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Pediatric Primary Antiphospholipid Syndrome: A Single Institution Experience.

Síndrome antifosfolípido primario en pediatría. Experiencia en una sola Institución

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Abstract

OBJETIVE: This study was to assess the clinical and immunological features, of children with primary antiphospholipid syndrome and highlight several unique clinical characteristics referred to as non-criteria manifestations of the disease.
MATERIALS AND METHODS: We retrospectively analyzed the medical records of prospectively collected data of 16 patients with vascular thrombosis that met the Sapporo and updated Sydney criteria for definite antiphospholipid syndrome, and of six patients with non-thrombotic manifestations, with follow-up at the hematology department of the Instituto Nacional de Pediatría, México, between January 2010 and December 2016.
RESULTS: Mean age was 8.9 years for patients with vascular thrombosis, and 15 years for patients with non-criteria manifestations. There was an equal female/male ratio in patients with vascular thrombosis and a high female predominance 5:1 in patients without thrombotic manifestations. Arterial thrombosis was the presenting event in nine patients (56.25%) and venous thrombosis in seven patients (43.75 %). One of the patients (11.1%) with arterial thrombosis had a recurrence, and four (57.1%) of the seven with venous thrombosis had one or more recurrences. IgG, IgM (or both) anticardiolipin and anti-b2glycoprotein I antibodies were detected in 44% and 66.6% respectively of the patients with arterial thrombosis and in 28.6% and 50% respectively of the patients with venous thrombosis. Lupus anticoagulant was present in 55.5% of the patients with arterial thrombosis and in 100% with venous thrombosis. Three patients with vascular thrombosis, two of them with arterial and one with venous thrombosis, expressed a high-risk antiphospholipid antibody profile (triple positivity) at presentation. Despite long-term anticoagulation treatment with vitamin K antagonists, there was a high rate of recurrent thrombosis after a first event in patients with DVT. Non-thrombotic hematologic manifestations showed an adequate response to corticosteroids or IgG.
CONCLUSIONS: The clinical spectrum of antiphospholipid syndrome in children has unique features not limited to vascular thrombosis, that cannot be explained only by a pro-thrombotic state, but also by the contribution of inflammatory mechanisms. Since currently there are no universally validated diagnostic criteria for pediatric antiphospholipid syndrome, some differences in important features between childhood and adult antiphospholipid syndrome, must be adapted for the diagnostic classification criteria in children.

KEYWORDS: antiphospholipid syndrome**,** antiphospholipid antibodies, high-risk antiphospholipid antibody profile, vascular thrombosis, recurrence, children.

Resumen

OBJETIVO: Este estudio fue registrar las características clínicas e inmunológicas de niños con síndrome antifosfolípido primario y resaltar varios rasgos clínicos distintivos, no incluidos entre las manifestaciones aceptadas de la enfermedad.

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MATERIALES Y MÉTODOS: Análisis retrospectivo de los expedientes clínicos de los datos recolectados prospectivamente de 16 pacientes con trombosis vascular que cumplían con los criterios de Sapporo y los actualizados de Sydney de diagnóstico de certeza de síndrome antifosfolípido y de seis pacientes sin manifestaciones trombóticas que tuvieron seguimiento en el Departamento de Hematología del Instituto Nacional de Pediatría de la Ciudad de México, entre enero de 2010 y diciembre de 2016.
RESULTADOS: La edad promedio fue de 8.9 años para pacientes con trombosis vascular y de 15 años para los pacientes sin manifestaciones trombóticas. La relación en cuanto al género fue similar en pacientes con trombosis vascular y se observó un gran predominio de 5:1 en los pacientes sin manifestaciones trombóticas. La trombosis arterial fue la manifestación inicial en nueve pacientes (56.25%) y la trombosis venosa en siete pacientes (43.75%). Uno de los pacientes con trombosis arterial tuvo una recurrencia, mientras que cuatro de los siete (57.1%) con trombosis venosa presentaron una o más recurrencias. Los anticuerpos: anticardiolipina (aCL) y anti-B2 glicoproteína I (anti-ß2GP I) de tipo IgG, IgM (o ambos) se detectaron en 44% y 66.6% respectivamente, de los pacientes con trombosis arterial y en 28.6% y 50% respectivamente, de los pacientes con trombosis venosa. El anticoagulante lúpico se detectó en 55.5% de los pacientes con trombosis arterial y en 100% con trombosis venosa. Tres pacientes con trombosis vascular, dos de ellos arterial y uno venosa, expresaban un perfil de anticuerpo antifosfolípido de "alto riesgo" (triple positividad) en el momento de presentación. A pesar de terapia anticoagulante de larga duración con antagonistas de la vitamina K, se observó una tasa elevada de recurrencias después del primer evento en pacientes con trombosis venosa profunda. Las manifestaciones hematológicas en pacientes sin trombosis, mostraron una respuesta satisfactoria a corticosteroides e IgG.
CONCLUSIONES: El panorama clínico del síndrome antifosfolípido en niños presenta características clínicas distintivas no restringidos o limitados exclusivamente a trombosis vascular, ya que no pueden ser explicadas simplemente por un estado pro-trombótico, sino que necesitan también la contribución de procesos inflamatorios. Dado que no existen actualmente criterios diagnósticos validados aceptados universalmente para síndrome antifosfolípido en pediatría, algunas de las diferencias entre la enfermedad de adultos y de niños, deberán incorporarse en el futuro en el criterio de diagnóstico y clasificación del síndrome antifosfolípido en niños.

