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Review Article

Thrombotic Thrombocytopenic Purpura: Diagnosis and Treatment

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ABSTRACT

Thrombotic Thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathic disease, associated with thrombocytopenia and hemolytic anemia. It is caused by an enzymatic dysfunction responsible in cleavage of blood clotting factors. In this study we have tried to review the available approaches in diagnoses of the disease as well as treatment strategies. Based on the what the current review has provided, treatment policy depends on accurate diagnosis, it seems that developing a diagnostic and treatment guide for this disease is currently essential. Also, it's necessary to study genetic types of TTP with more details because, hopefully, new techniques of gene therapy open a window to more stable treatments.

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Introduction

Thrombotic Thrombocytopenic purpura (TTP) is a heterogeneous group of thrombotic microangiopathic diseases which are diagnosed by microangiopathic hemolytic anemia with fragmented RBCs, thrombocytopenia, and organ dysfunction caused by disturbed blood flow in capillaries. TTP is caused by sever deficiency of an enzyme (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) ADAMTS-13 responsible for physiologic cleavage of von-wilberand factor (vwf). Thrombocytopenia and Hemolytic Anemia are laboratory findings of thrombotic microangiopathy.[1] In 1996 five common features of TTP (such as thrombocytopenic purpura, hemolytic anemia, neural symptoms, and renal diseases) were registered.[1] Lian and colleagues found that by incubation of patients' TTP plasma with normal plasma, platelets activity will decrease. Hence after 1979, platelet aggregation factor was introduced for the cause of TTP.[2] This factor was discovered by Moake and in 1982, it was considered as an unusual big complex containing Factor XIII and vwf multimers[3] which is now called a giant vwf. In 1966 the enzyme which is responsible for cleavage of vwf polymers into the smaller multimers was discovered and was introduced as metalloproteinase.[4] Also In 1988 it was determined that non-familial TTP is associated with inhibition of vwf cleaving proteasea.[5] In 2001 it was report that this protease gene locus is on chromosome 9q34 which is named as a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13).[6] There is usually severe anemia and hemoglobin concentration is lower than 10 mg/100 ml. Fragmented RBCs (schistocytes), burr cells, and helmet cells, are significant morphologies in

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peripheral blood smear. Hemolysis indicators are increase in LDH and free Hemoglobin in plasma, and low or undetectable haptoglobin level. Hyperbilirubinemia is common and reticulocytes count is regularly increased. Schiztocytosis and negative coombs test are the basic criteria for microangiopathic hemolytic anemia. Vascular platelet aggregation will reduces platelet survival and it is determined by creation of small blood clots in capillaries and arteries.[7] The decrease in vwf cleaving metalloproteinase activity is assumed the fundamental cause of disease mechanism in hereditary and acquired TTP.[8] Therefore, dysfunction in ADAMTS13 activity can be seen in different autoimmune situations. An auto-antibody may cause transient and relapsing acquired TTP. Disorder in immune system regulation and auto-antibody production lead to multiorgan manifestations like lupus erythematosus and antiphospholipid syndrome.[8] Terms of microangiopathic hemolytic anemia and thrombotic microangiopathy are used for the cases with infection, bone marrow transplantation, drug therapy, cancer, chemotherapy, and pregnancy.[9] The disease emerges suddenly and early clinical symptoms include: fatigue, joint pain, myalgia, and stomachache (like cold) can be found frequently.[10]

Epidemiology

Studies show the incidence rate of TTP in black people is sevenfold higher than non-blacks and more than threefold higher in women compared to men.[11] TTP can be diagnosed in all ages of adulthood. The highest incidence rate is in patients 18-49 years old.[11] TTP is a rare disorder, and the disease incidence is 5 per million per year.[12] TTP in adult patients is with acquired dysfunction and severe deficiency of ADAMTS13 which occurs in one per 100000 persons a year.[13, 14] Mostly early signs of TTP begins with pregnancy.[15] Pregnancy may be a risk factor for acute acquired TTP and reveals hereditary form of the disease.

