Eur J Pediatr
DOI 10.1007/s00431-011-1548-9

SHORT REPORT

Catastrophic antiphospholipid syndrome: first signs in the neonatal period

Marta Cabral · Clara Abadesso · Marta Conde · Helena Almeida · Helena Carreiro

Received: 14 June 2011 / Accepted: 2 August 2011

Abstract The term "catastrophic" antiphospholipid syndrome (CAPS) is used to define a subset of the antiphospholipid syndrome (APS) characterized by the clinical evidence of three or more organ involvement by thrombotic events in a short period of time and with laboratory confirmation of the presence of antiphospholipid antibodies. We describe a male infant first admitted at 17 days old for necrotizing enteritis complicated by cardiac and renal failure. Because of progressive renal function deterioration, a renal biopsy was performed at 8 months old, and histopathologic examination was compatible with renal venous thrombosis. Laboratory searching for vascular, prothrombotic, and metabolic disease was negative. Five months later, he developed two different episodes (20-day range) of ischemic stroke. Genetic test for thrombophilic conditions was positive for two different mutations, and repeatedly high titers of lupus anticoagulant, anticardiolipin, and anti-β2glicoprotein I antibodies were found. He was treated successfully with anticoagulants and showed a favorable clinical evolution. To the best of our knowledge, this is the youngest patient reported with probable CAPS. Although rare, APS/CAPS in the neonatal period or in the first year of life must be suspected in infants presenting with thrombotic phenomena. The present case illustrates the importance of an early diagnosis and treatment to enhance possibilities of survival.

Keywords Catastrophic · Antiphospholipid · Syndrome · Thrombosis · Infant

M. Conde
Pediatric Rheumatology Clinics, Department of Pediatrics,
Hospital Prof. Doutor Fernando Fonseca E.P.E,
Estrada da Venteira, IC19,
Amadora 2720-276, Portugal
e-mail: mssr.cabral@gmail.com

C. Abadesso · H. Almeida
Pediatric Intensive Care Unit, Department of Pediatrics,
Hospital Prof. Doutor Fernando Fonseca E.P.E,
Estrada da Venteira, IC19,
Amadora 2720-276, Portugal

H. Carreiro
Department of Pediatrics,
Hospital Prof. Doutor Fernando Fonseca E.P.E,
Estrada da Venteira, IC19,
Amadora 2720-276, Portugal

Present Address:
M. Cabral (✉)
Pediatric Rheumatology Clinics, Department of Pediatrics,
Hospital Prof. Doutor Fernando Fonseca E.P.E,
Estrada da Venteira, IC19,
Amadora 2720-276, Portugal
e-mail: mssr.cabral@gmail.com

Introduction

The antiphospholipid syndrome (APS) is a noninflammatory autoimmune disorder characterized by the association of thrombotic phenomena and/or recurrent fetal loss, in combination with elevated titers of antiphospholipid (aPL) antibodies [11]. The Sapporo criteria are the most acceptable diagnostic criteria for APS, and its last revision (2006) defines one clinical criterion and one laboratory criterion for its definite diagnosis (Table 1).

Despite the strong association between aPL antibodies and thrombosis, its pathogenic role in the development of thrombosis has not been fully elucidated [9]. These antibodies are not always pathogenic and can be present in several situations, for example, infections, autoimmune diseases, tumors, and even in 3–4% of healthy individuals, without being related to thrombotic phenomena [7]. An unusual

Published online: 16 August 2011

Table 1 Revised classification criteria for the antiphospholipid syndrome (2006)

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met

Clinical criteria

(1) Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

(2) Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: eclampsia or severe preeclampsia defined according to standard definitions, or recognized features of placental insufficiency, or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria

(1) Lupus anticoagulant (LA) present in plasma, on two or more occasions, at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Las/phospholipid-dependent antibodies)

(2) Anticardiolipin (Acl) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (> the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA

