Case Report

Catastrophic antiphospholipid syndrome - A case report

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Abstract

Catastrophic antiphospholipid syndrome (CAPS) is a rare, potentially life-threatening condition, acute in onset , characterized by diffuse vascular thrombosis, leading to multiple organ failure in a short period of time in the presence of positive antiphospholipid antibodies (aPL). Lupus anticoagulant and anticardiolipin antibodies are the predominant antibodies associated with CAPS. Treatment options for CAPS include anticoagulation, steroids, plasma exchange, cyclophosphamide therapy, and intravenous immunoglobulin therapy. The high rate of mortality warrants greater awareness among clinicians for early diagnosis and treatment of CAPS. In this case report, 30-year-old post-partum female presented with progressive weakness, shortness of breath of grade IV and swelling of all the four limbs of 15 days duration with an episode of seizure. Investigations revealed MRV - cortical sinus venous thrombosis (CSVT) of transverse and sigmoid sinus, Raised anti-ds DNA anticardiolipin and lupus anticoagulant, 24 hour urinary proteins – 540 mg/day indicating clinical lupus nephritis. Weakness of all the limbs with areflexia indicated acute inflammatory demyelinating polyneuropathy (AIDP). 2D echocardiography- post partum dilated cardiomyopathy (DCMP).

Key words

Catastrophic antiphospholipid syndrome, Cortical sinus venous thrombosis (CSVT), Acute inflammatory demyelinating polyneuropathy (AIDP), Lupus nephritis.

Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by the occurrence of the arterial and venous thrombosis and/or obstetric complications (miscarriage, fetal death in utero) associated with the presence of antiphospholipid antibodies [1]. The catastrophic antiphospholipid syndrome (CAPS) is most severe manifestation of antiphospholipid syndrome, and is characterised by the occurrence of thrombosis in multiple organs over a short period of time [2]. CAPS is rare, affecting less than 1% of patients with APS.

Case report

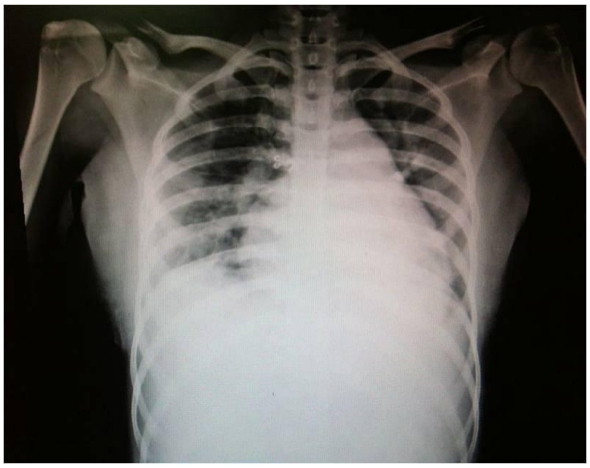
A 30 year old female, primi, delivered a 3 kg full term live male baby by normal vaginal delivery in a hospital one month ago. Pregnancy and delivery was uneventful. She presented with weakness of all the four limbs of 15days duration, swelling of upper and lower limbs 2 days duration.

Patient was apparently asymptomatic 15 days prior to the admission. Then she developed difficulty in walking, weakness progressed to the upper limbs, history of tingling and numbness was present. Patient had 3 episodes of seizures after admission. No history of urinary/bowel disturbances. No history of trauma. No history suggestive of cranial nerve involvement. No history of root pains. No history of fever, cough, cold. No history of vomiting, diarrhoea, abdominal pain. No history of hypertension, diabetes, bronchial asthma, epilepsy. No history of pre eclampsia, eclampsia.

On examination, patient was conscious, coherent, cooperative, afebrile, JVP was not raised. PR-84/min, BP-180/130 mmHg, RR- 36/min was present. No pallor, no icterus, no cyanosis, no clubbing, no lymphadenopathy. Bilateral pedal edema was present. Cardio Vascular System examination showed Apex –in 5^{th} intercostals space, forcible. S1, S2 heard, S3 present, no murmur. Respiratory System was normal, RR-36/min. Per abdomen- soft, non tender, no hepato-splenomegaly. CNS: higher mental functions normal, cranial nerves normal, Motor system- power decreased (3/5) in all the four limbs. Sensory system was normal. Reflexes- all deep tendon reflexes lost. Plantars- not-elicitable. Fundus examination- both eyes normal.

