Antiphospholipid Syndrome in Mexican Children

Alfonso Zamora-Ustaran MD[1], Ricardo O. Escarcega-Alarcón MD[2], Mario Garcia-Carrasco MD[3,4], Enrique Faugier MD[5], Samara Mendieta-Zeron MD[5], Claudia Mendoza-Pinto MD[3], Álvaro Montiel-Jarquin MD[3], Margarita Muñoz-Guarneros MD[6], Aurelio Lopez-Colombo[7] MD and Ricard Cervera MD[8]

[1]Department of Pediatrics, Hospital General Zona Norte, Puebla, México
[2]Department of Internal Medicine, Temple University Hospital, Philadelphia, PA, USA
[3]Systemic Autoimmune Diseases Research Unit, HGR 36-CIBIOR, Instituto Mexicano del Seguro Social, Puebla, Mexico
[4]Department of Rheumatology, Medical School, Benemerita Universidad Autónoma de Puebla, Puebla, Mexico
[5]Department of Rheumatology, Hospital Infantil de México "Federico Gomez", Mexico DF, Mexico
[6]Department of Pedriatics, Medical School, Benemerita Universidad Autonoma de Puebla, Puebla, Mexico
[7]Delegational Coordination of Research, Instituto Mexicano del Seguro Social, Puebla, Mexico
[8]Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain

ABSTRACT: **Background:** Data on pediatric antiphospholipid syndrome (APS) are very sparse.

Objectives: To describe the main clinical characteristics, laboratory data and complications of pediatric APS patients, and to analyze the differences between primary APS and APS associated with systemic lupus erythematosus (SLE).

Methods: We retrospectively reviewed clinical and laboratory data of 32 children at the Federico Gomez children's hospital in México. Nineteen patients had SLE, 12 (37.5%) had primary APS and 1 (3%) had immune thrombocytopenic purpura. We collected information on sociodemographic variables, vaccinations, age at onset, and family history of rheumatic disease, hematological disorders, skin disorders and non-thrombotic neurological disorders. Immunological features included immunoglobulin (Ig) G and IgM anticardiolipin antibodies, IgG and IgM anti-β2 glycoprotein I antibodies, lupus anticoagulant, and anti-dsDNA and antinuclear antibodies.

Results: The patients included 24 females and 8 males. The most common thrombotic events were small vessel thrombosis (44%), venous thrombosis (28%) mainly deep venous thrombosis (DVT) in lower extremities, and arterial thrombosis (25%). The most common clinical non-thrombotic manifestations were hematological (53%) and neurological disorders (22%). There were no significant differences between groups with regard to the site of thrombosis, non-thrombotic clinical manifestations or laboratory features.

Conclusions: There were some important differences between the clinical manifestations of APS in children compared with adults, but we found no significant differences between patients with primary and APS associated with SLE. Larger studies in Latin American APS children are necessary to determine whether there are differences between ethnic groups.

IMAJ 2012; 14: 286–289

KEY WORDS: antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE), Mexico

For Editorial see page 310

Antiphospholipid syndrome is a multisystemic autoimmune disorder characterized by arterial and venous thrombosis, recurrent fetal loss, thrombocytopenia and the persistence of circulating antiphospholipid antibodies [1]. The aPL test detects a group of antibodies with different pathogenic properties associated with reactions against serum phospholipid-binding proteins. The most common antibodies detected are the lupus anticoagulant, anticardiolipin antibodies and anti-beta2-glycoprotein I antibodies.

APS may be primary (when there is no other underlying autoimmune disease) or associated with other diseases, mainly systemic lupus erythematosus [2-4]. Recently, pediatric APS has been the subject of numerous studies [5-7]. The major differences between pediatric and adult APS are the absence of common acquired risk factors for thrombosis, no pregnancy-related morbidity, increased incidence of infection-induced antibodies, different cutoff values for determination of aPL, and specific factors regarding long-term therapy in children [5]. The classification criteria initially proposed in an international consensus in 1999 [4] cannot be fully applied in children. Because some clinical criteria, such as pregnancy morbidity and thrombotic risk factors (smoking, obesity, use of contraceptives) are absent in children, it is probable that the sensitivity and specificity of the criteria for aPL-related thrombosis are higher in children than in adults. Berkun et al. [5] analyzed the clinical and laboratory manifestations of pediatric APS and concluded that it has unique features, especially venous thrombosis, stroke and thrombocytopenia. The largest analysis of pediatric APS, recently published by Avcin and co-authors [6], found differences between primary APS and APS associated with another autoimmune disease. Primary APS patients were

