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Catastrophic antiphospholipid syndrome: Lessons from 14 cases successfully treated in a single center. A narrative report

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ABSTRACT

The study aimed to evaluate the clinical significance of laboratory findings in patients with catastrophic antiphospholipid syndrome (CAPS) and to report the effects of a well-defined treatment protocol in 14 consecutive cases.

Thirteen patients (12 presenting one and one presenting two episodes of CAPS) were consecutively treated and monitored between 1986 and 2017. Antiphospholipid antibody (aPL) characteristics of the patients were compared with those of 64 matched controls (45 antiphospholipid syndrome patients and 19 aPL carriers) who did not develop CAPS during the same mean follow-up period (12 years ± 9.9 SD).

Triple aPL positivity (IgG/IgM anticardiolipin + IgG/IgM anti-β2Glycoprotein I + lupus anticoagulants) significantly prevailed in the CAPS patients with respect to the controls ($p = 0.003$). IgG anticardiolipin and IgG anti-β2Glycoprotein I mean antibody titers of the CAPS patients were significantly higher than those of the controls ($p = 0.0018$ and $p = 0.003$, respectively). Triple therapy (anticoagulation + plasma exchange + steroids) was administered to all the CAPS cases except for one. Beginning in 2009, intravenous immunoglobulin infusion has also been included in the triple therapy protocol (six patients). All the patients recovered from CAPS; five showed renal failure and one a I-II class New York Heart Association (NYHA) dilated cardiomyopathy. Long-term outcomes of CAPS included a gradual worsening of renal failure in one patient who required hemodialysis 30 years after the acute episode. Renal function improved in the other four patients. The patient affected with dilated cardiomyopathy worsened to a II class NYHA over a five year period. Currently all the patients are alive.

A specific antiphospholipid antibody profile could be considered a risk factor associated to CAPS. Early use of a defined treatment protocol based on triple therapy either or not associated with IVIG was associated with recovery in all CAPS patients.

1. Introduction

Catastrophic antiphospholipid syndrome (CAPS) is a recognized subset of antiphospholipid syndrome (APS) characterized by multiple vascular occlusive events, usually affecting the small vessels supplying organs/tissues and presenting over a short period of time The term "catastrophic" was introduced by Asherson in 1992 [1], and in 2003 an international consensus stated for the first time the criteria for the classification of CAPS [2]. This severe variant seems to involve approximately 1% of APS patients [3]. According to most investigations, the majority of CAPS episodes are triggered by one or more precipitating factors including infections, surgery, malignancy, contraceptives, pregnancy/puerperium, withdrawal of warfarin or subtherapeutic (< 2.0) international normalized ratio (INR), Systemic lupus erythematosus flares and traumas [4–6]. From a clinical point of view CAPS is characterized by the involvement of several organs manly including kidneys (73%), lungs (60%), brain (56%), heart (50%), and skin (47%) [6].

Due to the rarity of CAPS, it has been impossible to carry out randomized controlled trials to define the optimal therapeutic approach. Data from the International CAPS Registry support a treatment strategy, termed triple therapy, based on a combination of anticoagulants + glucocorticoids + plasma exchange and/or intravenous immunoglobulins (IVIG) that should be the treatment of choice [6,7].

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The mortality rate decreased from 53% in the patients diagnosed before 2000 to 33% in those diagnosed from 2000 to 2005 [8]. This reduction can probably be explained by the more frequent use of the triple therapy. Mortality unfortunately continues to be high despite these interventions [6,7]. Several studies have shown that new therapeutic options such as rituximab or eculizumab may play a role in the treatment of CAPS, especially in patients refractory to triple therapy and in those with relapsing CAPS [9].

The study aimed to evaluate the clinical significance of laboratory findings in patients with CAPS and to report the effects of a well-defined treatment protocol in 14 consecutive cases.

2. Patients and methods

2.1. Study population

Thirteen patients with CAPS (12 with one and one with two episodes) were enrolled. Therefore, 13 patients and 14 episodes of CAPS were consecutively treated and monitored by the same medical team between 1986 and 2017 at the Rheumatology Unit of the University Hospital of Padua. All of the patients were diagnosed with definite CAPS on the basis of the following International Consensus Statement criteria: 1) evidence of involvement of three or more organs, systems and/or tissues; 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; 4) laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) [2].