On investigations, complete blood picture revealed: Hb%-11.7 gm/dl; WBC-8,800cells/cumm; platelets- 3,68,000 cells/cumm, blood urea- 21 mg/dl ; serum creatinine- 1.0 mg/dl. Serum electrolytes: Serum sodium- 132 mmol/lit, serum potassium- 3.2 mmol/lit, serum chloride-101 mmol/lit. Complete urine examination: 24 hour urinary proteins-540 mg/day (urine albumin was negative during delivery). Ultrasound abdomen showed Right Kidney – 9.5 x 4.5cm, Left Kidney 9.3 X 4.2. Chest x ray, revealed Cardiomegaly.(**Figure - 1**) ECG revealed left axis deviation with left ventricular hypertrophy, T-wave inversions in lead L 1, L 2, avF,V2 to V6 ; Deep Q waves in V2, V3. (**Figure - 2**), Anti cardiolipin antibodies-IgM 17 mpl (<12.5mpl), IgG 20 mpl (<15gpl), IgA 22 apl (<12apl) . Lupus anticoagulant- 50 seconds (28-40sec). Anti ds DNA- 300 IU/ml (N - 0-200 IU/ml). MRI- empty delta sign (**Figure - 3**). MR Venogram shows thrombosis of right transverse and sigmoid sinuses. (**Figure - 4**)

Figure – 1: Chest X- ray shows cardiomegaly.



Based on history, clinical examination and investigations patient was diagnosed as a case of

catastrophic anti phospholipid syndrome. Patient Had, CSVT, AIDP, Lupus Nephritis, Hypertension. Patient was treated with Inj. Solumedrol-1 gm iv OD -5 days Followed by Tab. Prednisolone-20 mg TID, Tab Nicardia retard 10 mg TID, Inj. Ampicillin 500 mg iv QID, Inj. Amikacin 500 mg iv BD, Inj. Metrogyl 500 mg iv TID, Inj. Optineuron 1 amp iv OD, I.V. Fluids.

Figure – 2: ECG shows -LAD+, LVH+ with T wave inversions in L1, L2, L3, AVL.

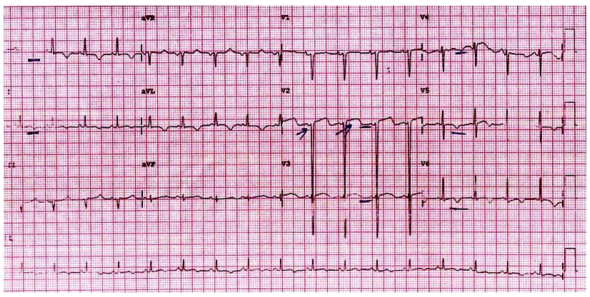
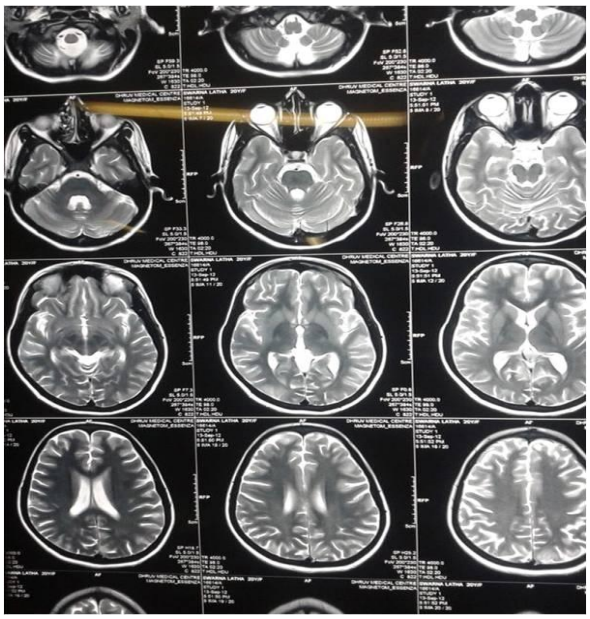


