

EXTENDED REPORT

Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome

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Objective: To describe the characteristics of patients with catastrophic antiphospholipid syndrome (APS) included in the International Registry of patients with this condition (CAPS registry) and to analyse the value of the recently proposed preliminary criteria for the classification of catastrophic APS.

Methods: A review of the first 220 patients included in the website based CAPS registry was undertaken and the preliminary criteria for their classification were tested; 175 unselected patients with systemic lupus erythematosus or APS, or both, acted as controls.

Results: The mean age of the patients was 38 (14 years (range 7 to 74)), with a female preponderance (F/M, 153/67). The main clinical manifestations included renal involvement in 154 (70%), pulmonary in 146 (66%), cerebral in 133 (60%), cardiac in 115 (52%), and cutaneous in 104 (47%); 114 patients (52%) recovered after the catastrophic APS event (mortality 48%). Patients who received the combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulins had the best survival rate (63%, $p=0.09$). Sufficient data could be analysed for application of the classification criteria in 176 patients. According to the preliminary criteria, 89 patients (51%) could be classified as having "definite" and 70 (40%) as having "probable" catastrophic APS, thus given a sensitivity of 90.3% with a specificity of 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively.

Conclusions: The preliminary criteria for the classification of catastrophic APS and the CAPS registry are useful tools for epidemiological studies.

In 1992, the "catastrophic" antiphospholipid syndrome (APS) was first defined as a potential life threatening variant of the APS which is characterised by multiple small vessel thrombosis that can lead to multiorgan failure.¹ Fortunately, this is an unusual form of presentation that represents fewer than 1% of the APS cases.² The recurrence rate is low with a stable clinical course if these patients are treated with adequate anticoagulation.³ Owing to the rarity of its presentation, an international registry of patients (the CAPS registry) was created in 2000 supported by the European Forum on Antiphospholipid Antibodies (aPL).

The heterogeneity of the different clinical forms of presentation led to the need to develop consensus criteria for the classification of this condition. In 2002, a pre-congress workshop at the Tenth International Congress on aPL held in Taormina, Italy, allowed the establishment of the preliminary criteria for the classification of catastrophic APS that were published recently.⁴ The objectives of the present study were to describe the characteristics of the patients with catastrophic APS included in the CAPS registry and to analyse the value of the preliminary criteria for their classification using the data from this registry.

METHODS

We reviewed the 220 patients who were included in the website based international registry of patients with catastrophic APS (CAPS registry) at 1 October 2003, and tested the recently proposed preliminary criteria for the classification of catastrophic APS⁴ in those patients whose clinical data were sufficient for application of the criteria. The CAPS registry compiles all the published reports as well as newly

diagnosed cases of catastrophic APS from all over the world. The diagnoses and data have been submitted by a wide variety of interested clinicians, but efforts were made in most cases to contact these clinicians and verify the accuracy of the data sent in. The basis for submitting patient data was clinical judgement, as no classification criteria were published until 2003. The different variables of the database are detailed at <http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM>.

Additionally, we analysed 175 unselected patients from our clinics as controls: 100 with systemic lupus erythematosus (SLE), classified according to the American College of Rheumatology (ACR) revised criteria⁵—all with positive aPL and 65 with associated APS—and 75 with primary APS, fulfilling the preliminary criteria for the classification of definite APS.⁶

Data analysis

Conventional Fisher's exact test was used for analysing qualitative differences. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was carried out for multivariate analysis in order to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered to be significant study results. The sensitivity,

Abbreviations: aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; APL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; HELLP, haemolysis, elevated liver enzymes, and low platelet count syndrome; SLE, systemic lupus erythematosus

Table 1 Previous antiphospholipid syndrome manifestations of the patients from the CAPS registry

Manifestation	n (%)
Deep vein thrombosis	44 (20)
Fetal loss	31 (20)*
Thrombocytopenia	29 (13)
Cerebrovascular accident	20 (9)
Skin ulcers	19 (9)
Pulmonary embolism	18 (8)
Livedo reticularis	17 (8)
Peripheral artery thrombosis	10 (5)
Myocardial infarction	9 (4)
Haemolytic anaemia	7 (3)
Seizures	7 (3)
Digital ischaemia	7 (3)
Valve lesions	5 (2)
No previous APS manifestations	104 (47)

