Spectrum of juvenile antiphospholipid syndrome in two siblings: Case reports and review of literature

Basil Fathalla (basilfathalla@hotmail.com)
Al Jalila Children's Specialty Hospital  https://orcid.org/0000-0002-5964-9088

Khulood W Khawaja
Sheikh Shakhbout Medical Center

Samina Afzal
Al Jalila Children's Specialty Hospital

Case Report

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Abstract

Background

Antiphospholipid syndrome (APS) in children together with familial APS is extremely rare, differs from adult APS, and has no validated diagnosis criteria. Use of adult APS classification criteria for the diagnosis of pediatric APS may result in missed or delayed diagnoses in children as non-thrombotic clinical manifestations may precede thrombotic manifestations for prolonged periods. We report rare triple positivity of antiphospholipid antibodies (aPL) in two siblings presenting with a variable spectrum of juvenile primary APS manifestations and a review of literature.

Case report

Two siblings presented with a variable spectrum of juvenile primary APS manifestations at 13 years of age. Both patients had high triple aPL positivity on multiple occasions at least 12 weeks apart including positive anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies, and lupus anticoagulant tests. The older brother, currently 16 years of age, had a spectrum of clinical manifestations during his disease course including cutaneous thrombotic microangiopathy, arthralgia, and pulmonary embolism. His sister is currently 14 years of age and she presented with non-thrombotic clinical manifestations, was immediately screened, and diagnosed with triple aPL positivity at 13 years of age. A seven years old healthy brother was screened once and had negative aPL test results. Systemic investigations including work up for systemic lupus erythematosus in both symptomatic siblings were unremarkable and whole exome sequencing was inconclusive. Human leukocyte antigen (HLA) screen revealed positive HLA-DR4 and DQB1*0302 tests for both symptomatic siblings but not for the healthy brother.

Conclusion

We conclude that non-thrombotic clinical manifestations may precede thrombotic manifestations in primary APS in children, and this may cause significant delays in the diagnosis. Familial primary APS is very rare but may occur and high index of suspicion is required to test relatives with subtle clinical manifestations. Our case reports further support possible HLA-DR and -DQ associations with aPL antibodies.

Background

Antiphospholipid syndrome (APS) is an autoimmune multisystem disease characterized by venous and arterial thromboembolic events and/or recurrent fetal loss in the presence of persistently positive antiphospholipid antibodies (aPL). Other systemic manifestations associated with APS include cardiac, hematological, neurological, cutaneous, and renal involvement [1]. APS is either an isolated clinical entity (primary APS) or a secondary disorder (secondary APS) occurring in association with other autoimmune diseases such as systemic lupus erythematosus (SLE) [1, 2]. The aPL antibodies are a heterogenous group of autoantibodies that are detected by immunoassays and functional coagulation tests.
Commonly measured aPL tests include lupus anticoagulant (LA), anticardiolipin (aCL) antibodies, and/or anti-\(\beta_2\)-glycoprotein 1 (anti-\(\beta_2\)GP1) antibodies [2, 3]. The exact incidence and prevalence of APS in children is unknown; however, it seems that primary and secondary APS occur in children with similar frequency [3]. Familial APS is very rare and juvenile primary APS in siblings is extraordinarily rare [4, 5]. We report the exceptionally rare presence of triple positive aPL antibodies in a brother and sister presenting with variable clinical manifestations of juvenile primary APS.