(3) Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma present in medium or high titer (> the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation. Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials

variant of the APS, termed the "catastrophic" antiphospholipid syndrome (CAPS), was first described by Asherson in 1992, and represents the extreme end of the APS spectrum, resulting in multiorgan failure [4, 18]. Although CAPS represents 0.8–1% of all patients with APS, it is usually a life-threatening medical situation that requires high clinical awareness [4]. The diagnosis of CAPS is based on the preliminary criteria for its classification, defined by the international consensus statement in 2003 (Table 2) [4]. Thrombotic events may present in patients as a free-standing condition (primary APS) or be associated with other autoimmune diseases, most commonly systemic lupus erythematosus (SLE; secondary APS) [5, 10, 12, 18, 20]. There are no prospective studies because of the rarity of the condition, and CAPS treatment is not currently standardized [4], but anticoagulation, corticosteroids, plasma exchange, intravenous gammaglobulins, and immunosuppressant agents are the most commonly used therapies [7]. Despite adequate therapy, the mortality remains high, approximately 50%, with cardiac problems as the main cause. Once recovery has ensued, patients usually have a stable course, but require continued anticoagulation [2]. A recent study has documented that 66% of CAPS patients who have survived the initial catastrophic event had remained symptom free for an average follow-up of 62.7 months, and 26% developed further APS-related events; however, there were no instances of further catastrophic events [8]. Because of pediatric CAPS' rarity, only individual case reports or small case series have been reported in the literature and, therefore, few information exist on the pediatric aspects and long-term outcome of this disorder [6, 10].

Case report

We present a male, caucasian neonate from healthy non-consanguineous parents, labor and delivery at 36th week of pregnancy, 50th percentile for weight and height, and Apgar score of 7/9. He was first admitted to the hospital emergency care at 17 days old with irritability, marked abdominal distension with tenderness, vomiting and bloody stool, and signs of shock (delayed capillary refill, persistent tachycardia, and hypotension). Laboratory findings include hemoglobin (Hgb) 15.6 g/dl, 22,700 leukocytes/mm^3, 500,000 platelets/mm^3, C-reactive protein (CRP) 1.26 mg/dl, and metabolic acidosis (pH, 7.0; $HCO3^-$, 12 mmol/L; alkaline excess, −18 mmol/L; lactate, 12.7 mmol/L). The abdominal ultrasonography showed increased amounts of intraperitoneal non-loculated purulent fluid and markedly distended small bowel loops. After stabilization in the intensive care unit, an exploratory laparotomy was performed. Extensive small bowel necrosis was found, and resection was made with ileostomies. The histopathology was compatible with the small bowel's transmural infarction (necrotizing enteritis). After surgery, septic shock evolved to multiorgan failure, with severe hypotension, cardiac dysfunction, and profound laboratory abnormalities (Hgb, 9.3 g/dl; 2,200 leukocytes/mm^3; 53,000 platelets/mm^3; CRP, 35 mg/dl; and

Table 2 Criteria for the classification of catastrophic APS by international consensus statement on classification criteria and treatment guidelines (2003)

(1) Evidence of involvement of three or more organs, systems, and/or tissues[a]
(2) Development of manifestations simultaneously or in less than a week
(3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
(4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]
Definite catastrophic APS
• All four criteria
Probable catastrophic APS
• All four criteria, except for only two organs, systems, and/or tissues involvement
• All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS
• 1, 2, and 4
• 1, 3, and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

[a] Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg), and/or proteinuria (>500 mg/24 h)

