Update on the Catastrophic Antiphospholipid Syndrome and the "CAPS Registry"

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Abstract

Although less than 1% of patients with the antiphospholipid syndrome (APS) develop the catastrophic variant known as catastrophic antiphospholipid syndrome (CAPS), its potentially lethal outcome emphasizes its importance in clinical medicine today. However, the rarity of this variant makes it extraordinarily difficult to study in any systematic way. To collate all the published case reports as well as the newly diagnosed cases from all over the world, an international registry of patients with CAPS ("CAPS Registry") was created in 2000 by the European Forum on Antiphospholipid Antibodies (www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). Currently, this database documents the entire clinical, laboratory, and therapeutic data of more than 350 fully registered patients.

Keywords

- catastrophic antiphospholipid syndrome
- Asherson syndrome
- antiphospholipid antibodies
- anticardiolipin antibodies
- lupus anticoagulant
- antiphospholipid syndrome

The descriptive adjective "catastrophic" was added in 1992 to define an accelerated form of the antiphospholipid syndrome (APS) to highlight a new subset of this syndrome resulting in multiorgan failure, which is often fatal.[1] This subset is now also referred to as Asherson syndrome,[2] to honor Ronald A. Asherson (who passed away in 2008) for his impressive work on this condition. Patients with catastrophic APS (CAPS) have in common: (1) clinical evidence of multiple organ involvement developing over a very short period of time; (2) histopathological evidence of multiple small vessel occlusions; and (3) laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titer. Furthermore, ~60% of the catastrophic episodes are preceded by a precipitating event, mainly infections.[3–10]

Although less than 1% of patients with APS develop this complication,[6] its potentially lethal outcome emphasizes its importance in clinical medicine today. The majority of patients with CAPS end up in intensive care units with multiorgan failure and, unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed, often resulting in a disastrous outcome for these patients.

"CAPS Registry"

Due to the rarity of this syndrome, an international registry of patients with CAPS ("CAPS Registry") was created in 2000 by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients.[11] This registry documents the entire clinical, laboratory, and therapeutic data of all published cases with CAPS as well as of many additional patients whose data have been fully registered. Currently, the database documents data of more than 350 patients. The main clinical features, treatment, and evolution of these patients can be consulted via the Internet

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(http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) and the periodical analysis of these data allows us to increase the knowledge of this condition.

Classification and Diagnosis

The heterogeneity of clinical presentation in CAPS led to the development of consensus criteria for the definition and classification of these patients. In September 2002, a presymposium workshop held during the 10th International Congress on aPL in Taormina, Sicily, Italy, established preliminary criteria for the classification of CAPS[7] (►**Table 1**) that were later validated.[8] These preliminary criteria with an accompanying "classification algorithm" (►**Fig. 1**) have been of major importance, as patients with a doubtful diagnosis of CAPS or with less severe disease ("probable" CAPS) are classified separately and distinctly from those with a "definite" diagnosis of CAPS. These criteria have provided a more consistent diagnostic paradigm for CAPS over the past 10 years.

However, when patients present with multiple organ thromboses in a "real-world" setting, multiple factors can impede the timely diagnosis of CAPS and, at times, the differential diagnosis cannot be narrowed to a single disease. To address this problem, in April 2010, during the 13th International Congress on aPL in Galveston, TX, a "Catastrophic APS Task Force" was developed by the meeting organization committee. This task force proposed the delineation of new diagnostic algorithms to help clinicians managing patients in who CAPS is suspected.[12] The goal of the updated CAPS diagnostic algorithms is to provide a "step-by-step" approach to clinicians and researchers while assessing patients with multiple organ thromboses. Important steps of the diagnostic algorithms include: (1) history of APS or persistent aPL positivity; (2) the number of organs involved in less than a week; (3) histopathological evidence of microthrombosis on biopsy(ies); and (4) other explanations for multiple organ thromboses and/or microthrombosis.[13]

Clinical Features

The detailed analysis of the first 280 patients included in the CAPS Registry shows that 72% are females, with a mean age of 37 years (range, 11 to 60 years). Of these 280 patients, 46% suffered from primary APS, 40% from systemic lupus erythematosus (SLE), 5% from lupus-like disease, and 9% from other autoimmune diseases.[9]

