Catastrophic antiphospholipid (Asherson's) syndrome

Catastrophic antiphospholipid syndrome is characterized by multiple organ involvement developing over a very short period of time, histopathological evidence of multiple small vessel occlusions, and laboratory confirmation of the presence of antiphospholipid antibodies. Knowledge of its treatment is vital as the outcome can be lethal.

The descriptive adjective 'catastrophic' was added to the term antiphospholipid syndrome in 1992 (Asherson, 1992) in order to highlight an accelerated form of this syndrome resulting in multiorgan failure. Patients with catastrophic antiphospholipid syndrome (also known as Asherson's syndrome) (Piette et al, 2003) have in common:

1. 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 (Asherson et al, 1998, 2001).

Although two positive antiphospholipid antibody readings taken 12 weeks apart are required for the diagnosis of definite antiphospholipid syndrome, as this is an acute condition, this requirement for obvious reasons is not mandatory in patients presenting with the catastrophic antiphospholipid syndrome.

Although less than 1% of patients with antiphospholipid syndrome develop this complication (Cervera et al, 2002), its potentially lethal outcome emphasizes its importance in clinical medicine today. The majority of patients with catastrophic antiphospholipid syndrome end up in intensive care units with multi-organ failure and, unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed, resulting in a disastrous outcome for these patients.

The rarity of this syndrome makes it extraordinarily difficult to study in any systematic way. In order to put together all the published case reports as well as newly diagnosed cases from all over the world, an international registry of patients with catastrophic antiphospholipid syndrome (CAPS Registry) was created in 2000. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 300 patients whose data have been fully registered. This registry can be freely consulted at www.med.ub.es/MIMMUN/FORUM/CAPS.HTM. Analysis of this registry has allowed the characterization of the clinical and laboratory features of the catastrophic antiphospholipid syndrome as well as the establishment of preliminary criteria for its classification and guidelines for its management (Asherson and Shoenfeld, 2000; Asherson et al, 2003; Cervera et al, 2005).

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Clinical features

Detailed analysis of patients included in the CAPS Registry shows that 70% are female, with a mean age of 37 years (range 7–76 years). Approximately 46% have primary antiphospholipid syndrome and 40% have systemic lupus erythematosus, with other conditions such as rheumatoid arthritis, Sjögren's syndrome or vasculitis making up the remainder of cases.

The clinical manifestations of catastrophic antiphospholipid syndrome mainly depend on two factors:

1. Organs affected by the thrombotic event and the extent of the thrombosis
2. Manifestations of systemic inflammatory response syndrome, which are presumed to be the result of excessive cytokine release from affected and necrotic tissues.

Thrombotic manifestations

Intra-abdominal thrombotic complications affecting the kidneys, adrenal glands, splenic, intestinal and mesenteric or pancreatic vasculature are most commonly encountered and the patient frequently presents initially with abdominal pain or discomfort. Renal disease is present in 70.6% of patients and pulmonary complications are next in frequency (63.9%), with acute respiratory distress syndrome and pulmonary emboli accounting for the majority of these. Cerebral manifestations (infarcts, encephalopathy, seizures or cerebral venous occlusions) are also frequent (62%). Skin complications, such as livedo reticularis, purpura and skin necrosis, are next, occurring in 50.2%. Cardiac problems occur in 51.4%, with valve defects (mitral, aortic) often present. Valvular vegetations may also be encountered making for diagnostic difficulties in such cases (e.g. as recurrent thromboembolism). Myocardial infarctions are a presenting feature in 25% of cases.

Additionally, other unusual organs may be occasionally involved, resulting in testicular or ovarian infarction, necrosis of the prostate, oesophageal rupture, gastric and colonic ulcerations, thrombotic pancreatitis, and adrenal infarction, among other clinical manifestations.

