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Thrombotic thrombocytopenic purpura in pediatric patients

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Abstract: Although thrombotic thrombocytopenic purpura (TTP) is rarely seen in pediatric patients, failure to recognize this condition often leads to severe consequences and poor outcomes. Classic features of TTP include thrombocytopenia, microangiopathic hemolytic anemia, acute kidney injury, fever, and central nervous system involvement. However, patients suffering from this condition may not present with all of the symptoms simultaneously. Therefore, it is of utmost importance for healthcare providers to have a high index of suspicion. Laboratory investigations may reveal the presence of schistocytes on peripheral blood smear, negative Coombs test, high lactate dehydrogenase levels and severely low platelet counts. The etiology of TTP is mainly due to insufficient cleavage of the large multimers of von Willebrand factor (vWF) secondary to decreased activity of ADAMTS13 (a disintegrin and metalloprotease with Thrombospondin type 1 repeats, member 13). TTP can be broadly classified into familial TTP (Upshaw Schulman syndrome) and non-familial TTP. Familial TTP is due to a congenital deficiency of ADAMTS13. Its mainstay of therapy is initiation of plasmapheresis during the acute phase, followed by regular fresh frozen plasma (FFP) infusions. Alternatively, non-familial TTP is due to a decrease in ADAMTS13 activity secondary to the presence of anti-ADAMTS13 antibodies. Once again, the primary treatment is plasmapheresis; however, recent anecdotal data also supports the use of rituximab in select cases. [**Chin J Contemp Pediatr, 2012, 14(11):803 - 810**]

Key words: Thrombotic thrombocytopenic purpura; ADAMTS13; Plasmapheresis; Child
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儿童血栓性血小板减少性紫癜

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[**摘 要**] 血栓性血小板减少性紫癜(TTP)在儿童病例中甚为少见,但如未能及时诊断及施予治疗,其后果则极为严重。其最常见之5种病症为:血小板减少、微血管溶血性贫血、急性肾衰竭、发热及中枢神经系统症状。但临床病例中,并不一定会同时出现上述5种症状。故此医疗人员对此病必须有极高之警觉性。TTP之病理特征包括:外周血涂片可见裂体细胞,Coombs试验阴性,血清乳酸脱氢酶增高及中度或重度血小板减少。TTP发病机理主因缺乏ADAMTS13,从而引发微血管溶血性贫血及血小板减少。TTP可概括分为家族性TTP(Upshaw Schulman综合征)和继发性TTP。家族性TTP是由于先天性ADAMTS13缺乏所致,其急性治疗法为血浆置换,当病情稳定后,可输注新鲜冰冻血浆以防止病情复发。继发性TTP是指患者因体内产生抗体而导致ADAMTS13功能减退,主要治疗方法亦为血浆置换,最新之临床文献显示rituxiamb对此症亦颇有治疗价值。 [**中国当代儿科杂志,2012,14(11):803 - 810**]

[**关 键 词**] 血栓性血小板减少性紫癜;ADAMTS13;血浆置换;儿童

Thrombotic thrombocytopenic purpura (TTP) is rarely found in the pediatric population[1]. Nevertheless, it is important for pediatricians and pediatric specialists to be familiar with the disease presentation, be-

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cause it is associated with a high mortality rate if it is not promptly and appropriately treated[2].

von Willebrand factor (vWF) is typically secreted as large multimers which are linked by covalent bonds. It has been suggested that the pathophysiology of TTP is related to decreased activity of ADAMTS13, a 190-kD metalloprotease of the M12B subfamily, responsible for the cleavage of these vWF multimers[3]. Decreased activity of this protease results in platelet activation, leading to a consumptive thrombocytopenia, systemic microvascular thrombosis and severe microangiopathic hemolytic anemia (MAHA) with schistocytosis[4]. The pentad of clinical features associated with TTP includes: fever, thrombocytopenia, MAHA, neurologic abnormalities and renal involvement[5]. However, the entire pentad is often not apparent at presentation, and therefore, physicians should consider TTP on the differential diagnosis for a patient presenting with any of these symptoms[6].