Patients may develop CAPS de novo, without any history of a thrombosis (46%). However, the database also shows that previous deep vein thrombosis, fetal loss, or thrombocytopenia are the most frequently encountered aPL-associated previous manifestations.[9]

A precipitating factor for the episode of CAPS was reported in 53% of the patients. The most common precipitating factors were infections (22%) and surgical procedures (10%). Other less common causes were anticoagulation withdrawal or low international normalized ratio (INR) (8%), other medications (7%), obstetric complications (7%), neoplasia (5%), and SLE flares (3%).[9]

The clinical manifestations of CAPS mainly depend on two factors: (1) organs affected by the thrombotic event and the extent of the thrombosis and (2) manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues. There are thus two separate and distinct sets of manifestations, each of which requires effective therapy.[14–16]

Thrombotic Manifestations

Intra-abdominal thrombotic complications affecting the kidneys, adrenal glands, splenic, intestinal, and mesenteric or pancreatic vasculature are most commonly encountered and the patients frequently present initially with abdominal pain or discomfort. Renal disease is present in 71% of patients, but these patients generally do not succumb from the uremia itself. Pulmonary complications are

Table 1 Preliminary Criteria for the Classification of CAPS

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 aPL antibodies (lupus anticoagulant and/or aCL antibodies).[c]

Note: Definite CAPS: All four criteria.
Probable CAPS:

- All four criteria, but with involvement of only two organs, systems and/or tissues.
- All four criteria, but with the absence of repeat detection of aPL at least 12 weeks apart, due to the early death of a patient who had never been tested for aPL before the CAPS event.
- Criteria 1, 2, and 4.
- Criteria 1, 3, and 4 and the development of a third event after more than 1 week but before 1 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 mm Hg) and/or proteinuria (> 500 mg/24 h).
[b]For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may occasionally coexist.
[c]If the patient had not been previously diagnosed as having APS, laboratory confirmation requires that aPL antibodies must be detected on two or more occasions at least 12 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.[31]
CAPS, catastrophic antiphospholipid syndrome; aPL, antiphospholipid antibodies; aCL, anticardiolipin antibodies; APS, antiphospholipid syndrome.

