Catastrophic Antiphospholipid Syndrome

Man-Chi Leung and Woon-Leung Ng

Abstract: The catastrophic antiphospholipid syndrome is a potentially life threatening rheumatological condition characterized by multiple small vessel thrombosis related to the presence of the antiphospholipid antibodies resulting in multiorgan failure that progresses within a short period of time. A high degree of clinical suspicion is required for early diagnosis and prompt initiation of aggressive therapy is necessary to improve the outcome. Despite intensive treatment, mortality rate remains as high as 44%. Combined treatment with anticoagulant, high dose corticosteroid, plasma exchange and/or immunoglobulin is associated with a better prognosis.

Keywords: Catastrophic antiphospholipid syndrome, Asherson’s syndrome

Introduction

The catastrophic antiphospholipid syndrome (CAPS) is a rare and accelerated variant of the antiphospholipid syndrome (APS) that is associated with high mortality.1 It was first documented in details by Asherson in 19922 and was therefore also known as the "Asherson's syndrome".3 This disorder is characterized by four cardinal features: (a) clinical evidence of rapidly progressive multiple organ dysfunction syndrome (MODS), mostly occurring within a week; (b) evidence of systemic inflammatory response syndrome (SIRS); (c) histopathologic evidence of multiple small vessel occlusions (with a minority having concomitant large vessel thrombosis); notably with unusual sites of involvement including the bone marrow and reproductive organs; and (d) laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titers.4 Although less than 1% of patients with APS develop this complication,5 almost all patients with CAPS ended up in intensive care units with multi-organ dysfunction. High level of clinical awareness and expedited diagnosis and intervention are paramount in improving the outcome of these patients.

Owing to the rarity of this syndrome, the European Forum on Antiphospholipid Antibodies has established an international registry for patients with CAPS in 2000 (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM).6 The entire clinical, laboratory, and therapeutic data of all published cases with CAPS, as well as of many additional patients are collected and charted. Currently more than 300 patients have been fully registered.

Etiopathogenesis

The pathogenesis of CAPS seems to be multifactorial. It is still uncertain why some patients develop the classic APS with recurrent thrombosis affecting mainly large vessels, while a minority develop a rapidly progressive microthrombosis and diffuse small-vessel ischemia that characterizes the CAPS. In the currently accepted model of APS and CAPS, a "second or third trigger" may be necessary for an asymptomatic aPL-positive patient to develop vascular events (the second-hit hypothesis).7 Around 60% of patients with CAPS have at least one identifiable "trigger" factor, with infection being on top of the list followed by trauma, surgery, anticoagulant withdrawal and obstetric complications. The various "triggers" for CAPS are depicted in Figure 1.8

Kitchens9 hypothesized that multiple thrombotic lesions may be responsible for on-going thrombosis, producing a "thrombotic storm" in patients with CAPS. These clots are a
source of activation products of coagulation including prothrombin activation products F1 and F2, thrombin-antithrombin complexes and protein-C activation peptide. There is simultaneous depression of fibrinolysis via an increase in plasminogen activator inhibitors ("fibrinolytic shutdown") and consumption of natural anticoagulant proteins including protein C, protein S and antithrombin III. In effect, "clots beget clots" in a self-perpetuating vicious cycle.

The role of complement and phenotypic abnormalities in toll-like receptors in patients with CAPS is currently being investigated. This is possibly another important pathogenetic mechanism. In half of the CAPS patients, no associated autoimmune disorders can be identified.

**Clinical Features**

Up to February 2005, 250 patients were registered in the CAPS registry. There are 177 (70.8%) women and 73 (29.2%) men. The mean age was 37±14 (range 7 to 76) years. Among them, 116 (46.4%) patients have primary APS; 100 (40%) patients have systemic lupus erythematosus (SLE); 12 (4.8%) patients have SLE-like syndrome; 22 (8.8%) patients have other autoimmune disorders, including rheumatoid arthritis, systemic sclerosis, ulcerative colitis, Crohn's disease, relapsing polychondritis, Behcet's disease and dermatomyositis.

