A Congenital Variant of Thrombotic Thrombocytopenic Purpura in Two Siblings

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We describe two siblings affected by chronic relapsing thrombotic thrombocytopenic purpura from infancy. The elder brother, a 12-year-old boy had 50 such episodes characterized by acute onset of fever, headache, drowsiness, vomiting, dark urine, thrombocytopenia and anemia. The younger sister, a 6-year-old girl, had 8 episodes with the same clinical manifestations. Petechiae and ecchymoses on the extremities were present throughout their lives. Furthermore, anemia with evidence of red blood cell fragmentation and thrombocytopenia were present chronically. Periodical transfusion of fresh frozen plasma prevented recurrent episodes. These cases suggest that there is a congenital variant of thrombotic thrombocytopenic purpura.

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Key words: thrombotic thrombocytopenic purpura, sibling, fresh frozen plasma

Introduction

Thrombotic thrombocytopenic purpura (TTP), first described by Moshcowitz in 1924 (1), is characterized by a pentad of clinical manifestations including microangiopathic hemolytic anemia, thrombocytopenia, fever, fluctuating neurological signs and renal dysfunction. Until the early 1960s, TTP had been a fulminant, fatal disease and fewer than five percent of patients with acute episodes survived (2). Once the efficacy of whole blood exchange transfusions, plasma infusions, or plasma exchanges had been demonstrated, the survival rate of TTP increased to about eighty percent (3-7). It was also revealed that a considerable number of patients who survive the first episode of the disease frequently relapse (8).

This report presents two siblings affected by an unusual variant of TTP. Both siblings have suffered from frequent episodes of TTP with clinical manifestations of headache, vomiting, drowsiness and dark urine since early childhood. The clinical symptoms were temporarily improved by whole blood or plasma infusions. Once the diagnosis of TTP was made, they received plasma transfusions to supplement the missing plasma factor. Periodical transfusions of fresh frozen plasma (FFP) controlled their disease. Reports of siblings affected by chronic relapsing TTP since early childhood are quite rare because TTP was usually a fulminant and fatal disease. The present cases may represent an important variant of the disease.

Case Report

Case 1

A 10-year-old Japanese boy was admitted to the Yamaguchi University Hospital on the 20th of August 1990. He was born after an uncomplicated 38-week pregnancy with a birth weight of 3,030 g to 30-year-old, gravida 2, para 2 mother. Thirty-eight hours after birth he received exchange transfusions because of hyperbilirubinemia. From the age of 3 months to 10 years he experienced 50 similar episodes characterized by the acute onset of fever, headache, drowsiness associated with vomiting, dark urine, severe thrombocytopenia and anemia. At an early age, episodes had been preceded by an upper respiratory infection, however, the recent episodes had no apparent precipitating event. Petechiae and ecchymoses were present throughout his clinical course. Recent episodes necessitated his receiving transfusions of either whole blood or packed red cells to which he always responded dramatically, being clinically well within 2 days. Occasionally he recovered spontaneously from some episodes without a blood transfusion, although this recovery was slower than when he received blood transfusions.

On admission, physical examination revealed a well developed, well nourished, slightly pale boy, who had several...
ecchymoses on the extremities. The enlarged liver and spleen were each palpable to two finger-breaths below the costal margin. There was no lymph node enlargement, jaundice, hypertension, neurological abnormalities, or any sign of renal insufficiency.

Laboratory data on admission are summarized in Table 1. The peripheral blood smear showed abnormal red blood cell morphology characterized by anisocytosis, poikilocytosis, spherocytosis, reticulocytosis and fragmentation (Fig. 1A). Urinalysis was weakly positive for occult blood and negative for proteinuria. Serum electrolytes were normal. A bone marrow aspirate revealed hyperplastic marrow with a 0.28:1 of myeloid to erythroid ratio and numerous megakaryocytes. The osmotic fragility test of red blood cells was normal. All studies of the activities in the red cells of enzymes in the Embden-Meyerhof pathway, pentose phosphate pathway and those involved in glutathione metabolism were normal. Screening test for abnormal hemoglobins was negative. Platelet aggregation tests revealed that his platelets did not respond at all to adenosine diphosphate, epinephrine or collagen. The chest film and electrocardiogram disclosed no abnormality. A computed tomogram of the brain showed no abnormality, however, the electroencephalogram revealed increased whole brain theta waves. A biopsy specimen obtained from his left auricle failed to demonstrate microthrombi or any abnormality of endothelial cells. Although lacking histological proof or evidence of renal insufficiency, we diagnosed the patient as having an unusual congenital form of TTP.