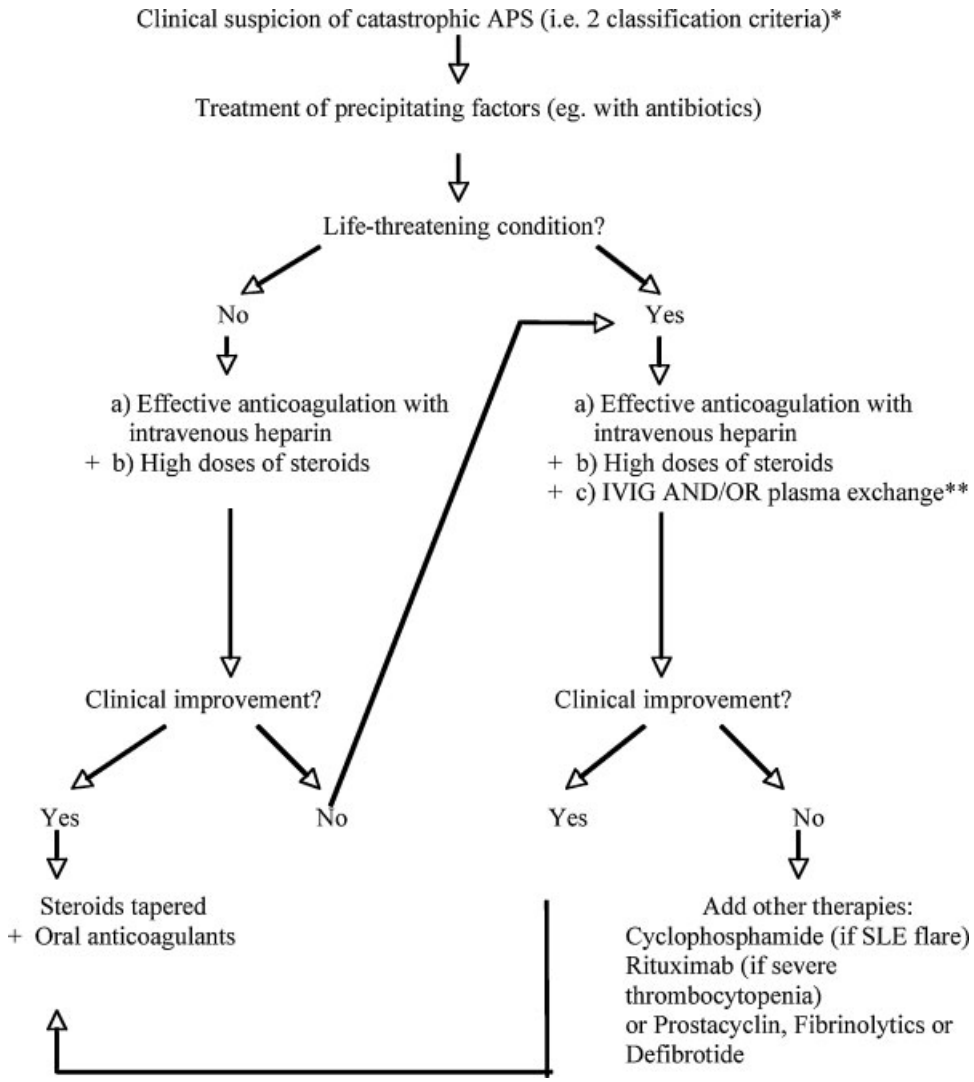

Figure 1 Treatment algorithm for catastrophic APS. *Need to exclude other microangiopathic syndromes (mainly thrombotic thrombocytopenic purpura and heparin-induced thrombosis/thrombocytopenia). **Plasma exchange should be performed with fresh frozen plasma as the replacement fluid. Plasma exchange is specially indicated if schistocytes are present. APS, antiphospholipid syndrome; IVIG, intravenous immunoglobulins; SLE, systemic lupus erythematosus.

next in frequency (64%), with acute respiratory distress syndrome (ARDS) and pulmonary emboli accounting for the majority of these patients, while pulmonary hemorrhage, microthrombi, pulmonary edema, and infiltrates occur in a minority of patients. Cerebral manifestations (infarcts, encephalopathy, seizures, or cerebral venous occlusions) are also frequent (62%). Small vessel cerebrovascular occlusive disease is probably more common than has been reported and may be the etiology of the encephalopathic features of the syndrome. Cardiac problems occur in 51%, often with valvular defects (mitral, aortic), while myocardial infarctions are a presenting feature in 25% of cases. Skin complications, such as livedo reticularis, purpura, and skin necrosis occur in 50% of patients.

Other organs may be occasionally affected, including testicular/ovarian infarction, necrosis of the prostate, acalculous cholecystitis, and bone marrow infarction.[9]

Manifestations of the SIRS

This multisystem inflammatory syndrome is due to cytokine activation and, although actual measurements of cytokine levels in very ill patients with CAPS have not been undertaken, it is assumed that this process occurs in the acute phase of the illness. Certainly, some of the nonthrombotic manifestations of CAPS, particularly ARDS,[17] are frequently encountered in SIRS. The cytokines involved include tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and macrophage-migration inhibitory factor and they are responsible not only for ARDS, but also for the cerebral edema, which may be a contributory factor in the initial confusion and deterioration of consciousness seen in these patients. These cytokines are also likely to contribute to myocardial dysfunction in some patients with CAPS. IL-18 is implicated in the pathogenesis of ARDS and acute lung inflammation due to its ability to increase neutrophil migration and lung vascular permeability. Furthermore, ARDS is often

complicated by disseminated intravascular coagulation (DIC).[18]

Laboratory Features

Thrombocytopenia was detected in 46% of cases from the "CAPS Registry." One-third of the patients had evidence of hemolysis and 15% had some of the features of DIC.[9] Schistocytes, if present, are usually scanty, unlike the abundant numbers seen in patients with thrombotic thrombocytopenic purpura (TTP).[19]

Immunoglobulin (Ig) G anticardiolipin antibodies (aCL) are usually positive in patients with CAPS with IgM aCL positivity being less frequent (isolated IgM aCL positivity was only occasionally found). Patients who also have a diagnosis of SLE typically have positive antinuclear antibodies, antibodies to double stranded DNA and to extractable nuclear antigens.

