Szydełko Magdalena, Szydełko Joanna, Szymczyk Agnieszka, Szymczyk Dominika, Chomczyńska Magdalena, Podhorecka Monika. Thrombotic thrombocytopenic purpura - a disease with multiple organ manifestations. diagnostic and therapeutic difficulties in clinical practice. Journal of Education, Health and Sport. 2018;8(8):430-450. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1318503
http://ojs.ukw.edu.pl/index.php/johs/article/view/5682

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 20.06.2018. Revised: 28.06.2018. Accepted: 21.07.2018.

Thrombotic thrombocytopenic purpura - a disease with multiple organ manifestations. Diagnostic and therapeutic difficulties in clinical practice

Magdalena Szydełko[1], Joanna Szydełko[2], Agnieszka Szymczyk[3], Dominika Szymczyk[1], Magdalena Chomczyńska[1], Monika Podhorecka[4]

[1]Students Scientific Association at the Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin

[2]Department of Endocrinology, Medical University of Lublin

[3]Independent Clinical Transplantology Unit, Medical University of Lublin

[4]Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin

Corresponding author:
Magdalena Szydełko

Students Scientific Association at the Department of Hematooncology and Bone Marrow Transplantation

Staszica 11 Str.

20-081 Lublin, Poland

phone: +48 81 53 45 468

e-mail: mszydelko@interia.pl

Key words: thrombotic thrombocytopenic purpura, symptoms, ADAMTS13, differential diagnosis, therapy strategies

Abstract

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a rare, heterogeneous and life-threating disease requiring prompt differential diagnosis. The most common form of that disease is idiopathic form affects usually young adults. The etiopathogenesis is most likely based on the excessive formation of platelet aggregates and microthrombosis in small vessels, capillaries due to the deficiency of a specific enzyme, ADAMTS13 (disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13).

Aim of the study: The aim of this review was to present the diagnostic difficulties of the TTP, which are mainly related to the range of multi-organ deficiency and symptoms that resemble lots of other diseases. Moreover, we discussed the current, as well as future perspectives of the treatment of thrombotic thrombocytopenic purpura.

Description of knowledge: The principal symptoms, which occur in TTP patient are caused by microangiopathic hemolytic anemia and thrombocytopenia. Moreover, that disease may also manifest by neurological, renal, cardiac abnormalities as well as abdominal disturbances, fever and flu-like symptoms. The other thrombotic microangiopathies, especially hemolytic-uremic syndrome, immune-mediated diseases, infections, stroke, myocardial infarction should

be taken initially in the differential diagnosis. The current management is based on plasma exchange therapy, steroids, rituximab, but the novel methods are investigated.

Conclusions: The differential diagnosis of hematological patients presenting clinical symptoms of thrombocytopenia, anemia associated with multi-organ dysfunction, especially when we suspect an autoimmune background of a given disease is crucial to implement the appropriate therapy and save the patient's life.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare, heterogeneous and life-threating disease requiring prompt diagnosis and implementation of appropriate treatment [1]. This entity was firstly described by Eli Moschowitz (*1924*) in a 16-year-old female patient with petechiae and hemolytic anemia manifesting as progressive, central pallor, rapidly involving to partial paresis, coma and death [2]. TTP is characterized by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia of various severity and multi-organ failure. There are two forms of this disease: acquired, which occurs more often and congenital also known as Upshaw-Shulman syndrome [3]. The latest epidemiological data shows that acquired TTP affects around 3-6/1 000 000 people in the world with a peak of incidence between 30 to 50 years old. Moreover, it is more common in women, particularly during or after pregnancy [4-6]. The etiopathogenesis of the above-mentioned disorders is based on the excessive formation of platelet aggregates and microthrombosis in small vessels and capillaries. This process is closely related to the deficiency of a specific enzyme,

