Catastrophic antiphospholipid syndrome: a narrative review

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Abstract

The catastrophic antiphospholipid syndrome (CAPS) is a life-threatening disorder characterized by the rapid development of multiple organs/systems thrombosis, in patients with persistently detectable antiphospholipid antibodies. The vascular occlusions predominantly affect small vessels, leading to a disseminated thrombotic microangiopathic syndrome. Most CAPS episodes are related to the presence of a precipitating factor, such as infections and malignant diseases, usually ending up in multiple organ failure. Clinical manifestations may vary according to the extent of the thrombosis, predominantly affecting kidneys, lungs, brain, heart, and skin. Treatment is based on the administration of anticoagulants, corticosteroids, plasma exchange and/or intravenous immunoglobulins. Cyclophosphamide is recommended in CAPS associated with systemic lupus erythematosus. Additionally, rituximab and eculizumab have been used in refractory cases. Overall mortality is still 36.9%, despite recent progress in the therapeutic approach.

Introduction

Catastrophic antiphospholipid syndrome (CAPS) is a rare and life-threatening disorder, characterized by the rapid development of multiple organs/systems thrombosis, in the presence of persistently detectable antiphospholipid antibodies (aPLs).[1,2] The thrombotic storm mainly involves small vessels. Asherson *et al.* first proposed the term *catastrophic* in 1992, referring to its high mortality rate (50%).[3,4] To date, more than 500 cases of CAPS have been reported, although its prevalence is probably underestimated because of multiple factors concurring to impede timely diagnosis.[5-7]

The periodical analysis of the CAPS Registry, that was set up in 2000 by the European Forum on Antiphospholipid Antibodies, has allowed to define the clinical and laboratory profile of CAPS patients, and to develop diagnostic and therapeutic guidelines.[5,8-10]

Hereby we summarize current knowledge on CAPS, trying to answer some questions regarding its therapeutic approach.

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Pathogenesis

CAPS pathophysiological mechanisms are still poorly understood, and the lack of studies on its pathogenesis mainly depends on its low prevalence.

It has been demonstrated that genetic and environmental factors play a role in the development of aPLs, and it is believed that exposure to environmental agents with β2-glycoprotein-I (β2GPI)-like peptides leads to the production of these antibodies in susceptible individuals.[11] Therefore, aPLs are a heterogeneous family of autoantibodies able to induce a pro-thrombotic and pro-inflammatory phenotype through different mechanisms of actions, mostly *via* β2GPI and complement activation.[11]

The presence of precipitating factors that share with aPLs an increased tendency to thrombosis has been strongly related to the development of the catastrophic scenario.[5,12,13] Therefore, in more than 50% of patients who developed CAPS a *trigger* event has been identified, including, in order of frequency, infections (49% of cases), surgical procedures (17%), malignancies (16%), anticoagulation withdrawal or sub-optimal international normalized ratio (INR) (8%), pregnancy complications (8%), drugs (5%), and flare activity of underlying autoimmune disorders (3%).[5,12,13] According to these data, it seems likely that a *second hit,* capable of leading to endothelial cells disruption/activation, is needed for the development of the catastrophic scenario in genetically susceptible individuals.

Laboratory features

Thrombocytopenia is commonly associated with CAPS, as it has been found in 67% of cases from the *CAPS Registry*.[5,10] Low platelet count may occur through a number of mechanisms, mostly because of direct binding of the aPLs to platelet-associated phospholipids, as well as of heparin-induced thrombocytopenia.[5] Microangiopathic hemolytic anemia (MAHA), defined as low platelet count, hemolysis features and schistocytes, can be associated with

CAPS. Interestingly, among the several prognostic factors related to the refractory forms, the evidence of MAHA, normally found in 16% of patients at first CAPS episode,[5] has been found in 72% of patients with the recurrent episodes.[14,15] Features consistent with disseminated intravascular coagulation (DIC) can also be detected, with an estimated prevalence of 11% in the CAPS Registry.[10]

