EXTENDED REPORT

Long term outcome of catastrophic antiphospholipid syndrome survivors

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Background: Catastrophic antiphospholipid syndrome (APS) is defined as life threatening multiple organ thromboses developing simultaneously or over a short period. The survival rate of catastrophic APS is about 50%, but the long term outcome of patients who survive is unknown.
Objective: To determine the long term outcome of patients with catastrophic APS and provide further information on patients who survived.
Patients and methods: The clinical characteristics and outcomes of 130 patients with catastrophic APS have been reported previously. Six new cases were recently added to this series. Based on these publications, the authors who reported patients who had survived were contacted. Each author was asked (*a*) what treatment they gave their patients after the catastrophic APS; (*b*) if their patients had any further thrombosis.
Results: 63/136 (46%) patients died at the initial event. Of the remaining 73 patients, information was available for 58 (79%). Thirty eight (66%) patients did not develop further APS related events during an average follow up of 67.2 months. Eleven (19%) patients developed further APS related events but were still alive. No patients developed further catastrophic APS. Nine (16%) patients died: due to multiple organ failure (three patients); myelofibrosis (one); pneumonia (one); and APS related events (four).
Conclusion: Sixty six per cent of patients who survive an initial catastrophic APS event remained symptom free with anticoagulation during an average follow up of 67.2 months. Twenty six per cent of the survivors developed further APS related events and the mortality rate of these patients was about 25%.

The antiphospholipid syndrome (APS) is a clinical syndrome associated with pregnancy morbidity (mostly fetal loss) and/or vascular thrombosis (venous, arterial) in the presence of circulating antiphospholipid antibodies, most commonly anticardiolipin antibodies and lupus anticoagulant.[1] The spectrum of APS related vascular events ranges from a superficial thrombosis to life threatening multiple organ system thromboses developing over a short period (catastrophic APS).

The term "catastrophic APS" was originally proposed in 1992, in which the major feature is the occlusion of small vessels supplying multiple organ systems.[2] After this initial description, the first comprehensive literature review of 50 patients with catastrophic APS was published in 1998.[3] Three years later, a second literature review described 80 additional patients with catastrophic APS.[4]

In both reviews patients were identified through published case reports after a computer assisted (Medline, National Library of Medicine, Bethesda, MD) literature search. The analysis of the clinical and serological features of these 130 patients with catastrophic APS significantly contributed to our understanding of this devastating syndrome. One of the major findings of these reviews was a mortality rate of about 50% at the time of the initial event.

However, the long term outcome of patients who survive catastrophic APS is unknown. As far as we know, there is no published report on the prognosis of patients with catastrophic APS which includes the anticoagulation regimens used, the development of further thrombotic or catastrophic events, or the mortality rates and functional outcomes.

Thus our primary objective was to determine the long term outcome of patients with catastrophic APS and provide further follow up information on patients who survived the initial event. Secondarily, we also examined the functional status of the survivors.

METHODS

Based on the two review articles on the clinical characteristics and outcomes of 130 patients with catastrophic APS,[3 4] we contacted, by email, regular mail, fax, or telephone, the first authors of the case reports in which patients had survived. Coauthors of the published reports were contacted when the first authors did not reply. We also added six recently reported patients with catastrophic APS to our data analysis.[5]

Authors were asked to provide the following information: (*a*) what treatment was given to their patients after the catastrophic episode and (*b*) if their patients had any further episode(s) of thrombosis or catastrophic APS during the follow up period.

Table 1 Total number of reported patients with catastrophic APS, the number of patients who survived, and the follow up information

Catastrophic APS	n
Total reported	136
Patients survived	73
Available follow up information	58
No further APS – alive	38
No further APS – dead	5*
Further APS – alive	11
Further APS – dead	4

*Three patients died after the initial catastrophic APS owing to multiple organ failure.

