Antiphospholipid syndrome and thrombocytopenia in childhood

Síndrome antifosfolípide e trombocitopenia na infância

Síndrome antifosfolípido y trombocitopenia en la infancia: relato de caso

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ABSTRACT

Objective: To report the case of a child diagnosed with antiphospholipid syndrome associated with severe thrombocytopenia, and to review the literature on the subject.

Case description: Child aged nine years and eight months old with severe thrombocytopenia associated with a positive anticardiolipin antibody. Data were collected by clinical history, physical examination, and laboratorial exams. Diagnosis was confirmed according to criteria established for the antiophospholipid syndrome, associated with the presence of the most common manifestations of the syndrome in children: livedo reticularis and thrombocytopenia.

Comments: The antiphospholipid syndrome is an uncommon pediatric disease, and clinical manifestations such as decreased platelet number should be considered.

Key-words: antiphospholipid syndrome; livedo reticularis; thrombocytopenia.

RESUMO

Objetivo: Relatar o caso de uma criança com diagnóstico de síndrome do anticorpo antifosfolípide associada à trombocitopenia grave e realizar uma revisão de literatura sobre o assunto.

Descrição do caso: Criança de nove anos e oito meses de idade com trombocitopenia grave associada a anticorpo anticardiolipina positivo. Os dados foram coletados por meio de anamnese, exame físico e exames complementares da paciente. O diagnóstico foi determinado de acordo com os critérios estabelecidos para a síndrome antifosfolípide, associados às manifestações mais comuns na faixa etária pediátrica: livedo reticular e trombocitopenia.

Comentários: A síndrome do anticorpo antifosfolípide é uma doença incomum na população pediátrica e suas manifestações clínicas, com a redução do número de plaquetas, devem ser consideradas.

Palavras-chave: síndrome antifosfolípide; livedo reticular; trombocitopenia.

RESUMEN

Objetivo: Relatar el caso de un niño con diagnóstico de síndrome del anticuerpo antifosfolípido asociado a trombocitopenia grave y realizar una revisión de literatura sobre el tema.

Descripción del caso: Niño de nueve años y ocho meses de edad, con trombocitopenia grave asociada a anticuerpo anticardiolipina positivo. Los datos fueron recogidos por medio de historia, examen físico y exámenes complementarios de la paciente internada en un hospital de Curitiba, en Paraná (Brasil). El diagnóstico fue determinado conforme a los criterios establecidos para el síndrome antifosfolípido, asociados a las manifestaciones más comunes en la franja de edad pediátrica: livedo recticular y trombocitopenia.

Comentarios: El síndrome del anticuerpo antifosfolípido es una enfermedad poco común en la población pediátrica, y su manifestación con reducción del número de plaquetas debe ser considerada.

Palabras clave: síndrome antifosfolípido; livedo recticular; trombocitopenia.

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Introduction

The antiphospholipid antibody syndrome or antiphospholipid syndrome (APS) is characterized by arterial, venous or microvascular thrombosis, fetal loss, recurrent spontaneous abortions, and thrombocytopenia, associated with the presence of circulating antiphospholipid antibodies (aPLs)[1-3].

Due to the fact that its incidence in the pediatric population is unknown, in the last years there has been an increase in the number of studies related to APS aiming to better define the prevalence and the clinical spectrum of this disease in children[4]. Whereas APS in adults has been well characterized, only a few studies on children with APS have been published, most of them case reports[5].

APS is called primary when it occurs in isolation, and secondary when it occurs in association with other diseases, commonly with juvenile systemic lupus erythematosus (SLE) [1]. Besides being associated with autoimmune or rheumatic diseases, aPLs have been reported to be associated with malignancies, hematological diseases, infections, neurological diseases, and drugs[6,7], as seen in Chart 1.

aPLs can be found in approximately 50% of SLE patients, and in percentages ranging from 1 to 5% of the healthy population, tending to occur more often in the elderly. Recent studies suggest that the occurrence of APS in SLE patients is between 34 and 42%. There is predominance in females (especially in secondary APS) and no race predominance; a higher incidence was observed in young individuals and middle-aged adults, although the syndrome can manifest in children and elderly. There are reports of its occurrence in infants of less than eight months of age[6,8].