aPL = antiphospholipid antibodies
APS = antiphospholipid syndrome

younger and had a higher frequency of arterial thrombotic events, whereas patients with APS associated with another autoimmune disease were older and had a higher frequency of venous thrombotic events and hematological and skin manifestations.

PATIENTS AND METHODS

We retrospectively reviewed the charts of 32 children diagnosed with APS at the "Federico Gómez" Hospital Infantil in Mexico DF, Mexico, between December 2007 and November 2008. Inclusion criteria included venous or arterial thrombosis at any site, and the presence of at least one of the following aPL: aCL, LA, and anti-β2GP1 antibodies.

The registry was the same as the Ped-APS registry [7], which includes general characteristics, clinical manifestations and immunological features. Information collected included sociodemographic variables, vaccinations, age at onset, family history of autoimmune disease, hematological disorders (thrombocytopenia < 100,000 mm^2), autoimmune hemolytic anemia (anemia plus elevated reticulocyte count and increase in indirect bilirubin), Evans syndrome (hemolytic anemia plus thrombocytopenia), lymphopenia (< 1500 mm^2), skin disorders (livedo reticularis, Raynaud's phenomenon, skin ulcers, pseudovasculitis), and non-thrombotic neurological disorders (epilepsy, migraine headache, choreoathetosis, aseptic meningitis). The immunological features that were evaluated included IgG and IgM aCL, IgG and IgM anti-β2GPI antibodies, LA, anti-double stranded DNA and antinuclear antibodies. These tests were performed using commercially available enzyme-linked immunoabsorbent assay kits. Results were considered positive if aCL titers were > 20 units on two or more occasions 6 weeks apart. The diagnosis of venous thrombosis was based on findings of Doppler ultrasonography scans. Arterial events included strokes, which were diagnosed using appropriate clinical presentation and confirmed by computed tomography and/or magnetic resonance imaging. The diagnosis of arterial thrombosis at other sites was confirmed clinically and by arteriography. Valve abnormalities were confirmed by echocardiography.

STATISTICAL ANALYSIS

The descriptive analysis used means and standard deviations. The association between categorical variables was evaluated using the chi-square or Fisher's exact tests. Comparisons between means were made using the Student *t*-test. A *P* value < 0.05 was considered statistically significant. The statistical analysis used the SPSS v16 for Windows statistical program.

aCL = anticardiolipin antibodies
LA = lupus anticoagulant
β2GP1 = anti-beta2-glycoprotein I

RESULTS

The study group comprised 24 females (75%) and 8 males (25%). Mean age at onset was 11.5 ± 4.6 years. Nineteen patients (59%) had SLE, 12 (38%) had primary APS and 1 (3%) had immune thrombocytopenic purpura. Four patients were initially diagnosed as having primary APS and developed SLE during the follow-up. The 32 patients reported thrombosis at different levels and persistence of aPL at the follow-up visits.

CLINICAL MANIFESTATIONS

Fourteen patients (44%) had small vessel thrombosis, 10 (31%) had venous thrombosis and 8 (25%) had arterial thrombosis. The most common presentation was digital ischemia (n=14), followed by deep vein thrombosis in the lower extremities (n=10) [Table 1]. Four patients (12%) had a family history of autoimmune diseases.

