

Antiphospholipid Syndrome in Mexican Children: Evolution, Laboratory and Clinical Characteristics: An 18-Year Experience

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Abstract

Introduction: Antiphospholipid syndrome (APS) is an autoimmune, multisystemic disease characterized by the presence of thrombotic events, gestational morbidity, as well as hematological, dermatological and neurological manifestations, in the presence of high titers of antiphospholipid antibodies. It can present as primary, an isolated clinical entity, or secondary, as a manifestation of a rheumatologic disease, primarily systemic lupus erythematosus. 35 years after its first description, the understanding of this pathology is still evolving and even more so in the presentation in children.

Objective: To do a demographic description of pediatric population with APS in our hospital, allowing us to establish diagnostic criteria and targeted therapeutic management. It will also allow a prompt diagnosis, avoiding the morbidity and mortality associated with this pathology.

Materials and Methods: We performed a descriptive cross-sectional study. We searched in our archives for patients under 16 years of age, evaluated at the Hospital Infantil de Mexico Federico Gomez from March 2000 to March 2018 that met Sapporo criteria for classification of antiphospholipid syndrome.

Results: By reviewing the archives, we documented 29 patients were met Sapporo criteria for classification of APS from March 2000 to March 2018 at Hospital Infantil de Mexico Federico Gomez. 52% of the patients were female, while 48% male. The average age of patients was 9.8 years, with a minimum of 2.2 and a maximum of 16 years. The mean age at diagnosis was 14.8 years, with a standard deviation of 4.56 (range from 6.2 to 14.2 years). Of the 29 patients, 48% were diagnosed with primary APS, while 52% with secondary. Systemic Lupus Erythematosus was the primary rheumatologic disease in all the cases of secondary APS.

Conclusion: Antiphospholipid syndrome is a complex and not well described pathology in pediatric population. Its variable presentation and unpredictable nature implies a diagnostic and treatment challenge for pediatricians. Epidemiological description of the pediatric population with APS at our hospital is very valuable for the development of diagnostic and therapeutic guidelines. Future reviews, in correlation with reviews from tertiary international rheumatologic centers are needed.

Keywords: *Antiphospholipid Syndrome (APS); Mexican Children; Arterial Thrombosis; Venous Thrombosis*

Introduction

Antiphospholipid syndrome (APS) is an autoimmune, multisystemic disease characterized by the presence of thrombotic events, gestational morbidity, as well as hematological, dermatological and neurological manifestations, in the presence of high titers of antiphospholipid antibodies. It can present as primary, an isolated clinical entity, or secondary, as a manifestation of a rheumatologic

disease, primarily systemic lupus erythematosus. 35 years after its first description, the understanding of this pathology is still evolving and even more so in the presentation in children. The presence of antiphospholipid antibodies has been widely reported in pediatric patients with thrombosis. APS is considered the most common acquired cause of a prothrombotic state of autoimmune etiology. At the moment, there are no reliable data on the incidence or prevalence of this syndrome in pediatric population, this is partly due to the absence of validated diagnostic criteria for pediatric patients. Although the incidence of thrombosis in children is lower than in adults, thrombosis attributable to antiphospholipid antibodies is proportionately higher. Hospital Infantil de Mexico Federico Gomez is a national reference center for autoimmune diseases [1-21].

Objective of the Study

There is no international description of the demographic characteristics of pediatric patients with APS. The demographic description of pediatric population with APS in our hospital will allow us to establish diagnostic criteria and targeted therapeutic management. It will also allow a prompt diagnosis, avoiding the morbidity and mortality associated with this pathology. We described the population with diagnosis of APS over the past ten years, the type and titles of antiphospholipid antibodies, and its correlation with arterial or venous thrombosis. We also describe the differences between demographic findings in Mexican pediatric population with international reports.

Materials and Methods

We performed a descriptive cross-sectional study. We searched in our archives for patients under 16 years of age, evaluated at the Hospital Infantil de Mexico Federico Gomez from March 2000 to March 2018 that met Sapporo criteria for classification of antiphospholipid syndrome. Epidemiological, clinical and laboratory data were captured at diagnosis. A statistical analysis was performed by describing variables correlating the information found. We described the findings of the demographic characteristics and correlated the information with international literature.