Pathophysiology

Vwf is synthesized by endothelial cells and megakaryocytes and it is stored as giant multimers of vwf. Multimers are in endothelial Weibel–Palade bodies and alpha granules of platelets. A metalloproteinase named ADAMTS13 is responsible for proteolytic cleavage of giant multimers of vwf.[16] Deficiency of ADAMTS13 activity in cells and blood flow can cause platelet aggregation and fibrin-platelet clot formation in blood vessels and consequently cause TTP.[16] Hereditary absence or acquired inhibition are the reasons of ADAMTS13 activity inhibition of this protease.[17, 18] Congenital disorder of ADAMTS13 is known as Upshaw-Schulman syndrome that includes thrombocytopenia, microangiopathic hemolytic anemia, and microvascular coagulation which is treated by plasma transfusion or exchange.[19] Immunosuppressive drugs can alter the antibodies and inhibit the ADAMTS13 in patients with TTP.[20] Laboratory findings of this disease include microangiopathic hemolytic anemia, schistocytes in peripheral smear, thrombocytopenia, and clinical symptoms such as fever, renal failure, and neural disorders.[16] Severe ADAMTS-13 deficiency is the result of antibodies inhibiting ADAMTS-13 activity or increasing ADAMTS-13 clearance in acquired TTP and homozygous or compound heterozygous ADAMTS-13 mutation in hereditary form of the disease.[21] If ADAMTS13's activity reaches lower than 10 %, giant vwf would not be cleaved and aggregate on the endothelium surface.[22] Studies show in acute TTP damaged endothelial cell markers will be released such as thrombomodulin, tissue plasminogen activator, intercellular adhesion molecules (ICAM), vascular adhesion molecules (VCAM), and endothelial microparticles.[23]

Classification

TTP must be differentiated from hemolytic uremic syndrome(HUS) which has similar clinical manifestation.[24] Autoantibody against Factor H and I in complement system is detected in some cases of HUS. Also, some patients had mutations in thrombomodulin and diacylglycerol kinase E.[22] Quinine was the first drug associated with thrombotic microangiopathic anemia (TMA). Lower doses of gemcitabine when in combination with docetaxel and oxaliplatin, are associated with thrombotic microangiopathic anemia (TMA).[25] Antiplatelet drug-like ticlopidine and clopidogrel develop TTP.[26] Sirolimus can cause thrombotic microangiopathic anemia (TMA) in transplantation.[27] Chemotherapy drugs such as mitomycin-c, gemcitabine, cisplatin, and carboplatin correspond with TMA.[28] Vit B-12 deficiency is related to TMA which is called TTP.[29]

Diagnosis Evaluation

Laboratory Technics for TTP diagnosis

TTP patients are diagnosed with severe thrombocytopenia, decrease in hemoglobin and hematocrit, indirect bilirubin increase, schistocytes presence in peripheral blood smear.[30, 31] Seeing schistocytes in peripheral blood smear is the easiest and the most important laboratory finding for diagnosis.[32] Although evaluation of ADAMTS13 level is significant for the confirmation of the disease, ADAMTS-13 activity test is not usually available so TTP treatment should be lingered because of laboratory test results.[33] If ADAMTS-13's activity level gets lower than 10 % confirm TTP diagnosis.[34] ADAMTS-13's activity level can reach higher than 10 % by using plasma containing ADAMTS-13 in patients with TTP (table 1).[35]

TTP Differential Diagnosis

Hereditary and immune TTP is a microangiopathic hemolytic anemia that platelets and fibrin block blood vessels which causes thrombocytopenia, anemia, and increase in LDH level. Fragmentation of RBCs because of platelet aggregation leads to anemia. Tissue necrosis and ischemia rise LDH level.[36] In Upshaw-Schulman syndrome (Hereditary TTP) ADAMTS-13's level decreases, in other words liver produces low ADAMTS-13. More than 100 mutation is discovered for this syndrome. Regarding to the kind of mutation patients

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Table 1: Laboratory tests for differential diagnosis of thrombotic microangiopathies[32]