TTP can often be confused with hemolytic-uremic syndrome (HUS), which is significantly more common in the pediatric population[7]. There is a risk of misdiagnosis as these two diseases have several characteristics in common, including MAHA, thrombocytopenia and the potential for renal or neurological abnormalities[8]. Patients with HUS are more likely to present with diarrhea and are more likely to develop severe renal failure, whereas neurological complications are more common in TTP[4]. Nevertheless, diarrhea is present in up to 30% of TTP cases[9]. Although typical HUS does not benefit from plasma exchange (PE) therapy, PE therapy is often initiated until TTP can be definitively ruled out[9]. Investigations that may aid in the distinction include: ADAMTS13 activity, stool cultures, and serology for *E. coli* 0157:H7[9].

TTP occurring in children can generally be divided into familial TTP or non-familial TTP. Familial TTP is due to significantly reduced ADAMTS13 activity and follows an autosomal-recessive inheritance pattern[10]. In non-familial TTP, autoimmune mechanisms have been implicated, in the form of autoantibodies against ADAMTS13[11].

The purpose of this report is to present a review of TTP cases found in the pediatric literature. An extensive search of the primary literature was conducted, specifically using the PubMed database. Since TTP is a rare occurrence in pediatric medicine, there is a lot to be learned from individual case reports. Each of these reports adds additional knowledge in regards to the diagnosis and management of TTP in children.

1 Familial TTP/Upshaw Schulman syndrome

Upshaw Schulman syndrome (USS) is a genetic form of TTP inherited in an autosomal recessive fashion[12]. One characteristic that distinguishes it from non-familial TTP is age of onset, as approximately 75% of children will have their first presentation of TTP as early as birth[13]. During the neonatal period, common presentations of TTP include thrombocytopenia, hyperbilirubinemia, and hemolytic anemia with schistocytosis[13].

Klukowska et al[14] reported two families in which more than one child experienced episodes of TTP. They subsequently were diagnosed with USS, confirmed by low activity levels of ADAMTS13, and the absence of enzyme inhibitors. Four out of the five affected children in this report presented in the neonatal period; all required exchange blood transfusions for neonatal hyperbilirubinemia[14]. Unfortunately, the diagnosis of familial TTP in these patients was not established until 10 years after presentation, as familial TTP was misdiagnosed as immune thrombocytopenia, Evans syndrome and HUS[14]. Therefore, the authors emphasize the benefits of early ADAMTS13 activity testing in cases of familial occurrence of immune thrombocytopenia, hemolytic anemia, severe neonatal hyperbilirubinemia requiring exchange blood transfusion and relapsing proteinuria and hematuria[14].

1.1 Investigation of familial TTP

Diagnosis of familial TTP is confirmed via a decreased ADAMTS13 activity, absence of ADAMTS13 inhibitors or autoantibodies, and ADAMTS13 gene sequencing[15]. Unfortunately, these investigations are not routinely available. Moreover, since presentation can be vague and non-specific, the diagnosis of familial TTP is often delayed or incorrect.

Schmugge et al[16] studied ADAMTS13 activity levels in healthy neonates, children and adults, and determined that generally, neonates had similar ADAMTS13 activity levels compared to children and adults. However, the authors found that 26% of neonates had reduced ADAMTS13 activity [(53.0 ± 1.1) %], but this normalized by 2-3 days of age[16]. This is important to keep in mind when measuring ADAMTS13 activity levels in neonates.

1.2 Approaches to the treatment of familial TTP

The treatment of choice for hereditary familial TTP may involve plasmapheresis during the acute phase,

followed by periodic FFP transfusions to maintain sufficient ADAMTS13 level, thereby preventing disease relapse[17]. Plasmapharesis therapy provides two benefits, as it replaces the deficient substance and also eliminates harmful substances[2]. Regular plasmapheresis is technically difficult in neonates because of small body size. However, as mentioned above, exchange transfusion has been used in cases of neonatal TTP presenting with hyperbilirubinemia[15].

Born et al[18] presented a case of inherited ADAMTS13 deficiency, in which the first presentation of TTP occurred at the age of three days. The patient's ADAMTS13 activity was < 4% at the time; and his mother and father's ADAMTS13 activity levels were 53% and 35% respectively, suggesting that they were asymptomatic carriers[18]. In this case, the authors treated the patient with FFP only in high risk situations, and this was done on three occasions when the patient had an infection[18]. From this case, the authors suggest that a reactive approach may be reasonable in certain circumstances of inherited familial TTP[18].