Clinical features

Clinical manifestations mainly depend on and vary according to the extent of the thrombosis and the involved organs, predominately affecting kidneys (73%), lungs (60%), brain (56%), heart (50%), and skin (47%).[5,16] Renal disease is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or proteinuria (>500 mg/24 h).[5] Pulmonary involvement can present with acute respiratory distress syndrome and pulmonary emboli in most of CAPS patients, although pulmonary hemorrhage, pulmonary edema with diffuse alveolar infiltrates have been reported.[16] Seizures and cerebral venous occlusions are frequent cerebral manifestations. Myocardial infarction and mitral and/or aortic defects can be also seen in patients with CAPS, whereas livedo reticularis, skin necrosis and purpura are the main skin complications. However, every organ/tissue may be potentially a□ected, and cases of intestinal ischemia, bone marrow infarction, gastric and colonic ulcerations, and thrombotic pancreatitis have reported.[16]

Diagnosis

Despite the heterogeneity of CAPS clinical/laboratory manifestations, in recent years, classification criteria have been developed, which are currently utilized for diagnosis (see Table 1).[1,17]

The most important clue is based on the careful exclusion of other systemic syndromes also involving small vessels and resembling CAPS. This notwithstanding, the coexisting thrombocytopenia and/or coagulation factors consumption[17,18] often impedes biopsy, so that a *definite* diagnosis is not reached.

A previous history of persistently detectable aPLs levels and/or of antiphospholipid syndrome (APS) may lead the diagnosis, even though less than 1% of patients with primary APS develop CAPS and this syndrome has been also associated with other autoimmune disorders, such as systemic lupus erythematosus (SLE) (30%), lupus-like disease (4%), and others (<6%).[5,6,7]

Moreover, the main triggers of CAPS episodes (*i.e.* malignancies and/or infections), are *per se* associated to the development of a transitory aPLs positivity,[11] and false-positive and false-negative LA tests can be seen in patients on anticoagulation.[11,19,20] In presence of multi-organ failure and clinical/laboratory findings of thrombotic microangiopathy (TMA), CAPS diagnosis also requires the exclusion of other systemic disorders, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), hypertension-related, pregnancy- and drug-related microangiopathic syndromes.[21,22]

In this context, the most important clue is to perform a careful clinical history and physical examination, looking for a history of uncontrolled hypertension, malignancies, recent enteritis, on-going pregnancy and exposure to some drugs. Indeed, heparin, ticlopidine, clopidogrel, chemotherapy agents, have been identified as probable causes of thrombotic microangiopathy.[5,22-24] A special attention to previous thrombotic episodes, aPLs positivity or history of another autoimmune diseases, may make the diagnosis of CAPS more probable.[5]

Funduscopic exam may help to rule out malignant hypertension; where TTP is suspected, a decrease in ADAMTS13 activity, up to lower than 5%, points to TTP as the most probable diagnosis.[5,22] Moreover, schistocytes on the peripheral blood smear are usually scantier in CAPS than in TTP.[5] In general, double or triple aPLs positivity or aPLs in high titers make the diagnosis of CAPS more probable.

Table 1. Diagnostic criteria for catastrophic antiphospholipid syndrome.

(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 antiphospholipid syndrome
- All four criteria
Probable catastrophic antiphospholipid syndrome
- All four criteria, except for only two organs, systems, and/or tissues involved
- All four criteria, except for the absence of laboratory confirmation owing to the early death of a patient never tested for antiphospholipid antibodies before the CAPS
- Criteria (1), (2), and (4)
- Criteria (1), (3), and (4) and the development of a third event between one week and one month after presentation, despite anticoagulation

Adapted from Cervera *et al.*, 2018.[5] *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 h). °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 antiphospholipid syndrome (APS), the laboratory confirmation requires that the presence of antiphospholipid 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.