StatPlus for Mac® program was used for descriptive and analytical statistics. Quantitative variables are analyzed by central tendency and dispersion measures. Qualitative variables are presented in percentages and counts.

Results

By reviewing the archives, we documented 29 patients were met Sapporo criteria for classification of APS from March 2000 to March 2018 at Hospital Infantil de Mexico Federico Gomez. 52% of the patients were female, while 48% male. The average age of patients was 9.8 years, with a minimum of 2.2 and a maximum of 16 years. The mean age at diagnosis was 14.8 years, with a standard deviation of 4.56 (range from 6.2 to 14.2 years).

Of the 29 patients, 48% were diagnosed with primary APS, while 52% with secondary. Systemic Lupus Erythematosus was the primary rheumatologic disease in all the cases of secondary APS.

Primary APS

In relation to patients with primary APS, 71% were male and only 29% female. The minimum age of presentation was 1.8 years and a maximum of 16.4 years, with an average of 8.17 years. Regarding the development of thrombosis, 28% presented arterial thrombosis and 72% venous thrombosis. Of the patients who developed arterial thrombosis, 100% had central nervous system thrombosis. Patients with venous thrombosis had deep vein thrombosis in lower extremities, followed by pulmonary embolism and finally thrombosis of the foot.

Immunological tests were performed on patients with primary APS, lupus anticoagulant was positive in 85%, anti-B2 glycoprotein isotype IgG in 25%, anti-B2 glycoprotein isotype IgM in 28% and Anticardiolipin IgG and IgM in 7%. None of the patients presented with triple marker positivity. However, 50% had a double positive marker, lupus anticoagulant and anti-B2 glycoprotein. Two patients had a second thrombosis event, one of them having double positive marker.

Regarding the levels of lupus anticoagulant in patients with primary APS, the initial determination had a maximum level of 4.7 and a minimum of 0. Presenting a standard deviation of 1,087, without statistical relevance. In the second determination, 12 weeks after the first one, values fluctuated from 0 to 2.34, showing a standard deviation of 0.66. The levels found for anti-B2 glycoprotein, IgG isotype, in patients with primary APS fluctuated from 0 to 34. Presenting a standard deviation of 1,087. In the second determination, 12 weeks after the first one, the values obtained increased from 0 to 72.4, with a standard deviation of 21.14. Anti-B2 glycoprotein, IgM isotype, the initial determination fluctuated from 0 to 70.86, with a standard deviation of 25. In the second determination, 12 weeks after the first measurement, the values were between 0 and 67.72, with a standard deviation of 24.98. Anticardiolipin isotype IgG had an initial measurement minimum of 0 and a maximum of 16.7, with a 4.4 standard deviation. The second measurement values obtained were between 0 and 28.2, with a standard deviation of 7.5. Anticardiolipin IgM isotype initial values fluctuated from 0 to 74, and second determination from 0 to 120, with a first standard deviation of 19.77, and a second of 32.15.

Secondary APS

Of the patients with diagnosis of secondary APS, 75% corresponded to female and 25% were males. The minimum age was 5.6 years and a maximum of 16.6 years, with an average of 12.05 years at diagnosis. More than half of the patients, 60% developed arterial thrombosis. Arterial thrombosis was presented in central nervous system in 66% of patients. Venous presentation occurred in 13% as pulmonary thromboembolism and 6% as deep venous thrombosis in the lower extremities.

Patients with secondary APS presented with positive lupus anticoagulant in 93%, anti-B2 glycoprotein subtype IgG in 33% and IgM in 26%. Anticardiolipin isotype IgG and IgM was positive in 13% and 26% respectively.

Of the patients with secondary APS, 26% had triple positive markers and 20% had double positive markers. A second thrombosis event was found in 26% of the patients, recurrence was twice as common in female population. Half of the patients with thrombosis recurrence had triple positive markers.