The clinical manifestations of individual patient are variable and dependent on two factors: a) the site and extent of thrombosis, and b) the systemic inflammatory response syndrome.

Most patients presented with multiple organ failure at the time of CAPS. The typical organ involvement included the kidney (70%), followed by lung (68%), brain (63%), skin (58%) and heart (51%). Other commonly involved organs included the gastrointestinal tract, liver, retina and reproductive organs.

The kidney is the most commonly affected organ. The cause of renal failure is manifold but mainly due to renal thrombotic microangiopathy. Other causes include occlusion of major abdominal vessels and hypotensive or hypertensive events.
Pulmonary involvement was reported in 68% of CAPS patients. Acute respiratory distress syndrome (ARDS) is the dominant manifestation with high mortality rate of 40% despite aggressive treatment. When ARDS developed in an APS patient, CAPS should be strongly suspected in the differential diagnosis.

Cardiogenic shock may occur as a result of myocardial infarction from coronary artery thrombosis, cardiac microthrombosis, acute valvular dysfunction or massive pulmonary thromboembolism.

Cerebral manifestations are frequent. Cerebral infarct with stroke is the most common neurologic presentations. Other neurologic presentations including encephalopathy, seizures, myelitis and mononeuritis multiplex are also seen in CAPS patients.

Other significant thrombotic manifestations include adrenal infarction or haemorrhage occurs in 10% to 26% of CAPS patients. Haematologic manifestations include thrombocytopenia (63%), haemolytic anaemia (32%) and disseminated intravascular coagulation (DIC). Infarctions may occur in unusual sites such as the bone marrow, testicles, uterus, ovaries and thyroid.

Laboratory Findings

In a review of 250 patients with CAPS, positive IgG anticardiolipin antibodies (aCL) were present in 84%, positive IgM aCL in 42%, and positive lupus anticoagulant in 78% of the patients. Thrombocytopenia was found in more than 60% of cases, and one third of patients had evidence of haemolysis. Schistocytes were usually scanty. At least 13% of patients had evidence of disseminated intravascular coagulation (DIC).

Diagnosis

The awareness of the diverse clinical presentation and a high index of suspicion are imperative in making a prompt diagnosis. Timely initiation of appropriate therapy is critical to survival of patients with CAPS. In 2002, proposed preliminary classification criteria for the CAPS (Table 1) were accepted during the 10th International Congress on Antiphospholipid Antibodies in Taormina, Sicily, Italy. In 2003, the international consensus statement was published. Cervera et al. validated the preliminary criteria for the classification of CAPS in 176 patients included in the CAPS registry. These criteria yielded a sensitivity of 90.3% with

<table>
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<tr>
<th>Table 1. International classification criteria for CAPS</th>
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<tr>
<td>1. Evidence of involvement of 3 or more organs, systems, and/or tissues*</td>
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<tr>
<td>2. Development of manifestations simultaneously or in less than 1 wk</td>
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<tr>
<td>3. Confirmation by histopathology of small vessel occlusion in at least 1 organ/tissueb</td>
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<tr>
<td>4. Laboratory confirmation of the presence of aPL (LA and/or aCL and/or anti-β2-glycoprotein I antibodies)c</td>
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Definite CAPS
- All 4 criteria

Probable CAPS
- All 4 criteria, except for involvement of only 2 organs, systems, and/or tissues
- All 4 criteria, except for the absence of laboratory confirmation at least 6 wk apart attributable 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 1 wk but less than 1 month, despite anticoagulation treatment

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% increase in serum creatinine, severe systemic hypertension (>180/110 mmHg), and/or proteinuria (>500 mg/24h).

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 APS, the laboratory confirmation requires that presence of aPL must be detected on 2 or more occasions at least 6 wk apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.
specificity of 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively.