[b] For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally

[c] If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipids must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event)

disseminated intravascular coagulation with hepatic insufficiency), requiring invasive ventilatory and inotropic support. Blood and intra-abdominal fluid cultures were positive for *Escherichia coli*. At the fourth day, the patient became stable and 4 weeks later underwent a second surgery to assess for viability of the remaining bowel. Twenty-four hours later, he suddenly developed shock with severe cardiac failure (dilated myocardiopathy with decreased ejection fraction of the left ventricle), with troponin (13.46 ng/mL) and activated partial thromboplastin time (aPTT) (>160 s) elevation. After a period of hypotension, he developed severe hypertension and oligoanuric acute renal failure (glomerular filtration rate (GFR), 16.07 ml/min/1.73 m^2) with macroscopic hematuria. The doppler ultrasonography showed an atrophic right kidney with poor corticomedullary differentiation, with its main artery not visualized. The patient required continuous venovenous hemodiafiltration for 20 days. Hypertension (average, 180/110 mmHg) was very difficult to control requiring a combination of eight antihypertensive drugs. The abdominal magnetic resonance (MR) angiography confirmed the right kidney's atrophy with marked hypoperfusion of its main artery, and radionuclide imaging with ^{99m} Tc-MAG3 showed its severe decreased function (7%). Screening for hereditary prothrombotic and metabolic diseases was negative (Table 3).

At 6 months old, he was discharged with a delayed growth, controlled hypertension, left ventricle hypertrophy, and mild-to-moderate renal insufficiency (GFR, 32 ml/min/1.73 m^2) under conservative treatment. Two months later, right nephrectomy was performed and hypertension stabilized. The histopathology documented a generalized cortical atrophy (Fig. 1), reduction of the main renal vein and its branches' lumen by chronic thromboses, with signs of recanalizing thrombi, and histological features of fibrous intimal hyperplasia of the interlobular and small arteries, abnormalities compatible with renal vein thrombosis, thrombotic microangiopathy, and subsequent chronic renal ischemia (Fig. 2).

At 13 months old, he presented with focal tonic-clonic seizures and right hemiparesis. Brain CT revealed an acute infarct involving the left frontal, temporal, and parietal lobes, without associated hemorrhage (Fig. 3). He was treated with acetylsalicylic acid 5 mg/kg/day and phenobarbital with improvement, but 20 days later, he developed left hemiparesis de novo accompanied by axial weakness, right eye exophoria, and generalized hyperreflexia. Brain CT and MR angiography showed multiple de novo acute ischemic infarcts in the frontal, right temporal, and parietal lobes (Fig. 3). Intracardiac, carotid, and vertebral arteries' thrombus/masses were excluded by doppler ultrasonography. Subcutaneous low-molecular-weight heparin (LMWH) 1 mg/kg/day was added. At that time, genetic test for thrombophilias showed two different mutations: heterozygosity for prothrombin gene mutation (*PT 20210G>A*) and homozygosity for plasminogen activator inhibitor-1 gene mutation (*PAI-1 675G>A*). Immunologic studies revealed positive antinuclear antibody (ANA) titer 1/640 and positive anticardiolipin (aCL; 1.8 U/mL (<1.1)) and anti-β2glycoprotein I (anti-β2GPI; IgM, 1.0 U/mL; IgG, 25.1 U/mL (<20)) antibodies (Table 3). Erythrocyte sedimentation rate was 22 mm/1sth.

At 24 months old, immunologic studies demonstrated persistent positive ANA titer 1/640, mild positive lupus

Table 3 Laboratory searching for prothrombotic, autoimmune, and metabolic diseases and its evolution