PALABRAS CLAVE: Síndrome antifosfolípido, anticuerpos antifosfolípidos, perfil de anticuerpos antifosfolípido con riesgo alto en cuanto a desarrollar trombosis, trombosis vascular, recurrencia, niños.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired multisystem autoimmune disorder characterized by arterial, venous or small vessel thrombosis, pregnancy morbidity, and persistent pathogenic circulating antiphospholipid (aPL) antibodies that bind to phospholipid antigens or that recognize phospholipid-binding proteins[1,2]. Preliminary classification criteria was formulated after an International Preliminary Consensus workshop held in 1998 by a panel of experts in Sapporo, Japan, and later addressed in the 2006 International Consensus statement for classification of Definite APS in Sydney, Australia[3, 4]. APS is a rare disease in children and it was not until the early 1990s, when there was an increasing clinical awareness of the disease, after the pub-

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lication of an editorial paper that highlighted the importance of characterizing APS in childhood, and three years later by a review of 50 published cases of APS in pediatric patients by Ravelli and Martini[5, 6]. In the last two decades, there has been a growing interest in APS in children, but given the rarity of the condition, most information comes from case reports and small series of cases, so that in 2004 a project of an International Registry of pediatric patients with APS (Ped-APS Registry) was established, to obtain data and better define the clinical and laboratory features and the long-term outcome of APS in childhood. As of December 1, 2007, 121 patients from 14 countries were registered and the results of the analysis of these initial cases published in 2009 and 2013[7, 8]. Whereas APS in adults has been well characterized, currently there are no universally specific validated criteria for the diagnosis and treatment of pediatric APS, but in recent years, the initiative, Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE) has proposed a series of evidence-based recommendations for diagnosis and treatment of APS in children[9,10]. Although the relevance of non-criteria clinical manifestations of APS were considered with very low quality of evidence to support their inclusion in APS classification criteria in adults[11], children often present some of these non-criteria manifestations such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), Fisher-Evans syndrome, and neurological disorders that often precede overt thrombosis[12-18]. APS can occur at any age in childhood starting in the neonatal period but is more frequent in adolescence, and can develop in patients with no evidence of an underlying disease, group known as primary APS (PAPS), or can occur mainly in the setting of systemic lupus erythematosus (SLE) or other related autoimmune diseases, or any other process that have the potential to promote cellular activation perturbing the vascular endothelial microenvironment (inflammation associated vasculopathy), as infections, drugs, and malignancy, known as secondary APS (SAPS)[14, 16-19]. There are few reports of APS in children in our country and the earliest report can be traced back to 1993[20-22], so given the rarity of the disease it is of utmost importance the need of multicentric prospective studies to characterize epidemiology of thromboembolic events and classification criteria and management of non-thrombotic manifestations of PAPS in children.

PATIENTS AND METHODS

We retrospectively analyzed the medical records of prospectively collected data from 16 patients one-year-old and less than 18 years with a diagnosis of venous, arterial or small vessel thrombosis and persistent pathogenic positive aPL antibodies detected in two or more occasions at least 12 weeks apart, and that fulfilled the classification of definite APS.3, 4 Patients with a high-risk aPL antibody profile were those that tested positive for a medium or high titer IgG aPL units (> 40GPL or >!00 GPL) aCL and anti-b2GPI antibodies and also expressed LAC activity. The study was conducted between January 2000 and June 2016, in patients with follow-up in the hematology department of the Instituto Nacional de Pediatría, México. We also included six children who had persistent positive aPL antibodies tests and non-thrombotic clinical manifestations.

Demographic data included gender and age at onset of clinical manifestations attributable to APS, family history of thrombotic and thrombotic related diseases, clinical associated manifestations, precipitating risk factors, and underlying autoimmune diseases. Routine laboratory tests included a complete white blood cell count (WBC), standard methods of coagulation and in specific settings search of hereditary pro-thrombotic risk factors. Lupus anticoagulant (LAC) was detected by prolongation of activated partial thromboplastin test (aPTT) that did not correct with mixing tests and confirmed by a positive

dilute Russell´s viper venom test (dRVVT). A positive result was indicated by a dRVVT screening test, mixing studies with pooled normal plasma and excess phospholipid test with a ratio greater than 1.2.[23, 24] A commercially available enzyme-linked immunosorbent assay (ELISA) was used to assess anticardiolipin (aCL) and anti-β2 glycoprotein1 (anti-β2GP1) antibodies according to the manufacturer´s instructions (Euroimmun). IgA, IgG and IgM antibody isotypes were measured and expressed in phospholipid units (APL, GPL or MPL U) respectively, and results were considered positive if medium titers >40 APL, GPL or MPL U or high titers ≥ 100 APL, GPL or MPL) concentrations were registered on two or more occasions at least twelve weeks apart. The diagnosis and the site, extent and outcomes (residual clot, progression/recurrence) of venous and/or arterial thrombosis were determined using Doppler venous ultrasonography (USG) scans, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans as clinically indicated, including pulmonary embolism protocol (high resolution computed tomography pulmonary angiography (CTPA) and magnetic resonance pulmonary angiography (MRPA).

