International Journal of Contemporary Pediatrics
*Janarthanan M et al. Int J Contemp Pediatr. 2019 Mar;6(2):243-247*
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20190070

**Original Research Article**

# Primary antiphospholipid syndrome in children: experience from two tertiary centres in South India

**Mahesh Janarthanan[1]*, Dhaarani Jayaraman[2], Julius Scott[2], M. S. Latha[2], Saravanan Margabandhu[3], Chitra Sundaramoorthy[3], S. Srinivas[3]**

[1]Department of Pediatric Rheumatology, [2]Department of Pediatric Hematology and Oncology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India
[3]Department of Pediatrics, Apollo Children's Hospitals, Chennai, Tamil Nadu, India

**Received:** 23 December 2018
**Accepted:** 08 January 2019

***Correspondence:**
Dr. Mahesh Janarthanan,
E-mail: maheshjanarthanan@hotmail.com



## ABSTRACT

**Background:** Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by the presence of episodes of vascular thrombosis, recurrent fetal loss and other clinical features in the presence of antiphospholipid antibodies. The aim of the study was to analyze the clinical manifestations and immunologic profile of children presenting with APS.
**Methods:** Authors did a retrospective case record study of patients admitted with thrombotic events between September 2013 and August 2018 and identified patients with positive antiphospholipid antibodies. Children who had clinical features of active lupus were not included.
**Results:** The clinical and immunologic profile of 7 pediatric patients presenting with APS over 5 years from 2013 to 2018 were analysed. Symptoms secondary to vascular thrombosis were limb swelling, stroke, gangrene of toes and Budd Chiari syndrome.
**Conclusions:** APS though rare should be considered in the differential diagnosis of children presenting with thrombotic events. They need long term anticoagulants to prevent further episodes.

**Keywords:** Children, Primary antiphospholipid syndrome, Thrombosis

## INTRODUCTION

Antiphospholipid antibodies are autoantibodies directed against phospholipid-binding proteins. This includes lupus anticoagulant (LA), anticardiolipin (aCL) antibody and anti-β2 glycoprotein 1 (anti-β2GP1) antibody. These antibodies maybe present in low dilutions in normal healthy young children.[1] The pathogenesis in this condition is similar to other autoimmune conditions and includes a triad of, individuals with a genetic susceptibility, autoimmunity and an environmental trigger.[2] To diagnose APS in children there should be an episode of venous or arterial thrombus with the presence of one the antibodies described. The presence of these antibodies should be checked 12 weeks apart for its persistence.[3] This is done to exclude conditions like infection which may cause false positive presence of antibodies. Primary APS is a very rare condition in children and secondary APS maybe part of an underlying connective tissue disorder the most common association being with systemic lupus erythematosus (SLE). The adult criteria for making a diagnosis of APS may not be applicable to pediatrics since recurrent fetal loss cannot be included in childhood APS. The symptoms may vary between adult and childhood onset disease. The clinical presentation in children are variable and may include

features of deep vein thrombosis, chorea, stroke, psychosis, cardiac manifestations, pulmonary embolism, renal artery thrombosis, ischemic manifestations of gastrointestinal tract, Raynaud phenomenon, livedo reticularis, digital gangrene, thrombocytopenia, autoimmune hemolytic anemia.[4] Catastrophic APS could be a potentially fatal manifestation.[5] Being a rare disease there are no clear guidelines regarding management of childhood APS. Long term follow up is vital as a small proportion of patients could develop lupus and also due to the risk of recurrent thrombosis.[6,7]

## METHODS

A retrospective study of case notes of pediatric patients with a diagnosis of antiphospholipid syndrome admitted in both tertiary centres between September 2013 and August 2018 was done.

***Inclusion criteria***

- To be included in this study the patient had to be under 18 years of age, presented with features of arterial or venous thrombosis and have the persistent presence of the antiphospholipid antibodies.

***Exclusion criteria***

- Authors excluded children who had active features of lupus or patients who developed features of lupus later.