Scully et al[19] presented yet another approach to treat familial TTP, which involves the use of plasma-derived factor VIII concentrate of intermediate purity (BPL 8Y) for both treatment and prophylaxis. In this case series, seven children with familial TTP were successfully managed with BPL 8Y, thereby suggesting that BPL 8Y is an effective alternative to FFP, and it offers unique benefits because the therapeutic volumes of BPL 8Y are smaller than that of FFP[19].

Jilma-Stohlawetz et al[20] examined the effectiveness of an aptamer targeted against vWF in three adult patients with chronic relapsing familial TTP. This aptamer, ARC1779, acts to inhibit vWF-mediated thrombosis and was shown to increase or stabilize platelet counts. Nevertheless, at the present time, it cannot be recommended for treatment of TTP, since complete clinical and laboratory improvement did not occur[20].

1.3 Familial TTP associated with Moyamoya syndrome

There are two case reports of Moyamoya syndrome associated with TTP in pediatric patients. One case is of an eleven-year-old boy with unilateral Moyamoya disease and familial TTP, which was confirmed by an ADAMTS13 activity of < 3% of normal, and an ADAMTS13 gene analysis demonstrating a splicing-donor-site mutation[21]. The second case is of a 3-year-old girl diagnosed with Moyamoya syndrome and familial TTP with evidence of severe ADAMTS13 deficiency[22]. In both of these cases, the patient's hematologic abnormalities were treated with regular fresh frozen plasma transfusions[21-22]. However, with only two case reports in the literature, it is difficult to account for the association between Moyamoya syndrome and TTP.

2 Non-familial/Idiopathic TTP

Non-familial TTP occurs about 15-fold more frequently in adults compared to children[23]. Clinical presentation can be similar to familial TTP; however, the age of presentation for non-familial TTP is rarely before one year old[24]. The diagnosis is confirmed by low levels of ADAMTS13 activity, together with either a positive assay for ADAMTS13 inhibitor, or a positive enzyme-linked immunosorbent assay for anti-ADAMTS13 IgG[25]. The gold standard of treatment is plasmapheresis to overcome the inhibitors[3], but individual case reports may offer additional insight.

2.1 Non-familial TTP treated with plasma exchange

Successful treatment of TTP with plasma exchange is well-documented in the adult literature, but there is only limited evidence for the use of plasma exchange in children with TTP. Lawlor et al[26] presented two children, aged 6 and 12 years, both successfully managed with plasma exchange for the first episode of non-familial TTP. Both originally presented with hematologic, neurologic and renal abnormalities. The first patient responded to plasma exchange with resolution of his hematologic and neurologic abnormalities, however, renal dysfunction persisted[26]. The second patient also benefited from plasma exchange, and had a full recovery other than requiring skin grafts for a leg wound[26].

2.2 Approach to TTP in a pediatric patient too small for plasmapheresis

Tripathi et al[27] presented a case of a 3-year-old child with TTP, who was deemed ineligible for plasmapheresis due to his small size. Instead he was successfully treated with prednisolone (1 mg/kg/day) and daily FFP infusions[27]. This case also suggests a potential risk associated with use of platelet transfusions in TTP, as the patient in this case had been given two units of platelets and subsequently suffered a cerebral infarct[27]. This is controversial because the TTP-HUS registry in adults showed no significant harm in terms of neurological sequelae or death[28].

2.3 Non-familial TTP requiring rituximab therapy

There is extensive evidence for the use of rituximab,

an anti-CD20 monoclonal antibody, in the treatment of TTP in adults[29]; however, experience for its use in children is more limited. Given the potential publication bias, rituximab treatment in pediatric patients with TTP seems to have a high success rate.

Curtillet et al[30] first reported successful use of rituximab in a 14-year-old patient with autoimmune TTP. The patient was initially treated with daily plasma exchange, and then subsequently treated with four weekly injections of rituximab. At day 89, the patient was still in remission[30].