Data Analysis

Descriptive statistics. Continuous variables were expressed as means, minimum and maximum or median, and categorical variables as frequencies and percentages.

RESULTS

Patient characteristics:

We identified 16 patients with PAPS, nine with arterial thrombosis (56.2%) and seven with venous thrombosis (43.7%), with a female-male (F-M) ratio 1:1 and six patients with non-thrombotic diseases and a F-M ratio 5:1. Mean age of patients with vascular thrombosis was 8.6 ± 5.6 (range 2-17 years), 8.9 ± 5.1 (range 2-17 years) for patients with arterial thrombosis, 8.4 ± 6,2 (range 2-16 years) for patients with venous thrombosis and 15 ± 1.6 (range 13-17 years) for patients with non-criteria manifestations. Time interval between the onset of symptoms and diagnosis was 9.5 days for patients with arterial thrombosis (range 1-60 days) and 88.9 days for patients with venous thrombosis (range 1-240 days). Two patients had a first-degree relative, one with an autoimmune disorder (rheumatoid arthritis) and the other with a vascular disease, acute ischemic stroke (AIS), and six patients had an underlying pro-thrombotic risk factor (trauma, central venous catheter [CVC], cardiac surgery, prolonged immobilization, and heterozygous protein C deficiency). Clinical and laboratory features are summarized in **tables 1-3**.

Arterial Thrombosis

Arterial thrombosis was the presenting symptom in nine children (56.2%), five of whom were girls. The mean age at diagnosis was 8.9 ± 5.1 (range 2-17 years). In five patients (55.5%) it was associated with typical symptoms of cerebral AIS, in two (22.2%) with small vessel thrombosis, and in one case each (11.1%) with an acute migraine attack, and an anterior ischemic optic neuropathy **(table 1)**. One that harbored a high-risk aPL antibody profile had a recurrence at a different site of the original event (case 2). Of the two patients who experienced digital peripheral arterial occlusions, one who expressed a high-risk aPL antibody profile, developed a first thromboembolic event (ischemic necrosis) that required amputation of distal phalanges after a trauma of the left hand (case 6). The other had a history of painful cool discoloration of toes and heel of the left foot for five days that progressed to the distal part of the leg in 24 hours. CT angiography revealed involvement of medium and small caliber vessels with reduced diameter of tibial, peroneal and jejunal arteries and diminished perfusion in the arteries of the dorsal arc of the left foot. He was a carrier of a double aPL antibody profile (case 7). Clinical (malar rash,

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Table I. Characteristics and evolution of patients with arterial thrombosis

No. Patient	Age (years) (sex)	Clinical manifestation	Site	Risk factor	aCL IgA/IgG/ IgM	anti-β2GP1 IgA/IgG/ IgM	LAC	Triple positivity	Treatment
1	2.5 (F)	Monoparesis, motor aphasia, facial paralysis	Cerebral Infarct in MCA territory	Mitral valve plasty	-/-/-	++/-/-	-	No	Acenocoumarin (indefinite)
2	14 (F)	Bilateral paresis of cranial nerves III, IV, VI Papilledema	Cerebral edema/ cerebral infarct	No	-/++/+++	++/+++/+++	2.7	Yes	Acenocoumarin and Hydroxychloroquine until 18 years old, and then unknown (referred to another institution)
3	5 (M)	Hemiparesis Complex partial epilepsy with difficult to control seizures	Cerebral Infarct	No	-/-/-	-/-/-	1.6 Three years later	No	Acenocoumarin (32 months) and continued with low dose ASA (indefinite)
4	10 (F)	Hemiparesis	Cerebral Infarct	No	+/-/+	-/-/-	-	No	Acenocoumarin until 18 years old, and then unknown (referred to another institution)
5	17 (M)	Hemiparesis	Cerebral infarct	No	-/+++/+++	N/-/+++	-	No	Acenocoumarin until 18 years old, and then unknow (referred to another institution)
6	10 (M)	Peripheral ischemic necrosis	Digital peripheral arterial thrombosis of left hand	Trauma	-/++/++	++/++/+++	1.8	Yes	Amputation of distal phalanges Acenocoumarin (indefinite)
7	9 (F)	Cool discoloration of toes and heel of left foot extending to distal part of the leg.	Digital peripheral arterial thrombosis with involving of tibia and fibula arteries.	No	-/+/+	+/+++/+++	2.8	No	Acenocoumarin (indefinite)
8	11 (F)	Acute migraine attack, Diplopia	Subarachnoid Hemorrhage / vasospasm of both vertebral arteries	No	-/-/-	-/-/+++	-	No	Acenocoumarin (27 months) and then discontinued .
9	1.5 (F)	Visual acuity impairment Abnormal ocular motility	bilateral optic nerve, optic chiasma, optic tracts involvement, basal ganglia infarcts		-/-/-	++/-/+	1.3	No	Pulse methylprednisolone IVGG, LMWH x 5 days, and then switched to Acenocumarin (indefinite)

aCL: anticardiolipin antibodies; CT: Computed tomography; F: female; IVGG: Intravenous gammaglobulin; LAC: Lupus anticoagulant; M: Male; MCA: Middle cerebral artery; MRA: Magnetic resonance angiography; MRI: Magnetic resonance image; (-) Negative: (+) 20 -40 U; (++) >40 U- 100; (+++) >100 U.