Five days after admission, he complained suddenly of headache and general fatigue, followed by drowsiness, dark urine and fever. As before, there was no apparent precipitating factor. Neurological examination revealed no abnormality associated with the drowsiness. The urine was “Coca-Cola”-like in color and contained hemoglobin and protein. Microscopic examination of the urine revealed no white blood cells, a few red blood cells and many red blood cell casts. Six hours after the onset of this episode, we initiated a 200 ml fresh frozen plasma (FFP) transfusion. When one half of the volume of FFP was trans-

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<th>Table 1. Laboratory Data on Admission</th>
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Fig. 1. Red blood cell morphology characterized with anisocytosis, poikilocytosis, spherocytosis, reticulocytosis and fragmentation in the peripheral blood smear of case 1 (A) and case 2 (B). The milder morphological changes were seen in the second sister, who had no episodes of TTP (C) (Wright stain, x600).

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Fig. 2. Hospital course of case 1. After transfusing 2 U of frozen fresh plasma (FFP), a significant recovery of the hemoglobin (Hb) concentration, platelet (PLT) number, and percent reticulocytes (Retic) was seen.

Fig. 3. Clinical course of case 1 after discharge. Cyclic changes in hemoglobin (Hb) and platelet (PLT) levels in peripheral blood were evident with preventive use of 100 ml (1 U) of frozen fresh plasma (FFP) given every 3 weeks.

test gave the same results as in case 1. The chest film, electrocardiogram and the computed tomogram of the brain disclosed no abnormality. However, the electroencephalogram revealed diffusely increased theta waves. Histological examination of the skin was not performed.

We had no opportunity to observe any episode in the hospital. The laboratory data, however, demonstrated clearly that the patient had a chronic active disease resembling TTP as did her elder brother. We resigned to give prophylactic transfusions of FFP because we could not obtain her parents' consent. She was discharged with her elder brother (case 1) on the 1st of September, 1990. At 6 months after discharge, she had a relatively severe episode associated with an intracranial hemorrhage. After that, she received preventive transfusions of 100 ml FFP and has not since experienced any similar episode. Thus, we concluded that both siblings had the same disease, a variant of...
TTP, although they differed in a few respects in the onset, frequency and clinical manifestations of their diseases.

**The family**

The two affected siblings were born into a family of four children (Fig. 4). The eldest sister died at 4 days after birth with a diagnosis of "Melena neonatorum". The details of her perinatal health could not be obtained, but suggested that she too had TTP. The second sister, a 14-year-old, has had no episode of TTP and has normal peripheral blood counts and normal blood chemistries. However, a low serum haptoglobin level (34 mg/dl), mild poikilocytosis and red blood cell fragmentation in this subject suggests a mild variant of TTP (Fig. 1C). The parents were unrelated and had no history of anemia, thrombocytopenia or jaundice. Screening tests of the parents, including peripheral blood counts, blood chemistries, and serum haptoglobin levels revealed no abnormality. The other family members were not examined. Human leukocyte antigen (HLA) typing was performed for subjects 1 and 2 and their mother and revealed that they shared at least DR4.

**Discussion**

Among a number of reports regarding thrombotic microangiopathic hemolytic anemia designated as TTP, hemolytic uremic syndrome (HUS), and other pathogenic microvascular thrombotic conditions, a very unusual subset of a congenital variant has also been reported by several investigators. Schulman and his associates reported a female patient who had frequent episodes of severe epistaxis, purpuric skin lesions, jaundice and precipitous thrombocytopenia usually preceded by an infection (9, 10). They disclosed marked improvement by plasma transfusion of the platelet count as it ceased the hemorrhaging during each episode in this patient. Thereafter, on a trial basis they transfused plasma at regular intervals of 20 to 23 days, and were able to eliminate the hemorrhagic manifestations. It was noted that the patient had a chronic active disease of thrombotic microangiopathic hemolytic anemia throughout her life time, even when she was not experiencing an acute episode. Upshaw reported a female patient who experienced 32 episodes from the age of 6 months to 11 years, which were characterized by high fever, generalized petechial rash, thrombocytopenia, hemolytic anemia and, usually, a prior clinically evident infection although 5 of the 32 episodes occurred spontaneously (11). Shinohara et al presented a Japanese female patient with recurrent episodes of petechial bleeding, thrombocytopenia and anemia due to microangiopathic hemolytic anemia (12). These three patients had several important, common characteristics that were documented clinically and on laboratory analysis, such as onset during infancy, chronic active disease with frequent episodes of thrombotic microangiopathic hemolytic anemia, and an excellent reproducible response to each plasma transfusion. Rennard and Abe proposed the name "Upshaw-Schulman syndrome" for the disease condition exemplified by these subjects (13).