Thrombocytopenia is a frequent finding in APS patients and is related to several mechanisms that have not been well defined[9]. Occasionally, this laboratory abnormality is the first and only manifestation of the syndrome in question, which leads to the initial diagnosis of idiopathic thrombocytopenic purpura (ITP)[10].

The specific justification for this work was to describe this uncommon pediatric disease, associated with severe thrombocytopenia, and to review the literature on the subject. The study was approved by the Human Research Ethics Committee of Hospital Pequeno Príncipe, Curitiba, state of Paraná, Brazil, under registration number 057/2011.

Case description

Patient aged nine years and eight months, female, Caucasian, born and living in Pinhais, state of Paraná, Brazil, was admitted to the emergency department of Hospital Pequeno Príncipe, Curitiba, in February 2011 complaining of strong nosebleed, as well as of slight gum bleeding on the

Chart 1 - Conditions associated with antiphospholipid syndrome[6,7]

Immune diseases	Systemic lupus erythematosus (25 to 50%), idiopathic thrombocytopenic purpura (30%), rheumatoid arthritis (33%), psoriatic arthritis (28%), Sjögren's syndrome (42%), giant cell arteritis/ rheumatic polymyalgia (20%), mixed connective tissue disease (22%), systemic sclerosis (25%), Behçet's disease (20%), polyarteritis nodosa, dermatomyositis/ polymyositis, autoimmune hemolytic anemia, autoimmune chronic hepatitis. ** Numbers in parenthesis represent patients with antiphospholipid antibodies and not necessarily the presence of clinical manifestations of antiphospholipid syndrome.*
Malignancy	Solid tumors, leukemia, lymphoproliferative disorders / Hodgkin's disease, multiple myeloma, and fungoid mycosis.
Hematologic diseases	Myelofibrosis, von Willebrand's disease.
Infectious diseases	Syphilis, hanseniasis, tuberculosis, mycoplasma, Lyme's disease, malaria, HIV infection, hepatitis A, hepatitis C, HTLV-1, mononucleosis, adenovirus infection, parvovirus infection, measles, varicella, parotiditis, bacterial infections (endocarditis and sepsis).
Neurologic diseases	Sneddon's syndrome, *miastenia gravis*, multiple sclerosis, migraine.
Medication	Chlorpromazine, phenytoin, hidralazine, procainamide, quinidine, clozapine, streptomycin, and phenothiazines.

previous day. She reported the onset of echymosis not related to trauma on her body, with no other associated complaints.

The patient has been admitted to the same hospital nine times since August 2010 due to the same symptoms (epistaxis and gingival bleeding). On her first admission, after undergoing a bone marrow test, she was provisionally diagnosed with ITP and was treated with prednisone 2mg/kg for 30 days, dosage that was then gradually reduced until suspension. She also had two previous episodes of vaginal bleeding.

Physical examination showed that her overall health status was good and she was alert, conscious, blushing, hydrated, and communicating well. Her vital signs were normal. The patient had a group of petechiae with a diameter of approximately 2cm on the right cervical region and diffuse petechiae on the right upper limb. She presented a 4cm ecchymosis on the right upper limb and another one measuring 2cm on the abdominal region, and diffuse ecchymoses with approximately 1cm of diameter were observed on the lower limbs. She presented with livedo reticularis on her hands. Physical examination did not show other abnormalities (Figures 1 and 2). The pictures from the lesions were taken three days after the beginning of the treatment, but the livedo reticularis was not present anymore.

In December 2010, the patient showed the following results for aPLs: IgG anticardiolipin 2.0 GPL (reference: <10) and IgM 21 MPL (reference: <7), negative lupus anticoagulant and anti-beta-2-glycoprotein I.

In February 2011, her laboratory tests showed hemoglobin of 13.1mg/dL, platelet count of 5,000/mm^3 (reference: from 150,000 to 400,000/mm^3), IgG anticardiolipin 40 GPL and IgM 20 MPL, negative lupus anticoagulant and anti-2-glycoprotein I. Antinuclear factor (ANF), anti-Smith, and Ro and La antibodies were also negative, and serum complement levels (C3 and C4) were normal. On that occasion, the child did not receive platelet transfusion and, after the results of the tests were obtained, the patient was treated with prednisone 20mg every eight hours and hidroxychloroquine 400mg orally, as a single daily dose.

