

ASK THE EXPERT

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome is a potentially fatal thrombotic disease that develops in a subset of patients with antiphospholipid syndrome. Survival of patients with the rare condition, which is characterized by the development of multiple organ thromboses over a short period of time, depends on the vigilance of the treating clinicians, early diagnosis, and aggressive therapy, all of which can be compromised by multiple factors including the overlap of clinical and laboratory features with other autoimmune and infectious conditions, according to rheumatologist Dr. Doruk Erkan.

Dr. Erkan (along with Dr. Gerard Espinosa and Dr. Ricard Cervera of the Hospital Clinic Barcelona) recently published a summary of the diagnostic challenges associated with catastrophic antiphospholipid syndrome (APS) and proposed updated diagnostic algorithms to streamline its management (*Autoimmun. Rev.* 2010;10:74-9). In this issue's column, Dr. Erkan discusses the critical diagnostic and management considerations necessary to improve the outcomes of catastrophic APS patients.

RHEUMATOLOGY NEWS: What are the characteristic signs and symptoms of catastrophic APS?

DR. ERKAN: Multiple organ dysfunction, driven mainly by thrombotic microangiopathy, is responsible for the majority of the clinical events in catastrophic APS, although large venous or arterial thrombosis can also occur. The three most commonly involved organs are kidneys (renal thrombotic microangiopathy, and renal artery/vein thrombosis), lungs (pulmonary infarction and/or hemorrhage, and acute respiratory distress syndrome), and brain (stroke, seizure, and encephalopathy). However, thromboses in atypical locations are common in catastrophic APS patients. Any organ system can be involved, including the myocardial, skin, hepatic, and adrenal systems. Intestinal infarctions and peripheral gangrene can also develop, and hematologic manifestations such as thrombocytopenia and schistocytic hemolytic anemia commonly occur, creating a diagnostic challenge for physicians.

RN: What risk factors, if any, have been identified for catastrophic APS?

DR. ERKAN: The presence of multiple thrombosis risk factors is associated with a higher risk of thrombosis in individuals with antiphospholipid antibodies (aPL) and even in aPL-negative populations. A "trigger event" such as surgery, pregnancy, infection, or oral contraceptive use is commonly identified in aPL-positive patients when they develop thrombosis. Similarly, about 50%-60% of patients with catastrophic APS have an identifiable "trigger event." However, it is not well understood why some aPL-positive patients develop only single-vessel thrombosis and others go on to develop the rapidly pro-

gressive microthrombosis and organ failure that are seen in catastrophic APS. Potential genetic risk factors that may predispose aPL-positive patients to catastrophic APS are under investigation (*Am. J. Med.* 2011;124:290-6).

RN: What are the key elements for establishing a timely, accurate diagnosis of catastrophic APS?

DR. ERKAN: The first step in diagnosis is to obtain an accurate history. Previous APS diagnosis and/or persistent clinically significant aPL positivity (as determined by a positive lupus anticoagulant [LA] test and/or moderate- to high-titer aPL on ELISA) is of great importance for



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DR. ERKAN

diagnosis. However, almost half of the patients who develop catastrophic APS do not have any previous history of a thrombosis or aPL positivity. In this group of patients, the diagnosis is a particular challenge as multiple factors can impede the timely diagnosis, as in the following examples:

- ▶ A positive aPL test can be associated with infections (usually low-titer aPL ELISA) or anticoagulation (positive LA test); thus, at times it can be difficult to exclude the possibility that positive aPL tests are occurring as bystanders, not necessarily as contributors for thrombosis.
- ▶ False-negative aPL results may occur during acute catastrophic APS events.
- ▶ A continuum of thrombotic microangiopathic conditions exists, accounting for patients with thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, and catastrophic APS.
- ▶ Both sepsis and heparin-induced thrombocytopenia share similarities with catastrophic APS, and these three conditions may overlap.