**Differential Diagnosis**

Diagnosis of CAPS is often challenging in a patient presenting with acute onset of multiorgan dysfunction, thrombocytopenia and microangiopathic haemolytic anaemia. Other medical conditions may share many of the same clinical features as CAPS. These include severe sepsis, thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS), DIC, heparin-induced thrombocytopenia (HIP) and HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets). Table 2 highlights some distinguishing features among the common differential diagnoses for CAPS. Furthermore, CAPS may occasionally coexist with the above mentioned conditions.

**Treatment**

Once CAPS is suspected, early and aggressive treatment is critical in order to improve the outcome. Owing to the rarity of the disease, there are no prospective randomized controlled trials to date that investigate the efficacy of various treatment regimes. The experience comes from the published case series and analysis of the International CAPS registry. A treatment algorithm for CAPS (Figure 2) has been proposed and reviewed.7,14

**General Management**

Since more than half of patients developed CAPS following an identifiable trigger factor, treatment and elimination of possible precipitating factors is essential. Infections should be treated with parenteral antibiotics after taking appropriate cultures. Debridement or amputation should be performed without delay if necrotic tissue is present. Amital et al16 reported 2 cases of CAPS which remitted following leg amputation. Surgical procedure in APS and CAPS patients require special attention. All patients undergoing surgical procedure should keep periods without anticoagulation as short as possible and parental anticoagulation should be used in the perioperative period and continued until the patient is fully ambulatory.17

Almost all CAPS patients were eventually treated in intensive care unit because of multiorgan failure. Mechanical ventilation is often required for respiratory failure especially if ARDS is present. Patients requiring respiratory support may need special mechanical ventilation strategies to minimize complications and facilitate weaning.7 Renal replacement therapy may be required for renal insufficiency. Inotropic support for circulatory failure also plays an important role in management of CAPS patients. Other

<table>
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<tr>
<th>CAPS</th>
<th>TTP</th>
<th>HUS</th>
<th>DIC</th>
<th>Malignant hypertension</th>
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<tr>
<td>Fever</td>
<td>+/-</td>
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<td>+</td>
<td>+/-</td>
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<tr>
<td>CNS involvement</td>
<td>++</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Renal involvement</td>
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<td>+</td>
<td>+++</td>
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<td>Thrombocytopenia</td>
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<td>Elevated PT</td>
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<td>Elevated aPTT</td>
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<td>FDP</td>
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<tr>
<td>aPL</td>
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CAPS – catastrophic antiphospholipid syndrome; TTP – thrombotic thrombocytopenic purpura; HUS – haemolytic uraemic syndrome; DIC – disseminated intravascular coagulation; PT – prothrombin time; aPTT – activated partial thromboplastin time; FDP – fibrin degradation product; aPL – antiphospholipid antibodies.
supportive measures include tight glycaemic control using insulin and glucose infusion; management of severe hypertension and stress ulcer prophylaxis. In case of adrenal insufficiency secondary to adrenal infarction or haemorrhage, intravenous corticosteroid replacement should be initiated.

Specific Therapies

Anticoagulants, corticosteroid, intravenous immunoglobulin and plasma exchange are the most commonly used therapies in CAPS patients.

1) Anticoagulant: Heparin accelerates the activity of antithrombin, resulting in inhibition of thrombin, factor Xa and other activated clotting factors. Heparin also inhibits complement activation and the binding of aPL to their target antigens. Intravenous heparin is usually administered for 7-10 days followed by oral anticoagulants once the patient is stabilized, aiming at an international
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normalized ratio (INR) of approximately 3.0. Heparin is then discontinued once INR reaches the therapeutic target. 7

2) Corticosteroids: Steroids are used to inhibit the excessive cytokine release due to widespread tissue injury. Steroids may also be necessary to replace possible adrenal hormone deficiency. The usual prescribed dosage is intravenous pulse methylprednisolone (1000 mg/day) for 3-5 days followed by high doses of methylprednisolone (1-2 mg/kg/d).18