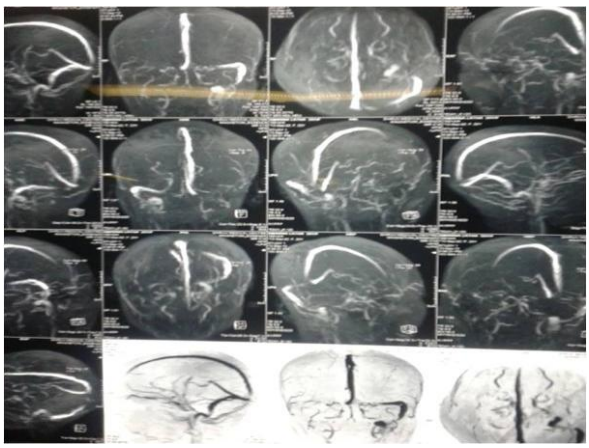
Figure – 3: MRI Brain shows empty delta sign.



Discussion

CAPS is a special form of APS described for the first time by Asherson in 1992 [4]. This rare condition affects less than 1% of patients with APS. An international registry has been established in the year 2000, which lists all reported cases [5, 6]. The classification criteria for a CAPS diagnosis have recently been revised [2, 7]. Diagnosis of "**definite CAPS**" is made in case of symptoms involving at least three organs or systems, appearing or constituting in less than a week, in the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-beta2GP1 antibodies, controlled at least 12 weeks after the initial diagnosis, with histological confirmation of microcirculatory thrombosis (**Table - 1**). Several patients are classified as "**probable CAPS**". This is most often due to a lack of histological evidence [6, 8], because of threatening thrombocytopenia, or anticoagulation that precludes biopsy sampling. In some cases, diagnosis is also missed. Diagnostic algorithms based on these criteria have recently been proposed [7] (**Algorithm – A, B, and C**).

Figure – 4: MR Venogram shows Thrombosis of RT transverse and sigmoid sinuses.



CAPS is a disease of young females, with a mean age of 37 ± 14 years. The sex ratio is 2.4/1 [5]. Some pediatric cases have also been reported in the literature. CAPS is found in patients with primary APS (46%), or associated to systemic lupus erythematosus (SLE) (40%). It has been described as appearing denovo in 46% of cases that is without any thrombotic history [9]. A precipitant factor is found in 53% of cases, including infection (22%), surgery (10%), withdrawal or sub-therapeutic anticoagulation therapy (8%), pregnancy (7%), medications (mainly estrogen and/or progesterone) (7%),

neoplasm (5%), or lupus flare (3%). This last entity associates weakness, fever, pain, nausea, dyspnea, or hematuria. CAPS pathophysiology is complex and not fully understood [10]. Some viral or bacterial peptide sequences would present a structural homology with the beta2-glycoprotein I (beta2-GPI), and would be recognized by anti-beta2GPI antibodies. Endothelial cells are activated by anti-beta2GPI through the toll-like receptor 4, resulting in the excessive production of cytokines (TNF-alpha, interleukin-6, and macrophage migration inhibitory factor). This would result in a systemic inflammatory response syndrome (SIRS), and in the acquisition of a procoagulant and prothrombotic endothelial phenotype, with increased synthesis and / or expression of tissue factor. The clinical manifestations are related to microcirculatory thrombosis and SIRS. The most common symptoms [5] involve the kidney, the lung, the central nervous system (CNS) and circulation (**Table - 2**). Renal involvement is present in 71% of patients [6]. It results from an acute vascular nephropathy, with severe or malignant hypertension, moderate proteinuria, hematuria, and some- times acute renal failure. Renal biopsy can be performed through a jugular route without interruption of anticoagulation.

Table – 1: Classification criteria for CAPS [6].