Authors collected the following details in a proforma which included age, sex, presenting complaints, disease manifestations, site of thrombosis, lab parameters including CBC, DCT, C3 C4 level, ANA, dsDNA, lupus anticoagulant, anticardiolipin antibody IgG and IgM, anti β2 glyoprotein1 antibody, details regarding treatment with steroids, anticoagulation agents, other medications, interventions and the duration of follow up. Lupus anticoagulant, anticardiolipin antibody and anti β 2 glyoprotein1 antibody status was rechecked after 3 months at follow up. No statistical analysis was done as the numbers were small.

## RESULTS

Seven patients were identified as having APS. The clinical and laboratory features of these patients are summarized in Table 1.

**Table 1: Summary of clinical and laboratory features of seven patients identified as having APS.**

| Age/ Sex | Presenting complaints | Pathology | ANA | C3C4 | DCT | LA | β2GP1 | aCL | Treatment and follow up |
|---|---|---|---|---|---|---|---|---|---|
| 2/F | Abdominal distension | Budd Chiari syndrome | - | N | - | + | - | - | Heparin, warfarin Hydroxychloroquine 4 years |
| 14/F | Right lower limb swelling | Thrombus in femoral vein extending to IJV | + | N | - | + | + | + | Heparin, steroids, rituximab Hydroxychloroquine 6 months |
| 15/M | Swelling of face and legs | Pulmonary thrombus partial thrombus in left renal vein | - | N | - | + | + | - | IV Steroids Anticoagulation Plasma exchange 1 year |
| 15/F | Discoloured toes | Gangrene of toes | + | Low | + | + | + | + | Steroids, anticoagulants, hydroxychloroquine, cyclophosphamide 2 year |
| 16/M | Stroke seizures | Cortical venous thrombus | + | N | + | + | - | - | Anticoagulants, hydroxychloroquine 4 years |
| 16/F | Right lower limb swelling, neck swelling | Thrombi in right axillary, subclavian vein extending to IJV and in femoral and popliteal veins | + | N | + | + | - | + | Steroids, anticoagulants, hydroxychloroquine 4 years |
| 16/F | Left hemiparesis | Pontine infarct | + | low | + | + | - | + | Steroids, anticoagulants, hydroxychloroquine 2 years |

The age group of these patients ranged from 2½ to 16 years. M: F ratio was 2:5. Clinical manifestations were variable. ANA was positive in 5/7, dsDNA was negative in all patients, hypocomplementemia was identified in 2/7, lupus anticoagulant was positive in all 7 patients, anticardiolipin IgG in 4/7and beta 2 glycoprotein antibodies in 3/7 patients, 2 patients were positive for all the three antibodies, Direct Coomb's test (DCT) was positive in 4/7 patients.

All patients had normal white cell count and platelet count except 1 patient who had thrombocytopenia. All patients were treated with heparin injections followed by warfarin and aspirin. All patients also received hydroxychloroquine. 5/7 patients received steroids. One patient received cyclophosphamide, one received rituximab and another patient underwent plasma exchange.

The duration of follow up ranged from 6 months-4 years. All patients have remained persistently positive for APS serology and they have not developed new features of SLE since presentation.

***Patient 1***

2½ year old female child presented with progressive abdominal distension and had extensive portal vein and hepatic vein thrombosis with cavernomatous malformation (Budd-Chiari syndrome). Lupus anticoagulant was detected, and she was treated with anticoagulants and hydroxychloroquine.

***Patient 2***

14-year-old female child presented with right lower limb swelling. She had thrombus in the right femoral vein extending up to the internal jugular vein. She was thrombocytopenic, ANA +ve and positive for all 3 APS antibodies. She was treated with steroids, heparin, hydroxychloroquine and rituximab.

***Patient 3***

15-year-old male child presented with facial puffiness, chest pain and swelling of legs had pulmonary and left renal vein thrombus. He was lupus anticoagulant, anti β 2 glycoprotein 1antibody positive. He was treated with steroids, anticoagulation, plasmapheresis, and hydroxychloroquine.

***Patient 4***

15-year-old female child presented with gangrenous toes (Figure 1). She was ANA +ve, lupus anticoagulant, anti β 2 glycoprotein 1antibody and anticardiolipin IgG antibody positive with low complements and positive DCT. She was treated with steroids, anticoagulation, hydroxychloroquine and cyclophosphamide.