Albaramki et al[31] reported the use of rituximab in two children. The first was a 15-year-old girl who failed to respond to 10 days of plasmapharesis, but responded rapidly to immunosuppression with prednisolone and rituximab. She remained in remission 12 months later[31]. Furthermore, her ADAMTS13 activity recovered from <10% before treatment to 100% at 6 months after remission[31]. The second case is of a 6-year-old boy who presented with his third relapse of non-familial TTP. The first two episodes were treated with plasmapheresis and prednisolone[31]. In the third relapse, he was initially treated with plasmapheresis, but this was complicated by infection of his vascath catheter. Therefore, rituximab was added, and he remained in remission 17 months later[31].

Jayabose et al[32] discussed a patient who developed TTP at the age of 10 years, and subsequently relapsed twice in a two year period. After her second relapse, being controlled with plasmapheresis, she was treated with vincristine, oral prednisone and a single dose of rituximab to prevent further relapse[32]. Her peak ADAMTS13 level achieved 99% at 24 weeks[32]. However, because her ADAMTS13 levels decreased to <15% over the next 38 weeks, she was then treated with rituximab 375 mg/m^2 weekly for four doses[32]. Her ADAMTS13 level remained above 97% at week 60[32].

There are other cases in the literature of non-familial TTP treated with rituximab (Table 1) with similar situations to the cases discussed above[33-35]. These cases highlight the importance of distinguishing familial from non-familial TTP, as patients with non-familial TTP can often benefit from immunosuppressive therapy, such as rituximab. The mechanism of action of rituximab involves the depletion of B-lymphocytes leading to decreased titres of inhibitory antibodies and subsequent increase of ADAMTS13 activity[31]. Specifically, rituximab seems to be an important addition in patients that do not respond effectively to plasma exchange therapy, or who suffer from TTP relapses.

Table 1 Characteristics of pediatric TTP patients treated with rituximab

Reference	Gender	Age (years)	Episode of TTP	Treatment	Reason for rituximab	Follow-up
[30]	Male	14	First	PE; 4 weekly injections of rituximab beginning on day 40.	Failed attempt to space out PE.	In remission at day 89.
[31]	Female	15	First	PE; prednisolone and 4 weekly injections of rituximab beginning on day 9.	Slow hematological and biochemical recovery with PE therapy.	In remission at 12 months.
[31]	Male	6	Third	PE; 4 weekly injections of rituximab after infection of vascath catheter.	Recurrence of disease following infection of vascath catheter.	In remission at 17 months.
[32]	Female	12	Third	PE, vincristine, oral prednisone, and one dose of rituximab; 4 weekly injections of rituximab were given at 38 weeks.	Prevent a third relapse.	In remission at week 60.
[33]	Male	10	First	PE; 4 weekly injections of rituximab beginning on day 20.	Refractory to PE therapy.	In remission at 18 months.
[35]	Female	16	First	PE and methyl-prednisolone; 4 weekly injections of rituximab beginning on day 13.	Refractory to PE therapy.	In remission at 3 months.

PE: plasma exchange

2.4 Non-familial TTP with spontaneous recovery

Moskowitz et al[36] reported a 5.5-year-old female who presented with anemia and thrombocytopenia. Throughout the course of her illness, she was not given any transfusions or treatments; instead, she was monitored with close observation and frequent blood counts[36]. Her diagnosis was only determined five months into her illness, with an ADAMTS13 inhibitor level of >8.0 inhibitor units and ADAMTS13 activity of <5%[36]. She experienced spontaneous recovery, with normal blood counts within six months of presenta-

tion, undetectable ADAMTS13 inhibitors at nineteen months after presentation, and ADAMTS 13 activity of 51% at nineteen months post-presentation[36].

These authors presented the first case report of a child with TTP who experienced spontaneous recovery[36]. They introduce the idea that plasma exchange therapy has several risks associated with it, including systemic infection, hypotension and catheter thrombosis[36]. However, since untreated TTP is associated with a high mortality rate, a "watchful waiting" approach cannot be recommended at this time.