*Percentage relates to the female patient population. APS, antiphospholipid syndrome.

specificity, and predictive values of the preliminary criteria for the classification of catastrophic APS were determined according to Galen and Gambino.⁷

RESULTS

General characteristics of patients with catastrophic APS

The mean (SD) age was 38 (14) years (range 7 to 74) with a female preponderance (F/M, 153/67); 106 (48%) suffered from primary APS, 88 (40%) from SLE, 11 (5%) from lupus-like syndrome, four (2%) from rheumatoid arthritis, four (2%) from systemic sclerosis, and the remaining seven (3%) from other autoimmune disorders (relapsing polychondritis, ulcerative colitis, Crohn's disease, dermatomyositis, and Behçet's disease).

Clinical presentation and precipitating factors

Fifty three per cent of the patients had previous APS manifestations (table 1). The main previous manifestations were deep vein thrombosis in 44 (20%), fetal loss (abortions or fetal deaths) in 31 female patients (20%), thrombocytopenia in 29 (13%), cerebrovascular accidents in 20 (9%), skin ulcers in 19 (9%), pulmonary embolism in 18 (8%), and livedo reticularis in 17 (8%).

In 58% of the patients, an identifiable precipitating factor was detected, including infections (20%), surgical procedures (biopsies, dental extractions, invasive procedures, transplantation) (14%), neoplasms (9%), anticoagulation withdrawal or low international normalised ratio (INR) (7%), obstetric complications (5%), lupus flares (4%), and the use of oral contraceptives (3%). Twelve patients had two identifiable precipitating factors and in one case three triggering factors were found (anticoagulant withdrawal and surgical resection for a neoplastic process).

The majority of patients presented with multiple organ involvement at the time of catastrophic APS. The combination of pulmonary, cardiac, and renal involvement was most commonly seen. Table 2 shows the thrombotic manifestations described in these patients. However, as some types of organ involvement were detected at necropsy or during surgical procedures and other types can only be scored as present if the clinician actively looks for them, the percentages given may be an underestimate.

Laboratory findings

The following antibodies were detected: IgG anticardiolipin antibodies (aCL) in 176 of 210 patients (84%) (in 68 cases in high titres, defined according to the APS classification

Table 2 Clinical manifestations at the time of presentation with catastrophic antiphospholipid syndrome in patients from the CAPS registry

Feature	n (%)
<i>Peripheral thrombosis</i>	74 (34)
Deep vein thrombosis	50 (23)
Femoral artery	8 (4)
Radial artery	4 (2)
Other arteries	19 (9)
<i>Cerebral</i>	133 (60)
Infarcts	97 (44)
Encephalopathy	17 (8)
Seizures	13 (6)
Microthrombosis	10 (5)
Venous cerebral thrombosis	5 (2)
Coma	4 (2)
Transient ischaemic attack	2 (1)
<i>Cardiac</i>	115 (52)
Valve lesion	56 (26)
Myocardial infarction	50 (23)
Heart failure	22 (10)
Microthrombosis	10 (5)
Mural thrombi	9 (4)
<i>Pulmonary</i>	146 (66)
Acute RDS	74 (34)
Pulmonary embolism	54 (24)
Pulmonary haemorrhage	16 (7)
Microthrombosis	10 (5)
Pulmonary oedema	7 (3)
Infarction	6 (3)
<i>Abdominal</i>	189 (86)
Renal	154 (70)
Hepatic	62 (28)
Splenic	41 (19)
Adrenal	33 (15)
Intestinal	27 (12)
Mesenteric	23 (11)
Pancreas	21 (10)
Portal vein thrombosis	7 (3)
Inferior cava thrombosis	7 (3)
Gallbladder thrombosis	6 (3)
<i>Skin</i>	104 (47)
Livedo reticularis	62 (28)
Skin ulcers	30 (14)
Digital ischaemia	21 (10)
Purpura	12 (6)
Necrosis	7 (3)
Microthrombosis	7 (3)
Splinter haemorrhages	5 (2)
<i>Other manifestations</i>	56 (25)
Retinal artery thrombosis	11 (5)
Bone marrow necrosis	7 (3)
Uterus	7 (3)
Neuropathy	7 (3)
Testicles	4 (2)
Retinal vein thrombosis	4 (2)
Thyroid thrombosis	3 (1)
Avascular necrosis	4 (2)
Others	8 (4)

