CASE REPORT OLGU SUNUMU

# An Adolescent Girl with the Recurrent Attacks of Different Type of Thromboses

## Farklı Tiplerde ve Tekrarlayıcı Trombozları Olan Adölesan Kız

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### Abstract

**Introduction:** Thrombosis is less common in childhood compared to adults and is usually acquired. Here, we present a patient who had recurrent thrombosis in different organs and was diagnosed with lupus secondary antiphospholipid syndrome (APS) when the lupus anticoagulant test was positive in the follow-up, which we treated quickly and effectively considering possible catastrophic prognosis due to kidney involvement in the same week.
**Case Report:** Fifteen-year-old girl who presented to the emergency department with complaints of sensitivity, pain, and swelling in her left leg. Her medical history revealed recurrent thrombosis attacks and development of mental retardation after a seizure at around the age of three, and no underlying disease had been identified to date. Her family history revealed that her aunt had complained of hand swelling after cold exposure. No significant finding was detected in her thrombophilia panel. A thrombophilia panel was conducted, but no significant findings were detected. Due to a positive lupus anticoagulant test, the patient was diagnosed with APS. The diagnosis of systemic lupus erythematosus was also considered secondary to APS after positive results for anti-nuclear antibody (ANA) and dsDNA tests. Due to the recurrent thrombosis attacks and kidney involvement, a possible catastrophic outcome was considered. In addition to the on going heparin, warfarin, and aspirin therapy, high-dose steroids, cyclophosphamide, intravenous immunoglobulin, and 5 sessions of plasmapheresis were administered, and all treatments were met with a positive response.
**Conclusion:** In this case presentation, we wanted to emphasize that despite the difficulties in the differential diagnosis of thrombosis in children and especially the diagnosis of catastrophic antiphospholipid syndrome (CAPS), prompt and effective treatment can be life-saving.

**Keywords**
Antiphospholipid antibodies, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, child, thrombosis

**Anahtar kelimeler**
Antifosfolipid antikor, antifosfolipid sendrom, katastrofik antifosfolipit sendrom, çocuk, tromboz

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### Öz

**Giriş:** Tromboz çocukluk döneminde erişkine kıyasla daha nadir görülmekte olup genellikle edinsel nedenlidir. Burada farklı organlarda tekrarlayan tromboza sahip ve aynı hafta içinde böbrek tutulumunun da olması nedeniyle olası katastrofik gidiş düşünerek hızlı ve etkin bir şekilde tedavi ettiğimiz, izleminde de lupus antikoagülan testi pozitif saptanarak lupusa sekonder antifosfolipit sendromu (APS) tanısı alan hastamızı sunuyoruz.
**Olgu Sunumu:** On beş yaşında kız hasta acil servise sol bacakta hassasiyet, ağrı ve şişlik yakınmalarıyla başvurdu. Öyküsünden tekrarlayan tromboz atakları ve yaklaşık üç yaşlarında geçirilen konvülziyon sonrası mental retardasyon geliştiği

ve günümüze kadar etiyolojiye yönelik herhangi bir hastalık tespit edilmediği öğrenildi. Soygeçmişinde halasında soğukla temas sonrası ellerde morarma şikayeti haricinde başka özellik yoktu. Trombofili panelinde anlamlı bulgu saptanmadı. Lupus antikoagülan test pozitifliği olması nedeniyle APS tanısı alan hastada anti nükleer antikor (ANA) ve dsDNA testleri pozitif saptanarak sistemik lupus eritamatozus tanısına sekonder APS düşünüldü. Hastanın tekrarlayan tromboz ataklarının olması ve böbrek tutulumunun da tespit edilmesi nedeniyle olası katastrofik gidiş düşünüldü. Başlanmış olan heparin, warfarin ve aspirin tedavisine ek olarak yüksek doz steroid, siklofosfamid, intravenöz immünoglobulin ve 5 seans plazmaferez uygulandı ve tüm bu tedavilere olumlu yanıt alındı. **Sonuç:** Bu olgu sunumumuzda çocuklarda trombozun ayırıcı tanı ve özellikle katastrofik antifosfolipid sendrom (CAPS) tanısındaki zorluklara rağmen, zaman kaybetmeden etkin bir tedavinin hayat kurtarıcı olduğunu vurgulamak istedik.