ADAMTS13 (disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), whose main task is to cleave large multimers of von Willebrand factor (vWF). The size of the vWF multimer is directly related to its binding capacity to the platelets: the larger the multimers, the higher the binding strength. The activity of ADAMTS13 may be decreased in a two main manners such as genetic mutation of the gene encoding this enzyme or due to the production of antibodies against ADAMTS13 protease as a consequence of variety of conditions including autoimmune diseases, hematopoetic stem cells transplantation, malignancy, pregnancy and drugs (clopidogrel, ticlopidine, mitomycin, tacrolimus, penicillin, cyclosporine) [7-8]. The mortality rate of this disease was dramatically reduced from about 80-90% to about 10-20% due to the introduction of fresh frozen plasma for treatment of TTP. Nevertheless, it remains a potentially fatal entity, especially due to the fact that approximately half of patients with congenital form of the disease did not present symptoms in neonatal, infancy or childhood period and that disorder is not often taken into account as the first in differential diagnosis due to the low prevalence of occurrence (over 100 cases described worldwide) [9-10]. Furthermore, thrombotic thrombocytopenic purpura is associated with a high incidence of recurrence, reaching even 30 to 50% of patients with acquired deficiency of ADAMTS13 enzyme. The relapse occurs most frequently in the first two months to a year from the time of the first episode and more often in younger patients with low ADAMTS-13 activity (<5-10%) and anti-ADAMTS-13 antibodies that persist after remission [11-12].

Thrombotic thrombocytopenic purpura is a disease with heterogeneous clinical manifestation, range from very uncharacteristic and little expressed to even very spectacular symptoms. Apart from the most frequent hematological disorders, TTP can also lead to various degrees of neurological, cardiological and digestive disorders. In addition, abnormalities in the functioning of the kidneys, visual disturbances and even changes in the osteoarthritis system are also observed [13-17]. Scientific observations prove that despite significant progress in understanding etiopathogenesis and diagnostic capabilities, TTP is misdiagnosed in almost 20% of cases. Main diagnostic errors were more frequently noted in females with a history of autoimmune disorder and had organ manifestation. It is also worth emphasizing, that differential diagnosis of major hematological disorders such as thrombocytopenia (51%) and hemolytic anemia (37%) posed many difficulties [18].

The aim of this review was to present the diagnostic difficulties of the TTP, which are mainly related to the range of multi-organ deficiency and symptoms that resemble lots of

other diseases. Moreover, we discussed the current, as well as future perspectives of the treatment of thrombotic thrombocytopenic purpura.

Materials and methods

The available literature was subjectively selected due to its usefulness in showing clinical approach to the symptoms, differential diagnosis and therapy of TTP. Moreover, literature which reveals inconsistency in results was shown as well. Articles in the EBSCO and the PubMed database have been analyzed using keywords: thrombotic thrombocytopenic purpura, symptoms, ADAMTS13, differential diagnosis, therapy strategies.

1. Symptoms

TTP is a disease that usually begins suddenly, typically in a 20–50 year age group with a slight preponderance in women, who is previously not burdened with other illnesses. The range of non-specific symptoms resulting from the end-organ ischemia due to platelet microthrombi varies from mild, often overlooked to very severe conditions that are a state of immediate life threat. For this reason, there is a need for a high level of suspicion in the diagnosis of thrombocytopenia and anemia in patients with concomitant multi-organ failure. On the basis of long-term, in-depth observation of patients diagnosed with acute TTP, the pentad of classic symptoms such as microangiopathic hemolytic anemia (MAHA), moderate-to-severe thrombocytopenia, neurological disorders, renal insufficiency and fever was highlighted [19-20]. However, clinical experience revealed that the occurrence of all these symptoms affecting one patient, and especially at the beginning of the disease is relatively rare, estimated from 4 to 30% [21-22]. The first signs usually appear about 12 days before the development of full-blown form of the disease [19]. Table 1. presents most frequently clinical presentation of acute TTP and the other diseases that may imitate similar symptoms, which should be taken into consideration as the first step in the differential diagnosis.

1.1. General symptoms

The clinical study revealed that general, non-specific symptoms such as fever (> 37,5^{o}C, usually low-grade) or flu-like signs initially was observed in many patients [10]. However, other authors suggest that increased body temperature may occur only in 25% of patients who develop the signs of TTP [3]. Furthermore, there are scientific reports, which show that some infectious diseases (viral – typically influenza A virus, bacterial, fungal), also

manifested with similar general symptoms, may induce the production of antibodies against ADAMTS13 and stand at the base of autoimmune TTP [23].