Treatment

Early diagnosis and aggressive therapies are essential in the management of CAPS. Unfortunately, despite such therapies, the mortality remains extremely high (around 30%).[5] An algorithm with treatment guidelines for the CAPS (►**Fig. 1**) has been proposed.[7] Treatment may be divided into three major categories: (1) prophylactic therapy, (2) specific therapies, and (3) nonspecific therapies.

Prophylactic Therapy

Particular attention should be given to APS patient according to the following guidelines:

- Any infection, however trivial, should be energetically treated with the appropriate antibiotics.
- APS patients undergoing surgical procedures, however minor, should all receive parenteral anticoagulation during the procedure instead of remaining on oral anticoagulation.
- The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants (e.g., subcutaneous heparin).
- Severe SLE "flares," although uncommonly associated with CAPS, should also be treated with parenteral anticoagulation.

Specific Therapies

First-Line Therapies

Anticoagulants

These are usually given in the form of heparin, which is the mainstay of treatment in patients with CAPS. In fact, the CAPS Registry analysis confirms the lower rate of mortality in anticoagulated patients compared with those who are not (36.9 vs. 77.8%, respectively; $p < 0.0001$).[4] The type of anticoagulation received during the acute phase of CAPS (unfractionated or low-molecular-weight heparin or oral anticoagulation) did not influence the survival of patients. Heparin is usually administered for 7 to 10 days followed by oral anticoagulants aiming for an INR of ~3.0. The dual effect of heparin (inhibition of thrombin generation and inhibition of complement activation) may explain its beneficial effect in APS patients.

Glucocorticosteroids (GC)

Based on the analysis of the CAPS Registry, there is no statistically significant difference in survival regarding the route, dose, and duration of GC therapy. Empirically in the case of a life-threatening condition, these should be administered for a minimum of 3 days (1000 mg methylprednisolone daily), but may have to be continued for longer duration depending on the patient's response. However, GC therapy alone did not improve outcome according to data from the CAPS Registry. The rationale for using GC in CAPS is based on their inhibition of nuclear factor-κB, which is an important mediator in both SIRS- and aPL-mediated thrombosis. Therefore, unless an absolute contraindication exists, GC should be considered in CAPS patients.

Second-Line Therapies

Plasma Exchange (PLEX)

This procedure removes aPL (most likely transiently) as well as cytokines, TNF-α, and complement products. Based on a literature search of the use of PLEX in patients with CAPS,[20] as well as analysis of the CAPS Registry,[5] the use of PLEX clearly improves patient survival. The current recommendation is to start PLEX if there is no response to anticoagulation and GC.[1] There are times when PLEX is used as part of the first-line management in patients with a particularly severe presentation.[7] It is important to note that most, but not all, reported patients with CAPS received PLEX together with fresh frozen plasma (FFP) as the replacement fluid. FFP contains natural anticoagulants, such as Antithrombin, and also clotting factors. It is not known if PLEX with a different replacement fluid, such as human albumin solution, would result in different outcomes. It is important to note that PLEX should be the treatment of choice in patients with features of microangiopathic hemolytic anemia and a prominent component of small vessel occlusive disease. The most often used procedure for PLEX is removal of 2 to 3 L of plasma per session, for a minimum of 3 to 5 days.

Intravenous Immunoglobulins (IVIG)

The daily dose recommended is 0.4 g/d/kg body weight for 4 to 5 days. IVIG may be of particular value in those patients who have severe thrombocytopenia, but may also possibly decrease the synthesis of aPL and increase the catabolism of circulating pathological immunoglobulins due to anti-idiotypic action. IVIG infusions are usually well tolerated, but there are a few reports of thromboembolic events (especially with rapid infusion of high doses in certain patients groups; see below), as well as a few cases of acute renal failure following IVIG therapy.[21] At present, analysis of treated patients with CAPS from the CAPS Registry does not show any evidence that IVIG on its own improves survival in patients with this condition. However, its combined use with PLEX might be more effective and therefore this combination could be considered for the most severe cases.