**Case 1**

A 13-year-old, previously healthy boy presented with new onset raised erythematous rash on the planter aspect of his feet associated with tenderness and a burning sensation for three months duration. He was evaluated by dermatology and neurology services without clear diagnosis; empiric colchicine followed by dapsone were prescribed for one month with no benefit. He had a partial response to a course of oral prednisone 2 mg / kg tapered over a period of two months. A skin biopsy was done one month later after recurrence of rash while on prednisone and showed acral skin with edema around the eccrine / vascular clusters with sparse neutrophils and eosinophils often transgressing walls of small vessels. A few small vessels or capillaries contain luminal thrombi made up of variably granular loose eosinophilic materials. Rare small vessels also show limited mural fibrinoid insudation. The eccrine ducts / glands were normal. The overall findings were consistent with thrombotic microangiopathy. APS was suspected and he was referred to adult rheumatology. APS work up included aCL-IgG level of > 120 GPL U/ml (positive > 12), aCL-IgM level of 5.8 MPL U/ml (positive > 12), anti-\(\beta_2\)GP1 IgG level of > 200 RU/ml (positive > 20), anti-\(\beta_2\)GP1 IgM level of > 19.79 RU/ml (positive > 20), and a positive LA test. Repeated tests 12 weeks later revealed aCL-IgG level of > 120 GPL U/ml (positive > 12), aCL-IgM level of 3.5 MPL U/ml (positive > 12), anti-\(\beta_2\)GP1 IgG level of > 200 RU/ml (positive > 20), anti-\(\beta_2\)GP1 IgM level of > 16.74 RU/ml (positive > 20), and a positive LA test. In the meanwhile, he was referred to neurology due to persistent paresthesia and pain in his right foot. Nerve conduction test and electromyography revealed features of chronic bilateral L5-S1 radiculopathy (right more than left) associated with an element of myelopathy. Brain and spine MRI studies with and without contrast were unremarkable. He was started on low dose aspirin with close follow up and tapering course of prednisone. He remained on low dose aspirin for 6 months, then he was switched due to abdominal pain to clopidogrel 75 mg daily for 18 months without any issues during that period and successfully tapered prednisone.

At the age of 15 years he had recurrence of severe erythematous raised rash as shown in Fig. 1A, both on the hands and feet, along with arthralgia, difficulty walking, and severe pain in his right calf but no clear evidence of deep vein thrombosis by vascular doppler study. He was hospitalized and switched to warfarin, received one course of daily intravenous immunoglobulin (IVIG) for 5 days, started hydroxychloroquine sulfate (HCQ), and received gabapentin followed by pregabalin for pain. Subsequently, he was transferred to Pediatric Rheumatology at one of our institutions after he developed sudden respiratory distress. He had shortness of breath with shallow breathing, and low oxygen saturation. He was transferred to intensive care and a chest CT scan confirmed a pulmonary embolism. He was treated with low molecular weight heparin (LMWH) and later switched to oral warfarin (target INR
2.5–3.5) once he became stable. He also received IVIG 2 grams/kg for one day and pulses of methylprednisolone 500 mg daily for three consecutive days.

Upon stabilization the family elected to go for a second opinion in the USA and the diagnosis of primary APS was upheld. He continued to have active skin lesions and pain in his legs. Adjustments to his medications included starting mycophenolate mofetil (MMF), rituximab, and a tapering course of prednisone. He continued to receive HCQ. In the USA, LMWH was combined with warfarin (target INR 2.5–3.5) then eventually switched to warfarin alone. He also underwent physical therapy management for his pain syndrome and eventually discontinued pregabalin. He returned from the USA to our second institution and was seen in follow up for seven months thus far. Laboratory investigations upon his return are summarized in Table 1. He had recurrent episodes of epistaxis and it was difficult to maintain INR within the target range, so he was switched back to LMWH due to personal preference. He had one episode of chest pain requiring hospitalization, and a thromboembolic work up including echocardiography, electrocardiogram (ECG), and chest CT scan studies were all normal. He is currently 16 years of age and continues to be stable, asymptomatic, and tolerating his medication for the last six months.
Table 1
Laboratory tests and medication in siblings with aPL antibodies and clinical features of primary APS.