Manifestations of systemic inflammatory response syndrome

This multisystem inflammatory syndrome is caused by cytokine activation and, although actual measurements of cytokine levels in very ill patients with catastrophic antiphospholipid syndrome have not been undertaken, it is assumed that this process is ongoing in the acute phase of the illness. Certainly, some of the non-thrombotic manifestations, particularly acute respiratory distress syndrome (Bucciarelli et al, 2006a), are frequently encountered in systemic inflammatory response syndrome. This may be superimposed on an underlying infective process, which itself may have been instrumental in 'triggering' catastrophic antiphospholipid syndrome.

The presence of systemic inflammatory response syndrome in patients with catastrophic antiphospholipid syndrome may in some way be related to interaction and activation of complement, as systemic inflammatory response syndrome is not a feature in other patients who present with similar clinical complications from other causes (e.g. bowel infarctions caused by vasculitis or ischaemic gangrene caused by atherosclerosis).

Laboratory features

Thrombocytopenia is usually present and was detected in more than 60% of cases from the CAPS Registry. One third had evidence of haemolysis and 14.9% had some of the features of disseminated intravascular coagulation (Asherson et al, 2005). Schistocytes may be present, but are usually scanty, unlike the abundant numbers seen in patients with thrombotic thrombocytopenic purpura (Espinosa et al, 2004). Immunoglobulin G (IgG) anticardiolipin antibodies are usually positive with IgM being less frequent. Patients with systemic lupus erythematosus demonstrate positive antinuclear antibodies, and antibodies to double-stranded DNA and extractable nuclear antigens.

Preliminary classification criteria

During the 10th International Congress on antiphospholipid antibodies in Taormina, Sicily, Italy, in 2002, proposed preliminary classification criteria for the catastrophic antiphospholipid syndrome (*Table 1*) were accepted (Asherson et al, 2003). This consensus statement is of major importance, as patients with a doubtful diagnosis or with less severe disease ('probable' catastrophic antiphospholipid syndrome) may now be classified separately and distinctly from those with a 'definite' catastrophic antiphospholipid syndrome. From the study of the initial 176 analysable patients included in the CAPS Registry (Cervera et al, 2005), it was found that the sensitivity of these criteria was 90.3% and the specificity 99.4%. Positive and negative predictive values were 99.4% and 91.1% respectively.

Treatment

Early diagnosis and aggressive therapies are essential in order to 'rescue' patients from succumbing to this

Table 1. Preliminary criteria for the classification of catastrophic antiphospholipid syndrome

1. Evidence of involvement of three or more organs, systems and/or tissues (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 hours))	
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 (For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally)	
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) (If the patient had not been previously diagnosed as having antiphospholipid syndrome, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite antiphospholipid syndrome)	
Definite catastrophic antiphospholipid syndrome	All four criteria
Probable catastrophic antiphospholipid syndrome	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 because of the early death of a patient never previously tested for antiphospholipid antibodies before the catastrophic antiphospholipid syndrome event
	Presence of criteria 1, 2 and 4
	Presence of criteria 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

From Bucciarelli et al (2006a)