The antiphospholipid antibody (aPL) profiles of the CAPS patients were compared with those of 64 controls matched for age, sex, medical history, and clinical criteria for APS classification who did not develop CAPS during the same mean follow-up period to examine their clinical significance (Table 1). As nine out of 13 CAPS patients were previously affected by APS, while four developed CAPS as the first manifestation of APS, the 64 controls were selected from 309 patients with APS and 177 aPL carriers. Statistical comparisons were performed on the data of the 13 patients studied. The CAPS clinical and laboratory characteristics, the treatment protocols used, and the outcomes of all 14 CAPS episodes were evaluated.

2.2. Patient management

Early diagnosis, controlling or if possible eliminating precipitating factors (e.g. antibiotics for infections) just as supportive treatment of multiorgan failure in an intensive care unit were considered essential for the survival of our CAPS patients.. Also initiating treatment within eight hours from the time of diagnosis was considered of utmost importance. Therapeutic anticoagulation except in the cases presenting hemorrhagic complications was the first and most important therapy for these patients. Given their short half-life and since it was possible to titrate dosage, intravenous unfractionated heparin or subcutaneous calcium heparin were the most frequently used anticoagulants. Plasma exchange sessions were performed according to the following timetable: once a day for three to five consecutive days, then it was suspended. Resuming sessions depended primarily on the patient's clinical response. Seventy to 100% of the plasma volume was exchanged at each session and the replacement fluid was a mixture of 70% albumin (4%) and 30% saline. Acid Citrate Dextrose Formula A anticoagulant used in a 1:12–1:15 ratio ensured anticoagulation. Antithrombin (1000 IU) was administered at the end of the session to compensate for the decrease in natural anticoagulants caused by plasma exchange removal when its post-treatment values were below the lower normal limit. To avoid bleeding (as plasma exchange temporarily removes blood clotting factors), the heparin dosage administered after the session was halved for 12 h. Corticosteroids were administered as intravenous pulses of 500–1000 mg/day of methylprednisolone but, in the presence of contraindications such as a severe infection, the dosage was reduced to intravenous 1–2 mg/kg/day. To avoid its removal each daily pulse was administered immediately after each plasma exchange session for three-five consecutive days. Then the dosage was decreased to 1–0.5 mg/kg/day to be tapered slowly depending on the patient's clinical condition. Just as for other autoimmune diseases [10], IVIG (400 mg/kg/day) were infused for five consecutive days. The procedures were scheduled promptly after the last plasma exchange session in order to avoid immunoglobulin removal by the plasma exchange. Immunoglobulin A deficiency, renal failure, and previous intolerance/allergy to IVIG were considered contraindications for this treatment. Low-dose aspirin was added for patients with important thrombophilia and low risk of bleeding. In cases refractory to this combined therapy, eculizumab was considered an additional option.

CAPS survivors relied on life-long warfarin treatment with an INR value that depended on the patient's characteristics (generally, ranging between 2.5 and 3.5). Antiplatelet drugs were also prescribed to the patients considered to be at high risk of thrombosis, but not presenting risk of bleeding.

The institutional review board for observational studies and the Audit Committee of the University Hospital of Padua approved the study design. Patients were informed and asked to sign informed consent forms. Their medical records were then retrieved and reviewed.

Table 1
Demographic and clinical features of CAPS patients and matched control subjects.

	CAPS patients n = 13 n (%)	Control subjects n = 64 n (%)
Mean age (years) at diagnosis ± SD (range)	32 ± 10.4 (13–50)	31 ± .8.4 (16–56)
Women	12 (92.3)	59 (92.2)
Men	1 (7.7)	5 (7.8)
Mean follow-up duration (years) ± SD (range)	12 ± 9.9 (1–32)	14 ± 9.2 (1–36)
Previous diagnosis		
Primary APS	6 (46.1)	30 (46.9)
APS + SLE	1 (7.7)	5 (7.8)
APS + SLE-like	2 (15.4)	10 (15.6)
Antiphospholipid antibody carriers	4 (30.8)	19 (29.7)
Previous APS clinical criteria	9	45
Vascular thrombosis	5 (55.5)	25 (55.5)
Pregnancy morbidity	1 (11.1)	5 (11.1)
Thrombosis + pregnancy morbidity	3 (33.3)	15 (33.3)

CAPS, catastrophic antiphospholipid syndrome; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.