Multiorgan failure and antiphospholipid antibodies: the catastrophic antiphospholipid (Asherson’s) syndrome

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Abstract

A review of 250 patients with the catastrophic antiphospholipid (Asherson’s) syndrome (CAPS) taken from the website organized by the Europhospholipid Group (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) is presented in this paper. A short historical overview of the antiphospholipid syndrome (APS) is followed by a description of the “triggering” factors, associated autoimmune diseases, clinical presentation, presumed pathogenesis, prognosis, mode of death and suggested therapies.

Triggering factors are present in approximately 50% of patients and consist predominantly of infections, trauma, including minor surgical procedures such as biopsies, obstetric-related multiorgan failure and malignancy-associated CAPS. The patients present mainly with multiorgan failure resulting from predominantly small vessel occlusions affecting mainly intra-abdominal organs such as bowel, liver, pancreas, and adrenals, although large vessel occlusions do occur and comprise mainly deep vein thromboses (DVT) of the veins of the lower limbs and arterial occlusions causing strokes and peripheral gangrene. They do not however dominate the clinical picture. The condition differs considerably from the simple/classic APS in several respects, viz. the rapid development of multiorgan failure following the above-mentioned identifiable precipitating factors, the involvement of unusual organs such as bowel, reproductive organs, and bone marrow, complicating features of disseminated intravascular coagulation in 20% of cases, the acute (adult) respiratory distress syndrome (ARDS) in one third of patients, and severe thrombocytopenia; these not being encountered in the simple/classic APS. Treatment consisting of regular and repeated plasma exchanges using fresh frozen plasma, and IV immunoglobulins in addition to parenteral steroids and anticoagulation are necessary to improve the survival in a condition where the mortality is still of the order of 50%. Treatment may have to be continued for several weeks. Parenteral antibiotics may be indicated where an underlying infection is suspected. Antifungal therapy may also be indicated with prolonged treatment and the use of the monoclonal anti-CD20 molecule, Rituximab, has proven useful in those patients where thrombocytopenia poses a major risk of hemorrhage.

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Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; β2GPI, β2-glycoprotein I; CAPS, catastrophic antiphospholipid syndrome; DVT, deep vein thrombosis; INR, international normalized ratio; PAPS, primary antiphospholipid syndrome; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenia purpura

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Introduction

This is a new disease and represents a major challenge to attending physicians in intensive care units where most of these patients are seen.

The antiphospholipid syndrome (APS) consisting of recurrent venous/arterial occlusions, recurrent fetal losses accompanied by a moderate thrombocytopenia and positive tests of the lupus anticoagulant, antibodies to cardiolipin (aCL) or β2-glycoprotein I (β2GPI), mainly was first defined by Harris et al. (1987) working at the Royal Postgraduate Medical School, the syndrome now referred to as the Hughes’ syndrome (Khamashta and Asherson, 1996) and latterly the systemic APS (Shoenfeld, 2003) replaces the earlier descriptions of these associations. Several years later, a “primary” syndrome, distinct from other connective tissue diseases was first recognized in 1985 (Asherson, unpublished data). It was first defined however some 3 years later in 1988 (Asherson, 1988) and three series of patients were then published in the following year (Asherson et al., 1989; Alarcon-Segovia and Sanchez-Guerrero, 1989; Mackworth-Young et al., 1989). The “primary” syndrome has now overtaken those patients with systemic lupus erythematosus (SLE) in frequency (Cervera et al., 2002).

Multiorgan failure is distinctly uncommon during the course of most connective tissue diseases.

In 1987, a single unusual case of a young female who had developed multiorgan failure associated with gangrene of all her extremities, elevated antiphospholipid antibodies (aPL) and features of disseminated intravascular coagulation was published (Bird et al., 1987), followed by several similar cases (Ingram et al., 1987; Greisman et al., 1991). The condition was defined as the catastrophic antiphospholipid syndrome (CAPS) in 1992 (Asherson, 1992). Since then, 250 cases have been analyzed and almost 300 have now been encountered and documented (Asherson et al., 1998; Asherson, 1992). It seems clear that many more cases remain unidentified and unpublished. The eponym “Asherson’s syndrome” was attached in 2003 (Piette et al., 2003).