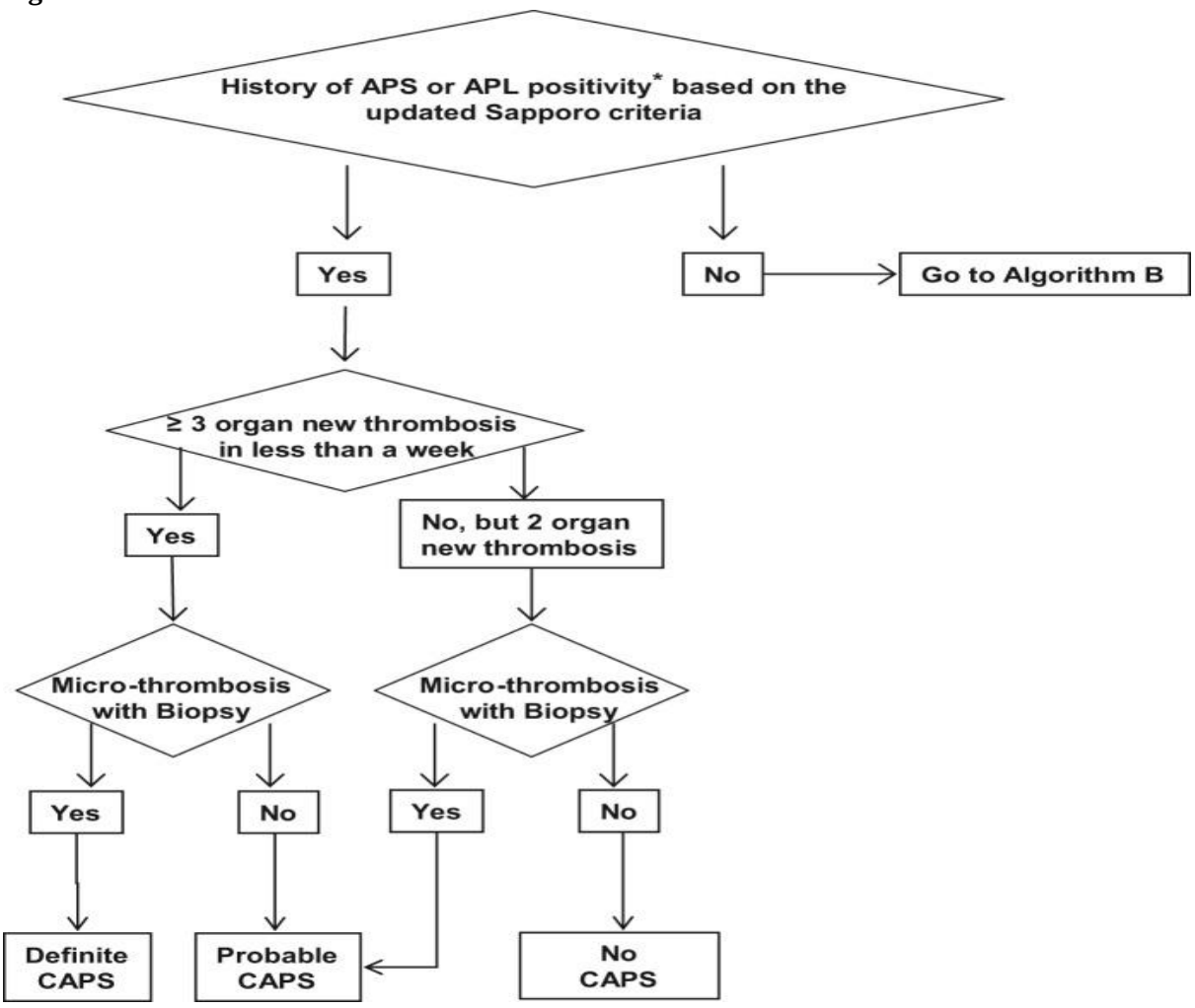
Criteria 1	Involvement of at least three organs, systems and/or tissues* (hematologic manifestations excepted)
Criteria 2	Development of manifestations simultaneously or in less than a week
Criteria 3	Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
Criteria 4	Laboratory confirmation of the presence of antiphospholipid antibodies
Classification [6]	
Definite CAPS	All criteria
Probable CAPS	Criteria 2, 3 and 4 but involvement of only 2 organs, systems or tissues Criteria 1, 2 and 3, but absence of laboratory confirmation at least 12 weeks apart due to the early death of a patient never previously tested for aPL prior to CAPS Criteria 1, 2 and 4 Criteria 1, 3 and 4 and the development of a 3d event in more than a week but less than a month, despite anticoagulation
Laboratory criteria for aPL confirmation (2 positive tests at least 12 weeks apart)	
	Positive lupus anticoagulant : DRVVT and sensible aPTT [14] Positive anticardiolipin antibodies (IgG and/or IgM) Positive anti-beta2GP1 antibodies (IgG and/or IgM)

aPTT: activated partial thromboplastin time. DRVVT: Dilute Russell's viper venom time. *Renal involvement: rise of serum creatinine by 50%, severe systemic hypertension (> 180/100 mmHg) and/or proteinuria (> 500 mg/day)