Lupus anticoagulant in patients with secondary APS, had an initial determination maximum level of 2.34 and a minimum of 0. Presenting a standard deviation of 10.61, In the second determination, 12 weeks after the first one, values fluctuated from 0 to 2.5, showing a standard deviation of 0.63. The levels found for anti-B2 glycoprotein, IgG isotype, in patients with secondary APS fluctuated from 0 to 200. Presenting a standard deviation of 64.60. In the second determination, 12 weeks after the first one, the values obtained increased from 0 to 98.65, with a standard deviation of 33. Anti-B2 glycoprotein, IgM isotype, the initial determination fluctuated from 0 to 200, with a standard deviation of 72. In the second determination, 12 weeks after the first measurement, the values as in the first determination. Anticardiolipin isotype IgG had an initial measurement minimum of 0 and a maximum of 88.12, with a 23.91 standard deviation. The second measurement values obtained were between 0 and 29.16, with a standard deviation of 10.68. Anticardiolipin IgM isotype initial values fluctuated from 0 to 55, and second determination from 0 to 67, with a first standard deviation of 17.44, and a second of 20.56.

Discussion

In the present review, we described the epidemiology of the patients with diagnosis of APS evaluated at Hospital Infantil de Mexico Federico Gomez, and its correlation with the scarce international information currently reported. We report 29 patients with APS assessed in the institution, from March 2000 to March 2018 that meet Sapporo criteria.

Internationally it is reported, that there is a predominance of female sex in pediatric patients with APS, in a ratio of up to 3: 1; in the population analyzed, a 1:1 presentation ratio was found, with a minimum female predominance in primary APS. The age reported at diagnosis in international literature is 10.7 years; the population analyzed had a presentation age similar to that reported internationally, with an average age of 9.8 years.

No	Sex F/M	Age at diagnosis	APS Clas- sification	Thrombosis (1 st event) Art 1 Ven 2		LAC1	LAC2	B2G IgG1	B2G IgG2	B2G IgM1	B2G IgM2	AC IgG1	AC IgG2	AC IgM1	AC IgM2
1	F	8.6	2	1	0	2.21	1.98	0	0	0	0	0	0	0	0
2	M	16.4	1	1	1	1.42	1.23	0	0	0	0	0	0	0	0
3	F	9.2	2	1	0	1.74	1.34	>200	56	0	0	0	0	55	67
4	F	9.7	2	1	0	1.28	1.34	84	67	43.8	34.2	0	0	0	0
5	F	15	1	2	0	1.45	1.31	0	0	0	0	16.7	28.2	0	0
6	F	14.4	2	1	2	1.4	1.26	0	0	123.8	89.1	38.2	25	0	0
7	F	14.6	2	1	1	2.33	2.22	0	0	0	0	0	0	0	0
8	M	9.4	1	2	0	0	0	34	24	0	0	0	0	74	22
9	M	8	2	1	0	1.88	1.74	0	0	0	0	0	0	0	0
10	M	13.8	1	2	2	1.39	1.51	0	0	49.4	58.6	0	0	0	0
11	M	2.2	1	2	0	4.7	1.36	28	32	0	0	0	0	0	0
12	M	14.3	1	2	0	1.74	1.84	0	0	0	0	0	0	0	0
13	F	14.4	2	2	0	0	0	105.76	98.65	0	0	0	0	0	0
14	F	3.1	1	2	0	1.29	1.39	0	0	33.48	67.72	0	0	0	0
15	F	11.2	1	2	0	1.69	1.21	0	72.4	70.86	0	0	0	0	0
16	F	12.4	2	2	2	2.13	1.9	0	0	>200	>200	12.66	29.16	27.48	36.34
17	M	5.5	1	2	0	1.27	1.28	0	25.9	33.8	20.96	0	0	0	0
18	M	9.8	2	2	2	2.34	2.21	0	0	0	0	0	0	0	0
19	M	11	2	1	0	1.55	2.3	0	26	36.93	0	0	0	0	0
20	M	3.2	1	1	0	1.31	1.55	0	0	37	0	0	0	0	0
21	F	14.2	2	1	0	1.69	1.63	0	0	0	0	0	0	0	0
22	F	16.6	2	1	0	1.28	2.32	139.9	56	>200	17.9	88.12	9.9	25.16	18
23	M	3.3	1	1	0	0	0	0	0	0	0	0	0	>120	>120
24	M	1.8	1	2	0	1.94	2.34	0	0	56	48.9	0	0	0	0
25	F	5.6	2	2	0	2.2	2.5	6	0	7.8	0	7.8	23	9.1	0
26	M	9	1	2	0	1.94	2.21	0	0	0	0	0	0	0	0
27	F	13	2	2	0	1.56	1.87	0	0	0	0	0	0	18.35	21.86
28	F	6.2	1	1	0	1.35	1.43	0	0	0	30.7	0	0	0	0
29	M	14.2	2	1	0	2.34	2.22	66	52	0	0	0	0	37.6	39