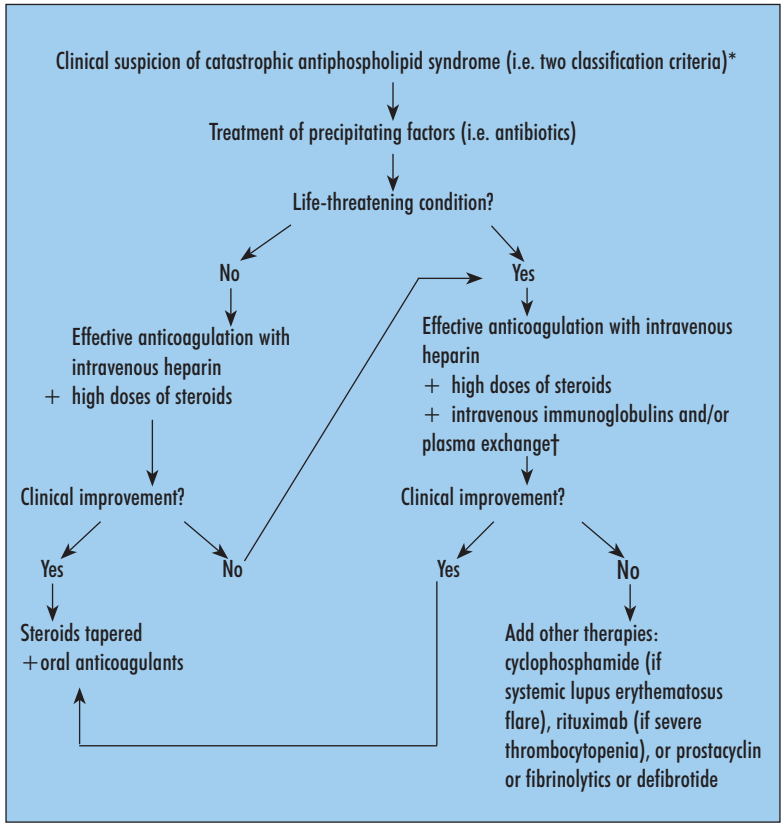

Figure 1. Treatment algorithm for catastrophic antiphospholipid syndrome. *Consider exclusion of other microangiopathic syndromes (mainly thrombotic thrombocytopenic purpura and heparin-induced thrombosis or thrombocytopenia). †With fresh frozen plasma; particularly indicated if schistocytes are present.

potentially rapidly fatal condition. It has been shown (Bucciarelli et al, 2006b) that although the mortality is still high despite all therapies, it has been considerably reduced over the past 5 years (from 53% to 33%) by the energetic therapies advised. An algorithm with treatment guidelines for the catastrophic antiphospholipid syndrome (*Figure 1*) has also been proposed (Asherson et al, 2003).

Prophylactic therapy

In any antiphospholipid syndrome patient, particular attention should be given to the following prophylactic guidelines:

1. Any infection, however trivial, should be energetically treated with the appropriate antibiotics
2. Antiphospholipid syndrome patients undergoing surgical procedures, however minor, should all receive parenteral anticoagulation during the procedure instead of remaining on coumadin
3. The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants (e.g. subcutaneous heparin)
4. Systemic lupus erythematosus 'flares', although uncommonly associated with catastrophic antiphospholipid syndrome, should also be treated with parenteral anticoagulation.

Specific therapies

First-line therapies

Intravenous heparin: This is usually administered for 7–10 days followed by oral anticoagulants to an international normalized ratio of approximately 3.

Corticosteroids: They should be administered for a minimum of 3 days but may have to be continued for longer depending on the patient's response. Steroids are not indicated for treatment of the ongoing thrombosis or to attempt to reduce the high levels of antiphospholipid antibodies, but to treat the manifestations of the presumed excessive cytokine release.

Second-line therapies

Intravenous immunoglobulins: The daily dose recommended is 0.4 g/day/kg body weight for 4–5 days. It may specifically be helpful in those patients who have severe thrombocytopenia but also possibly decreases antibody synthesis and increases the catabolism of circulating immunoglobulins in others. Intravenous immunoglobulins are usually well tolerated, but there are a few reports of thromboembolic events after intravenous immunoglobulin infusion and a few cases have described the association of acute renal failure with this therapy.

Plasma exchange: Pathogenic antiphospholipid antibodies as well as cytokines may be removed by this procedure. It is the treatment of choice in patients with schistocytes.

Third-line therapies

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

Cyclophosphamide: Theoretically, immunosuppressive therapy might be useful to prevent rebound of the antiphospholipid antibodies following plasma exchange.

Rituximab: This anti-CD20 monoclonal antibody has now been used with good results, particularly in patients with non-responsive severe thrombocytopenia.

Prostacyclin: This compound is a potent inhibitor of platelet aggregation and would thus theoretically be of benefit in the ongoing clotting process. It is also a vasodilator. The dose is 5 ng/kg/min for 7 days.