The cases described presently are very similar and probably identical to the three patients reported previously. In case 1 of the present report, however, there were several unique clinical
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These patients may be included in the
affected from birth by chronic thrombotic microangiopathic
age of one year (16). These patients appeared to have been
siblings with onset during infancy, all of which died before the
three siblings, at least one of which was affected by “the chronic
variant of TTP.

There are some other case reports probably belonging to
“Upshow-Schulman syndrome” in the previous literature. If the
patient does not survive the first few attacks, it is not possible
doctor its chronic clinical course. Elias et al presented
three siblings, at least one of which was affected by “the chronic
fatal variant of TTP” who died before the age of two years (14).
Wallace et al reported four siblings affected with fatal TTP from
early childhood (15). Kaplan et al also reported three HUS
siblings with onset during infancy, all of which died before the
age of one year (16). These patients appeared to have been
affected from birth by chronic thrombotic microangiopathic
hemolytic anemia. These patients may be included in the
disease category of “Upshow-Schulman syndrome”.

The pathogenes of TTP and HUS, while thought to be
identical (17), have not yet been elucidated. Several hypotheses
have been proposed. These include a quantitative abnormality
in large multimer von Willebrand factor (18), reduced
prostacyclin synthesis by endothelial cells (19), reduced tissue
plasminogen activator (20), presence of platelet aggregating
protein (21), presence of antibody to endothelial cells (22), and
hyperadhesion by neutrophilic leukocytes to endothelial cells
(23). In the 2 present cases, we found decreased von Willebrand
factor activities with normal multimer distribution and decreased levels of 6-keto prostaglandin F₁₀, a degradative product of prostacyclin.

On the other hand, a considerable number of reports regard-
ing familial occurrence of TTP and/or HUS (24–26) and our
demonstration of a congenital variant in siblings strongly
suggest that genetic predisposition plays an important role in
pathogenesis. Some investigators have indicated that family
members affected by TTP and/or HUS have common human
leukocyte antigens (HLA) (27, 28). Pirson et al however, found
no relationship between familial HUS and any specific HLA
phenotype (29) as demonstrated by the present cases. It is of
interest that the parents appear normal although genetic predis-
position is suggested. A single autosomal recessive segregation
may be causative as speculated by Wallace et al to explain how
4 children of 7 with normal parents were affected (15). In the
present cases, however, all 4 children were somehow affected.
Therefore, it is unlikely that a single autosomal recessive
mutation is responsible for their condition. Our cases suggest the
possibility that environmental factors may operate in addition
to a genetic factor. To exclude any environmental factor, such as a toxic agent, we carefully obtained the history of each
family member but did not find any prominent characteristics.
The mother had no unusual history of drug use. Thus, the fact
that our cases are siblings and were affected from infancy
suggests ambiguously a genetic cause to their condition.

Recently, Byrnes and Moake classified TTP into three
subgroups, mainly according to the frequency of episodes;
single episode, intermittent and chronic relapsing TTP (30).
Interestingly, Rose and Eldor suggested using their unique
scoring system that the episodes in frequently relapsing patients
were milder than those in patients with a single episode of TTP
(8). The present subjects also have normal renal function, which
is the most important prognostic factor in TTP and HUS (31),
in spite of frequent episodic hemoglobinuria. Furthermore, our
patients have experienced neither growth or mental retardation.

In conclusion, we report a congenital variant of TTP,
“Upshow-Schulman syndrome” in two siblings. Periodical
transfusions of FFP were effective for preventing recurrences.
Although the present cases suggest that there is a genetic basis
for this disease, an etiologic mechanism remains to be clarified.
It will be important to follow carefully the clinical course of
these patients as it may provide added insight into the
pathogenesis of TTP and HUS.

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