|                  | Patient 1                      | Patient 2                      | Normal sibling |
|------------------|--------------------------------|--------------------------------|----------------|
| **Gender**       | Male                           | Female                         | Male           |
| **Current age**  | 16 years                       | 14 years                       | 7 years        |
| **Age of onset** | 13 years                       | 13 years                       | N/A            |
| **Clinical Features** | Vasculitic rash (skin biopsy showing thrombotic microangiopathy) | Vasculitic rash | Arthralgia |
|                  | Arthralgia                      |                                |                |
|                  | Pulmonary embolism              |                                |                |
| **Laboratory tests** |                                |                                |                |
| CBC              | Anemia                         | Anemia                         | Normal         |
| ESR range (< 20 mm/h) | < 20                           | 25–45                          | 7              |
| CRP range (< 2.8 mg/L) | < 2.8–54                    | 1.45–3.35                      | 1.5            |
| LFT              | Normal                         | Normal                         | Normal         |
| RFT              | Normal                         | Normal                         | Normal         |
| ANA              | Negative                        | Negative                        | Negative       |
| Anti-DsDNA       | Negative                        | Negative                        | Negative       |
| ENA              | Negative                        | Negative                        | Negative       |
| ANCA             | Negative                        | Negative                        | Negative       |
| Coombs           | Positive                        | Positive                        | N/A            |
| WES ‡            | Not conclusive                  | Not conclusive                  | N/A            |

‡ WES (whole exome sequencing): Clinical Exome Sequence Analysis was done for the sample submitted by the proband (patient 1) at Gene Dx laboratory in USA. Samples submitted for analysis by next generation sequencing included father and mother, and targeted testing for sister (patient 2).

aCL: anticardiolipin antibodies, anti-β2GP1: anti-β2-glycoprotein 1 antibodies, ANA: anti-nuclear antibodies, ANCA: antineutrophilic cytoplasmic antibodies, CBC: complete blood count, CRP: C-reactive protein, dPT: dilute prothrombin test, dRVVT: diluted Russel viper venom test, ENA: Anti-extractable nuclear antibodies (including anti-Smith, anti-RNP, anti-SS-A, anti-SS-B, anti-SCL-70, anti-Jo-1, and Sm/RNP), ESR: erythrocytes sedimentation rate, HCQ: hydroxychloroquine sulfate, HLA: human leukocyte antigen, IVIG: intravenous immunoglobulins, LA: lupus anticoagulant, LMWH: low molecular weight heparin, MMF: mycophenolate mofetil, PTT: partial thromboplastin time.
|                     | Patient 1                                                                 | Patient 2                                                                 | Normal sibling |
|---------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------|
| **HLA**             | DR4, DR2, DR53, DQB1*0302                                                 | DR4, DR3, DR53, DR52, DQB1*0302                                           | DR2           |
| **LA**              |                                                                           |                                                                           |                |
| PTT-LA (0.0–51.9)   | 59.1/88.2                                                                 | 82.2/62.7                                                                | 34.6          |
| dRVVT Mix (0.0–47)  | 59.4/66.2                                                                 | 81/68.7                                                                  | 43.2          |
| dRVVT confirm (0.8–1.2) | 1.9/2.3                                                              | 2.6/2.4                                                                  | N/A           |
| dPT (0.0–55)        | 141.1/91.4                                                               | 102.9/71.4                                                               | 42.2          |
| Thrombin Time (0.0–23) | 19.2/25.2                                                              | 18.2/16.3                                                                | 19.1          |
| dPT Confirm ratio (0.0–1.4) | 1.25/1.31                                                              | 1.91/1.54                                                                | 1.06          |
| Lupus Reflex        | Present                                                                  | Present                                                                  | Absent        |
| Interpretation      |                                                                           |                                                                           |                |
| **Anti-β2GP1**      |                                                                           |                                                                           |                |
| IgA (< 19.0 U/ml)   | 8.1/13.7                                                                  | 53.7 / 37.5                                                              | < 0.6         |
| IgG (< 19.0 U/ml)   | > 160.0/>160.0                                                            | > 160.0/>160.0                                                           | < 1.4         |
| IgM (< 19.0 U/ml)   | 0.9/1.1                                                                   | 25.0/12                                                                  | < 0.2         |
| **aCL**             |                                                                           |                                                                           |                |
| aCL IgA (< 19.0 APL U/ml) | 4.7/9.3                                                                | 45.7/32.1                                                                | < 0.5         |

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|                  | Patient 1 | Patient 2 | Normal sibling |
|------------------|-----------|-----------|----------------|
| IgG (< 19.0 GPL U/ml) | >160.0/>160.0 | >160/>160 | <1.6           |
| IgM (< 19.0 MPL U/ml)  | 0.4/0.7   | 17.0/8.9  | <0.2           |