photosensitivity, alopecia, oral ulcers, arthritis, pleuritis, pericarditis, renal, neurologic and hematologic disorders) and serologic tests (anti-nuclear autoantibodies, anti-double stranded DNA antibody level, anti-Sm nuclear antigen antibody, C3 and C4 levels) were all negative.

Venous Thrombosis

Seven patients (32%) presented with venous thrombosis, five of them were males (83%) and four had an associated thrombotic risk-factor **(Table 2)**. The mean age at diagnosis was 8 .4 ± 6.2 (range 2–16 years). Five patients presented with deep vein thrombosis (DVT) in the lower extremities, one with right atrial thrombosis and one with pulmonary embolism. Four out of sixteen (25%) with vascular thrombosis had one or more recurrences, all in the group of venous thrombosis and the second recurrent event presented from three months to one year after the first event, and a third recurrence in one patient seven years later. There was a prolonged time-interval between the onset of symptoms and diagnosis in four patients, in whom no medical care was sought in the first thrombotic event **(table 2)**. One patient harbored a high-risk aPL antibody profile and experienced a DVT recurrence (case 12).

Non-criteria manifestations
Hematologic

Six patients (27%) without thrombosis had hematologic manifestations, the majority of whom were females (83%), with a mean age of 15 ± 1.6 (range 13-17 years). The most common non-thrombotic diseases were Fisher-Evans syndrome observed in three patients, an alloimmune hemolytic anemia in one patient with a previous history of unexplained spontaneous miscarriage and seizures, an isolated ITP in one patient, and a severe bleeding tendency in a patient who developed a left pharyngeal hematoma, and showed abnormal coagulation tests (aPTT, prothrombin time) that did not correct with mixing tests, and very low levels of prothrombin coagulation factor **(Table 3)**.

Immunologic features

Measurements of aPL antibodies were performed a mean of five times (range 3 to 12) Increased levels of IgG and IgM (or both) aCL and anti-b2GPI antibodies were detected in 44.4% and in 66.6% of patients with arterial thrombosis, and in 28.6% and 50% of patients with venous thrombosis **(table 4)**. LAC was detected in 55.5% of patients with arterial thrombosis and in 100% with venous thrombosis. Two patients with arterial and one with venous thrombosis had negative aPL antibodies tests by standard assays (cases 1, 3, 10) when first seen in the hematology department. The first patient only expressed IgA anti-b2GPI, the second patient suffered a cerebral AIS and a cerebral infarct one year earlier and expressed a LAC three years later; he was placed on long-term secondary thromboprophylaxis with aspirin and later developed prolonged general seizures managed with carbamazepine and valproate that reduced but failed to control the seizures after several months. The addition of further thromboprophylaxis with acenocoumarin provided complete control of the seizures after two years, and LAC concomitantly decreased progressively disappearing five years later. In the third patient diagnosis was suspected initially by a medium/high titer IgA anti-b2GPI antibody (71 APL U) and supported by the detection three months later of high titer IgG aCL antibody (118 GPL U) and high titer IgA, IgG and IgM anti-b2GPI antibodies, (APL, GPL and MPL > 200 U each respectively) and confirmed by the persistence of aPL antibody positivity in subsequent tests.

Two patients with arterial and one with venous thrombosis expressed a high-risk aPL antibody profile (triple positivity); in the three IgG aCL and anti-b2GPI medium or high (> 40 or > 100

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Table 2. Characteristics and evolution of patients with venous thrombosis

No. Patient	Age (years) (sex)	Site	Risk factor	aCL IgA/IgG/IgM	anti-β2GP1 IgA/IgG/IgM	LAC	Triple positivity	Treatment
10	2 (M)	CNS thrombosis at one year age/ DVT	Hip dysplasia/prolonged immobilization	-/-/-	-/-/+ Three months later	1.99 Three months later	No	In the first event without treatment / Acenocoumarin (indefinite)
11	2 (M)	DVT	CVC /AHAI pneumonia with pleural effusion	ND/-/-	-/-/+	1.46	No	LMWH x 10 days Acenocoumarin (28 months) and then discontinued
12	14 (M)	DVT	Heterozygous protein C deficiency	+++/+++/+++	ND/+++/++	2	Yes	Acenocoumarin until 18 years old, and then unknow (outside institution)
13	11 (F)	DVT	No	++/+++/-	-/-/+++	2	No	LMWH x 5 days and acenocumarin (indefinite)
14	12 (M)	DVT	No	-/+/+	ND/ND/ND	1.85	No	LMWH (15 days) and no oral anticoagulation, later intermitent (acenocoumarin, due to lack of compliance; discontinued treatment without medical indication
15	2 (M)	Right atrial thrombosis	CVC	-/-/-	+++/+++/-	1.26	No	Acenocoumarin (indefinite)
16	16 (F)	Chronic DVT / Pulmonary embolism	No	-/-/-	-/++/++	1.65	No	In the first event without treatment / Thrombectomy, LMWH (indefinite)