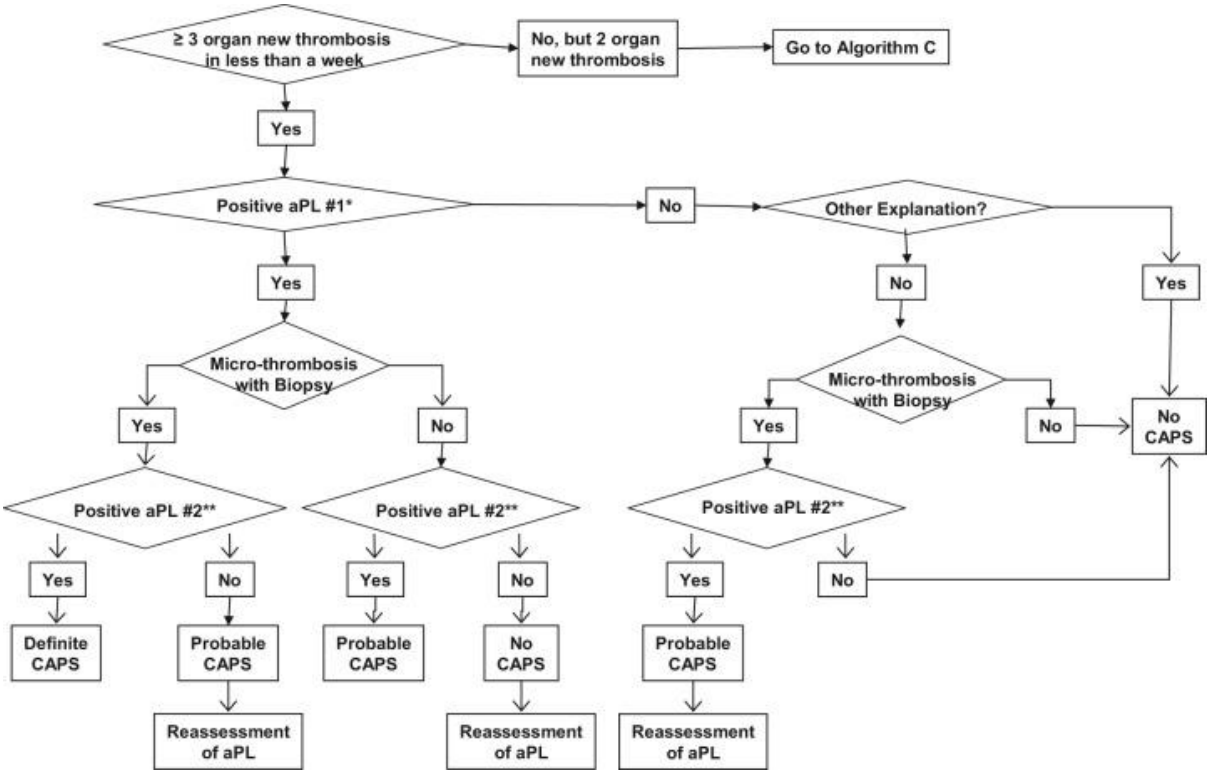
Histology reveals organized thrombi, like in other thrombotic microangiopathies [11]. Pulmonary involvement is found in 64% of cases. It can manifest as an acute respiratory distress syndrome (ARDS), and more rarely as pulmonary embolism (15%). Its mechanisms often mix microcirculatory thrombosis, SIRS, causal infection, and left ventricular failure. Pulmonary histopathologic examination, which is rarely attempted because of the bleeding risks, reveals lesions of thrombotic microangiopathy, and diffuse alveolar hemorrhage. CNS impairment is also common (62%). It can manifest as consciousness alteration, confusion