**Current anti-coagulation**

| Low dose aspirin | - | 81 mg daily | - |
| LMWH            | 60 mg BID | - | - |

**Past anti-coagulation**

| Warfarin        | INR 2.5–3.5 | - | - |
| Combination     | LMWH and Warfarin | - | - |
| Clopidogrel     | 75 mg daily | - | - |
| Low dose aspirin| 81 mg      | - | - |

‡ WES (whole exome sequencing): Clinical Exome Sequence Analysis was done for the sample submitted by the proband (patient 1) at Gene Dx laboratory in USA. Samples submitted for analysis by next generation sequencing included father and mother, and targeted testing for sister (patient 2).

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### Case 2

The previously healthy 13-year-old younger sister of the above patient presented with a two-week history of progressive pain in her left hand and finger. There was no preceding injury or illnesses. There was no associated fever or other systemic complaints. She had a rash on the fingers similar to that which her brother had at the time of his disease onset as shown in Fig. 1B. A systemic work up included laboratory tests as detailed in Table 1. She was found to have triple positive aPL antibodies including LA, aCL, and anti-β2GP1 that was confirmed at least 12 weeks later. Other investigations included a normal chest x-ray, abdominal ultrasound, renal Doppler study, ECG and echocardiography, pulmonary, and ophthalmology evaluations. We initiated HCQ and low dose aspirin, and she has been in follow up for the last 10 months.
with resolution of her rash and no episodes of thrombosis. Her more recent aPL work is still showing elevated aCL and anti-β2GP1 but LA is currently not detected.

**Family History**

The parents are Arabic and nonconsanguineous. They have seven offspring including four males and three females. The two siblings mentioned above have primary APS related manifestations, one other sibling has psoriasis, and the remaining four are healthy. The youngest child (seven years old) is healthy boy. We screened him for aPL as shown in Table 1. We also screened him along with the symptomatic siblings or human leukocyte antigen (HLA)-DR or -DQ associations also shown in Table 1. The remaining siblings are all adults. The father has rheumatoid factor negative rheumatoid arthritis. The paternal grandfather passed away at the age of 80 and had a history of recurrent erythematous rashes of unknown cause.

**Discussion**

Pediatric APS may occur at any age during childhood. There are no validated criteria for the diagnosis and using the adult classification criteria for the diagnosis of pediatric APS may result in missed or delayed diagnoses as non-thrombotic clinical manifestations may precede thrombotic manifestations [6]. The exact prevalence and incidence of APS in children is unknown. According to data from the International Pediatric APS Registry (APS-IPR) including 121 pediatric cases from 14 countries, the female to male ratio was 1:1 and the mean age at onset was 10.7 years [3]. Almost 50% of the patients in the registry had an underlying autoimmune disease. Primary APS was associated with younger age and a higher frequency of arterial thrombotic events, whereas secondary APS accompanied by an underlying autoimmune disease was associated with older age and a higher frequency of venous thrombotic events. Most frequent non-thrombotic clinical manifestations included hematologic, cutaneous, cardiac, and non-thrombotic neurologic manifestations [3]. The most common APL detected in these patients was aCLs (81%), followed by LA (72%), and anti-β2GP1 (67%). Multiple positivity of aPLs was detected in 42 patients who were simultaneously tested for all three subtypes, and only one third of these patients had triple positivity [3]. Both of our patients had high triple APL positivity on multiple occasions. Although the brother eventually fulfilled the updated international classification criteria for adult APS [7], the sister did not meet APS criteria while the diagnosis of non-thrombotic APS fits very well.