Treatment

Provided that clinical trials defining the optimal therapeutic approach for patients with CAPS are still lacking, the current recommendations rely on the revision of available data and authors' experiences. Organ-specific supportive measures should be promptly started, and patients should be closely monitored, since they often require a timely admission to intensive care units.[11,25]

Potential precipitating factors should be identified, including recent sickness and/or surgery, malignancies, on-going pregnancy, and medication changes. For patients with a suspected infection, the treatment should be preferably based on antimicrobial susceptibility tests, to maximize the control of the systemic inflammatory response (SIRS).[26]

The *first line* management strategy, established on the analysis of CAPS registry, is based on the combination of anticoagulation (AC), immunosuppression, plasma exchange (PE) and intravenous immunoglobulin (IVIG).[1,5,27] The use of intravenous cyclophosphamide has been recommended in patients with CAPS associated to SLE,[28] and more recently, rituximab and eculizumab have been employed as an add-on treatment for patients with refractory disorders.[29-39] During the acute phase, most CAPS patients are usually treated with unfractionated heparin, which prevents fibrin formation, and inactivate activated factor X, slowing down the thrombotic storm.[40] Its short time-of-action makes non-fractionated heparin a safe drug when treating patients with an elevate risk of bleeding.[5,40] Once clinical stability is achieved, unfractionated heparin can be switched to low-molecular-weight heparin, and then to oral anticoagulants, such as warfarin, maintaining the INR within 2 and 3.[5] The effectiveness of direct oral anticoagulants in CAPS is unknown.[5]

Pulse methylprednisolone at doses of 500-1000 mg/day (generally for 3 days) is recommended in the acute phase, followed by dose tapering with prednisolone, in keeping with the patient's clinical condition.[41]

PE is recommended in patients with features of microangiopathy (*e.g.* increased LDH levels, reduced aptoglobin levels, and schistocytes), as an add-on therapy to intravenous heparin and high dose steroids.[41] There is no recommendation about the duration of this procedure, which is generally continued for a minimum of 3-5 days.[41] The infusion rate of unfractionated heparin has to be increased by about 65% during PE to maintain the efficacy of anticoagulation.[42]

IVIG may be effective for reducing aPLs titers.[43] There is no firm recommendation about the dose, and IVIG have been used at doses of 200-400 mg/kg daily for 5 days, as in other autoimmune conditions.[5,41] When PE is performed, IVIG should be administered after the PE session.[42] Cyclophosphamide is recommended when CAPS is associated with SLE, as its addition to standard therapy seems to decrease mortality.[28] Doses of 750 mg/m^2 monthly or 500 mg every 15 days, over a period of 3-6 months, have been proposed.[5,43,44]

Rituximab has shown its utility in patients with poor response to initial treatment or recurrent episodes of CAPS.[29] Its effectiveness has been attributed to the rapid fall of pro-inflammatory cytokines, coming from the reduction of B cells numbers.[29] The proposed dosage consists of two administrations of 1000 mg every 15 days, followed by four weekly doses of 375 mg/m^2.[5,29]

Complement inhibition may also play an adjuvant role to the main therapy for patients with refractory CAPS, because aPLs are able to induce complementary activation through the classical, lectin and alternative pathways.[11] Therefore, the add on use of eculizumab, an anti-C5 monoclonal antibody, in CAPS is supported by a recent survey of published case reports.[30-39] The only registered ongoing phase II trial investigates the use of eculizumab in patients who develop end stage renal disease after an episode of CAPS (clinicaltrials.gov #:NCT01029587). Weekly doses of 900-1200 mg of eculizumab have been used in the acute phase, decreasing its frequency after the acute phase to 600-900 mg, administered every two weeks.[5,30] However, the optimal duration of this treatment is unknown.

Analyzed individually, only anticoagulation has shown a significant effect in improving survival.[5] However, the combination of anticoagulation, immunosuppression, plasma exchange and/or IVIG achieved the highest survival rate (70%).[45,46]

Conclusions

Catastrophic antiphospholipid syndrome is a rare disorder, characterized by the development of multiple vascular thrombosis over a short period of time, in patients with persistently detectable aPLs. Vascular occlusions, predominantly affecting small vessels, mandate its inclusion in differential diagnosis of thrombotic microangiopathies, which in turn include TTP, typical and atypical HUS, systemic infections, malignancies, pregnancy-related disorders, malignant hypertension, and drug-induced TMA. An accurate medical history and physical examination may suggest the appropriate workup for the differential diagnosis. The current widely accepted therapy is based on the combination of anticoagulation, steroids, plasma exchange and/or intravenous immunoglobulins that have achieved the best survival rate. Cyclophosphamide is recommended in patients with CAPS associated with SLE. Rituximab and eculizumab have been favorably employed as an add-on treatment for patients with refractory disorder.