Table 2 Anticoagulation regimens of patients without further APS related events

Treatment	No of patients (n=38)
Warfarin (INR not reported)	10
Warfarin (INR 2–3)	7
Warfarin (INR 2.5–3.5)	4
Warfarin (INR 3–4)	10
Warfarin + Clopidogrel	1
Fluindione	1
Acenocoumarol	1
Aspirin*	2
No treatment†	1
Heparin/aspirin‡	1

*Patient 1: End stage renal disease, receiving haemodialysis, waiting for renal transplantation. Patient 2: Aspirin for six years followed by no treatment for four years; †End stage renal disease, receiving haemodialysis, waiting for renal transplantation; ‡Stopped heparin six weeks post partum.

The follow up period was from the time of catastrophic APS event to the last contact with their doctor. Mortality from APS and all-cause mortality during the follow up period were also recorded. We recorded the information from authors using a standardised data form.

Mann-Whitney test was used to compare the continuous variables.

RESULTS

The initial review of 136 published patients with catastrophic APS showed that 63/136 (46%) died at the time of the reported event. Of the remaining 73 patients, we were able to obtain information on 58 (79%) patients, and 49/58 (84%) patients were still alive at the time of the study (table 1). The demographic characteristics of the 58 patients (41 female) from whom we were able to obtain information did not differ from those of the 15 patients (10 female) with missing information (mean (SD) age at the event 36.6 (15.9) *v* 35 (16); p=0.7 and the number of organ systems affected 4.1 (1.9) *v* 5.0 (1.7); p=0.1).

Thirty eight of 58 (66%) patients did not develop further APS related thrombotic events (mean (SD) follow up time 67.2 (44.0) months, median 54, range 12–186). Thirty five patients had follow up information until 2001 when our study was completed. For the remaining three patients, the last contacts with their doctor were five, three, and one years respectively. Table 2 demonstrates the anticoagulation regimens that patients without further events received during the follow up period.

Fifteen of 58 (26%) patients developed further APS related thrombosis after the initial catastrophic APS event (mean (SD) time to the event 37.7 (34.8) months, median 24, range 5–120) and the mortality rate of these patients was about 25% (4/15 patients). Table 3 shows the clinical characteristics and outcomes of these 15 patients. Six patients had recurrent events associated with a surgical procedure and one had recurrence with a sub-therapeutic international normalised ratio (INR). All 15 patients developed only one further thrombotic event during the follow up period except one patient who had recurrent events. None of the patients developed further catastrophic APS.

Of 15 patients who developed further APS related events, 11 (7 female, mean (SD) age at initial event 35.1 (12.3)) were still alive during the follow up. Antiphospholipid syndrome related events in the 11 patients included two pulmonary embolism; two arterial-venous graft thrombosis; one stroke; one recurrent deep vein thrombosis/pulmonary embolism; one myocardial infarction; one renal artery graft thrombosis; one penile artery thrombosis; one left arm amputation due to perioperative thrombotic complications, and one aortoiliac junction thrombosis.

Nine of 58 (16%) patients (six female, mean (SD) age at initial event 40.2 (17.2)) died during the follow up: three shortly after the event due to multiple organ failure; two due to non-APS related causes; and four due to APS related events. Non-APS related mortality causes in two patients included myelofibrosis more than 15 years after the initial event and pneumonia one year after the event, respectively. Causes of death due to the APS in four patients included: two perioperative complications four years (total knee replacement) and four months (mitral and aortic valve replacement) after the initial event, respectively; one pulmonary haemorrhage/infarcts seven years after the event; and one massive pulmonary embolism nine months after the event (table 3).

Eight (15%) patients were functionally impaired as a consequence of catastrophic APS: three had end stage cardiac failure; two had end stage renal disease requiring haemodialysis; one case of symptomatic arrhythmia; one chronic renal insufficiency; and one had gait abnormalities and visual symptoms.