Other fibrinolytics: These compounds (which include streptokinase, urokinase, tissue plasminogen activators, ancrod and defibrotide), theoretically, might have an important role to play in the management of refractory patients with catastrophic antiphospholipid syndrome but may be associated with haemorrhagic complications. Their judicious use is probably justified in difficult cases where a life-threatening situation is imminent because of ongoing clotting.

New therapies, directed against components of complement, are in development.

Outcome and prognosis

The mortality of the condition is high despite present day therapy. In an analysis of the CAPS Registry focused on mortality (Bucciarelli et al, 2006b), the major cause of death was identified in 81 out of 114 (71.1%) patients. Cerebral involvement was the most frequent cause of death, being present in 22 patients (27.2%). This included stroke in 15 (18.5%), cerebral haemorrhage in four (4.9%), and encephalopathy in three (3.7%) patients. Cardiac involvement was identified in 16 (19.8%) patients as major cause of death, including cardiac failure in 14 (17.3%) and arrhythmias in two (2.5%) patients. Infection was described as the main cause of death in 16 (19.8%) patients, including bacterial sepsis in 10 (12.3%), fungal sepsis in three (3.7%), *Pneumocystis carinii* pneumonia in two (2.5%) patients, and suppurative peritonitis in one patient (1.2%).

However, once patients with catastrophic antiphospholipid syndrome have recovered, they usually have a stable course with continued anticoagulation. Erkan et al (2003) documented that 66% of patients with catastrophic antiphospholipid syndrome who have survived the initial event had remained symptom free for an average follow up of 62.7 months. Twenty-six per cent of the survivors, however, developed further antiphospholipid syndrome-related events but there were no instances of further catastrophic events. Only a few patients have suffered relapsing catastrophic antiphospholipid syndrome (Bucciarelli et al, 2007). In these, clear precipitating factors were evident, e.g. recurrent infections and trauma. This is a rare event, unlike patients with the not superficially dissimilar condition of thrombotic thrombocytopenic purpura where recurrent episodes are common.

Conclusions

The reasons why some people (a minority only) with a history of previous thrombotic events related to the presence of antiphospholipid antibodies are catapulted into the multiorgan failure syndrome termed catastrophic antiphospholipid syndrome remains an enigma even today, 15 years after it was originally defined. The end result, however, is overwhelming small vessel occlusive disease affecting intrabdominal organs mainly as well as deep vein thromboses (complicated by thromboembolism to the lungs in some) and cerebrovascular occlusions with resultant strokes in approximately one third of patients. Studies of the pathogenesis are severely hampered by the absence of analyses on samples collected from acutely ill patients. The potential for future therapies is exciting but will require the active participation and collaborations of many physicians around the globe, particularly those involved in intensive care units. **BJHM**

Dr RA Asherson passed away in May 2008. This article is dedicated to his memory.

Conflict of interest: none.

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KEY POINTS

- Catastrophic antiphospholipid syndrome is a potentially life-threatening condition with a high mortality, the diagnosis of which requires a high degree of clinical awareness on the part of attending physicians.
- Patients with this syndrome have clinical evidence of multiple organ involvement developed over a very short time period, histopathological evidence of multiple small vessel occlusions, and laboratory confirmation of the presence of antiphospholipid antibodies.
- The combination of high doses of intravenous heparin, steroids, intravenous immunoglobulins and/or repeated plasma exchanges are the current basic treatment of choice for all patients with this severe condition.
- The role of antiphospholipid antibodies and the overproduction of cytokines (in the form of systemic inflammatory response syndrome) in the pathogenesis of catastrophic antiphospholipid syndrome hold much promise for future therapies.
- Once patients with catastrophic antiphospholipid syndrome have recovered, patients usually have a stable course with continued anticoagulation. Only a few patients have suffered relapsing catastrophic antiphospholipid syndrome.