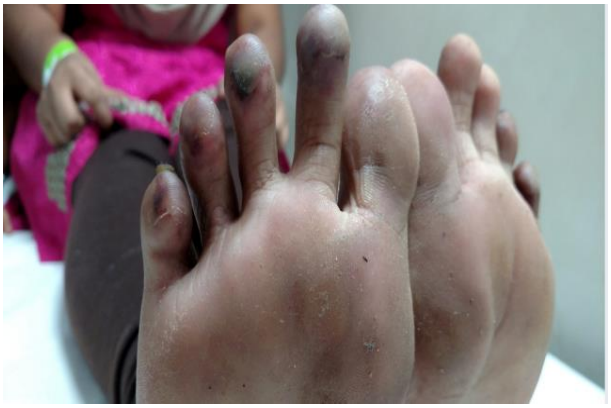

**Figure 1: Patient number 4 with gangrene of toes.**

***Patient 5***

16-year-old male child presented with stroke and seizures and had cortical venous thrombus. He was lupus anticoagulant, ANA and DCT positive. He was treated with anticoagulation and hydroxychloroquine.

***Patient 6***

16-year-old female child presented with neck and right lower limb swelling, had thrombi in right axillary vein, subclavian vein extending to IJV and in femoral and popliteal veins. She was lupus anticoagulant, anticardiolipin IgG antibody, ANA and DCT positive. She was treated with steroids, anticoagulation and hydroxychloroquine.

***Patient 7***

16-year-old female child presented with left hemiparesis and right pontine infarct (Figure 2). She was lupus anticoagulant, anticardiolipin antibody IgG, ANA and DCT positive. C3 C4 was low. Treatment for this child included steroids, anticoagulants and hydroxychloroquine.

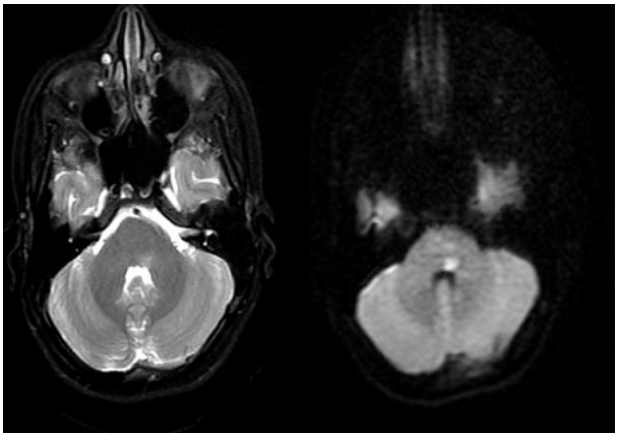

**Figure 2: MRI brain of patient number 7 with pontine infarct.**

## DISCUSSION

The actual incidence or prevalence date of childhood APS in India is virtually nonexistent. There is some Indian data regarding secondary APS in children with SLE and some case reports regarding primary APS.[8]

In present retrospective study over 4 years authors had only 7 patients with primary APS. Though small it's still a significant number considering the rarity of the condition. In a large cohort of 1000 patients only 28 (2.8%) of the patients were pediatric patients under 15 years of age and this included children with secondary APS.[9] In a multicentre European study which included 121 patients from 14 countries only about half the patients (60/121) had primary APS.[10] The male:female ratio was almost equal. The predominant presenting feature in this cohort was arterial thrombotic events and particularly stroke. The most common manifestation in our patients was vascular thrombosis in 3 patients followed by stroke in 2 and peripheral gangrene and Budd Chiari syndrome in 1 patient each. Budd Chiari syndrome as the presenting manifestation of APS though rare has been reported in a case series.[11] In the European study among the children with primary APS, 82 % were positive for aCL antibodies, 70% positive for anti β 2 GP1 antibodies and 72% had positive lupus anticoagulant. In present study all the 7 patients tested positive for lupus anticoagulant, 4 tested positive for aCL antibodies and 3 were positive for anti β2 GP1 antibodies. Although guidelines suggest the testing of both IgG and IgM antibodies to aCL and anti β 2 GP1 authors tested only IgG levels to reduce the cost of investigations. The plan was to check for IgM antibodies if they were negative for IgG antibodies and lupus anticoagulant.