Pathogenesis

It is still unclear as to why some patients will develop recurrent thromboses, mainly affecting large vessels, while others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels. Indeed, the preceding precipitating or “trigger” factors may be identical in either simple or classic APS patients and in those with CAPS. Clearly, other factors, as yet unidentified, must play important roles.

General factors implicated in the causation of thromboses including prolonged bed rest, sedentary situations (e.g. long-haul flying), dyslipidaemias, diabetes mellitus, nephrotic syndrome and obesity do not seem to be implicated in its pathogenesis and, interestingly enough, patients suffering from the hereditary coagulopathies (e.g. Protein C/S, antithrombin III deficiencies or mutations such as Factor V Leiden or Prothrombin gene mutations) do not appear to be prone to this complication. It seems to be a primary “autoimmune” situation associated with high levels of aPL, and, in many cases, is also accompanied by other severe autoimmune disturbances which may complicate the
clinical picture and a diagnosis of severe thrombocytopenia or microangiopathic hemolytic anemia may be entertained. Unlike the simple or classic APS where large vessel occlusions dominate the clinical picture, small vessel occlusive disease accounts for the major clinical manifestations of the condition in CAPS patients.

From Table 1 it can be seen that 60% of patients appear to have developed CAPS following an identifiable “trigger” factor, with infections dominating the list. A list of these infections encountered is shown in Table 2.

Postulated mechanisms by which infections may cause thrombosis have been a subject of much interest over the past 2 years and several reviews have been devoted to this topic. Asherson and Shoenfeld published an editorial in 2000 devoted to molecular mimicry in the pathogenesis of CAPS and the work undertaken in the laboratories of Yehuda Shoenfeld in Israel by Miri Blank particularly has made a significant contribution to the understanding of the many and diverse mechanisms which could be linking the structure and function of β2GPI itself, the main antigen against which the “antiphospholipid” antibodies are directed, to the role of infection and thrombosis. Credit must also be given to the work of the late Azzudin Gharavi and his coworkers (Gharavi et al., 2000) who identified seven proteins with sequence homology to the GDKU and GDKU2 proteins (which are the major phospholipid binding sites on β2GPI) and which formed part of many human viruses to which humans are exposed. Moreover, immunization of groups of mice with these peptides together with Freund’s adjuvant produced high levels of aPL and anti-β2GPI antibodies.

**Post-immunization CAPS**

A recent case from Israel has reported the development of CAPS following immunization of a patient with a vaccine against Japanese B encephalomyelitis (Chapman, personal communication), a case following inoculation against yellow fever was seen in Peru (Solimano, personal communication) and recently a patient who developed CAPS following vaccination against influenza was encountered in The Netherlands (Van Paassen, personal communication), again incriminating certain peptides as “triggers” for CAPS.

**Trauma/surgical procedures**

**Major:** hysterectomy, cholecystectomy, other abdominal surgical procedures, pelvic surgery, caesarian section, A/V shunt surgery.

**Minor:** lung/renal biopsies, dental extraction, dilatation and curettage, needle stick injury (angiography), fractures, minor procedures (ERCP).

The mechanisms by which trauma/surgical procedures may initiate CAPS are unknown, but might involve excessive cytokine production affecting endothelial cell function and the expression and up-regulation of procoagulant molecules as well as production of tissue factor.

**Malignancies and lymphoma**

In 16 patients (6.8%), malignancies appeared to be associated with the development of CAPS.

**Lupus “flares”**

The low prevalence of CAPS associated with lupus “flares” (seven patients only) is surprising but makes a case for alternative mechanisms involved in the pathogenesis of CAPS other than just the overproduction of antibodies. A possible case can be made for the use of anticoagulant therapy in patients with lupus “flares” who have high levels of aPL and who have not yet experienced any thrombotic episodes.