References

1. Asherson R, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530-4.
2. Schreiber K, Sciascia S, de Groot PG, et al. Antiphospholipid syndrome. Nature Rev Dis Primers 2018;4:17103.
3. Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508-12.
4. Espinosa G, Rodríguez-Pintó I, Cervera R. Catastrophic antiphospholipid syndrome: an update. Panminerva Med 2017;59254-68.
5. Cervera R, Rodriguez-Pinto I, Espinosa G. The diagnosis and clinical management of the catastrophic antiphospholipid syndrome: a comprehensive review. J Autoimmun 2018;92:1-11.
6. Cervera R, Piette J-C, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019-27.
7. Espinosa G, Berman H, Cervera R. Management of refractory cases of catastrophic antiphospholipid syndrome. Autoimmun Rev 2011;10:664-8.
8. Cervera R, Tincani A. European Working Party on systemic

lupus erythematosus and European Forum on Antiphospholipid Antibodies: two networks promoting European research on autoimmunity. Lupus 2009;18:18863-8.
9. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. Autoimmun Rev 2010;10:74-9.
10. Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS registry. Autoimmun Rev 2016;15:1120-4.
11. Erkan D, Salmon JE. The role of complement inhibition in thrombotic angiopathies and antiphospholipid syndrome. Turk J Haematol 2016;5:1e7.
12. Cervera R, Bucciarelli S, Plasín MA, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". J Autoimmun 2009;32:240-5.
13. Cervera R, Asherson RA, Acevedo ML, et al., Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004;63:1312-7.
14. Asherson RA, Espinosa G, Menahem S, et al. Relapsing catastrophic antiphospholipid syndrome: report of three cases. Semin Arthritis Rheum 2008;37:366-72.
15. Espinosa G, Rodríguez-Pintó I, Gomez-Puerta JA, et al. Relapsing catastrophic antiphospholipid syndrome potential role of microangiopathic hemolytic anemia in disease relapses. Semin Arthritis Rheum 2013;42:417-23.
16. Bucciarelli S, Espinosa G, Cervera R, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 2006;54:2568-76.
17. Cervera R, Font J, Gómez-Puerta J, et al., Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005;64:1205-9.
18. Cervera R, Rodríguez-Pintó I, Colafrancesco S, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on catastrophic antiphospholipid syndrome. Autoimmun Rev 2014;13:699-707.
19. Gómez-Puerta JA, Espinosa G, Cervera R. Antiphospholipid antibodies: from general concepts to its relation with malignancies. Antibodies 2016;5:pii:E18.
20. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003;101:1827-1832.
21. George JN, Charania RS. Evaluation of patients with microangiopathic hemolytic anemia and thrombocytopenia. Semin Thromb Hemost 2013;39:153-60.
22. Kello N, Khoury LE, Marder G, et al. Secondary thrombotic microangiopathy in systemic lupus erythematosus and antiphospholipid syndrome, the role of complement and use of eculizumab: case series and review of literature. Semin Arthritis Rheum 2018 [Epub ahead of print].
23. Tada K, Ito K, Hamauchi A, et al. Clopidogrel-induced thrombotic microangiopathy in a patient with hypocomplementemia. Inter Med 2016;55:969-73.
24. Jacob S, Dunn BL, Qureshi ZP, et al. Ticlopidine-, zlopidrogrel-, and prasugrel-associated thrombotic thrombocytopenic purpura: a 20-years review from the Southern Network on Adverse Reactions (SONAR). Semin Thromb Hemost 2012;38:845-53.
25. Vora SK. Care medicine catastrophic antiphospholipid syndrome. J Intensive Care Med 2006;21:144-59.
26. Cervera R. CAPS registry project group. Catastrophic antiphospholipid syndrome (CAPS): update from the "CAPS registry". Lupus 2010;19:412-8.