RDS, respiratory distress syndrome.

criteria)⁶; IgM aCL in 80 of 197 (41%) (in 20 cases in high titres and in 73 cases in association with IgG aCL); lupus anticoagulant in 154 of 203 (76%); antinuclear antibodies in 113 of 183 (62%); anti-double-stranded DNA antibodies in 60 of 168 (36%); and antibodies to extractable nuclear antigens in 29 of 128 (23%). Thrombocytopenia was found in 129 of 204 patients (63%), haemolytic anaemia in 63 of 196 (32%), disseminated intravascular coagulation (DIC) in 39 of 187 (21%), and schistocytes in peripheral smear in 21 of 174 (12%).

Table 3 Treatment in the patients from the CAPS registry

Treatment	n (%)
Anticoagulation	173 (79)
Steroids	158 (71)
Cyclophosphamide	66 (30)
Plasma exchange	60 (27)
IVI	42 (19)
Dialysis	30 (14)
Fibrinolysis	8 (4)
Use of defibrotide	4 (2)
Splenectomy	3 (1)
Prostacyclin	3 (1)
Leg amputation	2 (1)
Other treatments	9 (4)

IVI, intravenous immunoglobulin.

Treatment and outcome

The different treatments used in patients with catastrophic APS are summarised in table 3. One hundred and fourteen patients (52%) recovered after the catastrophic APS event, while the remaining 106 (48%) died. Some clinical manifestations were related to a worst prognosis (death), such as renal involvement (p = 0.004; odds ratio (OR) = 2.4 (95% confidence interval (CI), 1.21 to 4.76)), splenic involvement (p = 0.004; OR = 2.63 (1.2 to 5.84)), pulmonary involvement (p = 0.006; OR = 1.97 (1.06 to 3.69)), SLE diagnosis (p = 0.009; OR = 1.9 (1.01 to 3.56)), and adrenal involvement (p = 0.05; OR = 2.64 (1.1 to 6.44)). Those patients who received the combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulins had the best survival rate (63%, p = 0.09).

Analysis of the preliminary criteria for classification of the catastrophic APS

Preliminary criteria for the classification of catastrophic APS are shown in table 4. From the 220 patients included in the CAPS registry, we were able to analyse enough data for criteria application in 176 patients. In the remaining cases, data on the time of development of manifestations could not be obtained accurately. One hundred and seventy one patients (97%) fulfilled the first criterion, 175 (99%) the second, 133 (76%) the third, and 159 (90%) the fourth. With respect to the number of criteria fulfilled, 89 patients (51%)

fulfilled all four criteria, 74 (42%) fulfilled three, 11 (6%) fulfilled two, and two (1%) fulfilled only one criterion. According to definition of the preliminary classification criteria, 89 (51%) of the previously compiled catastrophic APS patients from the CAPS registry could be classified as having “definite” catastrophic APS (they fulfilled all four criteria) and 70 (40%) as having “probable” catastrophic APS.

The characteristics of patients classified as having “probable” catastrophic APS were as follows: two patients (3%) fulfilled all four criteria, except that only two organs, systems, or tissues were involved; nine (13%) fulfilled all four criteria, except for the absence of laboratory confirmation with at least six weeks owing to the early death of a patient never tested for aPL before the catastrophic APS; and 59 (84%) fulfilled criteria 1, 2, and 4.

Only one patient from the control group fulfilled criteria for “probable” catastrophic APS. According to these findings, the sensitivity of the preliminary criteria for the classification of catastrophic APS is 90.3%, the specificity 99.4%, the positive predictive value 99.4%, and the negative predictive value 91.1%.

DISCUSSION

Over the last 10 years, various different case reports and small series have described patients with catastrophic APS. Two major paper summarised the different characteristics of a total of 130 patients and provided information on the pathogenesis, clinical features, treatment, and outcome.^{8,9} The website based CAPS registry has also compiled a large amount of information but the present study indicates that additional efforts should be made in the future because the registry often receives insufficient data or information on patients who do not have “definite” or “probable” catastrophic APS from physicians all over the world.