## Introduction

Thrombosis is a rare condition in childhood compared to adults, and changes in blood flow, vessel wall and blood levels of coagulation factors play a role in its formation (1,2). It has been shown that acquired factors cause thrombosis more frequently than inherited factors in childhood thrombosis (3). Although antiphospholipid syndrome (APS) is rare in childhood and adolescence, it is one of the main acquired causes of symptomatic thromboembolism in the pediatric population (4). Catastrophic antiphospholipid syndrome (CAPS) is a disease that causes rapid development of thrombosis in various organs, leading to dysfunction and failure in the presence of antiphospholipid antibodies (aPL) (5). CAPS is a life-threatening condition that needs to be treated early (6). Anticoagulation, antiplatelet agents, corticosteroids, intravenous immunoglobulins (IVIG) and plasmapheresis are treatments with proven efficacy in CAPS (7). We present our patient, who was diagnosed with a possible CAPS, whose treatment was started quickly and effectively, and thrombosis was taken under control with plasmapheresis.

### *Case Presentation*

Fifteen-year-old girl initially presented to the emergency department with complaints of tenderness, pain and swelling in the left leg. The patient with mental retardation had discomfort and fever for the last few days. She had pain in her left leg and had no history of trauma. On physical examination, there was redness, tenderness, limitation of movement in the left thigh, and edema of the leg. Her fever was 37.8 °C, heart rate was 96/min, and blood pressure was 126/78 mmHg. In her past history, it was learned that she had convulsions at the age of three, and then the patient regressed mentally. No cranial radiological imaging was performed at that time. All neurometabolic tests were performed in this application for mental retardation in the patient and were found negative. The patient, who had no convulsions for ten years, was not using anticonvulsive drugs. In the family history, there were no other features except for her aunt; who experienced cyanosis in her hands after contact with the cold. The patient had no history of COVID-19 contact and COVID-19 PCR was negative. In laboratory examinations of the patient, the platelet value was 114,000/mm$^3$ and the erythrocyte sedimentation rate was 44 mm/hour. Of the coagulation tests, prothrombin time and activated partial thromboplastin time were found to be mildly elevated. In the thrombophilia panel; protein C 42 (55-111) and protein S 39.6 (52-92) levels were low, and antithrombin level 98.2 (79.4-112) was normal. The low levels of protein C and S detected in our patient were probably due to consumption during the acute thrombosis period and control examination was planned during the remission period of the disease. No mutation of factor V-Leiden and Prothrombin G20210A was detected. Homocysteine level, lipoprotein (a) level, factor VIII, IX, X, XI activities was normal. In the examinations made during this period MTHFR C677T heterozygous and MTHFR A1298C heterozygous mutations were detected. There was no evidence of hemolysis in the peripheral smear of our patient. Direct Coombs test was negative and reticulocyte count, LDH and haptoglobulin were normal. Kidney ultrasonography was normal. Low molecular weight heparin (100 IU/kg/dose) treatment was started for the patient who was hospitalized. Warfarin (0.1 mg/kg) treatment was started in the follow-up of this treatment. The patient, whose deep vein thrombosis improved in the follow-up, was admitted to our hospital again in the second week due to cyanosis, pallor and coldness on the fingertips of both hands while under antithrombotic treatment. On examination, the patient's general condition was good and vital signs were normal. The capillary filling time was very prolonged on the fingertips of both hands, the

skin was cold, and there was cyanosis, especially on the distal phalanges of the 4th fingers (Figure 1). Pulses were detected in both upper and lower extremities, and the flows were normal in the upper extremity Doppler examination. Having a family history of Raynaud's phenomenon, mental retardation and previous seizures [lupus with possible central nervous system (CNS) involvemen], mild hematuria and proteinuria (lupus with possible kidney involvement) in our patient suggested the diagnosis of antiphospholipid antibody syndrome (APS). When hematuria and proteinuria were detected, Doppler US performed to the patient revealed no pathology in the renal arteries and veins. To confirm the diagnosis of APS, lupus anticoagulant and anti cardiolipin antibodies tests were performed (about 12. week) and found positive. All laboratory tests performed on the patient are given in Table 1.

In our patient, a probable diagnosis of CAPS was considered because of the presence of aPL, the development of clinical findings within one week, venous thrombosis in the leg, arterial thrombosis in the fingertips of both hands and kidney involvement (8). In addition to antithrombotic and hydroxychloroquine treatments, two doses of IVIG 1 g/kg, three doses of pulse methyl prednisolone every other day, and one dose of pulse cyclophosphamide (750 mg/m$^2$) were administered, and the thrombosis in the fingertips improved. However, despite all these treatments, a very dramatic response was obtained with five sessions of plasmapheresis treatment applied to the patient due to the recurrence of her findings in the follow-up (Figure 2).