Seven days after the beginning of the treatment, the child was discharged with a platelet count of 30,000/mm^3 and returned to the outpatient clinic after seven days, clinically stable and maintaining the platelet count.

Discussion

SPA is defined based on the presence of one clinical criterion (vascular thrombosis or fetal loss) and one laboratory criterion (anticardiolipin and anti-beta-2-glycoprotein-I IgG and/or IgM antibody at medium or high titers, or positive lupus anticoagulant test)[1,11]. Autoantibodies must be detected on at least two occasions, six to 12 weeks apart, in order to distinguish persistent from transient responses, which may be caused by infection or drug exposures[2,11,12]. Other important and common manifestations of the syndrome that are not included in the diagnostic criteria for APS in adults are: livedo reticularis, chorea, and thrombocytopenia[13]. These clinical findings lead to the diagnosis of pediatric APS, despite the lack of validation in children[5].

There might be some important differences in the clinical spectrum of APS related to the age at the onset of the disease. Several issues are unique to the pediatric population:

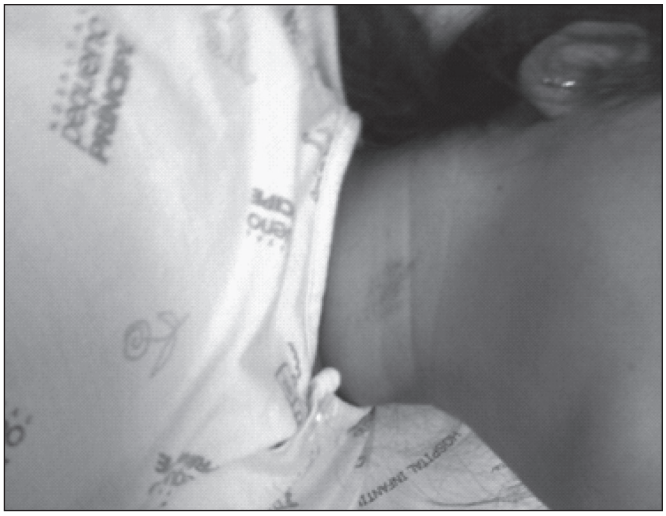

Figure 1 - Cluster of petechiae on the right cervical region

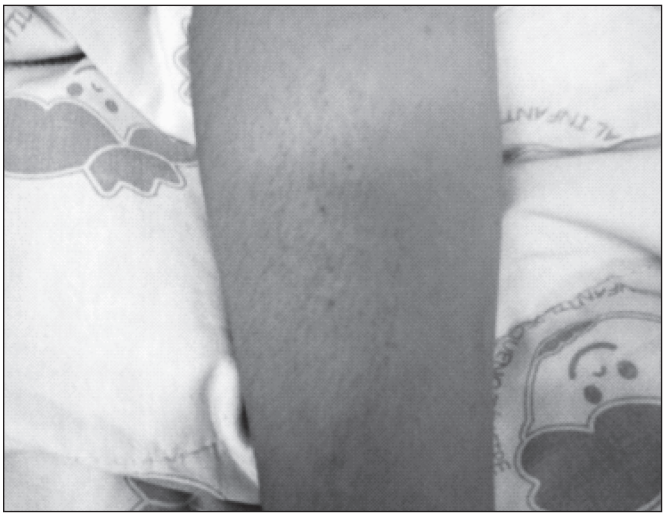

Figure 2 - Petechiae on the right forearm

absence of prothrombotic risk factors present in adults, increased incidence of infection-induced aPLs, and prevalence of disease manifestations[14]. In clinical practice, a diagnostic investigation for aPLs should be considered in patients with arterial or venous thrombosis and fetal loss for which there is no alternative explanation, particularly in the presence of recurrent manifestations. Likewise, unexplained thrombocytopenia, hemolytic anemia, and prolongation of coagulation tests should lead to determination of aPL levels[2].

The most common clinical manifestation of APS is thrombosis, which can affect the vessels of any organ. Venous thrombosis, most commonly affecting the deep veins of the lower limbs, is the most prevalent in pediatric patients. Arterial thrombosis results mainly in strokes and transient ischemic attacks (50%)[3,5,15]. Other anatomic sites for arterial thrombosis are the heart (25%), causing coronary occlusion, and the eye, kidney, and peripheral arteries (25%) [2], as observed in Chart 2.