3) Plasma Exchange (PE) with fresh frozen plasma (FFP): The most often regime is removal of 2 to 3 litres of plasma for a minimum of 3 to 5 days with FFP as replacement fluid. PE is proposed to remove pathogenic aPL, cytokines or other inflammatory mediators. Espinosa et al19 studied 46 patients with thrombotic microangiopathic haemolytic anaemia (TMHA) associated with the antiphospholipid antibodies. Amongst these patients, those treated with PE had a recovery rate of 73%. Therefore PE was recommended as a first line of treatment for all patients with TMHA associated with aPL.1,7,19

4) Intravenous immunoglobulin (IVIG): The usual daily dose is 0.4 g/day/kg body weight for 4 to 5 days. IVIG can neutralize patient’s pathogenic antiphospholipid antibodies in short term via anti-idiotypic activity and reduce antibody production in long term via inactivation of idiotypic B cell clones.20 It has an added advantage for having a broad spectrum antibacterial and antiviral activity. IVIG are usually well tolerated but severe anaphylactic reactions can occur in patients with IgA deficiency in whom it is contraindicated. There are a few case reports of thromboembolism after IVIG infusion and a few cases reported acute renal failure after the therapy.

Most patients received multiple therapeutic modalities. According to a recent review of the mortality and treatment regimens in CAPS patients by Bucciarelli et al,1 patients with suspected or confirmed CAPS should be treated with a combination of anticoagulants and corticosteroid plus plasma exchange as first-line therapy. IVIG can be considered if there is no clinical improvement. If both IVIG and plasmapheresis are used in the same patient, IVIG is usually administered after the last day of plasma exchange. The regimen may have to be continued for several weeks before improvement occurs. Intensive supportive measures should be given to all patients.

In refractory patients with CAPS, several investigational medications with variable reported effectiveness may be considered. These include rituximab,21 prostacyclin22 and defibrotide.23 Cyclophosphamide was found to have no added benefit except in patients with SLE or other patients with vasculitic "flares".18

While there is a recent advocate towards the use of anticoagulation at moderate intensity (INR 2.0 to 3.0) for prevention of recurrent thrombosis in APS; higher intensity anti-coagulation (INR 3.0-4.0) is generally recommended for CAPS patients even though no prospective evidence for this approach is currently available. The most appropriate level of anticoagulation for Chinese patients is unknown.

Outcome and Prognosis

In a recent review on the mortality in CAPS, the overall mortality rate is as high as 44% despite all endeavors. The major causes of death include cerebral involvement (mainly consisting of stroke), cardiac involvement, and infections. Higher mortality is observed in patients with SLE. However, no differences between fatal and survived patients were observed in terms of age, sex, presence of precipitating factors or any of the clinical and laboratory features.1

Despite the high mortality in CAPS, the long term prognosis is good once patients survive the initial episode. They usually have a stable course with anticoagulation. Erkan et al24 documented that 66% of patients (38 out of 58) who survived a CAPS event remained symptom free with an average follow-up of 62.7 months. Nineteen percent of patients had further non-fatal APS related events but none of them have recurrent CAPS.24

Summary

Catastrophic antiphospholipid syndrome is a rare rheumatological emergency with high mortality. Growing physician awareness and heightened clinical alertness are crucial to the early diagnosis and prompt initiation of
aggressive intervention to alter the dismal outcome of these patients.

*Human history becomes more and more a race between education and catastrophe.*

H. G. Wells, *Outline of History* (1920)

Nearly a century has passed but the words of H.G. Wells’ ring truer than ever. The challenge put forth by CAPS calls forth more dedicated effort in scientific research and medical education.

*It takes a good man to prevent a catastrophe, but a great man to make use of one.*

Cardinal Richelieu

## References