**Warfarin withdrawal/low international normalized ratio (INR)**

Warfarin withdrawal prior to major surgical procedures or minor procedures (e.g. biopsies), or because of hemorrhagic complications usually attributable to anticoagulation therapy, may be followed within a short time either by recurrent thrombosis or by CAPS, particularly

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<tr>
<th>Table 1. Precipitating factors</th>
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<td><strong>Unknown</strong></td>
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<td><strong>Infections</strong></td>
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<td><strong>Trauma</strong></td>
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<td><strong>Anticoagulation problems</strong></td>
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<td><strong>Neoplasia</strong></td>
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<td><strong>Obstetric</strong></td>
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<td><strong>Lupus “flares”</strong></td>
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<td><strong>Others</strong></td>
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<th>Table 2. Infections and CAPS (55 = 22%)</th>
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<td><strong>Respiratory</strong></td>
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<td><strong>Cutaneous</strong></td>
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<td><strong>Urinary</strong></td>
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<td><strong>Abdominal</strong></td>
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<td><strong>Sepsis</strong></td>
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<td><strong>Others</strong></td>
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if other “trigger” factors are also present (e.g. underlying carcinoma, infection).

This is the so-called “double” or “treble” hit hypothesis, which applies to any patient with multiorgan failure.

Great care should be taken by attending physicians/surgeons to ensure that any APS patient is adequately covered during any procedure no matter how trivial (e.g. biopsy, dental extraction) by adequate parenteral anticoagulation.

Kitchens (1998) advanced the hypothesis that clots themselves may be responsible for the on-going clotting which he referred to as a “thrombotic storm” seen in CAPS patients.

These clots continue to generate thrombin, fibrinolysis is depressed by increase in plasminogen activator inhibitors (fibrinolytic “shutdown”) and there is simultaneous elevation of coagulation activation products comprising prothrombin activation products F1 and F2, thrombin–antithrombin complexes and protein-C activation peptide. There is consumption of the natural anticoagulant proteins such as protein C, protein S and antithrombin III. That clot removal may indeed be associated with remission of CAPS evidenced by the report of two patients in whom amputation of gangrenous limbs was associated with complete recovery (Amital et al., 2001).

The various “triggers” for CAPS are summarized in Fig. 1.

**Clinical features**

The demographic characteristics of the patients were 175 females (70%) and 75 males (30%). The mean age was 38 years (range 7–76 years).

A diagnosis of primary antiphospholipid syndrome (PAPS) was made in the majority (49.6%), with SLE in 40%, lupus-like disease in 5%, systemic sclerosis in 1.6%, rheumatoid arthritis in 1.2%, ulcerative colitis in 1.2%, Crohn’s disease in 0.4%, two patients with vasculitis (polychondritis, Behcet’s) (0.4% each), and single patients suffering from dermatomyositis, and discoid lupus.

The majority of CAPS patients developed this illness as a complication of APS associated with SLE or were patients previously diagnosed with a PAPS and were already on anticoagulation therapy for previous thrombotic episodes in addition to low-dose steroids (in the case of SLE patients). In some patients, the disease developed “ab initio” in someone who was not suspected as having APS, but who might have had a deep vein thrombosis (DVT), stroke or myocardial infarction in the past. In 60%, a “triggering” factor was elicitable (see Table 1). Small vessel occlusive disease dominates the clinical picture but large vessel occlusions do occur at the same frequency as they do in the simple/classic APS, viz. DVT in 23% only. Unusual organs are involved, particularly the reproductive and gastrointestinal tract, in addition to bone marrow necrosis, etc. The clinical picture depends on two major pathogenetic factors (a) effects of multiple small vessel occlusions on organs particularly, and (b) the systemic inflammatory response syndrome, the major manifestation of which is the acute (adult) respiratory distress syndrome (ARDS).

Renal involvement predominates (73%), followed by pulmonary (68%), cerebral (63%), skin (58%), cardiac (51%), hepatic (34%), other gastrointestinal (e.g. bowel infarctions) (24%), splenic (18%), and adrenal (14%). Involvement of the pancreas, retina, and peripheral nerve involvement with mononeuritis multiplex have also been reported.

**Laboratory findings**

IgG anticardiolipin antibodies were elevated in 82% of patients, IgM elevations were seen in 43% and positive lupus anticoagulants were present in 76%.

No patients were aPL negative.

