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PRIORITY REPORT
Inherited ADAMTS13 Deficiency: Unique Presentation and Treatment

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A 3-year-old male presented with severe thrombocytopenia and microangiopathic hemolytic anemia in conjunction with severe bilateral otitis media. After laboratory analysis, a diagnosis of inherited ADAMTS13 deficiency was proven. Rather than treating with prophylactic fresh frozen plasma, to date the patient has been successfully treated with single-donor, directed plasma infusions in response to early signs of relapse. It may be reasonable to consider observational and reactive care rather than prophylactic care in some cases of inherited ADAMTS13 deficiency. Pediatr Blood Cancer 2008;50:956–957. © 2008 Wiley-Liss, Inc.

Key words: ADAMTS13; thrombotic thrombocytopenic purpura; von Willebrand factor

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a disease characterized by microangiopathic hemolytic anemia and thrombocytopenia caused by the abnormally high activity of the ultra large von Willebrand factor molecules (vWF). It most frequently results from decreased activity of the vWF-cleaving protease, ADAMTS13. This decreased activity is due to either an acquired inhibitor of ADAMTS13 or a congenital genetic mutation, which causes a deficiency of the active protein [1,2]. Inherited ADAMTS13 deficiencies present themselves at birth in 50–60% of cases, in childhood in 10–20% of cases, and in adolescence or adulthood in 30–40% of cases [2].

TTP is generally treated using either plasma exchange or plasma infusion [3]. TTP caused by inherited ADAMTS13 deficiency, otherwise known as Upshaw–Schulman syndrome, is generally treated prophylactically with fresh frozen plasma (FFP) infusions every 2 or 3 weeks [2]. This approach is designed to supply the ADAMTS13 protein and prevent the microangiopathic hemolysis that leads to end-organ damage.

CASE REPORT

A previously healthy 3-year-old white male presented with a fever. Physical examination revealed severe bilateral otitis media and ecchymotic lesions over his trunk and lower extremities. Although fussy with fever, the child seemed neurologically sound with no evidence of altered mental status or focal deficits. Initial laboratory tests revealed a white blood cell count of 14.1 K/μl with a normal differential, a hemoglobin concentration of 7.6 g/dl, and a platelet count of 8,000/mm^3. Reticulocyte count was within reference range at 33.8×10^9/L. The partial thromboplastin time (PTT) value was 30.2 sec and the international normalized ratio (INR) was 1.0 (both normal). Other coagulation studies revealed an elevated fibrinogen level of 480 mg/dl and an elevated D-dimer concentration of 913 fibrin equivalent units (FEU) μg/L (reference range 90–499 μg/L). Lactate dehydrogenase (LDH) level was elevated at 1,437 U/L (reference range 130–340 U/L). Creatinine level was normal (0.3 mg/dl). Total bilirubin was elevated, although the direct bilirubin was normal (1.4 and 0.3 mg/dl, respectively), suggesting hemolysis. A urinalysis was normal with the exception of 1+ albumin and 25 red blood cells per high power field. This was thought to be related to his thrombocytopenia. A Coombs test was negative. Peripheral blood smear (PBS) review demonstrated a significant population of schistocytes (5 per high power field). An ADAMTS13 level was ordered.

At the time of presentation, differential diagnoses included hemolytic uremic syndrome, although this possibility seemed unlikely given the patient's normal renal function and lack of diarrhea. TTP was considered as well, but given the patient's normal renal and neurologic function other etiologies were explored. It was suspected that the patient had early, disseminated, intravascular coagulation secondary to the otitis media and presumed sepsis. The patient was treated supportively with red blood cell and platelet transfusions. There were no adverse effects from these transfusions. Blood counts subsequently normalized, and the patient was discharged home 3 days after presentation.