or neurological deficit. It is related to diffuse brain ischemia or stroke [12]. Malignant hypertension can also lead to a posterior reversible encephalopathy (PRES). Cardiac involvement is present in 51% of cases. Heart failure can be due to a microcirculatory diffuse disease, valvular dysfunction, either mitral or aortic, or to pericardial effusion. Myocardial infarction occurs in 25% of cases. Histology consists of microcirculatory thrombotic lesions, and, more rarely, of valvular lesions or intracavitary thrombus. Skin involvement is observed in 50% of cases. Manifestations are variable, mainly including ischemic necrosis of the extremities, livedo racemosa [13] or sub-ungual hemorrhages flames [2, 12]. Skin biopsy can be performed easily in order to prove microvascular damage. Liver damage is found in 30% of cases. It is linked to hepatic microvascular ischemia, which results in biological cytolysis. Liver failure can be related to an ischemic hepatitis due to thrombosis of large hepatic arteries, or to the occurrence of a Budd-Chiari syndrome characterized by the occlusion of the hepatic veins [12]. Gastrointestinal involvement is observed in 23% of cases. It can manifest as ischemic abdominal pain, acalculous cholecystitis, or pancreatitis [14, 15]. Splenic rupture is a rare but dreadful complication [16]. Adrenal disease is rare (13%) and consists of hypo- tension, abdominal or back pain, and electrolyte disorders including hyponatremia, and hyperkaliemia. It is also often associated to hypoglycemia. Adrenal insufficiency is related to adrenal infarction or hemorrhage. Other organs may even be more rarely affected. Testicular or ovarian infarction, prostate necrosis, bone marrow infarction esophageal rupture, giant gastric ulcer, or colonic ulcer has been reported.