2.5 TTP associated with systemic lupus erythematosus

There are more than 20 reports of TTP associated with systemic lupus erythematosus (SLE) in pediatric patients. Although TTP is rare in children, the association of TTP with SLE is more common in the pediatric population compared to adults[37]. Brunner et al[37] studied 35 cases of childhood-onset TTP and concluded that the proportion of incipient or definite SLE in pediatric patients with TTP ranges from 35% to 49%, which is significantly greater than that in adults. Furthermore, severe proteinuria in these patients is considered a risk factor for SLE[37].

On the other hand, it is also essential to maintain a high suspicion for TTP in patients with SLE. Thampi et al[38] reported a 9-year-old girl initially diagnosed to have SLE. The diagnosis was later changed to TTP due to significant numbers of schistocytes on the peripheral smear and a low ADAMTS13 level. Since both SLE and TTP can cause hemolysis, the presence of schistocytes is an important distinguishing feature between the two[38]. In contrast, Yuen et al[39] presented a case of an 8-year-old boy diagnosed with both SLE and TTP, and subsequently experienced nine relapses of TTP in a two-year period. Interestingly, eight of the relapses were associated with low activity index of SLE[39].

3 Non-familial TTP secondary to other comorbidities

The literature describes several cases of non-familial TTP secondary to other comorbidities. Specifically, in the pediatric literature, there are reports of TTP secondary to liver transplantation, stem cell transplantation, surgical operation, hemoglobinopathies and infection.

3.1 Transplant-associated TTP

Transplant-associated TTP likely results from extensive endothelial damage caused by chemotherapy, calcineurin inhibitors, graft versus host disease (GVHD), cytomegalovirus, or veno-occlusive disease (VOD)[40]. Moreover, cyclosporin may increase the release of VWF from endothelial cells, thus imposing additional risk in this setting[41].

Lee et al[42] reported an association between liver transplantation and TTP in pediatric patients. Out of 400 liver transplant patients (including 146 pediatric patients), four (1%) developed TTP, and all four of these patients were children[42]. In three of the children, the etiology of the TTP was due to cyclosporin therapy, while in the fourth, the etiology of TTP was due to VOD[42]. Unfortunately, despite reductions or removal of cyclosporine therapy and treatment with plasma exchange, only one of these patients survived, illustrating the high fatality rate of post-transplant TTP[42].

Reports from the adult literature also indicate poor prognosis in patients who develop thrombotic microangiopathy following liver transplantation. Nishi et al[43] discussed 18 patients who developed thrombotic microangiopathy following living-donor liver transplantation and were treated with plasma exchange. Although 56% responded to the plasma exchange therapy, one year survival rate was only 30%[43].

Similarly, there is an association between stem cell transplantation and TTP in pediatric patients. Sawant et al[44] reported a 17-year-old female with acute myeloid leukemia who received an allogenic hematopoietic stem cell transplant, and was treated with methotrexate, cyclosporine-A, and methyl prednisolone for prophylaxis against graft versus host disease (GVHD)[44]. On post transplant day 42, she was diagnosed with TTP and treated with plasma exchange, which led to improvement in her renal function and hematological markers[44].

Plews et al[41] reported a 2.5-year-old female with stage IV neuroblastoma who developed TTP secondary to bone marrow transplantation and pneumococcal sep-

sis. Early intensive treatment was begun with manual whole blood exchange due to challenges associated with the child's small size and venous access[41]. Since no clinical improvement was witnessed, she was subsequently treated with daily plasma exchanges with cryosupernatant for 34 days[41]. At three months after transplant, the patient had no evidence of disease sequelae, and she never experienced any TTP relapses[41].

The reports by Plews et al[41] and Sawant et al[44] all reemphasize the need to retain a high suspicion for TTP in patients receiving stem cell transplants, which can be controlled by early initiation of plasma exchange therapy.

In contrast, a case from the adult literature reports successful treatment of transplant-associated microangiopathy without the use of plasma exchange therapy[45]. The patient was a 26-year-old woman who developed transplant-associated microangiopathy following an allogeneic bone marrow transplant for aplastic anemia[45]. In this case rituximab was administered instead, justified by the patient's rapid deterioration[45].