**Causes of death**

In 71% (81/113) of patients, the clinical cause of death was determinable. Cerebral (19.5%), mainly strokes in 13.3%, cardiac (14.1%), infections (13.3%), pulmonary (7.1%), abdominal (4.5%), and multigorgan failure (12.4%) were the major causes of death. Necropsy findings were available in 52.2% (59/113) of patients. These findings consisted predominantly of microthrombosis in 89% of cases examined (53/59): renal (89%), cerebral (62%), pulmonary (45.7%), cardiac (45.7%), intestinal (30.5%), splenic (28.8%), hepatic (20.3%), cutaneous (20.3%), others (35.5%). Infarcts were found in 54.2% with cerebral infarcts predominating (54.2%), myocardial (20.3%), splenic (10.2%), renal (8.4%), hepatic (3.3%) and others (11.2%). Other findings of importance and interest at
autopsy were the presence of Libman–Sacks endocardi-
tis in 27.1%, pulmonary embolism in 16.9%, infections
in 10.2%, ARDS (6.8%), pulmonary alveolar hemor-
rhage (5%), carcinoma (3.3%) and Budd Chiari (1.6%).
In many patients, combinations of microthrombotic
lesions and infarcts were found. Infections found at
necropsy consisted of bacterial infections in 8.8%,
candidiasis in 2.6%, cerebral abscess in 0.9% and
Pneumocystis carinii in 0.9%.

It was not possible to determine if in fact these
infections had been present initially as part of the
“triggering” process or had developed during the course
of the illness and were due to the treatments with large
doses of steroids and in some cases, immunosuppressant
therapies, e.g. with cyclophosphamide. It is of major
clinical importance in the therapy of these patients for
clinicians to be alerted not only for the presence of
bacterial infections but also for development of compli-
cating fungal infection, e.g. with candidiasis necessitat-
ing the introduction of the appropriate antifungal agent
to the therapeutic armamentarium.

Treatment

Management of CAPS is challenging for all attending
physicians. Early diagnosis and aggressive therapies are
essential in order to “rescue” such patients from
succumbing to this potentially fatal condition. Unfortu-
nately, at this time, despite all therapies advised, the
mortality is extremely high (>50%). Treatment guide-
lines were recently published (Asherson et al., 2003).

The treatment may be divided into three major
categories: (a) prophylactic therapy, (b) primary specific
therapies, and (c) secondary non-specific therapies.

Prophylactic therapy

As it is unclear why some patients with an APS will
develop recurrent episodes, and others (a minority) will
be catapulted into multiorgan failure. In any APS
patient, therefore, particular attention should be given
to the following circumstances:
1. Any infection, however trivial, should be energeti-
cally treated with the appropriate antibiotics.
2. APS patients undergoing surgical procedures, how-
ever minor, should all receive parenteral anticoagula-
tion 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. SLE “flares”, although uncommonly associated
with CAPS, should also be treated with parenteral
anticoagulation.

Specific therapies

Aggressive treatment of any possible precipitating
factors, e.g. parenteral antibiotics should be adminis-
tered if underlying infection is suspected. If necrotic
tissue is present, debridement should be performed
without delay. Medications may be listed in three
categories (see also Table 3):

First-line therapies

*Intravenous heparin:* It is usually administered for
7–10 days followed by oral anticoagulants to an INR 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 the treatment of the ongoing throm-
bosis or to attempt to reduce the high levels of aPL, but
to treat the manifestations of the presumed excessive
cytokine release because of the widespread tissue
necrosis. ARDS is a prime example of this. It is
recommended that 1000 mg of methylprednisolone be
administered daily.

Second-line therapies

*Intravenous immunoglobulin (IVIG):* The daily dose
recommended is 0.4 gm/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
immunoglobulin in others. There is no evidence, judging
from the analysis of treated patients with CAPS, that IVIG
on its own improves survival but its combination with
plasma exchange might be more effective.

*Plasma exchange (PE):* Pathogenic IgG aCL and
β2GPI as well as cytokines such as IL-1, IL-6, tumor
necrosis factor α and complement may be removed by this
procedure. It has been reported as improving the outcome
in patients with classic APS and, of course, is the treatment
of choice in patients with thrombotic thrombocytopenia
purpura (TTP) where the emphasis is on small vessel
occlusive disease. It has been recommended that fresh
frozen plasma be used in this procedure.