**Figure 1.** Cyanosis seen especially in the 4th distal phalanx.

Table 1. Blood and urine analysis values of patient

| | Value (reference) |
|---|---|
| Blood | |
| Hb (g/dL) | 10.7 (13.6-17.2) |
| Htc (%) | 33.5 (38-44.1) |
| White blood cell count (mm$^3$) | 9.8 (4.3-10.3) |
| Platelet count (mm$^3$) | 114 (156-373) |
| Erythrocyte sedimentation rate (mm/h) | 44 (1-20) |
| Blood urea nitrogen (mg/dL) | 17 (5.1-16.8) |
| Creatinine (mg/dL) | 0.5 (0.57-1.25) |
| C3 (mg/dL) | 111 (83-193) |
| C4 (mg/dL) | 13 (15-57) |
| Cardiolipin IgM (MPL U/m)-basaline and 12. week | 18.3-18.4 (0-18) |
| Cardiolipin IgG (GPLU/mL)-basaline and 12. week | 6.7-<3 (0-18) |
| Antinuclear antibody | 2.6 (0-1.2) |
| Antibody to ds-DNA | 127 (0-20) |
| Anti-beta 2 glycoprotein 1 IGM | 2.3 (>18 Positive) |
| Anti-beta 2 glycoprotein 1 IGG | 5.4 (>18 Positive) |
| Lupus anticoagulant-basaline and 12. week | 1.91-2.14 (0-1.2) |
| Lupus anticoagulant confirmatory test-basaline and 12. week | 55.3-41.0 (30-38) |
| Prothrombin time- | 12.6 (10-14) |
| Prothrombin time-International normalized ratio (PTZ-INR) | 1.1 (0.8-1.2) |
| Activated partial thromboplastin time (APTT) | 35.4 (23-35) |
| Protein C (%) | 42 (55-111) |
| Protein S (%) | 39.6 (52-92) |
| Antithrombin-% | 98.2 (79.4-112) |
| Fibrinogen (mg/dL) | 204.53 (150-350) |
| D-Dimer (mg/dL) | 0.37 (0-0.55) |
| Dipstick urine analysis | |
| Specific gravity | 1.015 |
| pH | 6 |
| Blood | +2 |
| Protein | +1 |
| Protein/creatinine (mg/mg) | 1 |

## Discussion

In this case report, we are highlighting that thrombotic diseases, which occur less frequently in children than in adults, can be severe and potentially fatal. They also mention that different mechanisms are involved in the development of venous and arterial thrombosis, with factors such as endothelial damage and platelet function being more important in the case of arterial thrombosis, while stasis and disorders in the coagulation-fibrinolytic system are more relevant in venous thrombosis (1,2). Our patient experienced both venous and arterial thrombosis at separate occasions.

It has been shown that acquired factors cause thrombosis more frequently than inherited factors in childhood thrombosis (3). The most common cause of thrombophilia among genetic disorders is the Factor V Leiden mutation (8). Factor V Leiden mutation was not detected in our patient. The prothrombin gene mutation is the second most common genetic change, and this mutation was not detected in our patient (9). In our patient, protein C and S levels were low. Considering that these values may be low at the time of acute thrombosis and during heparin and warfarin treatment, it is planned to repeat these tests at the end of the treatment and/or when the patient is in complete remission.

The patient without a family history of thrombosis was assessed for the presence of APS common cause of acquired thrombophilia, and APS was also considered because the lupus anticoagulant test and antiphospholipid antibodies were positive. Childhood APS is a rare, acquired multisystem autoimmune condition with venous and arterial thromboembolic events (10). It may occur secondary to an autoimmune disease such as systemic lupus erythematosus (SLE) or as a primary clinical syndrome. Although APS is rare in childhood and adolescence, it is one of the main acquired causes of symptomatic thromboembolism in the pediatric population (4). Our patient's ANA and dsDNA test results were positive and had borderline CNS and kidney involvement, it was considered to be APS secondary to SLE. At the same time, convulsion at the age of 3 years old was evaluated as CNS involvement of lupus. Thrombosis is a well-known clinical entity in SLE, and it is multifactorial. The most important risk factor is the presence of APL antibody. However, approximately 40% of adults with SLE who are negative for APL antibody are diagnosed with thrombosis, indicating the importance of other risk factors such as inflammation and disease activity (11).

**Figure 2.** Post-treatment image.

For the clinical and laboratory diagnosis of APS, one or more anti-phospholipid antibodies [lupus anticoagulant (LA), anti-cardiolipin (aCL) IgG/IgM, anti-ß2 glycoprotein I (anti-ß2 GPI) IgG/IgM] should be positive twice with an interval of at least 12 weeks at medium or high titer (12). aPL and LA values of our patient were planned to be checked after 12 weeks and acute treatment was started.

