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## Rare initial manifestation of antiphospholipid antibody syndrome: A clinical case report

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### Abstract

Antiphospholipid Antibody Syndrome (APS) is a rare autoimmune disease in the pediatric population, characterized by the combination of thrombotic events and the persistent presence of circulating antiphospholipid antibodies (aPL), such as anticardiolipin (aCL), anti-beta2 glycoprotein (B2GP), and lupus anticoagulant (LAC). In this study, we present the case of an 11-year-old male adolescent with no significant medical history, who was brought to the emergency department due to sudden vision loss in his right eye (RE). On examination, a relative afferent pupillary defect was observed in his RE. Retinal examination demonstrated venous occlusion and occlusion of the superior and inferior temporal branches of the retinal artery. Further investigation depicted a positive aCL and B2GP, and LAC and APS were suspected. The patient was placed on low-molecular-weight heparins for anticoagulation therapy. In this particular case, hyperbaric oxygen therapy was also administered, resulting in mild improvement. Follow-up examinations at 12 weeks confirmed persistent high titers of circulating aPL, supporting the diagnosis of primary APS. At discharge, decreased visual acuity in the RE persisted; however, there were no other signs of connective tissue disease. The patient remained on multidisciplinary care and oral anticoagulation therapy with warfarin, and no more thrombotic events were registered. This case highlights a rare initial presentation of APS in an adolescent and the importance of early recognition and management of this condition. It emphasizes the need for a comprehensive multidisciplinary approach to treat APS in pediatrics, considering the potential long-term complications associated with this condition. Further research is warranted to enhance our understanding of APS in the pediatric population and optimize treatment strategies.

**Keywords:** Antiphospholipid antibody syndrome, thrombosis, anticoagulation, autoimmunity, visual acuity, adolescent

### Introduction

Antiphospholipid Antibody Syndrome (APS) is a rare autoimmune disease characterized by the association between vascular thrombosis or obstetric complications and the persistent presence of circulating antiphospholipid antibodies [anticardiolipin (aCL), anti-beta2 glycoprotein (B2GP), and lupus anticoagulant (LAC)]<sup>[1]</sup>. APS can take two forms: primary or secondary. Secondary APS is usually associated with a connective tissue disease (CTD), with Systemic Lupus Erythematosus (SLE) being the most frequent CTD seen in pediatric cases. Primary APS accounts for 40–50% of pediatric APS cases; however, a significant number of cases eventually progress to SLE or another autoimmune pathology<sup>[2, 3]</sup>. Unlike secondary APS, primary APS is characterized by an earlier onset, predominance in males, and association with ischemic events and/or arterial thrombosis. On the other hand, it is associated with a lower frequency of venous thrombosis, hematological disorders, or dermatological manifestations<sup>[4]</sup>.

The diagnosis of APS in pediatric age is hindered by the fact that the diagnostic criteria used in adults are not reliable for children. This is because they include obstetric morbidity as a key factor; thus, the Revised Sapporo Criteria of 2006 (Table 1) is used to define cases in pediatric age<sup>[4]</sup>. Antibodies should be present at least 12 weeks following the initial positive test since they can often appear transiently in other conditions, such as infections. *Mycoplasma pneumoniae*, for example, is a major cause of respiratory infections in school-aged children and young adults, and in recent times, several pediatric cases with thrombotic

events with positive aPL have been reported [5]. Testing for other antiphospholipid antibodies directed at other antigens (e.g., antiphosphatidylserine/prothrombin antibodies) remains controversial, and their routine use is not recommended [1].

The management of APS involves three key aspects: primary prophylaxis to prevent the first thrombotic event,

secondary prophylaxis for venous and arterial thrombotic events, and the management of recurrent thrombosis. The management of obstetric complications, due to the age of pediatric patients, is usually not included. Despite the advances in medical care and pharmacology, long-term anticoagulation remains the cornerstone treatment for children with a thrombotic event caused by an APS [6].

**Table 1:** Revised and Adapted Sapporo Criteria [14]

	Vascular Thrombosis	≥1 Clinical episode of arterial, venous, or small vessel thrombosis.
Clinical criteria	Obstetric Morbidity	a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10 <sup>th</sup> week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus. b) One or more premature births of a morphologically normal neonate before the 34th week of gestation due to (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency. c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria		Presence of aPL on ≥2 occasions at least 12 weeks apart: a) Presence of Lupus Anticoagulant (LAC) in the plasma b) High titers (>40U or P>99) of anticardiolipin IgG or IgM antibodies (aCL) c) High titers (>40U or P>90) of anti-beta2 glycoprotein (B2GP) IgG or IgM antibodies

**Note:** APS is present if at least one clinical criterion and at least one laboratory criterion are met.

### Case Report

We report a case of an 11-year-old male adolescent who had experienced non-herpetic viral meningoencephalitis at the age of 4, characterized by cerebrospinal fluid pleocytosis, fever, and a seizure episode, and vernal keratoconjunctivitis with the first episode presenting at 5 years of age. Aside from these conditions, he had no other significant previous medical history. On admission, he was undergoing treatment with an ophthalmic application of 0.05% cyclosporine, twice a day, for approximately 1 year.

He was brought to the emergency department due to a sudden decrease in visual acuity in his right eye (RE). No discoloration was observed, and there were no reports of pain with eye movements. The day before admission, he had a mild trauma in the right malar and infraorbital region caused by a soccer ball. Examination revealed a relative afferent pupillary defect in the RE, while the remaining physical examination yielded no remarkable findings.