Metabolic disease											
Ammonia, pyruvate, lactate, carnitine and acylcarnitine, uric acid, purine and pyrimidine blood levels, quantitation of plasma and urinary amino acids, organic acids and mucopolysaccharides, redox potential, genetic test for Williams syndrome, and muscular biopsy											Normal/negative
Prothrombotic disease											
Patient's age (months)	2	13	24	27	33	42	48	60	72	75	Units (reference values)
PT (max.)	13.3	10.2	11.5	11.2	10.7	11.1	12	11.1	11.7	11.7	s (10–14)
aPTT (max)	>160	28.7	>120	48.9	>160	32	33.2	34.5	45.3	28.3	seconds (26.1–33.2)
D-dimers (max)	780	123.5	–	–	175	–	–	–	–	–	μg/L (<190)
Protein C	45.1	71	–	–	–	–	–	–	–	–	% (40–92)
Protein S	80.2	69	–	–	–	–	–	–	–	–	% (33–69)
Factor V Leiden	118.1	–	–	–	–	–	–	–	–	–	% (50–150)
PAI-1	–	5.64	–	–	–	–	–	–	–	–	U/ml (0.3–3.5)
Antithrombin III	74.6	99	–	–	–	–	–	–	–	–	% (82–139)
Homocysteine	–	9.88	–	–	–	–	–	–	–	–	μmol/L (5–12)
Factor VII	–	70	–	–	–	–	–	–	–	–	% (70–130)
Factor VIII	–	113	–	–	–	–	–	–	–	–	% (50–150)
Lupus anticoagulant	–	35.5	47.3	36.8	–	32.7	26.6	46.5	55.1	37.8	s (<45)
aCP ab total titer	–	1,8	5.4	0.6	–	–	–	–	–	–	U/mL (positive, total titer >1.1, or IgM or IgG >15)
IgM	–	–	–	–	–	–	–	–	3.8	2.4	
IgG	–	–	–	–	10.6	4.4	10	11.8	6	7.2	
Anti-β2GPI ab											
IgM	–	1.0	2.0	0.1	0.1	19	2.3	31.7	12	7.4	U/mL (positive, IgM or IgG >10)
IgG	–	25.1	>150	1.7	9.7	7.3	0.1	10.4	5.2	4.1	
Autoimmune disease											
ANA	–	1/640	1/640	–	Neg	1/640	Neg	1/320	Neg	1/160	
Anti-dsDNA, anti-SM, anti-RNP, anti-SSA, anti-SSB and ANCA antibodies	–	Neg	Neg	–	Neg	Neg	Neg	Neg	Neg	Neg	
C3, C4, CH50	–	Normal	–	–	–	–	–	Normal	–	–	

PT prothrombin time, *aPTT* activated partial thromboplastin time, *PAI-1* plasminogen activator inhibitor type 1, *aCP ab* anticardiolipin IgG antibodies, *Anti-β2GPI ab* anti-β2glicoproteinI antibodies, *ANA* antinuclear antibody, *ANCA* anti-neutrophil cytoplasm, *Neg* negative

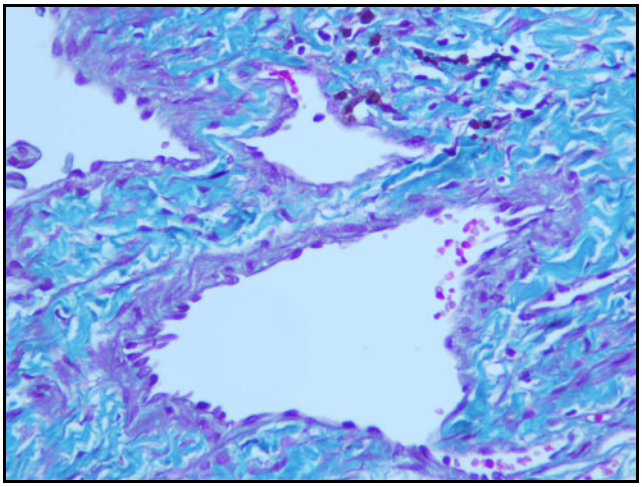

Fig. 1 Generalized cortical atrophy, with preservation of glomerular structures (fetal isotype) in more than 2/3 of the cortical thickness

anticoagulant (LA) (screening test, 47.3 s (<45); confirmatory test, 32.4 s (<38)), and positive aCL (5.4 U/mL) and anti-β2GPI (IgM, 2 U/mL; IgG, >150 U/mL) antibodies. Three months later, LA, aCL, and anti-β2GPI antibodies became negative. At that time, the patient's mother, previously healthy and with no previous history of fetal losses or thromboembolic events, was tested negative for immunologic studies, including aPL antibodies. Additionally, there was no family history of thrombotic disorders or fetal losses.