Table 3 Clinical characteristics and outcomes of 15 patients with catastrophic APS who developed further APS related events

No	Sex	Age	Disease	Catastrophic manifestations	Anticoagulation	APS related thrombosis	Trigger	Outcome
1	F	33	SLE	Hepatic, renal, portal vein, skin	ASA	Arterial-venous graft	Surgery	Recovery
2	F	25	PAPS	Hepatic, renal, splenic, bone, marrow, nose, skin	War (3–4)	Cardiac	Surgery	Death
3	M	37	PAPS	Hepatic, renal, pancreatic, pulmonary	War (3–4)	Aortoiliac junction	No	Recovery
4	F	33	PAPS	Renal, pulmonary, cerebral,	War	Pulmonary	No	Death
5	M	22	PAPS	Peripheral (v and a), prostate	War	Penile artery	Low INR	Recovery
6	F	30	SLE	Hepatic, renal, cerebral, bone	ASA	Renal artery graft	Surgery	Recovery
7	M	47	PAPS	Peripheral (a), renal, cerebral, cardiac, pulmonary, skin	War	Pulmonary	No	Recovery
8	M	52	PAPS	Peripheral (a), renal, cerebral, cardiac, pulmonary, skin	War (2–3)	Cerebral	No	Recovery
9	F	17	SLE	Peripheral (v), renal, cerebral, pulmonary, skin	War	Peripheral (v), pulmonary	No	Recovery
10	F	51	SLE	Renal, splenic, pancreatic, cardiac	War (>3)	Cardiac	No	Recovery
11	F	25	PAPS	Hepatic, renal, cardiac	War/ASA	Arterial-venous graft	Surgery	Recovery
12	F	23	PAPS	Peripheral (v), pulmonary, retinal	War (2–2.5)	Pulmonary	No	Recovery
13	F	49	PAPS	Peripheral (v), hepatic, cardiac	War (3–4)	Peripheral (a)	Surgery	Recovery
14	M	30	PAPS	Cerebral, adrenal	LMWH	Pulmonary	No	Death
15	M	62	PAPS	Renal, cardiac, cerebral	War (3–4)	Renal*	Surgery	Death

F, female; M, male; SLE, systemic lupus erythematosus; PAPS, primary antiphospholipid syndrome; a, artery; v, vein; ASA, aspirin; War (target INR), warfarin; LMWH, low molecular weight heparin.
*Worsening renal failure followed by retroperitoneal bleeding secondary to renal artery aneurysm.

DISCUSSION

Sixty six per cent of patients who survive an initial catastrophic APS event remained symptom free with anticoagulation during an average follow up of 67.2 months. Twenty six per cent of the survivors developed further APS related events and the mortality rate of these patients was about 25%.

Doctors have been increasingly recognising catastrophic APS but still many unresolved questions exist. The optimal treatment combination at the time of a catastrophic APS event is controversial,[6] but anticoagulation is the preferred treatment in the long term. Although short term outcomes of catastrophic APS are documented in two different series,[3 4] the long term outcomes are unknown. This is the first study demonstrating that catastrophic APS recurrence is unusual and patients treated with anticoagulation generally have a stable course.

Long term anticoagulation with warfarin is the standard of care to prevent a recurrent vascular event in patients with APS. The recurrence rate in untreated patients is 44–55% after the first vascular event,[7–9] and approaches zero in patients treated with high intensity warfarin.[10] In our study one quarter of patients with catastrophic APS developed a recurrent thrombotic event despite anticoagulation.

Of 15 patients who developed further thrombotic events, six (40%) occurred during the perioperative period, which emphasises the fact that patients with APS are at additional risk for thrombosis when they undergo surgery.[11] Stasis, intimal injury, and hypercoagulability are the three major factors that contribute to postoperative thromboembolic events.[12] During the perioperative period, patients with APS possess all these factors, and the risk of a thrombotic event is further increased by the discontinuation of warfarin. Thus, when a patient with APS or catastrophic APS undergoes a surgical procedure, the most effective pharmacological methods should be combined with physical methods such as intermittent venous compression, and patients should be closely observed for the signs and symptoms of thrombotic clinical events.[11]

In the absence of underlying connective tissue disorder, APS is defined as "primary APS".[13 14] Functional prognosis is poor in patients with primary APS with prolonged disease. A retrospective study showed that after 10 years of disease, one third of patients with primary APS had organ damage and one fifth were functionally impaired.[15] Although there are studies reporting the functional status of surviving patients with APS after prolonged disease, the functional outcome of surviving patients with catastrophic APS has not been reported. Thus, we secondarily analysed the functional outcome and found that 15% were significantly functionally impaired owing to the initial catastrophic APS event.

