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HIGHLIGHT

by James N. George, MD*

Congenital Thrombotic Thrombocytopenic Purpura: Lessons for Recognition and Management of Rare Syndromes

(Commentary on Peters et al., page 956)

Case reports are a critical contribution to medical education. They tell stories of patients who provide important lessons, such as the lessons provided by the case reported by Born et al. in this issue of *Pediatric Blood and Cancer*. A 3 year-old male with acute otitis media had unexpected severe thrombocytopenia and microangiopathic hemolytic anemia. HUS was the first consideration, which is appropriate in a 3-year-old, but he had normal renal function. TTP was considered, but his physicians thought that the normal renal and neurologic function seemed inconsistent with this diagnosis. The patient was treated for his infection, given red cell and platelet transfusions, and recovered in 3 days. Born et al. later made the diagnosis of TTP when they learned that the patient had absent ADAMTS13 activity in a sample drawn before his transfusions. The diagnosis of congenital TTP was confirmed by the persistent absence of ADAMTS13 activity over 5 months without a detectable (autoantibody) inhibitor, together with mild deficiencies of ADAMTS13 activity in both parents. ADAMTS13 is a plasma protease required for cleavage of von Willebrand factor. The absence of ADAMTS13 results in accumulation of large multimers of von Willebrand factor, which contribute to the systemic microvascular platelet thrombi that are the pathologic feature of TTP.

The diagnosis and management may have been different if Born's patient had been 33 years old rather than 3. Among adults, TTP is recognized with increasing frequency. When I was training 40 years ago, TTP was rare and fatal; I remember only one patient and he died quickly. With availability of effective plasma exchange treatment in the 1980s, the diagnosis of TTP increased nearly 10-fold [1]. Current diagnostic criteria for TTP are only thrombocytopenia and microangiopathic hemolytic anemia defined by fragmented red cells on the peripheral blood smear, elevated serum lactate dehydrogenase (LDH) levels, and a negative Coombs test without an apparent alternative etiology [2]. Many patients have no neurologic abnormalities or renal failure. At age 33, Born's patient would have been diagnosed as having TTP, triggered by the acute infection, and he would have been treated with plasma exchange. Although many adult patients do not have ADAMTS13 deficiency [2], acquired ADAMTS13 deficiency caused by an autoantibody inhibitor is a well defined etiology.

But TTP is rarely diagnosed in young children. Much more common is the clinically and pathologically similar disorder, hemolytic-uremic syndrome (HUS), defined by thrombocytopenia, microangiopathic hemolytic anemia, and renal failure and typically preceded by diarrhea caused by *Escherichia coli* O157:H7 [3]. TTP, rather than HUS, becomes the diagnosis in the absence of renal failure [2]. In children, the distinction between TTP and HUS is important, as typical diarrhea-associated HUS is most often managed with supportive care [3] while TTP is typically fatal without plasma treatment [2]. Plasma exchange is required for acquired TTP; plasma infusion is sufficient for ADAMTS13 replacement in congenital TTP.

Congenital TTP, often described as the Upshaw–Schulman syndrome, was first known from case reports. In 1960, Schulman et al. [4] reported an 8-year-old female who had had episodes of thrombocytopenia and hemolytic anemia since birth that responded to plasma infusions. They postulated that she lacked a factor in normal plasma required for platelet production [4]. She had periods of up to a year without need for plasma infusions, but for most of her life she required plasma infusions every 2–3 weeks. Years later, in spite of regular plasma infusions, her renal function progressively declined and she became dialysis dependent (Moake JL, personal communication). In 1978, Upshaw [5] reported a 29-year-old female who had had episodes of thrombocytopenia and microangiopathic hemolytic anemia since age 6 months. During his 11 years of observation, she had 32 episodes at intervals of 3 weeks to 20 months [5]. All but 5 episodes had a recognized precipitating factor: infections were the most common (similar to Born's patient); other trigger events included pregnancy, surgery, and pancreatitis. She required only 2 units of plasma to respond; her platelet count often began to increase with a few hours [5]. Upshaw interpreted her abnormality as a congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia [5]. Both of these patients were included in the landmark study in 1982 that identified unusually large multimers in patients with congenital TTP and predicted the absence of a factor required for the normal processing of VWF [6,7]. This factor was identified as ADAMTS13 in 2001 [8].

Initial case reports always describe classic features of a disorder. With more experience, more variability is inevitable. Now it is recognized that patients with congenital ADAMTS13 deficiency may present at any age. In women, an initial episode may not occur until late during a pregnancy [9]. Adult siblings of patients with congenital TTP may have absent ADAMTS13 activity but no signs of TTP [9]. Patients described as congenital HUS may have deficiencies of complement regulatory proteins [10]. But since renal

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failure may also occur in patients with congenital ADAMTS13 deficiency, as in Schulman's original patient, the clinical distinction between congenital syndromes described as HUS or TTP is negligible.

The diagnostic lesson of Born's report is to be aware of congenital TTP. The management lesson is that their patient has not required regular plasma infusions. He has required plasma infusions only 3 times during the subsequent 2.5 years. These episodes were only apparent because of thrombocytopenia and the presence of schistocytes on the peripheral blood smear; hemoglobin and LDH levels were normal. These observations emphasize how subtle the clinical manifestations of congenital TTP may be. Born et al. propose that this is safer than regular plasma infusions to maintain ADAMTS13 activity over 5%. However their plan requires intelligent, motivated parents and responsive physicians to provide careful evaluation at the first sign of any illness. In addition to plasma infusions for evidence of TTP, the patient is regularly assessed for renal or neurologic abnormalities that could develop due to microvascular thrombosis that is not clinically apparent (Peters AM, personal communication).

In all patients, TTP must be recognized as dangerous. For many years, Upshaw's patient had effective treatment for her acute episodes of TTP. Then, as Dr. Upshaw wrote to me, ''Unfortunately she wearied of this, and in 1998 she expired from full-blown TTP after refusing to come in for plasma'' (Upshaw JD Jr., 2000, personal communication).

Perhaps the greatest value of Born's report is to increase awareness of these congenital syndromes. Increased awareness will lead to increased frequency of diagnoses. Increased diagnosis is critical for disorders that can be simply and effectively treated but that can be fatal without treatment.

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