A retrospective diagnosis of "probable" CAPS was made. The clinical evolution was favorable, and after 5 years of follow-up, the patient is asymptomatic while anticoagulated (LMWH), despite intermittent laboratory signs of disease's activity (Table 3) and the residual sequelae: developmental delay, systemic hypertension, and mild renal insufficiency.

Discussion

In children, the frequency of aPL-related thrombotic events is generally lower than in adults, but several common infections are likely responsible for higher percentage of nonpathogenic and transient aPL antibodies in childhood [6]. Nevertheless, most of the clinical features that occur in adults with aPL antibodies have also been described in children [6]. In pediatrics, the incidence peak for thrombotic events occurs in the neonate. The use of central catheter, asphyxia, septicemia, and dehydration are major risk factors for thrombosis in most studies [19]. We believe that the first thrombotic event, and the first manifestation of APS in this patient, was the small bowel's transmural infarction, which took place during his first month of life. Both thrombosis and APS should be a differential diagnosis

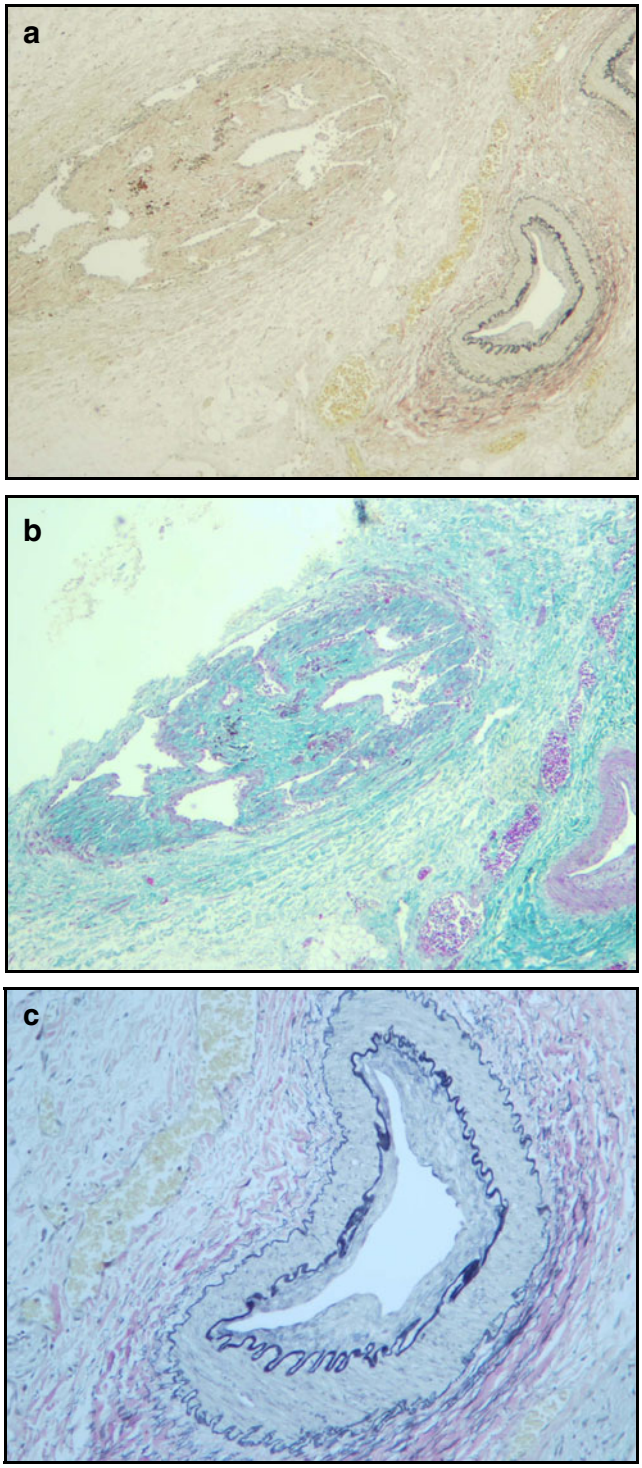

Fig. 2 **a**, **b** Reduction of the main renal vein and its branches' lumen by chronic thromboses, with signs of recanalizing thrombi, **c** histological features of fibrous intimal hyperplasia of interlobular and small arteries, abnormalities compatible with renal vein thrombosis, thrombotic microangiopathy, and subsequent chronic renal ischemia

on necrotizing enterocolitis (NEC) at that time, but it was initially assigned to the prematurity, even being a near-term infant. Although more common in premature infants, NEC