*Rituximab:* The recent use of this biological agent, an
anti-CD20 molecule (in use for several years in the
successful therapy of patients with non-Hodgkin’s
lymphoma) for severe thrombocytopenia has prompted

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<th>Table 3. Summary of treatments in 250 patients</th>
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<td>Treatment</td>
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<td>Anticoagulation</td>
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<td>Cyclophosphamide</td>
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<td>Plasma exchange</td>
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<td>IV immunoglobulin</td>
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its successful use in several patients with severe thrombocytopathy caused by CAPS (Ehresmann et al., 2004).

Third-line therapies

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

Cyclophosphamide: This powerful immunosuppressive agent has not been shown to be effective in an analysis of 130 patients with CAPS (Asherson et al., 1998, 2001). Theoretically, it might be useful to prevent rebound of the aPL following plasma exchange. However, it is still being used frequently by ICU physicians and its use may in fact be contributing to the high rate of complicating and life-threatening infections seen in these patients.

Prostacycline: 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. Only one case has been reported where this treatment has been used and the patient relapsed once it was discontinued (Kovacs et al., 1991; Tedeschi et al., 1998).

Ancrod: This compound has also only been used in a single patient. It is a powerful fibrinolyte.

Other fibrinolytics (e.g. streptokinase, urokinase, tissue plasminogen activators): have been used in isolated cases only and also correct plasminogen activator deficiencies. There is a danger of hemorrhagic complications with this group of compounds.

Defibrotide: This is an alkali metal salt of single-stranded DNA and has antithrombotic properties. Because of its polypharmacological properties, indications are that it may have an important role to play in the management of refractory patients with CAPS and has been successfully used in one patient. It acts as an endothelial “repair” fluid as well as down-regulating cytokines. It is currently being used by the Dana Farber Cancer Institute in Boston to treat hepatic veno-occlusive disease associated with transplantation and also at the University College Hospital in London for resistant cases of TTP. The manufacturers (Crinos Pharmaceuticals, Milan) have been totally resistant to funding or sponsoring any meaningful clinical trials to date (Burcoglu-O’Ral et al., 2002).

These compounds, theoretically, might have an important role to play in the management of refractory patients with CAPS. Their judicious use in difficult cases where a life-threatening situation is imminent because of ongoing clotting is probably justified.

Secondary non-specific therapies

Most patients end up in intensive care units because multiorgan failure has supervened. If renal failure is present, hemodialysis may be required. Mechanical ventilation for respiratory failure is often indicated particularly if ARDS is present. Inotropic drugs for circulatory failure need to be administered. Severe hypertension due to renal vascular occlusive disease may necessitate aggressive antihypertensive therapy. If hypotension is present due either to myocardial depression (SIRS), microangiopathy of small cardiac vessels or hemorrhagic infarction of the adrenal glands, parenteral steroids are necessary. This is another reason for inotropic drugs.

Outcome and prognosis

The mortality of the condition is high despite present-day therapy. Mortality is of the order of 50%. In the present series of patients, there was a 54% recovery (135 patients) and 45% demise (115 patients). Once they have recovered, patients usually have a stable course with continued anticoagulation. It has recently been shown (Erkan et al., 2003) 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. Twenty-six percent of the survivors, however, developed further APS-related events but there were no instances of further catastrophic events (Erkan et al., 2002). Only five patients have suffered “recurrent” CAPS. In three of these, clear precipitating factors were evident, e.g. recurrent infections and trauma. One patient had had three recurrences. One of these recurrences followed cataract surgery, a relatively minor procedure. Recurrent CAPS is a rare event, unlike patients with the not superficially dissimilar condition of TTP.

The treatment of the APS itself, particularly those patients who require surgical treatments is clearly of major importance in the prevention of this rapidly and often fatal complication. (Erkan et al., 2002).

There is no doubt that most documented patients with CAPS were not given the possible benefit of plasma exchange and IVIG early on (75% of cases) and far too many patients succumbed from septic shock, either unrecognized or inadequately treated.

It is hoped that attending physicians will take note.

References