All the 7 patients were treated depending on their presenting manifestations. All patients received anticoagulation with heparin followed by warfarin and aspirin. One patient with pulmonary embolism needed plasma exchange and another patient with deep vein thrombosis needed rituximab as she had persistent thrombocytopenia which did not respond to steroids and IVIG. Authors treated 1 child who developed gangrene of the toes with cyclophosphamide as she also had hypocomplementemia and a positive DCT. Authors considered the possibility of secondary APS in this child. This patient received 6 cycles of cyclophosphamide and followed up with low dose steroid and hydroxychloroquine and she has not developed new clinical features of SLE. Authors treated all children with hydroxychloroquine though there is no strong evidence for or against it. The absence of a uniform regimen is because of varied presentations, different treating clinicians and lack of strong published evidence for treatment in children with this disease. The recommendations for diagnosis and treatment of pediatric APS: the SHARE initiative has recently been published and this could provide a basis for future work in this field.[12]

The limitations in the study are that the data was collected from 2 different centres and treated by different physicians with varying protocols over a long duration and the small patient numbers. Considering the rarity of the disease these limitations are acceptable. The study also highlights the need for cooperation and collaboration between different centres in India so that the data can be collated and published. In the long term this helps in sharing experiences and information regarding best practices of management of this disease.

## CONCLUSION

Pediatricians and physicians need to be aware of this rare but potentially serious condition when dealing with young children with thrombotic events. Long term follow up of these patients is vital to monitor disease and therapy.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

## REFERENCES

1. Berkun Y, Kenet G. Pediatric antiphospholipid syndrome. IMAJ. 2008;10:45-7.
2. Cimaz R, Descloux E. Pediatric antiphospholipid syndrome. Rheum Dis Clin North Am. 2006;32:553-73.
3. Meroni PLM, Borghi O, Raschi E, Tedescoet F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol. 2011;7:330-9.
4. Aguiar CL, Soybilgic A, AvcinT, Myones BL. Pediatric antiphospholipid syndrome. Curr Rheumatol Rep. 2015;17:27.
5. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12:530-4.
6. Go´mez-Puerta JA, Martı´n H, Amigo MC, Aguirre MA, Camps MT, Cuadrado MJ, et al. Long-term follow-up in 128 patients with primary antiphospholipid syndrome. Do they develop lupus?. Med. 2005;84(4):225-30.
7. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, et al. Antiphospholipid syndrome and recurrent thrombosis in children. Arthritis Rheumatism. 2006;55(6):850-5.
8. Ahluwalia J, Singh S, Naseem S, Suri D, Rawat A, Gupta A, et al. Antiphospholipid antibodies in children with systemic lupus 3 erythematosus: a long-term clinical and laboratory follow-up 4 status study from northwest India. Rheumatol Int. 2014;34:669-73.
9. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome. Clinical and immunologic manifestations

and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheumatism. 2002;46(4):1019-27.
10. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, a Garay S, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an International registry. Pediatr. 2008;122(5):e1100-7.
11. Espinosa G, Font J, Garcia-Pagan JC, TÀssies D, Reverter JC, Gaig C, et al. Budd-Chiari syndrome secondary to antiphospholipid syndrome: clinical and immunologic characteristics of 43 patients. Med. 2001;80(6):345-54.
12. Groot N, de Graeff N, Avcin T, Bader-Meunier B, Dolezalova P, Feldman B, et al. European evidence-based recommendations for diagnosis and treatment of paediatric antiphospholipid syndrome: the SHARE initiative. Ann Rheum Dis. 2017:1-5.

**Cite this article as:** Janarthanan M, Jayaraman D, Scott J, Latha MS, Margabandhu S, Sundaramoorthy C, et al. Primary antiphospholipid syndrome in children: experience from two tertiary centres in South India. Int J Contemp Pediatr 2019;6:243-7.