The associated non-thrombotic clinical manifestations at the time of the initial thrombotic event are shown in Table 2. The most common manifestations were hematological dis-

SLE = systemic lupus erythematosus

Table 1. Thrombotic events at the onset of pediatric APS

Thrombotic event	
Small vessel thrombosis	14 (44%)
Digital ischemia	14 (44%)
Venous thrombosis*	10 (31%)
DVT in lower extremities	9 (28%)
IVC thrombosis and DVT	1 (3%)
Arterial thrombosis*	8 (25%)
Ischemic stroke	6 (19%)
Pulmonary artery	1 (3%)
Mesenteric artery	1 (3%)
Total	32 (100%)

Values presented are number of patients (%)

*One patient presented both venous (DVT) and arterial (mesenteric artery) thrombosis

IVC = Inferior vena cava

Table 2. Associated non-thrombotic clinical manifestations at the time of the initial thrombotic event

Hematological disorders	17 (53%)
Evans syndrome	5 (16%)
Thrombocytopenia	3 (9%)
Hemolytic anemia	3 (9%)
Leukopenia/lymphopenia	2 (6%)
Hemolytic anemia/lymphopenia	2 (6%)
Lymphopenia/thrombocytopenia	2 (6%)
Neurological disorders	7 (22%)
Epilepsy	5 (16%)
Chorea/athetosis	1 (3%)
Aseptic meningitis	1 (3%)
Skin disorders	2 (6%)
Skin ulcer	1 (3%)
Raynaud's phenomenon	1 (3%)
Valvular disorders	2 (6%)
Tricuspid insufficency	2 (6%)

Values are number of patients (%)

Table 3. Immmunological findings

	Primary APS		APS associated with SLE		Total	
	No. tested	No. (%) positive	No. tested	No. (%) positive	No. tested	No. (%) positive
aCL	12	7 (58%)	20	13 (65%)	32	20 (62%)
IgG/IgM	10	6 (60%)	18	11 (61%)	28	17 (61%)
IgG	1	1 (100%)	2	2 (100%)	3	3 (100%)
IgM	1	0 (0%)	0	0 (0%)	1	0 (0%)
Anti-β2GPI	6	2 (33%)	2	1 (50%)	8	3 (38%)
IgG/IgM	4	1 (25%)	2	1 (50%)	6	2 (33%)
IgG	2	1 (50%)	0	0 (0%)	2	1 (50%)
LA	2	2 (100%)	6	4 (66%)	8	6 (75%)
ANA	11	4 (36%)	19	17 (89%)	30	21 (70%)
DNA	10	2 (20%)	16	13 (81%)	26	15 (58%)

aCL = anticardiolipin antibodies, Ig = immunogloublin, β2GP1 = anti-β2-glycoprotein I, LA = lupus anticoagulant, ANA = antinuclear antibodies

orders (53%), including Evans syndrome (16%), thrombocytopenia (9%) and hemolytic anemia (9%). The second most common manifestation was neurological involvement (22%), of which epilepsy was the most frequent (16%). One patient aged 4 months presented with aseptic meningitis, together with thrombosis and no other cause of primary thrombophilia. Two patients (6%) had skin disorders, such as Raynaud´s phenomenon and skin ulcers. Of note, two patients had tricuspid regurgitation in the absence of pulmonary hypertension, one related to primary APS and the other to Libman-Sacks endocarditis.

No statistically significant differences were detected between the clinical manifestations of patients with primary APS and those with APS associated with SLE.

IMMUNOLOGICAL FEATURES

Immunological findings are summarized in Table 3. In patients with primary APS, aCL were positive in 58% and anti-β2GPI antibodies in 33%. Only two patients were tested for LA and both were positive. ANA were positive in 36% and anti-dsDNA in 20% (in these two cases the children did not fulfill classification criteria for SLE). In patients with APS associated with SLE, aCL were positive in 65%, anti-β2GPI in 50%, LA in 66%, ANA in 89% and anti-dsDNA in 81%. One patient, aged 4 months, who presented with thrombosis, was tested for inherited prothrombotic disease. Proteins C and S and antithrombin deficiencies were not detected and IgG aCL were positive.

DISCUSSION

To our knowledge, this is the largest study of APS in Latin American children. Pediatric APS was more frequent in girls than in boys (3:1), but this ratio was closer to that reported in Latin American adults (5:1) [2], in contrast to a European study on pediatric APS [6] where the ratio was 1.2:1. However, these differences may be due to the small number of patients in this Mexican cohort (32 patients) as compared to the European study (121 patients).