In European pediatric APS registries, the rate of venous thrombosis is 60%, arterial thrombosis is 30%, mostly in small vessels, and both arterial and vein involvement is reported at an even lower rate (13). Arterial involvement was observed in our patient after venous involvement. Hematological findings are seen in 30-50% of non-thrombotic involvements in APS. Among these, there are conditions such as Evans syndrome, autoimmune hemolytic anemia, and immune thrombocytopenia. Livedo reticularis and Raynaud's phenomenon may also occur (13). Our patient had only the findings of Raynaud's phenomenon among these findings.

CAPS is a disease that causes rapid development of thrombosis in various organs, leading to dysfunction and failure in the presence of aPL (5). CAPS is a rare condition seen in 1% of patients with APS (7). Classification criteria for CAPS were established in 2002 and validated in 2005 (5,14). However, these

criteria were created for classification, not diagnosis. CAPS criteria; it is defined as clinical involvement of at least three organ systems and/or tissues with histopathological evidence of small vessel occlusion and laboratory confirmation of the presence of aPL antibody (11). According to the updated Sapporo criteria, at least one clinical and one laboratory criteria are required for the definitive diagnosis of APS (15). In our patient, a possible diagnosis of CAPS was considered because of the presence of aPL antibodies, the development of clinical findings within one week, venous thrombosis in the leg, arterial thrombosis in the fingertips of both hands and kidney involvement. Hematuria and proteinuria were evaluated as renal involvement even though the Doppler was normal and biopsy could not be performed. Anticoagulation, antiplatelet agents, corticosteroids, IVIG and plasmapheresis are treatments with proven efficacy in CAPS (7). It is stated in the literature that rituximab can be used in patients who do not respond to all of these treatments.

In conclusion, we present a possible CAPS case who received high-dose steroids, cyclophosphamide, IVIG and five sessions of plasmapheresis in addition to heparin, warfarin and aspirin treatment and received a positive response from these treatments. It is aimed to emphasize that tombophilia tests in the acute phase of the disease may be misleading in children with recurrent thrombosis and there may be more serious underlying acquired conditions.

*Ethics*

*Conflict of Interest:* No conflict of interest was declared by the authors.

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## References

1. Celkan T, Dikme G. Thrombosis in children: Which test to whom, when and how much necessary? Turk Pediatri Ars 2018;53:1-9.
2. Heleen van Ommen C, Middeldorp S. Thrombophilia in childhood: to test or not to test? Semin Thromb Hemost 2011;37:794-801.
3. De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. Thromb Haemost 2013;110:697-705.
4. Ishiguro A, Ezinne CC, Michihata N, Nakadate H, Manabe A, Taki M, et al. Pediatric thromboembolism: a national survey in Japan. Int J Hematol 2017;105:52-8.
5. Berman H, Rodríguez-Pintó I, Cervera R, Gregory S, de Meis E, Rodrigues CE, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "CAPS Registry". Autoimmun Rev 2014;13:157-62.
6. Nayer A, Ortega LM. Catastrophic antiphospholipid syndrome: a clinical review. J Nephropathol 2014;3:9-17.
7. Kazzaz NM, McCune WJ, Knight JS. Treatment of catastrophic antiphospholipid syndrome. Curr Opin Rheumatol 2016;28:218-27.
8. Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS, et al. 16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends. Lupus 2020;29:1571-93.
9. Kaçar AG, Celkan T. Trombofili ve trombozda hangi tetkik, ne zaman istenmeli? Orhaner B (editör). Çocukluk Çağında Tromboz. 1. Baskı. Ankara: Türkiye Klinikleri; 2020. s.20-8.
10. Munshi R, Panchal P, Kulkarni V, Chaurasia A. Methylene tetrahydrofolate reductase polymorphism in healthy volunteers and its correlation with homocysteine levels in patients with thrombosis. Indian J Pharmacol 2019;51:248-54.
11. 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;76:1637-41.
12. Al-Hamood IA. Thrombosis in systemic lupus erythematosus: a review article. ISRN Rheumatol 2012;2012:428269.
13. Tumian NR, Hunt BJ. Clinical management of thrombotic antiphospholipid syndrome. J Clin Med 2022;11:735.
14. Rosina S, Chighizola CB, Ravelli A, Cimaz R. Pediatric Antiphospholipid Syndrome: from Pathogenesis to Clinical Management. Curr Rheumatol Rep 2021;23:10.
15. Demir S, Keskin A, Sağ E, Kaya Akca Ü, Atalay E, Cüceoğlu MK, et al. The challenges in diagnosing pediatric primary antiphospholipid syndrome. Lupus 2022;31:1269-75.