Cutaneous manifestations are generally explained by vascular occlusion and should be an indicator for diagnosis and for the need for extensive systemic investigation, since in 41% of APS patients they constitute the first clinical sign of the disease. The most common manifestation is livedo reticularis, which presents as persistent purplish, reddish or bluish lesions, maybe showing a mottled aspect, is irreversible with reheating, and generally affects the trunk, arms, and legs. Besides livedo, cutaneous ulcerations, purpuras, ecchymoses, subungual hemorrhages may also be present[6,15,16].

Thrombocytopenia in APS is often mild and benign (70-120×10^3/mm^3) and is rarely associated with hemorrhagic complications; moreover, it generally does not require treatment. The prevalence of thrombocytopenia in APS estimated in the literature ranges from 20 to 40%, with no significant difference between primary and secondary cases. A study in a series of 171 APS patients reported a percentage of 23.4% of thrombocytopenia cases; additionally, severe thrombocytopenia (<5x10^3/mm^3) was observed in only six patients from the series (17.6%)[17].

The frequent finding of thrombocytopenia and thrombosis in patients with APS suggests that aPLs interact with platelets in a manner that triggers platelet aggregation and thrombosis[9,18,19]. The mechanism of thrombosis in patients with aPLs is still unknown[3]. Some studies suggest hypotheses such as: aPL interference with endogenous anticoagulant

Chart 2 - Manifestations of antiphospholipid syndrome[6,7]

Cardiovascular manifestations	**Central nervous system manifestations**
• Valvulopathy	• Chorea
• Intracardiac thrombosis	• Dementia
• Coronary disease	• Migraine
• Cardiomyopathy	• Intracranial hypertension
	• Neurocognitive deficit
Gastrointestinal manifestations	• Psychosis
• Budd-Chiari's syndrome	• Depression
• Esophageal and intestinal ischemia	• Epilepsy
• Colonic ulcers	• Guillain-Barré's syndrome
• Hepatic infarction	• Transverse myelopathy
• Cholecystitis	• Optic neuritis
• Portal and mesenteric vein thrombosis	
	Cutaneous manifestations
Vascular manifestations	• Livedo reticularis
• Deep venous thrombosis in limbs	• Cutaneous ulcers
• Thrombosis of portal, renal, adrenal, retinal and intracranial vessels	• Thrombophlebitis
	• Subungual hemorrhages
• Thrombosis of cerebral, subclavian-coronary, mesenteric, renal and retinal arteries	• Ecchymoses
	• Painful nodules
	• Erythematous macules

mechanisms; binding and activation of platelets; interaction with endothelial cells; induction of the expression of adhesion molecules and tissue factor; as well as activation of the complement cascade[6,9,18].

Perinatal APS is rare and manifests in infants born to mothers with APS or positive aPL tests. It is generally characterized by multiple arterial and venous thrombosis in several locations and has a similar clinical presentation to that of adult patients[5].

A minority of patients (0.8%) might present with thrombosis of rapid onset affecting multiple organs, associated with high mortality, called catastrophic APS[15,19], which can be defined as the involvement of at least three different organ systems, with symptoms developing over days to weeks, caused by an acute thrombotic microangiopathy affecting small-caliber blood vessels[3,7]. In slightly more than a half of cases of catastrophic APS, it is possible to identify a triggering factor, the most important of which are infection, trauma, surgical procedures, neoplasias, oral anticoagulation, and obstetric complications[7,15].

The main differential diagnoses of APS associated with thrombocytopenia and with hemorrhagic manifestations are: SLE, leukemia, hemophilia, infectious diseases, ITP, thrombotic thrombocytopenic purpura, and others (Charts 1 and 3)[20-22]. It is known that there is a strong relationship between SLE and APS, and the presence of aPLs is the diagnostic criterion for SLE. Negative ANF and negative results for specific antibodies, such as anti-Sm and anti-DNA, practically rule out SLE.

Therefore, three different forms of evolution for APS are described:

- Isolated or associated clinical manifestation in a single episode (isolated livedo reticularis and livedo reticularis plus cerebral ischemia).
- Recurrent episodes: anticardiolipin antibody titers greater than 40 units, associated with a previous thrombosis episode, are independent risk factors for a new episode. The presence of SLE and positive anticardiolipin antibodies also increase the predisposition to recurrent thrombotic events. Maximum time between the first and the second episode should be three years.
- Catastrophic APS may occur in three distinct forms: initial event of APS, primary evolution of APS (most common form), or secondary evolution of APS (commonly associated with SLE)[6].