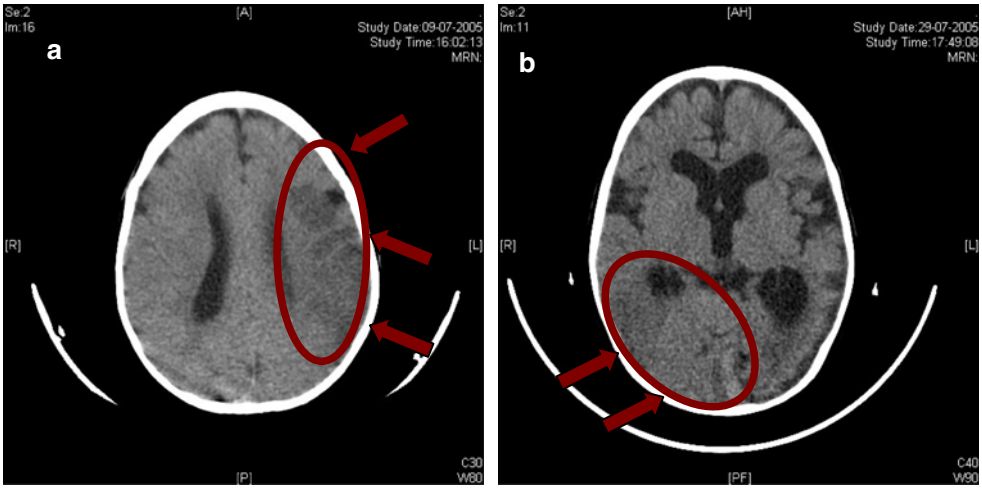

Fig. 3 **a** Acute infarct involving the left frontal, temporal, and parietal lobes, without associated hemorrhage, **b** multiple de novo acute ischemic infarcts in the frontal, right temporal, and parietal lobes

can occur in term and near-term babies, being its incidence inversely associated to birth weight and gestational age [21]. Unfortunately, aPL antibodies were not performed but, retrospectively, we can reasonably suspect they were already present at that time. Considering this episode as the first manifestation of CAPS in this patient, and to the best of our knowledge, this is the youngest patient (17 days old) with probable CAPS [13, 17].

According to Asherson, precipitant factors for APS have been recognized in 45% of patients, most commonly infections (20%). Other "trigger" factors that have been reported include trauma and surgical procedures (14%), drugs (5%), or autoimmune diseases' flares (3%) [2]. In this patient, possible precipitant factors could have been: (1) infection/septic shock preceding the small bowel's infarction, (2) the last surgery, and therapeutic procedures he was submitted during septic shock preceding right renal vein thrombosis. Both vascular cerebral accidents were not related to an apparent "trigger" factor.

Special concern is needed when dealing with aPL-positive children who have other congenital or acquired prothrombotic risks, and APS patients should be stratified according to that [6, 16]. This patient had both central lines and a positive prothrombin gene and PAI-1 mutations, which probably contributed as additional risk factors for thrombosis, as it was seen in another infantile APS published recently [14].