Laboratory Tests	Measured Parameters	Possible Diagnosis
Hematology	Complete blood count (peripheral blood smear, identifying schhiztocytes)	Microangiopathic hemolytic anemia
Biochemistry	Creatinine, urine protein, LDH, haptoglobin level	Hemolytic uremic syndrome (HUS)
Coagulation evaluation	Prolonged PTT, low fibrinogen level, increased D-Dimer	-severe fibrinolysis -Disseminated intravascular coagulation
Microbiology/virology	Investigating shigga toxin in urine and stool, blood culture, HIV, HBS, and HCV tests	-Shiga toxin associated HUS -Strep. Pneumonia associated HUS -HIV associated HUS
Pregnancy Test (for women in age of fertility)	BHCG	-HELLP Syndrome -Eclampsia
Immunologgy	Positive Direct coomb's test, Low ADAMTS-13 Ag level, ADAMTS-13's low activity, identifying inhibitor of ADAMTS-13	-Autoimmune hemolytic anemia -Evan's syndrome -Immune TTP -Hereditary TTP

LDH: Lactate Dehydrogenase. PTT: Partial Thromboplastin Time. BHCG: Human Chorionic Gonadotropin. HCV: Hepatitis C virus. HIV: Human immunodeficiency virus. HUS: Hemolytic–uremic syndrome

indicate clinical signs in childhood(50 to 60 % of the cases), early adulthood, third or fourth decade of their life,[37] in (table 2) Microangiopathic hemolytic anemias Classification is showing.

Hemolytic Uremic Syndrome (HUS) Associated with Shiga Toxin

E-coli O157 is the most common organism produces shiga toxin.[38] This organism can cause dysentery with or without HUS.[39] Shiga toxin induces vwf secretion from endothelial cells, consequently rises thrombotic activity and inflammation.[40] Unlike TTP, in HUS associated with shiga toxin there is not a decline in ADAMTS-13 activity level. After entering the intestine, E-coli attaches to the glomerular capillary epithelial cells, mesenchymal cells, and tubular epithelial cells result in acute damage and renal failure.[41, 42]

Microangiopathic Hemolytic Anemia Associated with Complement

Microangiopathic hemolytic anemia associated with Complement also called unusual HUS caused by getting out of control of Complement alternative pathway activity. This is because of deficiency in complement regulating system with inhibition of regulatory proteins such as Factor H, I or CD46 which is the result of hereditary disorders or immune antibodies.[43, 44] Gain of function mutation has similar effects C3 and Factor B coding genes.[45, 46] In contrast with TTP, there is no specific laboratory diagnostic test for microangiopathic hemolytic anemia associated with complement since normal amount of complement factors like H, B, C3, and C4 would dismiss the diagnosis.[47, 48]

Drug Dependent Microangiopathic Hemolytic Anemia

Quinine was the first drug introduced for inducing microangiopathic hemolytic anemia.[49] Other causes of microangiopathic hemolytic anemia are consecutive contact with quetiapine and gemcitabine.[25, 50] Antiplatelet drugs like ticlopidine and clopidogrel has similar chemical structure. In ticlopidine dependent microangiopathic hemolytic anemia, ADAMTS-13 activity usually decreases for auto-antibody production against ADAMTS-13, and it responses to plasma exchange.[51] Therefore In clopidogrel dependent microangiopathic hemolytic anemia, ADAMTS-13's activity doesnt decrease and no inhibitor is seen so plasma exchange wont be effective, the treatment is discontinuing the medication.[52] Another cause of microangiopathic hemolytic anemia is taking sirolimus in transplanted patients which leads to vascular endothelial growth factor reduction.[53] Other drugs may induce microangiopathic hemolytic anemia include mitomycin, medication uses before bone marrow transplantation such as cytarabine, etoposide, cyclosporine, teniposide, carmustine, and whole-body radiotherapy.[54]

Microangiopathic Hemolytic Anemia Associated with Vit B12

Cobalamin known as Vit B12 is a vital water-soluble compound. Common metabolism disorders of Vit B12 are methylmalonic aciduria and homocystinuria.[22] Cobalamin C deficiency give a rise to homocysteine, methylmalonyl coA and a decrease in methionine level. Homocysteine increased level damages endothelial cell, multiply platelet activity and consumption, dissemination of coagulation for increased Tissue Factor expression and Factor V & 12, and decreases thrombomodulin and anti-thrombin 3 expression; consequently leads to renal microangiopathic hemolytic anemia.[55]