aCL: anticardiolipin antibodies; AHAI: Autoimmune hemolytic anemia; CNS: Central nervous system; CT: Computed tomography; DVT: Deep venous thrombosis;
LAC: Lupus anticoagulant LMWH: Low molecular weigh heparin; MRI: Magnetic resonance image; ND: Not done; (-) Negative: (+) 20 -40 U; (++) >40 U- 100; (+++) >100 U.

Table 3. Characteristics and evolution of patients with hematological manifestations

No. Patient	Age (years) (sex)	Clinical manifestation	aCL IgA/IgG/IgM	anti-β2GP1 IgA/IgG/IgM	LA	Triple positivity (Yes / No)	Treatment
Estefania Mayorka 499279	13 (F)	Fisher- Evans syndrome	+/+/+++	+++/+/+++	2.8	No	Methylprednisolone pulses, Prednisone, Hydroxychloroquine
Claudia Aleman 501331	16 (F)	Thrombocytopenia Alloimmune hemolytic anemia	+/++/++	+++/-/+++	1,86	No	Prednisone IVGG Hydroxychloroquine
19	17 (F)	ITP	-/+++/+	+/+++/+++	ND	No	Prednisone (2 months)
20 Alicia Valdez 502760	16 (F)	Fisher Evans syndrome	-/-/-	-/-/+	2	No	Methylprednisolone pulses, Prednisone, IVGG Hydroxychloroquine
21	13 (M)	Mucocutaneous bleeding, pharyngeal hematoma	-/-/++	++/+/+++	3.1	No	Prednisone, FFP Hydroxychloroquine
22	15 (F)	Fisher Evans syndrome	-/-/-	-/-/+++	1.3	No	Methylprednisolone pulses, Prednisone, IVGG Hydroxychloroquine

aCL: anticardiolipin antibodies; IVGG: Intravenous gammaglobulin; LAC: Lupus anticoagulant; (-) Negative: (+) 20 -40 U; (++) >40 U- 100; (+++) >100 U.

Table 4. Frequency of aPL in the whole group of patients (continued on next page)

	Total	Arterial no. patients (%)	Venous no. patients (%)	Hematological no. patients (%)
LAC				
Positive	17 (80.9%)	5 (55.5%)	7 (100%)	5 (100%)
Negative	4 (19.1%)	4 (45.5%)	0	0
aCL				
Positivos	12 (54.5%)	5 (55.5%)	3 (42.8%)	4 (66.6%)
Negativos	10 (45.5%)	4 (44.5%)	4 (57.2%)	2 (33.4%)
aCL IgA				
Positive	5 (26.3%)	1 (12.52%)	2 (40%)	2 (33.3%)
Negative	14 (73.7%)	7 (87.5%)	3 (60%)	4 (66.7%)
aCL IgG				
Positive	10 (45.4%)	4 (44.4%)	3 (42.8%)	3 (50%)
Negative	12 (54.5%)	5 (55.6%)	4 (57.2%9	3 (50%)
aCL IgM				
Positive	11 (50%)	5 (55.5%)	2 (28.5%)	4 (66.6%)
Negative	11 (50%)	4 (45.5%)	5 (71.5%)	2 (33.4%)

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Table 4. Frequency of aPL in the whole group of patients

	Total	Arterial no. patients (%)	Venous no. patients (%)	Hematological no. patients (%)
anti-β2GP1				
Positivos	19 (90.4%)	7 (77.7%)	6 (100%)	6 (100%)
Negativos	2 (9.6%)	2 (22.3%)	0	0
anti-β2GP1 IgA				
Positive	10 (52.6%)	5 (62.5%)	1 (20%)	4 (66.6%)
Negative	9 (47.4%)	3 (37.5%)	4 (80%)	2 (33.4%)
anti-β2GP1 IgG				
Positive	9 (42.8%9	3 (33.3%)	3 (50%)	3 (50%)
Negative	12 (57.2%)	6 (66.7%)	3 (50%)	3 (50%)
anti-β2GP1 IgM				
Positive	17 (85%)	6 (66.6%)	5 (100%)	6 (100%)
Negative	3 (15%)	3 (33.4%)	0	0

GPL) antibody levels were associated with LAC activity (cases 2, 6, 12). IgM anti-b2GPI antibody isotype was predominant in patients with arterial thrombosis and in non-criteria patients with hematologic manifestations. LAC activity and aPL antibodies titers remained stable during follow-up in approximately 75% of the patients, but slight to moderate variations were observed in the remaining 25%.