The diagnosis of CAPS is still controversial because of its recent description and the few number of cases reported [4]. Clinically, the patients present predominantly with small vessel occlusions involving parenchymal organs, but large vessel occlusive disease can also occur [2]. In a series of 50 patients with CAPS, Asherson et al. reported that the kidney (78%), lung (66%), and central nervous system (56%) are the most affected organs [1, 18]. In our patient, two of these main groups of organs were affected. Hypertension is a well-documented complication of APS and CAPS. In the series reported by Nochy et al., hypertension was present in 93% of the APS patients; in some of them, it was the only clinical sign of nephropathy, and it can be very difficult to treat [22], as was seen in our patient. In case of kidney involvement, good control of systemic hypertension and adequate anticoagulation may have important prognostic implications in preventing progression to end-stage renal disease [22]. In our patient, nephrectomy of the atrophic kidney was necessary to control hypertension because anticoagulation was postponed until thrombosis has been confirmed by histopathology. Several other clinical features are relatively common in these patients, predominantly during disease's acute phase, such as thrombocytopenia, seizures, mesenteric inflammatory vaso-occlusive disease with secondary small bowel infarctation, intrarenal vascular lesions (thrombotic microangiophaty), livedo reticularis, or hemolytic anemia [3, 11, 15, 20]. The first four of these recognized manifestations associated with CAPS were present in our patient.

The clinical features depend on which organs are affected and on the extent of thrombosis [2]. Because of tissue necrosis, excessive cytokine release leads to a systemic inflammatory response accountable for some of the CAPS' non-thrombotic manifestations, particularly the acute respiratory distress syndrome (ARDS) and myocardial dysfunction [2]. Our patient never had ARDS, but myocardial dysfunction complicated by acute cardiac collapse was present.

The preliminary criteria for CAPS classification define probable and definite CAPS (Table 2) [4]. Definite CAPS is considered when all four criteria are met. Our patient presented as a "probable CAPS" with three of the four defined criteria: three-organ involvement (small bowel, right kidney, and brain), histopathologic evidence of thrombosis (renal vein thrombosis), and positive aCP and anti-β2GPI antibodies on two occasions at least 6 weeks apart. The occurrence of different thrombotic episodes

simultaneously or in less than 1 week was not recognized. However, Asherson et al. emphasized that these criteria are mostly empirical, have been accepted for classification purposes, and are not intended to be used as strict diagnostic criteria in a given patient [4].

We believe that our patient's aPL antibodies (aCL and anti-β2GPI) had been produced de novo by himself instead of transplacental passage of antibodies from his mother [19], who was tested negative for aPL antibodies. Additionally, serum patient's determination occurred when a maternal origin for these antibodies would be improbable (14 and 24 months old).

Lack of prospective and randomized treatment trials has led to considerable debate on the appropriate management of children with CAPS [6]. It has three clear aims: to treat any identifiable precipitating factor, to prevent and treat the ongoing thrombotic events, and to suppress the excessive cytokine "storm" [4, 7]. There is a general agreement that long-term anticoagulation is needed in a child who experienced an aPL-related thrombosis to prevent recurrences, but there is no consensus about the duration and intensity of this therapy [6].

In regard to this patient, the hypertension and the renal failure were considered a consequence of the unexpected renal vein thrombosis in the first months of life, but his neurologic sequelae could have been avoided with an earlier diagnosis. Nevertheless, after 5 years of follow-up under anticoagulation, he had no more thrombotic events. It is essential to start treatment as soon as this condition is suspected [7], and we think that the non-progressing clinical evolution in this patient was the result of an appropriate treatment initiated as soon as the diagnosis was established.

Finally, although rare, CAPS in neonatal period or in the first year of life must be suspected in infants presenting with thrombotic phenomena, even if they have been born from a mother without SLE or APS [19].

Conflict of interest The authors declare that they have no competing interests.