Microangiopathic Hemolytic Anemia Associated with Coagulation

Autosomal recessive mutation in diacylglycerol kinase E's gene is associated with microangiopathic hemolytic anemia.[56, 57] Diacylglycerol kinase E is present on endothelial cells, platelets, and podocytes. Unfortunately, loss of function of this enzyme causes prothrombotic situation that is because of increase in vwf, plasminogen-1 activator inhibitor, platelet-activating factor and tissue factor.[56]

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Table 2: Microangiopathic hemolytic anemias Classification[68]

Disease	Laboratory Findings/ Pathogenicity Mechanism	Clinical Manifestations	Treatment
Immune TTP	ADAMTS-13's activity less than 5% (usually with identifiable ADAMTS-1 inhibitor)	Local neural symptoms, seizure, renal involvement	Plasma exchange, Steroids, Rituximab
Hereditary TTP: Upshaw-schulman syndrome	-ADAMTS-13's deficiency -autosomal recessive	-more than 50% in childhood, and in adult pregnant females	-plasma exchange is acute phase -plasma transfusion in chronic phase
HELLP syndrome Preeclampsia	-increased trans-aminase -normal ADAMTS-13 -complement factors mutation	- seizure -tachycardia	-Preterm Cesarean section
Autoimmune microangiopathic hemolytic anemia	-systemic lupus erythematous -TTP: sudden ADAMTS-13 decrease	Renal involvement	-plasma exchange -use immuno-suppressive drugs if ADAMTS-13's activity goes less than 10 IU/dl
Metastatic Cancer	-leukoerythoblastic reaction -ADAMTS-13's activity more than 10 IU/dl	-cancer record -bone marrow involvement	Basic disease Treatment
Cobalamin-C deficiency	Homozygous or compound heterozygous mutation in methylmalonyl urea and homocystinuria (type C protein)	Clinical manifestations of abnormal HUS	-hydroxycobalamin -folic acid
Coagulation associated Microangiopathic hemolytic anemia	-thrombomodulin mutation -diacylglycerol Kinase E mutation -plasminogen mutation	Clinical manifestations of abnormal HUS	-ecolizumab -plasma exchange, in case of recurrence use ecolizumab
Drug dependent microangiopathic hemolytic anemia(dose dependent, endothelial damage)	-Tacrolimus, cyclosporine A -mitomycin C, gemcitabine, bevacizumab	-Clinical manifestations of abnormal HUS -liver failure	Supportive treatments, discontinue medication -ecolizumab[69]
Drug dependent microangiopathic hemolytic anemia(antibody dependent, dose independent)	-ticlopidine: anti ADAMTS-13 antibody -quinine: antibody against endothelial cells	-renal failure -liver poisening	If antibody identified plasma exchange must be done and discontinue medication
Transplant associated microangiopathic hemolytic anemia	-endothelial cells damage -complement activation -C5b-9 increase	-renal failure -seizure -tachycardia -heart failure	Supportive treatment(ecolizumab)
HIV associated microangiopathic hemolytic anemia	-normal ADAMTS-13's activity -rare decrease in ADAMTS-13's activity -identified antibody against ADAMTS-13	-local neural symptoms -seizure -renal involvement	-plasma exchange -anti retroviral drugs [32]
Abnormal HUS/ HUS associated with complement	-complement alternative pathway activation -anti factor H antibody -factor H, CD46, factor I and C3 mutation	Chronic micronagiopathic hemolytic anemia recurrence	-ecolizumab -if anti factor H presents, plasma exchange and immune suppressive drugs is necessary
HUS	-E Coli	Usually seen in children	
Shiga toxin associated HUS	-shigella -citrobacter	-renal failure -dysentry	Supportive treatment
Strep. Pneumonia associated HUS	-strep. Pneumonia (neuraminidase)	-sepsis -strep. Pneumonia meningitis	-antibiotics -supportive treatment

TTP: Thrombotic thrombocytopenic purpura. ADAMTS-13: A disintegrin and metalloproteinase with thrombospondin motifs 13. HELLP: Hemolysis, elevated liver enzyme levels, and low platelet levels. HUS: Hemolytic–uremic syndrome