For these reasons, the timely diagnosis of catastrophic APS can be challenging. At times, the differential diagnosis cannot be narrowed to a single disease during the acute period, and thus continuous assessment of patients is warranted. The most recent updated algorithms provide a "step-by-step" approach for clinicians in the assessment of patients with multi-organ thrombosis. Important steps of the diagnostic algorithms include the assessment of a history of APS or persistent aPL positivity; three or more new organ new thromboses developing in less than a week; biopsy diagnosis of microthrombosis; and other explanations for multiple organ thromboses and/or microthrombosis.

RN: Once a diagnosis has been established, what are the most important management considerations?

DR. ERKAN: If catastrophic APS is suspected, aggressive multimodal treatment is required without any delay. The most important treatment consideration is the timely administration of the right combination of medications in addition to the elimination of the potential triggers. Although there are no controlled studies, based on the analysis of the International CAPS (catastrophic APS) Registry, patients who receive the combination of anticoagulation plus corticosteroids plus plasma exchange or intravenous immunoglobulins have the highest survival rate. In the case of a deteriorating clinical situation, an additional agent, such as cyclophosphamide (especially in lupus patients) or rituximab (especially in patients with severe thrombocytopenia or hemolytic anemia) can be considered. Despite optimal therapy, the mortality rate is estimated to be approximately 30%, and may be higher if publication bias is considered.

The most pressing treatment challenges in catastrophic APS include delay in diagnosis for the reasons discussed above, ongoing thrombosis despite anticoagulation, high risk of simultaneous thrombosis and bleeding, and high prevalence of accompanying comorbidities (such as sepsis) that directly affect the mortality.

RN: How has the availability of the International CAPS Registry changed the understanding and management of catastrophic APS?

DR. ERKAN: Our current knowledge of catastrophic APS is mostly based on the

international Web-based registry, coordinated by Dr. Cervera. Patients with a catastrophic APS diagnosis have been included in this registry since 2000 through published or voluntary physician reports. The registry, which can be accessed freely (www.med.u.b.es/MIMMUN/FORUM/CAPS.HTM) contains clinical, laboratory, and therapeutic data on all reported cases of catastrophic APS, with approximately 300 patients as of May 2011; the most recent descriptive analysis of the registry reported by Dr. Cervera on behalf of the CAPS Registry group was published in April 2010 (*Lupus* 2010;19:412-8).

Because of the rarity of catastrophic APS, it is very difficult to study this life-threatening disease. The CAPS Registry is currently the only source that allows researchers to systematically analyze the demographic and clinical characteristics of these patients. Furthermore, there are no randomized, controlled trials evaluating the efficacy of various therapies, and the treatment outcome data are also based on the analysis of the registry. Thus, the registry has been crucial in our understanding as well as the management of catastrophic APS.

—Interview by Diana Mahoney

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Autoimmune Disease in Moms Ups Likelihood of Tics, OCD in Kids

FROM THE ANNUAL MEETING
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DENVER – Maternal autoimmune disease might be a risk factor for the development of obsessive-compulsive disorder or tics or both in children.

Autoimmune disorders were present in 17.8% of the biological mothers of 107 children, average age 9.2 years, with a primary diagnosis of a tic disorder, OCD, or both. This is a substantially higher figure than the 5% prevalence of autoimmune disease typically cited in the general population of women, Dr. Tanya K. Murphy noted. Moreover, the prevalence of autoimmune disease was greater among the mothers of children considered to be likely cases of Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcus (PANDAS) than in the mothers of children who were considered unlikely to have PANDAS, according to Dr. Murphy, director of the Rothman Center for Pediatric Neuropsychiatry at the Uni-

versity of South Florida, St. Petersburg.

The most common maternal autoimmune diseases in this study were Hashimoto's thyroiditis, with a prevalence of 11.9%; SLE, 3%; rheumatic fever, 3%; rheumatoid arthritis, 2%; and Graves' disease, 2%.

One hypothesis on the mechanism underlying the observed association is that prenatal exposure to maternal immune activation and inflammatory cytokines could produce significant effects upon CNS development and behavior. The PANDAS link suggests a genetic susceptibility to autoimmunity involving transmission of immune vulnerability and resistance genes. Group A strep is a potent inducer of inflammatory cytokines. One popular theory is that PANDAS arises because of molecular mimicry, with antibodies that are intended to attack group A strep targeting brain proteins instead.

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—Bruce Jancin