References

1. Asherson R (1998) Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Balt) 77:195–207
2. Asherson R (2005) The catastrophic antiphospholipid (Asherson's) syndrome in 2004—a review. Autoimmun Rev 4:48–54
3. Asherson R, Cervera R (2003) The antiphospholipid syndrome: multiple faces beyond the classical presentation. Autoimmun Rev 2:140–151
4. Asherson R, Cervera R, Groot P, Erkan D, Boffa M, Piette J et al (2003) Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 12:530–534
5. Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RH, Machin SJ, Barquinero J, Outt HH, Harris EN, Vilardell-Torres M, Hughes GR (1989) The primary antiphospholipid syndrome: major clinical and serological features. Medicine (Balt) 68:366–374
6. Avcin T, Cimaz R, Meroni PL (2002) Recent advances in antiphospholipid antibodies and antiphospholipid syndromes in pediatric populations. Lupus 11:4–10
7. Campos L, Kiss M, D'Amico E, Silva C (2003) Antiphospholipid antibodies and antiphospholipid syndrome in 57 children and adolescents with systemic lupus erythematosus. Lupus 12:820–826
8. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, Lockshin MD (2003) Long-term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 62:530–533
9. Espinosa G, Cervera R, Font J, Shoenfeld Y (2003) Antiphospholipid syndrome: pathogenic mechanisms. Autoimmun Rev 2:86–93
10. Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, Resti M, Picco P, Martini A (2003) Outcome of primary antiphospholipid syndrome in childhood. Lupus 12:449–453
11. Hanly J (2003) Antiphospholipid syndrome: an overview. CMAJ 168:1675–1682
12. Harris E, Pierangeli S (2004) Primary, secondary, catastrophic antiphospholipid syndrome: is there a difference? Thromb Res 114:357–361
13. Iglesias-Jiménez E, Camacho-Lovillo M, Falcón-Neyra D, Lirola-Cruz J, Neth O (2010) Infant with probable catastrophic antiphospholipid syndrome successfully managed with rituximab. Pediatrics 125:1523–1528
14. Kim H, Hwang H, Chae J, Kim K, Hwang Y, Lim B (2010) Ischemic stroke in a 7-month old infant with antiphospholipid antibody and homozygous c677t MTHFR polymorphism. Journal Child Neurol 25:1047–1050
15. Krause I, Blank M, Fraser A, Lorber M, Stojanovich L, Rovensky J, Shoenfeld Y (2005) The association of thrombocytopenia with systemic manifestations in the antiphospholipid syndrome. Immunobiology 210:749–754
16. Miyakis S, Lockshin M, Atsumi T, Branch D, Brey R, Cervera R, Derksen RH, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4:295–306
17. Navarrete N, Macías P, Jaén F, Hidalgo C, Cáliz R, Jiménez-Alonso R (2005) Two cases of catastrophic antiphospholipid syndrome. Lupus 14:907–909
18. Olguin-Ortega L, Jara LJ, Becerra M, Ariza R, Espinoza L, Wilson W, Barile-Fabris L (2003) Neurological involvement as a poor prognostic factor in catastrophic antiphospholipid syndrome: autopsy findings in 12 cases. Lupus 12:93–98
19. Rolim S, Castro M, Santiago M (2006) Neonatal antiphospholipid syndrome. Lupus 15:301–303
20. Soltész P, Veres K, Lakos G, Kiss E, Muszbek L, Szegedi G (2003) Evaluation of clinical and laboratory features of antiphospholipid syndrome: a retrospective study of 637 patients. Lupus 12:302–307
21. Springer S, Annibale D (2011) Title of subordinate document. In: Pediatric necrotizing enterocolitis. Medscape reference. Available via DIALOG. http://wwwhttp://emedicine.medscape.com/article/977956-overview of subordinate document. Accessed 21 July 2011
22. Uthman I, Khamashta M (2006) Antiphospholipid syndrome and the kidneys. Semin Arthritis Rheum 35:360–367