Transplantation Dependent Microangiopathic Hemolytic Anemia

Patients who had organ or bone marrow transplantation may indicate microangiopathic hemolytic anemia caused by infection, graft versus host disease (GVHD), transplant rejection, and drug. Transplantation-dependent microangiopathic hemolytic anemia mainly affects kidneys, but there are evidences of respiratory, gastrointestinal, neural and cardiac systems involvement. Thus ADAMTS-13's activity is normal or slightly low. Therefore, rare cases of severe ADAMTS-13 deficiency has been reported in kidney lung transplantation.[58, 59]

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Microangiopathic Hemolytic Anemia Associated with Autoimmune Disorders

Vascular coagulation is seen in young patients (mainly in pregnant) with antiphospholipid syndrome. Prolonged Prothrombin Time and antibody against phospholipid-binding proteins can be found. In catastrophic antiphospholipid syndrome, uncontrollable coagulation is the main feature of microangiopathic hemolytic anemia in these patients. Some sources discuss uncontrollable complement classical pathway and complement inhibitors are the causes of this disease.[60]

Microangiopathic Hemolytic Anemia Associated with Pregnancy

Thrombocytopenia with increased LDH level can present in pregnancy which is caused by HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets), Fatty liver or preeclampsia. Peripheral blood smear analysis is necessary to observe schistocytes which indicates microangiopathic hemolytic anemia.[61] Sometimes preterm cesarean section is the only treatment for microangiopathic hemolytic anemia. If needed other treatments such as plasma transfusion, plasma exchange, and anti-complement may be applied.[62]

HIV-associated Microangiopathic Hemolytic Anemia

In patients with HIV infection, different reasons like TTP, HHV8, and cytomegalovirus infection, malignancies (Kaposi's sarcoma), and antiviral drugs are the causes of microangiopathic hemolytic anemia. Moreover using Highly Active Antiretroviral Therapy (HAART) increases IL-6 and IL-8's level, inhibiting the ADAMTS-13's activity, and leads to microangiopathic hemolytic anemia.[63, 64]

Cancer-associated Micronagiopathic Hemolytic Anemia

In developed cancers microangiopathic hemolytic anemia occures after using drugs such as bevacizumab, mitomycin-C, and gemcitabine. In cases of bone marrow metastatic cancers or tumor cells drainage into the blood vessels, microangiopathic hemolytic anemia, sometimes with severe fibrinolysis can be seen.[65] ADAMTS-13's activity in cancer-associated microangiopathic hemolytic anemia is usually normal or slightly low(35-84 IU/dl).[66] In limited cases, severe deficiency of ADAMTS-13's activity (less than 10 IU/dl) with IgG presence has been reported.[67]

Treatment Management

TTP is a medical emergency and requires immediate diagnosis and management. In old ages, increase in LDH level(for organ damage and hemolysis) and cardiac troponin levels are in association with death and recurrence of treatment.[70, 71] Once TTP diagnosed, the patient and the therapist must be educated enough to recognize clinical signs on time. When clinical signs appear patient must be transferred to hospital for plasma transfusion and a physician or a hematologist should observe the patient regularly to evaluate treatment with plasma transfusion.[72]

Plasma Transfusion Treatment

Plasma transfusion is one of the ways of treating Hereditary TTP. To prevent acute onsets, 5 mg/kg of plasma every other two weeks is enough. therefore if acute TTP develops, 10 mg/kg of plasma is required every 7 to 14 days.[73, 74]

Plasma exchange is usually applied before accurate diagnosis of TTP. For immune TTP plasma exchange is better than plasma transfusion because it restores ADAMTS-13, removes autoantibodies against ADAMTS-13 and also cleans giant vwf multimers.[75, 76] Suggestive volume for plasma exchange is 1 to 1.5 times of plasma volume. This should be continued every day until platelet count gets normal ($150*10^3$) for two consecutive days, hemolysis reduces and organ dysfunction becomes ordinary.[31, 32, 77]

