG 1.72 ratio over control	Y	Warfarin and aspirin No recurrence
	Korematsu et al. (7)	Case report	5-year and 8-month old female Left PCA	Anti-phosphatidylcholine IgG 1.54 ratio over control	Y	Dipyridamole No recurrence
Anti-phosphatidylserine	Korematsu et al. (7)	Case report	1-year and 1-month old female Right vertebral and right PICA	Anti-phosphatidylserine IgG 1.77 ratio over control	Y	Warfarin and aspirin No recurrence

	Korematsu et al. (7)	Case report	5-year and 8-month old female Left PCA	Anti-phosphatidylserine IgG 1.38 ratio over control	Y	Dipyridamole No recurrence
	Krelza et al. (58)	Cross-sectional	47 children with acute ischemic stroke	IgG anti-phosphtdylserine 4/47 (8.5%)	N	NA
Anti-phosphatidylinisitol	Korematsu et al. (7)	Case report	1-year and 1-month old female Right vertebral and right PICA	Anti-phosphatidylinisitol IgG 1.67 ratio over control	Y	Warfarin and aspirin No recurrence
	Korematsu et al. (7)	Case report	5-year and 8-month old female Left PCA	Anti-phosphatidylinisitol IgG 1.33 ratio over control	Y	Dipyridamole No recurrence

Table 9. Literature data describing the prevalence of some non-criteria antiphospholipid antibodies among children with ischemic stroke.
PCA: Posterior cerebral artery; PICA: Posterior inferior cerebellar artery; Y: Yes; N: No; NA: Not available

2.4.3. Pediatric sinovenous thrombosis

Some non-criteria aPL, such as anti-phosphatidylethanolamine, were associated with mesenteric vein thrombosis in adults (71). Other non-criteria aPL, such as anti-phosphatidylcholine and anti-phosphatidylethanolamine, have been linked to central retinal vein occlusion in children with SLE (72). However, the independent role of non-criteria aPL in inducing vein thrombosis is limited to case reports. Only one case report highlighted positive titers of anti-phosphatidylcholine among a 1-month old female with internal cerebral vein thrombosis (7). Similar to cases of arterial thrombosis, there was no recurrence.

3. Management

3.1. Arterial

The optimal treatment for the thrombotic complications of APS has not been yet elucidated. Except in infants with congenital heart disease or thrombophilia where recurrence of acute arterial ischemic stroke can happen, initiation of anticoagulation agents or antiplatelet therapy is not recommended without identifiable risk factors (73, 74). However, the high probability of stroke complications (75-77) and possible risk of recurrence might implicate the need of long term anticoagulation. So far, few studies have assessed the impact of long term anticoagulation or antiplatelet on the risk of cerebral arterial thrombosis complications and recurrence. While the use of aspirin can lead to the prevention of recurrent events and a neurological recovery in some patients (43), other patients with same type of aPL positivity had recurrence and neurological deficits on follow-up (10). Low-molecular-weight heparin (LMWH) had beneficial outcomes whenever combined with aspirin (33), although systemic complications were reported with LMWH monotherapy (54). However, these observations are based on few cases. As for warfarin, the data is promising. Children who were treated with warfarin, regardless of the aPL type, had favorable outcomes (7, 30, 33). In certain cases, the use of antiplatelet or anticoagulant was not related to future aPL titer or neurological outcome (44). Even with observation, aPL sometimes fades away spontaneously and no recurrence occurs (24, 78).

Apart from aPL, the data on anticoagulation/antiplatelet and cerebral ischemic stroke in neonates and children is also still limited. In Boffa and Lachassinne review (79), low-dose aspirin was given in one infant which led to resolution of thrombus, whereas the combination of heparin and aspirin did not prevent death of another infant (79). More recently, Peixoto et al. (80) also reviewed literature cases of neonatal thrombosis and aPL, and found that aspirin had a favorable outcome in the three scenarios when used, similar to the two cases who received LMWH (80).

3.2. Venous

Although rare, spontaneous vein thrombosis in previously well children can present dilemma in terms of determining the optimal prophylactic or therapeutic anticoagulation. For venous thromboembolism, the evidence on anticoagulation use is inferred from adult practice. Regarding unfractionated heparin, there are no published studies in children that establish the ideal dose and frequency of monitoring. Therefore, the selection is based on expert opinion. On the other hand, better robust evidence exists for LMWH, although exact dosing is under investigation (81). Furthermore, vitamin K antagonists (VKAs), such as warfarin, had been studied in children with venous thromboembolism. Data on international normalized ratio (INR) ranges and dose adjustments for children is inferred from adult practice. VKAs are usually avoided in infants because vitamin K dependent factors plasma levels are decreased and change physiologically, and because of the interaction with infant formula (81). In addition, the tablet form of VKAs is unsuitable for neonates. For aPL positive sinovenous thrombosis, the data is very limited regarding the outcome of anticoagulation or antiplatelet use. Only a single case report noted that a child with sinovenous thrombosis who was positive for LAC was started on lifelong aspirin

(38). However, the recurrence rate or neurological outcome was not reported. The optimal need for lifelong anticoagulant or antiplatelet in neonates and children is still to be determined.

4. Conclusion

As in adults, pediatric APS can have thrombotic manifestations such as cerebral arterial or venous thrombosis. Despite the limitation, more data exists on childhood APS than neonatal APS. In neonates, the transient nature of aPL, transplacental passage of aPL, and lack of confirmatory tests are functional limitations to test for the contribution of aPL to cerebrovascular thrombosis. The persistence of LAC after perinatal ischemic stroke has been associated with worst neurological outcomes, in contrast to aCL, which led to mild long term complications in cases that had aCL positivity mainly at low titers. In terms of long term complications for neonates, anti-β2GPI seem to be associated with better outcomes than other criteria aPL. Likewise, non-criteria aPL have been linked to good neurological outcomes, especially when long term anticoagulation was started after the thrombotic event. In certain cases, the titers of aPL tend to decrease after thrombosis in neonates which needs to be followed for possibility of thrombotic recurrence. In the pediatric population, other pro-coagulative risk factors, such as genetic thrombophilia, can sometimes play a role in inducing arterial or venous events, which makes deduction about the real association harder. While few case reports highlighted unusual arterial involvement in anti-β2GPI positive children, more large studies are needed to confirm the hypothesis. Despite the preliminary data, the optimal anticoagulant or antiplatelet choice along with the dose are still unknown and requires further studies and investigations.

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