He was primarily examined by ophthalmology, and the ocular findings (i.e., venous engorgement, tortuosity with localized hemorrhages in the macular area, edema, microhemorrhages in the retinal periphery, and retinitis around the optic disc) were interpreted as a possible case of neuroretinitis.

A cranioencephalic computed tomography (CT) scan was performed, showing no abnormalities. A thorough investigation began as the patient was admitted to the adolescent department for further diagnostic evaluation. He was administered intravenous methylprednisolone at a dose of 30 mg/kg/day and oral azithromycin 500 mg due to positive IgM for *Mycoplasma pneumoniae*. On the second day, a worsening of the condition was noticed. Following the ophthalmology evaluation, an eye angiography was performed, and a venous and arterial occlusion of the retina of his RE was detected. He was immediately started on low molecular weight heparin (LMWH) anticoagulation (1.3 mg/kg/day). After the confirmation of arterial occlusion and due to the previously successful cases in the literature [7], hyperbaric oxygen therapy was also given to the patient. However, it only resulted in mild improvement and the course was halted after a total of 10 sessions.

An etiological investigation of possible causes of arterial and venous thrombosis was also performed (Table 2). On the fifth day, following the positive results of the three aPL, the primary suspicion shifted toward APS. Hence, the patient began taking warfarin and completed 5 days of azithromycin and 5 days of methylprednisolone, followed by corticosteroid weaning with oral prednisolone. After achieving a therapeutic INR, LMWH was discontinued and he was discharged on oral anticoagulation. By the time of the discharge, after 17 days of hospitalization, he still had decreased visual acuity in his RE. No other abnormalities were registered, and no clinical indications of a Connective Tissue Disease (CTD) were observed.

Follow-up laboratory tests were performed 12 weeks later and confirmed the persistence of triple positivity for circulating aPL, confirming the diagnosis of a primary APS. Currently, the patient remains under oral anticoagulation with warfarin, being followed multidisciplinary (Pediatric, Ophthalmology, Immunohematology, and Rheumatology). He did not show any new thrombotic episodes and still does not fulfill the criteria for CTD, namely LES.

### Discussions

Despite its rarity, pediatric APS poses a significant morbidity risk in children and currently lacks sufficient information. The criteria employed are derived and modified from those used in adults, which highlights the need for the future development of dedicated criteria for the pediatric age group [2]. Unlike adults, pediatric APS is more frequently associated with neurological or hematological manifestations, especially in the context of SLE or primary APS. Therefore, it is imperative to consider the possibility of APS when encountering less common clinical presentations, such as the case presented in this study.

The current treatment recommendations for children with at least one thrombotic event and persistent positivity of circulating antiphospholipid antibodies involve long-term anticoagulation [6]. However, promoting anticoagulation in a child is not an ideal scenario; hence, there is a need for further studies to assess the risk and prognosis, especially in asymptomatic children with persistently positive antibodies.

The treatment for the acute phase does not differ from other possible causes of thrombosis and consists of

anticoagulation with LMWH, as conducted in the presented case [8].

**Table 2:** Etiological study results carried out during hospitalization and in the ambulatory (12 weeks after the initial event).

	Hospitalization	Ambulatory (12 weeks after the initial event)
IgG anticardiolipin (aCL)	Positive	Positive
IgM anticardiolipin (aCL)	Negative	
Antibody anti-beta2 glycoprotein (B2GP)	Positive	Positive
Lupus anticoagulant (LAC)	Positive	Positive
Antinuclear antibodies	Positive (1/160) – speckled pattern 2, 4 e 5.	
CH50, C3 and C4	Negative	
ANCA (Antineutrophil cytoplasmic antibodies)	Negative	
ASCA (Anti-Saccharomyces cerevisiae antibodies)	Negative	
Rheumatoid factor	Negative	
Anti-factor VII	Normal.	
Anti-factor X	Normal.	
Antithrombin III	136%.	
Factor VIII C	305%.	
IgM Mycoplasma Pneumoniae	Positive	Negative
Mutation MTHFR	Mutation C677T and A1298C in compound heterozygosity.	

In addition, the use of direct oral anticoagulants (DOACs), such as rivaroxaban, is not advised, especially as a first-line treatment, due to insufficient clinical information. Previous studies have stated that patients with a history of arterial thrombosis and triple positivity (Positivity of all three classification laboratory criteria) have more risk of thrombosis if treated with DOACs as opposed to warfarin. [9]. A recent study comparing rivaroxaban to warfarin was prematurely terminated due to an increased number of thrombotic events in the rivaroxaban arm [10, 11]. Subsequently, the European Medicines Agency and the European League against Rheumatism guidelines recommended against the use of DOACs in APS patients, especially those at high risk with triple positivity [12, 13].

In summary, the authors present this case to highlight the rarity of both the clinical presentation and the pathology of APS. Given the arterial thrombotic event and triple positivity, the patient must continue treatment with warfarin and requires regular monitoring. The considerable constraints imposed by the pathology, coupled with the initial event leading to a significant decline in visual acuity in the right eye (RE), and the subsequent treatment, bear exceptional significance, especially within the pivotal age group of adolescence.

#### Conflict of Interest

Not available

#### Financial Support

Not available

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