Follow-up

The mean follow-up of patients with arterial and venous thrombosis was 5 years. All patients received low molecular weight heparin (LMWH) for the acute management of the thrombotic event, followed by oral anticoagulation with acenocoumarin, adjusted to a target international normalized ratio (INR) of 2.0-3.0. All patients were placed on indefinite secondary thromboprophylaxis, and three patients with arterial thrombosis received in addition, one an antiaggregant agent, acetylsalicylic acid (ASA), one hydroxychloroquine, and one methylprednisolone for three days for an AIS. During this period five out of 16 (31.2%) patients with vascular thrombosis had a recurrence, one in patients with arterial thrombosis, and four (55.5%) in the group with venous thrombosis, who experienced one or more recurrences. Three of these patients had not sought medical care at the first episode and developed a local chronic progressive thrombosis (cases 12, 14, 16). In three patients the second episode was in the same vascular bed (venous), and in two at a different site from the original thrombotic event. Recurrences occurred at a mean time of 22 months (range 3 to 84 months). Four patients with venous thrombosis had underlying risk factors (table 3). In most patients we were unable to reach the target INR therapeutic range, by frequent discontinuation of anticoagulation due to side effects, lack of compliance, and in one patient recurrence occurred in spite of an adequate INR. In two patients with arterial thrombosis oral anticoagulation was discontinued, in one after 32 months of treatment with acenocoumarin, followed by low dose ASA for another 20 months (case 3), and in one because she developed a serious adverse event (major bleeding), after twenty-seven months of treatment (case 8), both without recurrence. In one patient with DVT oral anticoagulation was withdrawn because LAC became negative after six months of treatment and anti-β2GP1 after one

year, and Doppler USG showed recanalization of venous thrombosis and there was disappearance of coexistent risk-factors for thrombosis after 28 months of treatment (case 11). He remains well with no new thrombotic episode 18 months after suspension of therapy (case 11). Patients with hematologic non-criteria manifestations responded well to corticosteroids and IgG, and the patients with LAC-Hypoprothrombinemia syndrome had a good response to methylprednisolone and fresh frozen plasma (FFP) after seven days of treatment.

DISCUSSION

APS is rare in childhood as shown in the largest adult APS cohort where only 28 (2.8 %) of 1000 analyzed patients, the disease occurred before age 15 [25] and although less frequent in children than adults, it appears to be more common than was initially realized, as suggested by studies in the early 1990s when Manco-Johnson and Nuss identified LAC in 25% of 79 consecutive children admitted with venous or arterial thrombosis in their institutions[26, 27] . In contrast Tavil *et al*. identified the presence of aPl antibodies in only 16 of 138 (11.6%) Turkish children with thrombosis, many of whom had associated prothrombotic risk factors.[28] The prevalence of PAPS in children is not known but is probably very rare as suggests the Ped APS Registry in which patients with the disease represented 49.5% of all cases, that included 28 of 41 (68%) previously published cases, while in more recently diagnosed cases, PAPS only represented 40% of all cases (32 of 80 cases) [7]. A similar observation has been reported in Mexico in a small cohort of 32 cases of APS in which 12 (38%) were classified as primary[21], and in a recent large series of cases from China in which PAPS only represented 24% of the cases (14/58)[29]. The lower proportion of PAPS seen in children may be due to the low incidence or rarely occurrence of pregnancy morbidity, although it could also be related to selection biases (including referral and ascertainment bias)[12,13]. Mean age at presentation in our cohort (10.4 ± 5.4) is slightly lower than the reported mean age of 10.7 years of the Ped-APS Registry [7] and of several pediatric series, including two recent retrospective series that reported a mean older age of 15 ± 3, probably because in one of these studies there was a high prevalence of SAPS (76%) especially SLE, but is similar to mean age of patients in our cohort with non-criteria manifestations, some of them high-risk patients for developing SLE or other autoimmune disease after long-term follow-up[29,30]. In contrast to adult and pediatric series of APS that report a high female predominance, in our study we found an equal female/male ratio, in accordance with the Ped-APS Registry that reported a 1.2:1 ratio[7]. There was also a slight predominance of arterial thrombosis similar to that reported in other studies[21,28,31,32], in contrast to most pediatric series that report a striking predominance of venous thrombosis, DVT affecting 43 to 65% of patients[6,7,22,29,30]. Vascular thrombosis is the hallmark of APS, and several studies have demonstrated that the pattern of disease expression can be quite heterogeneous, depending mainly on the type of organ or vessel (arterial or venous) involved, the vessel size and the rapid or slow course of the thrombotic process, as shown in our study[6,7, 30,32] . In children with arterial thrombosis, cerebral arteries are more frequently involved, with most patients presenting with AIS or transient ischemic attack (TIA)[29, 31, 33-35], though a wide range of CNS features have been reported, such as optic neuropathy, central retinal artery thrombosis, chorea, migraine, headache and seizures, as in our cohort[7,12-19]. In our study arterial thrombosis was the presenting symptom in 56.2% of the cases, which is higher than that reported in adults[29]. Of particular interest was one patient who suffered a cerebral AIS and developed a partial complex epilepsy with uncontrollable seizures, who improved dramatically when anticoagulant therapy was added to ASA, and there was a clinical correlation of seizure activity with antibody levels, as has been previously reported[36]. In most pediatric series, PAPS was