Familial APS is extraordinarily rare but has been reported. Among the earliest reports of familial APS was the occurrence of LA in two pairs of siblings with a spectrum of autoimmune manifestations and clear evidence of LA positivity; the pair of brothers aged 18 and 20 years and the pair of sisters aged 46 and 50 years were reported in 1980 (8). In 1990, nine individuals with an age range of 21–64 years, from four different generations in a large kindred, were reported to have aPL antibodies associated with a spectrum of clinical manifestations including stroke, deep venous thrombosis, and recurrent abortions (9). Another report in 1997 describes a family with aPL in whom HLA-DRB gene associations were observed. Patients had a spectrum of manifestations including arthritis, sagittal vein thrombosis, glomerulonephritis,
congestive heart failure, and interstitial lung disease. The youngest patient was 33 years old and had symptoms of lupus for ten years [10]. Many of these reported cases predate the publication of APS classification criteria. Subsequent studies have reported that first-degree relatives of patients with SLE or primary APS had a higher incidence of aCL antibodies, suggesting a genetic predisposition to the development of these antibodies. Identification of several kindred with an increased frequency of aPL antibodies and the associated clinical manifestations further supports the presence of familial forms of APS [11].

In 2013, Jelušić et al. [4] reported a case of a 17-year-old girl with primary APS developing subacute signs of hand and leg ischemia caused by radial and popliteal artery occlusions associated with triple APL positivity. The mother of the girl presented just months later with symptoms of superficial thrombophlebitis and blood tests showed triple APL positivity with possible secondary APS related to evolving SLE. In 2016, Islam et al. [5] reported three familial primary APS adult patients from Malaysia. The three patients comprised two sisters and one male cousin with a mean age of 26.3 years. The first diagnosis was made between 2005 and 2009, and all patients demonstrated deep vein thrombosis, high levels of IgM and IgG aCL antibodies, and received warfarin treatment. Follow up in 2014 showed that the patients became seronegative. There were no available genetic studies done for this family. Our reported siblings are among the youngest to present with APS manifestations, at 13 years of age. To our knowledge, there are no cases of familial APS reported in the large pediatric APS cohorts [3, 12].

No clear gene association has been identified for APS. Although raised levels of aPL antibodies have been described in a few families, the characterization of the APS, coexisting autoimmune diseases, and clinical complications are more heterogeneous, not well defined, and difficult to study. Not only is there rarity of multiplex families with APS to study, many reported cases have other comorbidities such as an autoimmune disease or some other hereditary prothrombotic feature [11]. Whole exome sequencing (WES) was done for our patients but was inconclusive. To our knowledge, WES was not done for families with familial APS reported in the literature, in part because many cases predate the availability thereof. Multiple human leukocyte antigen (HLA)-DR or -DQ associations with aPL antibodies have been described including HLA-DR4, Drw53, DQw7, and DQB1*0302 [11, 13]. However, these associations are difficult to interpret because of small patient sample size and questions regarding appropriate ethnically matched control populations [11]. Of interest, our two reported siblings with APS had positive HLA-DR4 and DQB1*0302 tests compared to the healthy brother as shown in Table 1.

**Conclusion**

Pediatric APS is a rare disease that differs in many ways from APS in adults. Non-thrombotic clinical manifestations may precede thrombotic manifestations, and this may cause significant delays in the diagnosis of APS in children. Familial APS is very rare but may occur. A high index of suspicion is required to test relatives with subtle clinical manifestations and, although it may be too early to conclude the need for screening of all family members, such an approach may be needed in some cases. Our cases further support possible HLA-DR and -DQ associations with aPL antibodies.
Abbreviations

aCL
anticardiolipin antibodies
aPL
anti-phospholipid antibodies
APS
Antiphospholipid syndrome
anti-β2GP1
anti-β2-glycoprotein 1 antibodies
ANA
anti-nuclear antibodies
ANCA
antineutrophilic cytoplasmic antibodies
dRVVT
diluted Russel viper venom test
HLA
human leukocyte antigen

Declarations

Ethics approval and consent to participate

Not required for case report

Consent for publication

Written informed consent was obtained from the patient's legal guardian/parents for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and material

Data sharing was not applicable to this article, as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding
Authors' contributions

FBM contributed to patient care, medical record review, drafting the manuscript, and the literature search. KWK contributed to patient care, editing the manuscript, and the literature search. AS contributed to patient care, editing the manuscript and literature search.

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Figure 1

A) Vasculitic erythematous rash on the planter aspect of the foot (Case 1), and B) on the palm of the hand (Case 2), associated with a burning sensation and arthralgia. The rash was the earliest
manifestation in both patients and preceded a pulmonary embolism in Patient 1. The lesions are erythematous and raised.