Recognition of catastrophic APS has increased over the past years, and it is now clear that it is not only associated with SLE or primary APS, but also with other autoimmune conditions such as rheumatoid arthritis, systemic sclerosis, intestinal inflammatory diseases, and Behçet’s disease, among others. Despite earlier recognition and better knowledge of the pathophysiology, the mortality rate is still unacceptably high (48%), specially in SLE patients and in patients with cardiac, pulmonary, renal, splenic, and adrenal involvement.

Table 4 Preliminary criteria for the classification of catastrophic antiphospholipid syndrome⁴

- (1) Evidence of involvement of three or more organs, systems, and/or tissues*
 - (2) Development of manifestations simultaneously or in less than one week
 - (3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
 - (4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)‡
- Definite catastrophic APS:** all four criteria
Probable catastrophic APS—any of the following:
- (a) All four criteria, except for only two organs, systems, and/or tissues involved
 - (b) All four criteria, except for the absence of laboratory confirmation (within at least 6 weeks) owing to the early death of a patient never tested for aPL before the catastrophic APS
 - (c) Criteria (1), (2), and (4)
 - (d) Criteria (1), (3), and (4) and the development of a third event between one week and one month after presentation, despite anticoagulation

*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 hours).

†For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

‡If the patient had not previously been diagnosed as having an APS, the laboratory confirmation requires that the presence of antiphospholipid antibodies must be detected on two or more occasions at least six weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Recently, Erkan *et al*³ evaluated the clinical outcome of 58 survivors of a catastrophic APS event. Thirty eight patients (66%) did not develop further APS related events, 15 (26%) developed a new thrombotic episode (in 13 cases during anticoagulation therapy), but none of them developed further catastrophic APS episodes.

The clinical approach to the treatment of catastrophic APS will depend on the site and extension of the vascular occlusions and the degree of systemic inflammatory response. The cornerstone of the treatment includes readiness to suspect the condition and the treatment of any precipitating factor, especially adequate antibiotic therapy for related infections based on the clinical setting, appropriate anticoagulant management, and the use of immunosuppressive drugs (especially steroids), plus third line therapy (plasma exchange or intravenous immunoglobulins) for the treatment of the thrombotic and cytokine “storm”.⁴ Finally, a series of life support measures are needed, such as mechanical ventilation, inotropic drugs, and continuous haemodialysis.¹⁰

The differential diagnosis in some circumstances is very difficult, specially with other microangiopathic syndromes that are capable of producing multiorgan thrombotic events. These conditions include thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, heparin induced thrombocytopenia, and the HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome.¹¹ In these critically ill patients there is a high chance that their blood samples may show false positive results in lupus anticoagulant assays (for example, coagulation factor deficiencies or heparin use), or that treatment decisions have to be made before the results of laboratory tests are available. However, the presence of persistent positive levels of aPL in a patient with these conditions will lead to the diagnosis of concomitant catastrophic APS. In fact, several patients in the CAPS registry fulfilled criteria for thrombocytopenic purpura or HELLP as well. Thus we only analysed patients with aPL as controls—including both SLE and primary APS patients—and for this reason we did not include controls with multiorgan thrombotic events (for example, thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, or HELLP) but without aPL.

Though microthrombosis is one of the typical markers of a catastrophic APS event, it may be difficult to confirm, and many patients could only be labelled as “probable” catastrophic APS based on large vessel multiorgan thrombotic involvement over a short period of time in the presence of aPL. Because of these difficulties in the confirmation of a definite catastrophic APS event, we included both “definite” and “probable” catastrophic APS in the evaluation of the classification criteria. According to our results, the International Consensus Statement on Preliminary Classification Criteria for the catastrophic APS is a useful tool for epidemiological studies and it is hoped that these criteria will be tested in future prospective multicentre studies, and that modifications or additions to the criteria will be made at subsequent workshops. It should be emphasised that these criteria are mostly empirical and have been accepted for classification purposes only. They are not intended to be used as strict diagnostic criteria in a given patient.

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APPENDIX

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