The ADAMTS13 assay drawn at the time of presentation subsequently revealed a severe deficiency of ADAMTS13 activity (<4% of normal) without a detectable inhibitor (<0.4 inhibitor units). ADAMTS13 assays were repeated at 2 weeks, 2 months, and 5 months from presentation when the child was asymptomatic and always were <4% without a detectable inhibitor level. ADAMTS13 activity levels in the patient's mother and father were found to be 53% and 35%, respectively (reference range = >67%). This established the diagnosis of TTP secondary to non-immune ADAMTS13 deficiency and strongly suggested that both parents were asymptomatic carriers. Because the patient presented at age three without renal or neurologic dysfunction, it was deemed reasonable to monitor the patient's hemogram values, PBS, urinalysis, and LDH level during times of stress to determine the need for plasma infusions.

The patient's parents were instructed to seek medical attention at signs of bruising or pallor or in situations of stress (e.g., infection or trauma). Excluding the initial visit, the patient has been evaluated six times in a 2-year period for infectious symptoms, including fever. Three of these episodes (upper respiratory infection, gastroenteritis, streptococcal pharyngitis) have required treatment with FFP infusions after mild drops in platelet counts developed and schistocytes were noted on peripheral blood smear. Nadir platelet counts were 48,000/mm^3, 31,000/mm^3, and 69,000/mm^3 in these three episodes. Single-donor directed plasma has been administered to minimize risk associated with blood component transfusions. The

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LDH level has not been elevated during any of the patient's relapses and is not a reliable early indicator for this case. Hemoglobin also remained normal during relapses. Urinalyses revealed trace or 1+ albumin at times of relapse but were normal during times of health. Routine checkups at 6-month intervals have failed to demonstrate renal or neurologic abnormality.

DISCUSSION

Inherited ADAMTS13 deficiency is generally treated prophylactically. A regimen of bi- or tri-weekly FFP infusions is the preferred treatment in order to maintain a functional level of the ADAMTS13 protein. Less frequently, therapy is provided reactively (10 of 59 cases in one series). In these cases, there are typically long intervals (several years) between episodes, or the episodes have been mild [2].

Due to our patient's relatively late initial presentation and his lack of end-organ compromise, it was deemed reasonable to observe the patient's clinical course and treat with FFP reactively rather than committing to regularly scheduled plasma infusions. As described by Loirat et al., this is an unusual approach for a patient with regular relapses. However, in the case of our patient, given judicious parents who can facilitate early intervention, it has proven to be safe (i.e., minimizing transfusions, avoiding end-organ damage), effective, more convenient, and less expensive.

Physicians should be aware of this treatment option and carefully consider the circumstances of each patient. If end-organ compromise is absent or minimal, it may be reasonable to consider reactive treatment rather than prophylactic treatment [4]. Perhaps patient age at first episode should also be taken into account. Further investigation is needed to determine if a relationship exists between patient age at first presentation and clinical severity for inherited ADAMTS13 deficient patients.

The observational approach requires parents capable of identifying early signs of illness. Parental concerns must be followed with close monitoring by the medical team. We monitor blood counts daily and intervene early in the event of a progressive fall in platelet count when a small population of schistocytes is found on the PBS. To date, all episodes have followed infectious illness, which has been the most consistent indicator of possible relapse and has allowed for early intervention. If future episodes occur with no obvious trigger resulting in late presentation, or if episodes become associated with end-organ damage, we may need to reevaluate our treatment approach.

Healthcare providers would typically suspect inherited ADAMTS13 deficiency in very young patients with severe episodes of microangiopathic hemolytic anemia and thrombocytopenia combined with renal or neurologic abnormalities. Physicians must be aware that oligosymptomatic cases do occur regularly [4]. Also, since it is generally diagnosed in the neonatal period, many practitioners would dismiss the possibility of this diagnosis in a patient of childhood age [2]. ADAMTS13 levels should be obtained in the work-up for all patients presenting with thrombocytopenia and microangiopathic hemolytic anemia, as well as for those with isolated thrombocytopenia where the diagnosis is unclear.

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