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characterized by younger age, more male predominance, AIS, and arterial thrombosis, when compared with patients with SAPS who are older, have a higher frequency of venous thrombosis, hematologic and skin disorders[6,8,14,16]. In our cohort there were marked differences between patients with vascular thrombosis; arterial thrombosis was characterized by brief time interval between onset of symptoms and diagnosis, female prevalence, F-M ratio of 2:1, median age 9.5 years, frequent CNS manifestations and one recurrences, in contrast to patients with venous thrombosis in whom there was a long time interval between onset of symptoms and diagnosis, male prevalence, a F-M ratio of 1: 2.5, mean age 6.5 years, less CNS manifestations, and more frequent recurrences. An interesting finding in our study was IgM anti-b2GPI antibody isotype predominance in patients with arterial thrombosis and in non-criteria manifestation patients with hematologic diseases. This finding was reported 25 years ago by Pengo and coworkers in a small subgroup (6%) of patients who expressed IgM aCL and anti-b2GPI as prevalent isotypes and that differed from the IgG positive ones in that they were significantly older, had more frequently arterial thrombosis and only one of them had experienced a recurrent event during follow-up. These findings led Galli to postulate the hypothesis that risk factors other than IgM aPL antibodies may have favored thrombosis[37-39]. Some of these features were found in some patients in our study and may explain the prevalence in patients with arterial and non-criteria manifestations. Classification of risk to develop thrombosis is based on the aPL profile (isotype, level, persistence, number, and intrinsic differences with respect to epitope specificity and avidity), the coexistence of inherited or acquired thrombotic risk factors, the presence of an underlying systemic inflammatory condition (infectious or autoimmune disorders), the duration and intensity of anticoagulation treatment, and time in the therapeutic range in those on secondary thromboprophylaxis[40-48].

There is a paucity of reports of long term outcome of pediatric APS in children, recurrence rates of thrombosis varying from 19% for a first venous event and 21% for those with a first arterial event of the Ped Reg,[7] to higher recurrence rates, 38.5% for DVT and 27.2% for arterial thrombosis in the Berkun *et al* study[31], to 58.8% in the series of Nageswara *et al*.[30] and lower (12.5 to 28.5%) of two small pediatric series[28, 29]. In our cohort recurrent thrombosis occurred in 25% of patients with vascular thrombosis, all in the group with venous thrombosis. In accordance to the Ped Reg that reports that recurrent events tend to present in the same vascular bed as the original event, in our study thrombosis occurred in the same vascular bed (venous) in three patients, including two of the three who had not sought medical care at the first episode and developed a local chronic progressive thrombosis and only in one at a different site, most of them with presence of several risk factors to develop thrombosis, though additional causes mainly insufficient anticoagulation, lack of compliance, and genetic thrombophilia undoubtfully played a significant detrimental role as has been previously documented[13-19,30]. In our cohort, six patients (37%) had associated pro-thrombotic risk-factors, four in the group of venous thrombosis mainly infectious diseases, AIHA, prolonged immobilization, CVC, traumatism, and inherited thrombophilia (heterozygous PC deficiency), but lacked typical pro-thrombotic risk factors seen in adults, which suggests a higher genetic burden to break through natural antithrombotic mechanisms as has been emphasized in several reports[12,16]. In only one of 12 patients investigated, was hereditary thrombophilia documented (heterozygous protein C deficiency) in a patient with triple aPL antibody profile who suffered a vascular recurrence. There is an increased relative risk of thrombosis associated with coincident inherited thrombophilia and aPL antibodies; the presence of aPL antibodies was associated with a greater than sixfold risk of stroke, and the heterozygosity for factor V Leiden increased the risk of stroke

by almost fivefold[45]. Since a high rate 53% of at least one thrombophilic marker was found in the Kenet *et al*. study and 45.5% in the Berkun *et al*. study, these results underline the importance of further characterization of the genetic and molecular signatures in all children with APS especially in geographic and clinical settings where a high prevalence of these pro-thrombotic risk factors have been reported[31, 45].

Some children who initially present as PAPS may later develop overt SLE. In the Ped-APS Registry cohort 30% of those with SLE initially presented with PAPS but progressed to full blown SLE during the 6.1 years of follow-up[7,8]. A similar rate of progression has been published previously in pediatric patients, four out of 12 (33%),[21] though a lower rate of progression has been reported more frequently in other series, rates varying from 0% [22, 28- 30] to 17.8% (5/28)[31], and 21.4% (3/14)[32], results that suggest that there may be a higher rate of progression from PAPS to SAPS in children as compared to the 7.2% to 13% registered in adults[49-51]. To date none of our patients has developed SLE in accordance with other series, probably because of the small sample size, the short follow-up period (mean 5 years), and the relatively low rate of progression to SLE or lupus-like disease reported, and when it does it usually is in the first or second year after diagnosis, especially in patients with high risk aPL antibody profile, though in occasional adults patients with PAPS, SLE developed after 8 and 10 years of follow-up, findings that highlight the need for long-term clinical and serologic monitoring for such potential development[13-19,49-51].