A total of 38% of patients had primary APS, a prevalence slightly lower than the prevalence in adults in the largest APS study (53%) [9]. In our study the most common autoimmune disease associated with pediatric APS was SLE (95%), followed by immune thrombocytopenic purpura. Thus, in pediatric APS patients, when there is a high suspicion of SLE it is very important to look for anti-dsDNA antibodies as well as to monitor for thrombocytopenia in order to improve the management and the outcome of these patients, because the presence of aPL in pediatric SLE can modify the disease expression and may be an important predictor of the development of irreversible organ damage.

The most-frequent thrombotic event was small vessel thrombosis (44%) – in contrast to DVT of the lower limbs reported by Avcin et al. [6] and in adult studies [2] – followed by DVT of the lower extremities (28%). The rate of ischemic stroke (19%) was similar to that reported in adults [2] and half of that reported by Avcin et al. [6].

The most common non-thrombotic clinical manifestations were hematological disorders (53%); of those, Evans syndrome was the most frequent (16%), higher than reported by Avcin's group [6] (12%) and lower than that reported in adults, where thrombocytopenia is the most frequent manifestation (22%–42%) [6,9,10].

Lupus anticoagulant was the most common immunological finding (75%), higher than that reported in adults (40–54%) [2,8,10]. This may be due to the higher number of SLE patients in our cohort.

The group of primary APS patients was slightly younger than that of APS associated with another autoimmune disease (9.7 ± 4.8 vs. 12.7 ± 4.1), although this difference did not reach statistical significance. The rate of female:male ratio in the primary APS was 2:1 vs 4:1 in the APS associated with another autoimmune disease. The site of thrombosis and the clinical associated manifestations did not show statistical differences.

CONCLUSIONS

We found a higher prevalence of APS associated with autoimmune diseases, mainly SLE, than primary APS. Most of the known risk factors, such as atherosclerosis, smoking, hypertension and contraceptive hormonal treatment, are not present in childhood, but there are some important features, such as migraine, thrombocytopenia, livedo reticu-

ANA = antinuclear antibodies

DVT = deep vein thrombosis

laris, and cardiac valve disease, that may be reconsidered in the criteria of APS in children. The increased frequency of infectious processes in childhood could be responsible for the prevalence of non-pathogenic and transient aPL, but in our cohort even the patients with primary APS had other ongoing manifestations. We found no important differences in thrombotic and non-thrombotic clinical manifestations and immunological features between the patients with primary APS and those with APS associated with SLE, although this may be a sample bias or a feature of Mexican children.

Corresponding author:
Dr. R. Cervera
Servei de Malalties Autoinmunes, Hospital Clinic, Villarroel, 170, 08036-Barcelona, Catalonia, Spain
Phone: +34 93 227-5774, **Fax:** +34 93 227 1707
email: rcervera@clinic.ub.es

References

1. Shoenfeld Y. Systemic antiphospholipid syndrome. *Lupus* 2003; 12: 497-8.
2. Garcia-Carrasco M, Galarza M, Gomez-Ponce M, et al. Antiphospholipid syndrome in Latin American patients: clinical and immunologic characteristics and comparison with European patients. *Lupus* 2007; 16: 366-73.
3. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002; 346: 752-63.
4. Wilson WA, Gharabi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an International Workshop. *Arthritis Rheum* 1999; 42: 1309-11.
5. Berkun Y, Padeh S, Barash J, et al. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum* 2006; 55: 850-5.
6. Avcin T, Cimaz R, Silverman ED, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics* 2008; 122: e1100-7.
7. Avcin T, Cimaz R, Rozman B; Ped-APS Registry Collaborative Group. The Ped-APS Registry: the antiphospholipid syndrome in childhood. *Lupus* 2009; 18: 894-9.
8. Myakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definitive antiphospholipid syndrome. *J Thromb Haemost* 2006; 4: 295-306.
9. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002; 46: 1019-27.
10. Uthman I, Godeau B, Taher A, Khamashta M. The hematologic manifestations of the antiphospholipid syndrome. *Blood Rev* 2008; 22: 187-94.