Primary APS represents in our institution 48% of the total population, being consistent with what is reported in the literature. Similarly, patients with primary APS were younger at diagnosis, but presented predominantly with venous thrombosis and not with the expected arterial presentation. Patients with secondary APS presented associated with systemic lupus erythematosus, with an older age at diagnosis, but with arterial thrombosis. The site with higher frequency of venous thrombosis reported is deep veins in lower extremities, which is consistent with our population with primary APS. In patients with secondary APS, it is not. In them, the main site of venous thrombosis was pulmonary thromboembolism. In the literature, as in the population analyzed, the more frequent site of arterial thrombosis is central nervous system.

The presence of positive lupus anticoagulant by its own confers an increased risk of thrombosis, as reported in international literature. Lupus anticoagulant was the antibody persistently present in patients with APS. All patients with recurrent thrombosis events had positivity of lupus anticoagulant. The detection of lupus anticoagulant is considered very useful in the risk staging of thrombosis, mainly in patients with systemic lupus erythematosus and secondary APS.

Literature states that the greatest risk for thrombosis development is the presence of triple immune marker. In our experience, no patient with primary APS presented triple positivity. However, half of the patients presented a double positive marker and this conditioned an increased risk of 10% for the presentation of a second thrombosis event. One third of the patients with secondary APS presented triple marker, and half of those patients presented a second event of thrombosis. Patients with triple marker presented predominantly with arterial thrombosis. In our experience the presence of triple marker implies an increased risk of thrombosis and specifically of the development of arterial thrombosis, as well as for recurrence of thrombosis, being consistent with what is reported in the literature.

At present, it has been identified that the presence of IgG isotype positivity for Anticardiolipin and anti-B2 glycoprotein is associated with a higher risk of thrombosis. In the population analyzed, patients with primary APS had a higher percentage of IgM positivity for Anticardiolipin and anti-B2 glycoprotein, as well as a greater persistence of positivity compared to IgG isotype. Patients with secondary APS, had higher levels and positivity of IgG isotype anti-B2 glycoprotein and of IgM isotype Anticardiolipin. It has been reported that the detection of the same isotype for different types of antibodies increases the risk of APS diagnosis, this was not evident in our population. As reported in the literature, patients with higher antibody titers had more thrombosis and recurrence events.

Conclusion

In the last eighteen years, at Hospital Infantil de Mexico Federico Gomez, 29 patients have been diagnosed with APS. The amount of patients may be higher if the pediatric population with thrombosis events and seronegativity for traditional antibodies is taken into account. That is the reason why it is necessary to implement the measurement of non-traditional antibodies in the pediatric population with thrombosis of unidentified cause, this would allow us to diagnose patients with seronegative APS. As reported in the literature, a higher percentage of patients are women and have secondary APS. The majority of patients with primary APS are men. In our population, unlike what the literature reports, secondary APS presents with a higher percentage of arterial thrombosis. The main site of venous thrombosis was lower extremities and arterial thrombosis was cerebrovascular events. The presence of lupus anticoagulant implies an increased risk of thrombosis, as well as the presence of double or triple marker. Antibody titers and their persistence also correlate with the risk of thrombosis.

The social and economic condition of our population, being a Federal Hospital in a third world country, confines a challenge for the clinician. Attachment to treatment and follow up appointments, as well as the availability of complementary studies is limited. Treatment choice is also influenced by the economic status of the population, with the need to modify therapeutic strategies to make them affordable. Controlled studies are required in these aspects, which allow us to obtain reliable statistical data in our population.

It is important to make a correlation with our findings and adult patients with APS in Mexican population. The present study gives rise to the performance of multicenter analyzes in pediatric population with APS, which allow the development of targeted diagnostic and therapeutic guides that allow us to identify and manage pediatric patients in a timely manner and thus reduce the morbidity and mortality associated.

Antiphospholipid syndrome is a complex and not well described pathology in pediatric population. Its variable presentation and unpredictable nature implies a diagnostic and treatment challenge for pediatricians. Epidemiological description of the pediatric population with APS at our hospital is very valuable for the development of diagnostic and therapeutic guidelines. Future reviews, in correlation with reviews from tertiary international rheumatologic centers are needed.

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