Physicians should be aware that thrombosis with IVIG use has been reported when high doses of IVIG are delivered rapidly, especially in elderly patients with comorbidities such as diabetes, hypertension, or hypercholesterolemia. Thus, if anticoagulation needs to be interrupted in the patient (e.g., because of bleeding), physicians should be cautious with the use of IVIG. Some of the strategies to reduce the risk of thrombosis include avoiding other intravenous products with a high osmotic load, reducing the rate of IVIG infusion (to avoid the delivery of a large osmotic load), adequate hydration, and using nonsucrose IVIG products (especially in patients with renal failure). When IVIG and PLEX are to be used simultaneously in the same patient, to prevent the removal of IVIG by PLEX, IVIG should be administered after the last day of the PLEX.

Third-Line Therapies

These comprise several agents that have either been used fairly often (cyclophosphamide) or only in a few cases (rituximab, prostacyclins, ancrod, defibrotide), and may have contributed to the recovery of the patient.

Cyclophosphamide

This may be beneficial in CAPS patients with SLE but not in primary APS patients, as has been demonstrated in a recent multivariate analysis of the CAPS Registry.[22] However, these results may have been confounded by the fact that cyclophosphamide was usually administered earlier in the course of management of SLE-associated CAPS patients than in primary APS patients with CAPS. Nevertheless, physicians should have a relatively low threshold to use cyclophosphamide in CAPS patients with SLE, especially in the presence of active lupus disease.

Rituximab

This is an anti-CD20 monoclonal antibody that has been used successfully in a limited number of APS patients with thrombocytopenia[23–25] or autoimmune hemolytic anemia.[24] However, it is not possible to evaluate if rituximab had any direct or indirect antithrombotic effect as all rituximab-treated CAPS patients also received anticoagulants and multiple immunosuppressive agents.[26–28]

Prostacyclin

This compound is a potent inhibitor of platelet aggregation and would thus theoretically be of benefit to mitigate the ongoing prothrombotic process. It is also a vasodilator. The usual dose is 5 ng/kg/min administered over 7 days.

Ancrod

This is a powerful fibrinolytic and also corrects plasminogen activator deficiencies. However, it is seldom used today.

Defibrotide

This is an alkali metal salt of single stranded DNA and has antithrombotic properties. Because of its polypharmacological properties, it may play an important role in the future in the management of refractory patients with CAPS. In the CAPS Registry, its use has been reported to be associated with a successful outcome in one patient.[29]

Other Fibrinolytics

Other fibrinolytics compounds such as streptokinase, urokinase, and tissue plasminogen activators, theoretically, might have an important role to play in the management of refractory patients with CAPS, but may be associated with hemorrhagic complications. Clinicians therefore need to weigh up the pros and cons of these compounds' judicious use in difficult cases where a life-threatening situation is imminent because of ongoing clotting.

Relapsing CAPS

Relapsing CAPS is distinctly uncommon compared with the not dissimilar condition of TTP, in which relapses frequently occur. In the CAPS Registry, relapses were reported in only 9 of 280 patients (3%). A total of 35 episodes of CAPS were described in these patients (6 patients presented 2 recurrences, 2 patients suffered 3 relapses, and 1 patient developed 17 relapses), with an overall mortality rate of 33%. The mean age of these patients was 45 $\pm$ 16 years. Five patients (55%) were females and 8 patients (88%) suffered from primary APS. A precipitating factor was identified in nine episodes (55% infections, 45% related with anticoagulant treatment). The most common organs involved were the brain, kidney, heart, and lung. Interestingly, laboratory features of microangiopathic hemolytic anemia (schistocytes) were present in 13/18 episodes (72%). Therefore, although relapse is a rare complication in patients with CAPS, the presence of schistocytes may be a useful indicator of the development of a relapse.[30]

Conclusion

The CAPS is an uncommon but potentially life-threatening condition for which clinicians need to have a high degree of awareness. It is clear that the majority of patients with this condition have manifestations of microangiopathy, namely occlusive vascular disease affecting predominantly the small vessels of different organs, particularly kidney, lungs, brain, heart, and liver. A minority of CAPS patients only experience the large vessel type occlusions typically seen in the non-CAPS patients. It is highly likely that there is a fundamental, profound, and sudden disturbance of the coagulation or fibrinolytic systems induced by the aPL in this group of patients, but the precise precipitating factors remain unknown in most cases. The therapeutic connotation of such a disturbance is that it may be corrected with the combination of anticoagulation, GC, and attempts to achieve a prompt reduction in the levels of circulating aPL (via PLEX and/or IVIG).

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