An interesting finding in three patients, was that they had all the features of APS and yet tested negative for aPL standard assays[41, 52-54]. For these patients, the definition of seronegative APS (SN-APS) has been proposed. However, the negativity to standard aPL assays does not mean that other antibodies are not present. In one patient diagnosis was suspected by an intermediate/high IgA anti-b2GPI and confirmed three months later by the appearance of high titer IgG aCL and IgG and IgM anti-b2GPI antibodies positivity that persisted on two subsequent determinations. One of the first longest cohort in the literature, by Murphy *et al*, showed that 4.3% of 5892 patients were positive for the IgA anti-b2GPI and less than 1% isolated positive, and described that there was a significant pathogenic role to develop thrombotic events in this subgroup[55,56]. In this and the other short transient negative case, it is possible that previously positive aPL antibodies titers became undetectable by consumption during the acute thrombotic episode and reappeared three months later, and in the other patient LAC was discovered three years later as has been reported previously[51]. In our cohort LAC was positive in 55.5% of patients with arterial thrombosis and in 100% with venous thrombosis. A positive LAC appears to be more specific for APS than an elevated anticardiolipin antibody, and to have a higher predictive value in the development of thrombosis as shown in a meta-analysis and in a systematic review of the literature. Three patients expressed a high-risk aPL antibody profile (triple positivity), all of them with a prevalent high titer IgG aCL/anti-b2GPI antibody and LAC activity; the rationale behind the triple positivity resides in the reactivity of IgG anti-b2GPI antibodies directed against an antigen specific epitope, the Gly40-Arg43 in the first domain of b2GPI, which are obviously aCL positive, The immune recognition requires the binding of b2GPI on an adequate surface (not necessarily phospholipids) in order to undergo the conformational change necessary to uncover the Gly40-ARG43 sequence. There is a high degree of concordance between aCL and anti-b2GPI antibodies as prevalent isotypes in APS. aCL tests usually detect antibodies reacting against cardiolipin complexed with b2GPI and are thus referred to as "b2GPI dependent aCL". When IgG anti-b2GPI antibodies are present in high titers, they induce the "in vitro" prolongation of clotting times, phenomenon known as LAC

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that is due to the interference of antibodies with PL functions of essential cofactors in coagulation, as has been demonstrated in the studies of Pengo and coworkers and de Laat *et al*. [43, 45, 47] The first authors found in a study of 104 patients with a high-risk aPL antibody profile followed up for a mean of 4.5 years, an incidence of thrombosis of 25 cases (5.3 cases per year) and a cumulative incidence of 37% after 10 years. In a larger cohort of 160 patients, 12.2% developed a first thromboembolic event at one year, 26.1% at 5 years and a cumulative incidence of 44,2% at 10 years. Immunologic features of three of the patients with triple positivity in our cohort, resemble the features previously reported, one with an incident thrombosis and one with a recurrence.

Although the standard of care for patients with APS is indefinite anticoagulation, we suspended treatment in three patients, with persistent negative aPL antibodies tests, disappearance of prothrombotic risk factors, and negative D-Dimer test and to date, none has experienced a recurrent thrombotic event. In two small series anticoagulation was discontinued in patients with persistent negative aPL tests and investigators suggested it could be relatively safe, but in a more recent report, patients with similar features suffered 45,8% of thrombotic recurrences[19, 57-59].

Another interesting finding in our study was that we found 27% of non-thrombotic clinical manifestations, which is slightly lower than the 38% of the pediatric APS Registry, and the 33.3% reported in the small series of primary APS of Amulya and colleagues and hematologic disorders were similar as those reported in the Registry and other series, except that the patients in our cohort have not developed thrombosis during their short follow-up[8,18,21,22,30,31]. Principal non-criteria manifestations were Fisher-Evans syndrome, AIHA, ITP, and hypoprothrombinemia-LAC syndrome which is characterized by serious bleeding, profound acquired hypoprothrombinemia, and the presence of circulating, high-affinity antibodies that bind prothrombin, low levels of this protein probably resulting from a rapid clearance of prothrombin antigen-antibody complexes. There was a good response to corticosteroids and immunomodulatory agents (IgG) in patients with hematologic manifestations and in the patient with hypoprothrombinemia-LAC syndrome to methylprednisolone and FFP[11-19, 60-63].

CONCLUSIONS

In summary, we describe the similarities and differences between definite APS in children and adults, and unique clinical features beyond thrombosis, that cannot be explained only by a prothrombotic-state but also by the contribution of inflammatory mechanisms, that need to be included in future classification criteria in children. Given the rarity of the disease it is of utmost importance the need of multicentric prospective studies to characterize the epidemiology of thromboembolic events and classification criteria and management of non-thrombotic manifestations in PAPS in children.

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