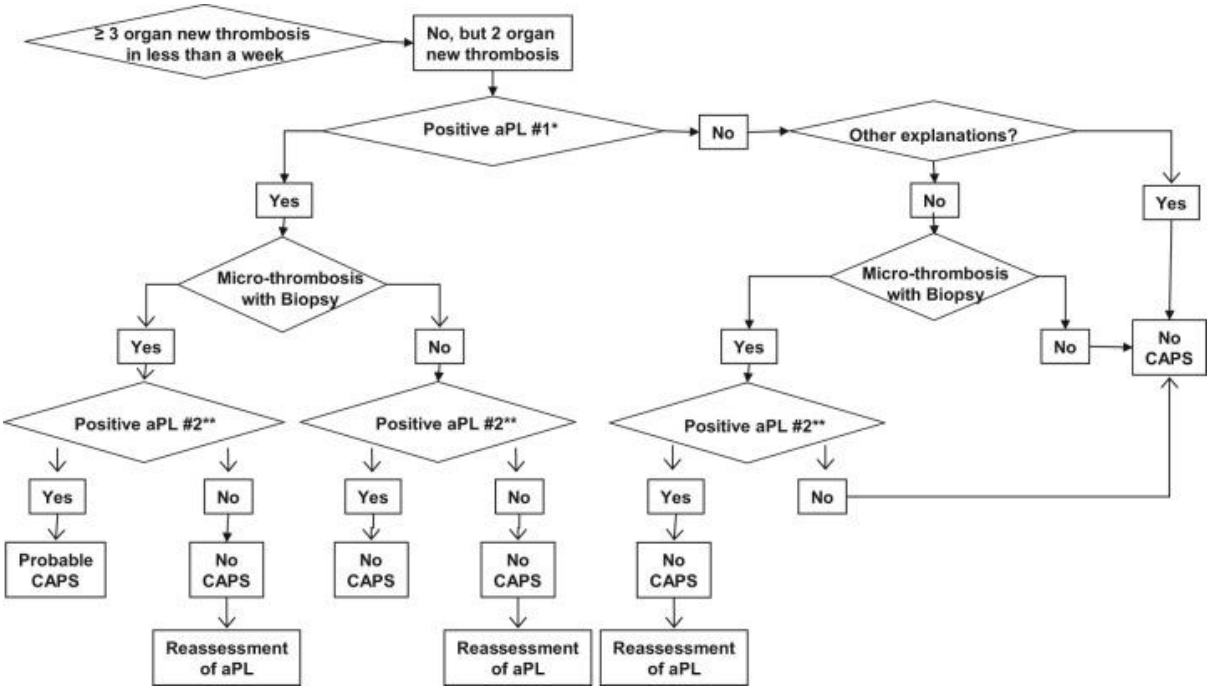
Algorithm - A



Algorithm – B



Algorithm – C



Specific laboratory tests can confirm the diagnosis of CAPS [11]. Lupus anticoagulant, evidenced through DRVVT and a sensible activated partial thromboplastin time (aPTT) [17] is positive in 82% of cases. Antiphospholipid antibodies (aPL) include anticardiolipin (IgG and/or IgM), and anti-beta2G- PI antibodies (IgG and/or IgM). They are found in 83% of cases. Since immunological tests are not available in an emergency setting, research of aPL should not delay management. Thrombocytopenia with platelet counts of less than 100,000 /mm3 is

found in 46% of cases [6, 12]. Hemolytic anemia is observed in 35% of cases, sometimes with schistocytes (16%) or biological signs of disseminated intravascular coagulation (DIC) (15%). Antinuclear antibodies can be found in 66% of cases [12], reflecting an underlying lupus. Useful laboratory tests in the differential diagnosis of multi-organ thrombotic diseases are summarized in **Table - 3**. The main differential diagnosis for CAPS are thrombotic microangiopathies, especially primary APS with deficits in ADAMTS13 [18], heparin induced thrombocytopenia [19], endocarditis, left atrium myxoma, and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count). Infection may cause transient appearance of non-thrombogenic aPL [20]. The prospective study by Wenzel, et al. [21] showed that, during a prolonged ICU stay, a lupus anticoagulant may appear in more than half of the patients, within an average delay of 13 days. This finding was not associated with the reason for an admission to the ICU, but correlated well with the occurrence of sepsis, or the need for treatment with catecholamine. It was not the cause of any thromboembolic event, and aPL tended to disappear from the blood of most surviving patients within 4 weeks. Anticoagulation therapy may also cause a false positive or false negative lupus anticoagulant [22]. The overall mortality of CAPS is important [12, 23] but currently tends to decrease with improved early detection. Mortality rate is now estimated to be 30% [24, 25]. Main causes of mortality are cardiac complications (14.1%), infections (14.1%), and stroke (13.3%). Prognostic factors associated with higher mortality are age over 36, SLE, pulmonary and renal involvement, positive antinuclear antibodies, and absence of anticoagulation therapy. In patients who survived the initial CAPS event, new thrombotic episode may occur despite anticoagulation with VKA (34%), mostly during the perioperative course of surgery (40%). CAPS relapse frequency is low, and estimated to be around 3% [24, 25].

Table – 2: Clinical manifestations of CAPS.

System involved (frequency)	Clinical symptoms
Renal (71%)	Hypertension (mild to malignant) Proteinuria and microscopic hematuria Acute renal failure Renal vein thrombosis Renal infarction
Pulmonary (64%)	Acute respiratory distress syndrome (ARDS) Pulmonary embolism
CNS (62%)	Lack of awareness Confusion syndrome Neurologic deficit (stroke) Posterior reversible encephalopathy (PRES)
Cardiac (51%)	Cardiac failure Valvular dysfunction (mitral, aortic) Pericardial effusion Myocardial infarction
Skin (50%)	Ischemic necrosis of the extremities Livedo racemosa Subungual hemorrhages flames
Hepatic (30%)	Biological cytolysis by microvascular ischemia
Gastrointestinal (23%)	Ischemic abdominal pain Acalculous cholecystitis Pancreatitis Splenic rupture
Adrenal gland (23%)	Hypotension (atypical in CAPS) Abdominal or lumbar pains Electrolyte disorders

Table - 3: Differential diagnosis of multi-organ thrombotic disorders.