3.2 Post-operative TTP

Although there is an increasing number of post-operative TTP cases being reported in the adult literature, Schiller et al[46] presented the first case of post-operative TTP in a pediatric patient. The patient was a 14-month-old infant who developed TTP several days after surgical removal of a large pelvic tumor[46]. The TTP was successfully treated with double-volume plasma exchange, beginning on post-operative day five[46]. The patient was also treated with chemotherapy for the malignancy (diagnosed as malignant yolk sac tumor), and at follow-up 48 months later, the child was doing well with no relapses[46]. The authors encourage a high index of suspicion for TTP in any post-operative child presenting with signs such as fever, anemia, renal failure and thrombocytopenia[46].

In contrast, Naqvi et al[47] presented a review of post-operative TTP in adults, and found that approximately 79% of cases occurred following vascular surgeries, with only 17% of cases complicating gastrointestinal surgeries. Typically, patients presented with MAHA and thrombocytopenia, sometimes accompanied by changes in mental status, fever, and renal impairment[47]. The majority of these patients were treated with plasma exchange, with 74% survival noted[47]. Unfortunately, even in adults, this diagnosis can be missed due to the timely association with surgery[47].

3.3 TTP in association with hemoglobinopathies

TTP complicating sickle cell disease has been reported in the adult literature, but Majjiga et al[48] presented the first case of TTP in association with sickle cell-hemoglobin C disease in a pediatric patient. This patient presented with the classic pentad of TTP[48]. He responded appropriately to plasma exchange therapy, and recovered without any sequelae, including no TTP relapses within a 3-year follow-up period[48].

Difficulty in diagnosing TTP in patients with sickle cell hemoglobin C has also been reported in the adult literature. Chinowsky et al[49] discussed a 22-year-old woman with fever and deteriorating mental status initially treated with IV acyclovir and IV antibiotics. She was subsequently treated with red blood cell exchange transfusion, IV folic acid therapy and IV Solu-Medrol, resulting in no improvement[49]. Clinical and laboratory improvement was achieved once plasma exchange therapy was initiated, helping to confirm a diagnosis of TTP[49].

3.4 TTP associated with brucellosis

Akbayram et al[50] reported the first case of TTP associated with brucellosis occurring in a child[50]. The patient, a 7-year-old girl, had risk factors for brucellosis, including living in a rural area and consumption of unpasteurized dairy products. The TTP was treated with methylprednisolone and fresh frozen plasma replacement, as plasma exchange could not be performed due to technical insufficiency[50]. Her brucellosis was treated with rifampisin and trimethoprim-sulfamethoxazole[50]. Unfortunately, the patient suffered from a pulmonary hemorrhage on her third day of hospitalization, and did not survive[50].

Despite this being the first case report of TTP associated with brucellosis in a child, there are a few case reports in the adult literature[50]. The mechanism by which brucellosis causes TTP is believed to be via circulating endotoxins[50]. In two different case reports of adults with brucellosis-induced TTP, both adults were successfully treated with plasma exchange[51-52], suggesting that this may be the preferred treatment in children as well.

4 Conclusions

The pentad of TTP applies to both children and adults; however, in both populations, clinical presentation can be vague, with MAHA (including presence of schistocytes on peripheral blood smear) and thrombocytopenia as the most common features[53]. The criterion for initiation of plasmapheresis therapy is based only on the presence of these two laboratory abnormalities[53].

In children, there is a higher chance of misdiagnosis, since HUS is a more common cause of MAHA and thrombocytopenia[53]. In contrast, in adults, TTP is more common than HUS[53]. However, if in doubt, the patient should be treated for TTP, because the mortality can be dramatically reduced by early initiation of plasmapheresis.

In both children and adults, untreated TTP carries a high risk for mortality. Plasma exchange therapy is indicated in non-familial TTP of all ages; however, experience with adjunctive treatments, such as rituximab, is more limited in the pediatric literature.

Since TTP in pediatric patients is a rare entity, much of our knowledge comes from small studies and case reports. A review of the available literature has illustrated that pediatric TTP can present in many different clinical contexts. One imperative message that was consistently stressed throughout the literature is the importance of maintaining awareness of TTP even in the absence of obvious symptoms, and to watch for comorbid illnesses that may mask underlying TTP. Alertness of the key distinguishing features of TTP is required, including schistocytosis on peripheral smear, negative Coombs test, elevated serum lactate dehydrogenase, and moderate-to-severe thrombocytopenia[53].

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