The major limitations of our study are the data collection, which were dependent on a retrospective questionnaire, and missing information on certain patients. Recall bias from the authors might have occurred and the information could not be confirmed because of lack of direct access to patient charts. Furthermore, the different management characteristics between institutions might have affected the outcomes of patients, but no one institution had enough patients for a meaningful comparison. The open ended format of the questionnaire is a strength of our study, which allowed us to capture details that might have been limited by a more standardised approach. Another strength of this study is that we collected a large body of data on a very uncommon and potentially fatal syndrome.

In summary, this is the first study that considers the long term prognosis of patients with catastrophic APS after the initial event. Further prospective studies, preferably using large scale registries, will help us to better understand the long term prognosis of catastrophic APS.

Appendix: The Catastrophic Antiphospholipid Syndrome Registry Project Group

The members of the Catastrophic APS Registry Project Group who contributed to this study are as follows: Christopher Davidson, Department of Cardiology, Royal Sussex Hospital, Brighton, UK; Alex E Denes, Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, USA; Ronald H W M Derksen, Department of Rheumatology and Clinical Immunology, University Medical Centre, Utrecht, The Netherlands; J F Diaz Coto, Caja Costarricense del Seguro Social, San Jose, Costa Rica; Patrick Disdier, Service de Medecine Interne, Centre Hospitalier Universitaire Timone, Marseille, France; Rita M Egan, Department of Medicine, University of Kentucky Medical Center, Lexington, USA; R Enriquez, Nephrology Section, Hospital General de Elche, Spain; Fernanfa Falcini, Department of Paediatrics, University of Florence, Italy; Leslie S Fang, Renal Associates, Massachusetts General Hospital and Harvard Medical School, Boston, USA; John T Grandone, Neenah, Wisconsin, USA; Anagha Gurjal, Division of Hematology/Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, USA; Gilles Hayem, Department of Rheumatology, CHU Bichat-Claude-Bernard, Paris, France; Graham R V Hughes, Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, UK; Sohail Inam, Riyadh Armed Forces Hospital Riyadh, Saudi Arabia; K Shashi Kant, Department of Internal Medicine, University of Cincinnati College of Medicine, Ohio, USA; Craig S Kitchens, Department of Medicine, University of Florida, Gainesville, USA; Michael J Kupferminc, Department of Obstetrics and Gynaecology, Lis Maternity Hospital, Tel Aviv University, Tel Aviv, Israel; Roger A Levy, Department of Rheumatology, Faculdade de Ciencias Medicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; Siu Fai Lui, Department of Medicine, Prince of Wales Hospital and Chinese University of Hong Kong, Shatin, Hong Kong; Peter J Maddison, Gwynedd Rheumatology Service, Ysbyty Gwynedd, Bangor, UK; Yoseph A Mekori, Department of Medicine, Meir Hospital, Kfar Saba, Israel; Takako Miyamae, Department of Paediatrics, Yokohama City University School of Medicine, Yokohama, Japan; John Moore, Department of Haematology, St Vincents Hospital, Sydney, Australia; Francisco J Munoz-Rodriguez, Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain; Ayako Nakajima, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan; Michael C Neuwelt from Medical Service, VA Palo Alto Health Care System, USA; Ann Parke, Department of Internal Medicine, Division of Rheumatic Diseases, University of Connecticut Health Center, Connecticut, USA; Jorge Rojas-Rodriguez, Department of Rheumatology, Specialties Hospital, Manuel Avila Camacho National Medical Centre, Puebla, Mexico; Allen D Sawitzke, Division of Rheumatology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, USA; Cees G Schaar, Department of Haematology, Leiden University Medical Centre, The Netherlands; Yehuda Shoenfeld from Chaim-Sheba Medical Centre, Tel-Hashomer, Israel; Alex C Spyropoulos from Clinical Thrombosis Center, Albuquerque, New Mexico, USA; Carlos Vasconcelos from Hospital Geral de San Antonio, Poro, Portugal; and Margaret Wislowska, Outpatients Department of Rheumatology, Central Clinical Hospital, Warsaw, Poland.

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