	CAPS	**TTP**	**DIC**
Thrombotic mechanisms	Antibody mediated thrombosis	Antibody mediated thrombosis	Sepsis, neoplasia, drug induced
Thrombotic site	Microvascular	microvascular	Microvascular
Haemorrhagic manifestations	-	±	+
Hematological manifestations			
Anemia	±	+	±
Schistocytes	±	++	±
Thrombocytopenia	±	++	+
Laboratory tests			
Prolonged PT	-	-	+
Prolonged aPTT/DRVVT	+if lupus anti coagulant	-	+
Low Fb	-	-	+
Positive FDP	±	-	+
Immunological tests			
Positive Apl	++	±	±

Treatment of CAPS is largely empirical, given the rarity of the syndrome. Current treatment guide- lines cannot be based on large prospective studies, but on case reports of successfully treated patients, and on data from the International CAPS Registry. Early diagnosis and aggressive therapies are mandatory. Besides treating the trigger, including infection, specific treatment targets thrombosis and SIRS. Early anticoagulation is of utmost importance, re-gardless of the severity of thrombocytopenia [26]. Intravenous unfractionated heparin is usually preferred to low molecular weight heparin in case of renal failure. If the patient has a lupus anticoagulant, monitoring is based on heparin blood level instead of aPTT. Heparin is followed by VKA for an INR of approximately 3. Corticosteroids inhibit aPL mediated thrombosis [6]. Some authors suggest very high doses (250 to 500 mg/day of methylprednisolone), before a relay with usual doses of 1 mg/Kg/day methylprednisolone equivalent. Duration depends on the clinical response. Plasma ex- changes complete the first line of treatment [27, 28]. They remove cytokines and aPL. Initial setting is once in a day, followed by 1 to 3 times a week when clinical and biological remission has been obtained. Intravenous immunoglobulin (IVIG) are proposed instead of plasma exchanges in case of hemodynamic instability [29, 30], usually at a dose of 2 g/Kg in 4 to 5 days [6, 9]. Association of anticoagulation with corticosteroids and plasma exchanges give the highest recovery rate, attaining 77.8%. The combination of anticoagulation with corticosteroids and IVIG provides 69% of success [31]. Some treatments have a specific indication. Cyclophosphamide is indicated only in CAPS with SLE, particularly in the presence of lupus flare [3, 32]. Rituximab is a monoclonal antibody directed against the CD20 antigen present on the surface of B cells. Rituximab has been reported to be beneficial in the treatment of refractory cases [33, 34]. Recent results of a pilot study [35] and a recent analysis of the CAPS registry [36] confirm its interest in refractory CAPS. Rituximab recommended intravenous usual dose is 1 g, followed by a second administration fifteen days later. Other adjuvant therapies have been proposed, but are still poorly evaluated. Eculizumab is a monoclonal antibody that inhibits terminal complement activation [37]. Other molecules affecting coagulation or fibrinolysis have been

proposed [38]. Defibrotide is a DNA derivative that has an anticoagulant effect. Mechanisms of action include an ability to increase levels of prostaglandin I2, E2, and prostacyclin. This alters platelet activity, increases tissue plasminogen activator function, and decreases the activity of tissue plasminogen activator inhibitor. Ancrod is derived from the venom of the Malayan pit viper. Its anticoagulation effect is related to cleavage of circulating plasma fibrinogen, and the action of fibrinogen degradation products.

Conclusion

APS is a systemic autoimmune disease with both thrombotic and non thrombotic manifestations in which non-aPL thrombosis risk factors as well as the importance of the 'clinically significant' aPL profile should be kept in mind for diagnosis. CAPS is the most severe form of APS with multiple organ thromboses, usually accompanied by microthrombosis and hematologic manifestations. The clinical manifestations of CAPS may evolve gradually, commonly overlapping with other thrombotic microangiopathies, requiring a high index of clinical suspicion. it is critical to initiate the treatment urgently if the diagnosis of CAPS is clinically suspected, even without the confirmatory aPL tests. Treatments may involve the following steps:

- Prevention includes the use of antibiotics for infection and parenteral anticoagulation for susceptible patients.
- Specific therapy includes the use of intravenous heparin and corticosteroids [1], and possibly plasma exchanges, intravenous immunoglobulin.
- Additional steps may have to be taken to manage circulatory problems, kidney failure, and respiratory distress.
- When maintaining survival of the disease treatments also include high doses of Rituxan (Rituximab) to maintain stability.

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