Patients who are positive for aPLs but have no history of thrombosis are not candidates for prophylactic treatment with drugs; however, studies by Giannakopoulos and Krilis suggest that the use of acetylsalicylic acid may be beneficial[23]. Nonetheless, risk factors associated with thrombosis, such as hypertension, smoking, hypercholesterolemia, contraceptive

Chart 3 - Differential diagnosis of thrombocytopenia[20]

Disease	Clinical presentation	Laboratory analysis
ITP	History of cutaneous or mucosal bleeding(s). Absence of adenomegaly and hepatosplenomegaly, no general symptoms.	Thrombocytopenia and normal results for the other series, myelogram (optional) with no hypoplasia or abnormal cells; antiplatelet antibodies (optional) in more than 80% of the cases.
Purpura in the newborn	Maternal history of ITP, similar clinical features to ITP.	Autoimmune antibodies.
Systemic lupus erythematosus	Thrombocytopenia can be the first manifestation of the disease, anemia, fever, and arthropathy.	Presence of antinuclear and anticardiolipin antibodies, hemolytic anemia in most cases, positive Coombs.
Leukemia	Weakened general state, fever, anemia, hepatosplenomegaly, and adenomegaly.	Myelogram with neoplastic cells.
Infectious diseases: toxoplasmosis, Epstein-Barr virus, cytomegalovirus, rubella, and HIV	Suggestive history and physical examinations.	Positive serologies, detection of the agent.

ITP: idiopathic thrombocytopenic purpura

use, and prolonged immobilization, should be eliminated. In the presence of venous thrombosis, full anticoagulation therapy is indicated due to the high risk of thromboembolism[6].

Hydroxychloroquine, frequently used in the treatment of patients with SLE, may also provide some protection against thrombosis in secondary APS. Besides its anti-inflammatory effects, hydroxychloroquine has a antithrombotic effect, which inhibits platelet aggregation and arachidonic acid release by stimulated platelets[24]. In a study with mice that received injectable aPLs, hydroxychloroquine has shown to reduce the size of the thrombi and their persistence time, according to the dosage used[25].

Catastrophic APS is normally treated with full anticoagulation, and some authors suggest that plasmapheresis may improve patients' survival[2].

There are no studies evaluating the optimal management of thrombocytopenia associated with APS, and there are no guidelines on when to treat and which treatments are required. In such cases, therapy is generally indicated in the presence of bleeding or when the risk of hemorrhage overweighs the risks associated with treatment. Patients with APS-associated thrombocytopenia are treated in a similar manner to patients with ITP since there are few reports suggesting that anticoagulation is an effective therapy for thrombocytopenia in these patients. Treatment options include: glucocorticoidis, intravenous immune globulin, immunosuppressive (azathioprine and cyclophosphamide), and rituximab. There are individual reports of successful treatment using danazol, aspirin, dapsone, and chloroquine[9].

Hemorrhage is a less common complication than thrombosis in patients with APS. Severe thrombocytopenia can result in bleeding; less frequently, patients with APS may have antibodies directed against prothrombin, resulting in increased clearance of this coagulation factor, which thus decreases its levels.

The site and severity of bleeding will dictate how the treatment will be conducted. If the bleeding results from antithrombotic therapy, the antithrombotic agent needs to be discontinued; additionally, an antidote can be administered and a transfusion support given, according to deficiency type. When the bleeding is associated with thrombocytopenia, or if the patient is taking aspirin, platelet transfusions may be given in addition to treatments that increase platelet count[9].

There is still no consensus on the treatment of pediatric patients with APS. The knowledge on anticoagulation in children is still insufficient, and there has been debate over the intensity and duration of this treatment approach[1]. The prognosis of patients with APS is related to the severity of initial clinical manifestation, to the previous disease history (previous thrombotic episode), to high antibody levels, to proper therapy (use of anticoagulants), and to the association with neoplasias during APS evolution[2,6].

It was concluded that, according to data from the literature, APS is not a frequent disease in the pediatric population. Its association with severe thrombocytopenia worsens the patient's clinical status, and there is a lack of consensus on the best treatment for children.

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