Drug Therapy

Corticosteroid

Among immuno-suppressive treatments with plasma exchange, beginning with cortisol is a standard plan to manage immune TTP primarily. 1 gram of methylprednisolone or 10 mg per Kg should be given intravenously for 3 days with plasma exchange, nevertheless, oral therapies can cause different problems for patients.[78] Corticosteroids mechanism of action is not clearly distinguished; however, it is almost known for antibody production suppression and reduction of cytokines associated with endothelial activity. Using steroids and plasma exchange concurrently can reduces plasma exchange side effects.[79]

Cyclosporine A

Cyclosporine A increases ADAMTS-13 activity and prevents recurrence of immune TTP.[80] By comparing cyclosporine A and corticosteroids as an alternative treatment for plasma exchange, it's indicated that there is no difference in disease relapse. However, corticosteroids are better than cyclosporine A to suppress autoantibody production and increase ADAMTS-13's activity level.[81]

Cyclophosphamide

One of the options for regulating the immune system in refractory the immune TTP is cyclophosphamide. It is used when plasma exchange, steroids, rituximab, and vincristine don't work, moreover, it can rise platelet count and ADAMTS-13's activity. For its side effect such as bone marrow suppression, infection, and fertility reduction, cyclosporine is not used as a first-line treatment.[82]

Rituximab

Rituximab is a monoclonal anti-CD20 antibody used in different hematological malignancies and autoimmune conditions like TTP and rheumatologic diseases. In a study patients with immune, refractory, or relapsed TTP were given rituximab (375 mg per 1 square meter of body surface every week for one month) in 1-3 week after the first dose, they had complete hematological and clinical remission, this happened by IgG level reduction and increase in ADAMTS-13's activity.[83] Significantly rituximab reduces

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immune TTP relapse by decreasing auto-antibodies against ADAMTS-13 and removing peripheral B lymphocytes, so ADAMTS-13 restores rapidly.[84, 85]

New Treatments

N-acetylcysteine

N-acetylcysteine decreases disulfide bonds in A1 domains (binds to platelet GP1b) of vwf in animal models. This material reduces the number of giant vwf and inhibits platelet adhesion & aggregation.[86] If N-acetylcysteine applies simultaneously with plasma exchange, prevents platelet aggregation and microangiopathic hemolytic anemia but it doesn't disintegrate clots, moreover, it is useful when applied with plasma exchange. The benefits of this drug had been studied for refractory TTP along with plasma exchange and steroids with increased platelet count.[87, 88]

TTP Targeted Therapy

A-1 domain of vwf and platelet GP1b are the target in molecular technology. ARC1779 is an aptamer or oligo nucleic acid binds to A-1 domains of vwf and blocks vwf-platelet reaction. Using this aptamer among with plasma exchange can increase platelet count.[89]

GBR600 is a humanized monoclonal antibody against vwf studied in apes. This inhibiting antibody rise platelet count in TTP and also protects apes from developing TTP.[90]

Caplacizumab (ALX-0081) and ALX-0681 are bivalent humanized single stranded Nanobody binding to N-terminal of A-1 domain of vwf and blocks vwf-GP1b interaction. ALX-0081 is an active intravenous drug while ALX-0681 is taken subcutaneous. There is no sign bleeding when these two apply with plasma exchange.[91, 92]

Recombinant ADAMTS-13

Recombinant ADAMTS-13 (rADAMTS-13) enhanced as an alternative product for hereditary TTP expected to be a potential alternative for plasma exchange.[93] Before indication of any clinical signs by using rADAMTS-13 (BAX930), all of ADAMTS-13s had been destructed in animal models and platelet count remained stable without any destructive effect, but producing auto-antibody against ADAMTS-13 was continued. This issue may not be clinically important in human body because many cases of hereditary TTP was for compound of heterozygous mutations.[94]

Conclusion

In 1966 TTP was introduced and still different aspects of the disease are enhancing. Although biological mechanisms, extrinsic factors, and genetic predisposing factors of TTP are known, there are, however, diagnosis challenges. Therefore, because choosing treatment policy depends on accurate diagnosis, it seems that developing a diagnostic and treatment guide for this disease is currently essential. Also, it's necessary to study genetic types of TTP with more details because, hopefully, new technics of gene therapy opens a window to more stable treatments.

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