27. Rodriguez-Pintó I, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: the current management approach. Best Pract Res Clin Rheumatol 2016;30 239-49.
28. Bayraktar UD, Erkan D, Bucciarelli S, et al. Catastrophic Antiphospholipid Syndrome Project Group. The clinical spectrum of catastrophic antiphospholipid syndrome in the absence and presence of lupus. J Rheumatol 2007;34:346-52.
29. Berman H, Rodríguez-Pintó I, Cervera R, et al., Rituximab use in the catastrophic Antiphospholipid syndrome: descriptive analysis of the CAPS registry patients receiving rituximab. Autoimmun Rev 2013;12:1085-90.
30. Tinti MG, Carnevale V, Inglese M, et al. Eculizumab in refractory catastrophic antiphospholipid syndrome: a case report and systematic review of the literature. Clin Exp Med 2019;19:281.
31. Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Arthritis Rheum 2012;64:2719-23.
32. Barratt-Due A, Fløisand Y, Orrem HL, et al. Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. Rheumatology 2016;55:1337-9.
33. Kronbichler A, Frank R, Kirschfink M, et al. Efficacy of eculizumab in a patient with immunoadsorption-dependent catastrophic antiphospholipid syndrome: a case report. Medicine (Baltimore) 2014;93:e143.
34. Lonze BE, Singer AL, Montgomery R. Eculizumab and renal transplantation in a patient with CAPS. N Engl J Med 2010;362:1744-5.
35. Lonze BE, Zachary AA, Magro CM, et al. Eculizumab prevents recurrent antiphospholipid antibody syndrome and enables successful renal transplantation. Am J Transplant 2014;14:459-65.
36. Strakhan M, Hurtado-Sbordoni M, Galeas N, et al. 36-year-old female with catastrophic antiphospholipid syndrome treated with eculizumab: a case report and review of literature. Case Rep Hematol 2014;2014:704371.
37. Zikos TA, Sokolove J, Ahuja N, Berube C. Eculizumab induces sustained remission in a patient with refractory primary catastrophic antiphospholipid syndrome. J Clin Rheumatol 2015;6:311-3.
38. Wig S, Chan M, Thachil J, et al. A case of relapsing and refractory catastrophic anti-phospholipid syndrome successfully managed with eculizumab, a complement 5 inhibitor. Rheumatology (Oxford) 2016;55:382-4.
39. Guillot M, Rafat C, Buob D, et al. Eculizumab for catastrophic antiphospholipid syndrome - a case report and literature review. Rheumatology 2018;57:2055-7.
40. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. Arterioscler Thromb Vasc Biol 2001;21:1094-6.
41. Espinosa G, Cervera R. Current management of catastrophic antiphospholipid syndrome. Int J Clin Rheumatol 2011;6:297-303.
42. Peedin AR, Karp JK. Revisiting the role of therapeutic plasma exchange in the management of catastrophic antiphospholipid syndrome. J Thromb Haemost 2019;17:1179-80.
43. Sciascia S, Giachino O, Roccatello D. Prevention of thrombosis relapse in antiphospholipid syndrome patients refractory to con-

ventional therapy using intravenous immunoglobulin. Clin Exp Rheumatol 2012;30:409-13.
44. Rodríguez-Pintó I, Espinosa G, Cervera R. The catastrophic antiphospholipid syndrome, in: P.L. Meroni (Ed.), Antiphospholipid Antib. Syndr. Bench to Bedside. Berlin: Springer International Publishing; 2015. pp 249-62.
45. Rodriguez-Pinto I, Espinosa G, Erkan D, et al. The effect of triple therapy on the mortality of catastrophic anti-phospholipid syndrome patients. Rheumatology (Oxford, England) 2018;57:1264-70.
46. Espinosa G, Bucciarelli S, Asherson RA, Cervera R. Morbidity and mortality in the catastrophic antiphospholipid syndrome: pathophysiology, causes of death, and prognostic factors. Semin Thromb Hemost 2008;34:290-4.