1.2. Hematological disturbances

One of the most common abnormalities, essential to raise suspicion and make a diagnosis of TTP, are symptoms resulting from microangiopathic hemolytic anemia and thrombocytopenia. They are occurring with a frequency of approximately 70-100% [3].

At the basis of the pathogenesis of MAHA, the coagulation of platelets in the vascular leads to destruction of red blood cells flowing through it, is considered. Patients frequently present symptoms of weakness, fatigue, pallor of the skin and mucous membranes, tachycardia as well as jaundice. However, it is worth noting, that this pathologic process may accompany other diseases including hemolytic-uremic syndrome, pregnancy associated conditions such as severe preeclampsia, HELLP syndrome, disseminated intravascular coagulation, malignancy, Evans syndrome, sepsis, malignant hypertension and drug-induced (e.g. tacrolimus, gemcitabine, anti-VEGF, mitomycin) hemolytic anemia [11,22]. Additionally, the above symptoms caused by the mechanical destruction of erythrocytes may be associated with non-immune processes such as the presence of prosthetic heart valves and ventricular assist devices [24-25].

The signs of thrombocytopenia in the course of TTP usually fluctuating from moderate to severe. Most commonly physical examination revealed the relapsing epistaxis, bruises, gingival bleeding, multiple petechial hemorrhages in the skin of lower extremities or back and less frequently gastrointestinal bleeding, hematuria, menorrhagia, retinal hemorrhage [10]. Although a group of conditions in the course of which there is a decrease in blood platelets, such as hemolytic-uremic syndrome, disseminated intravascular coagulation, immune thrombocytopenic purpura, preeclampsia, HELLP syndrome, heparin induced thrombocytopenia or Evans syndrome, comorbidity of thrombocytopenia with MAHA, multi-organ ischemia allow for accurate and instant diagnosis [22].

1.3. Neurological disorders

According to the scientific reports, neurological abnormalities may fluctuate from minor to severe, however in 50-25% of patients no neurological symptoms were observed [20,22]. Approximately in one third of cases of TTP, patients presented only moderate,

transient signs including headache, dizziness, blurred vision, reduced cognition, altered personality. The serious conditions usually resulting from reversible focal brain lesions such as motor deficits, paresis, aphasia, dysarthria, seizure, encephalopathy, ischemic stroke and finally coma are described in about 8-39% of cases [3,26]. Although, the clinical experience confirm that permanent neurological damage is not often in patients with TTP rapidly treated with PEX, even in cases with severe neurological manifestations [27]. It is considered that a cerebral angiopathy leading to reduction of cerebral blood flow and hypoperfusion of neurons in combination with endothelial disturbances, impaired reactivity of the small cerebral arteries, damage to the blood-brain barrier and vasogenic edema underlined of the pathogenesis of neurological abnormalities in the course of TTP [28-29].

1.4. Renal insufficiency

Renal insufficiency and the pathogenesis of this process in TTP patient has remained a mystery until recently. It was reported that more than half of patient manifest the renal abnormalities of varying degrees of advancement of which nearly 46% present grade III acute kidney injury (AKI) [16]. Other study investigated that AKI has occurred in only 9% of patient [22]. The symptoms, which were most frequently reported by patients were oliguria, hematuria, lumbar pain and less frequent urine foaming due to increasing proteinuria [30]. It seems to be crucial to perform an accurate differential diagnosis in the group of patient manifest impairment of kidney together with signs of MAHA and thrombocytopenia, since changes in the kidney may be irreversible and patients may require constant renal replacement therapy [16]. Other pathologic condition requiring taking into consideration are hemolytic-uremic syndrome, urosepsis, diabetic non ketotic hyperosmolar acidosis, hemolysis, blood pressure variability, drug-related renal toxicity, glomerulonephritis and connective tissue disease [31].

1.5. Cardiac symptoms

Clinical evidence of cardiac involvement have not been clarified in the scientific reports, although there is a valid extremity to be awareness of the most life-threatening complications of TTP such as high risk of myocardial infarction (MI), arrhythmias or sudden cardiac death [32]. The level of MI incidence in the course of TTP was determined by various research to range from 15 to 41% [33]. Autopsy studies of patients died of sudden cardiac death in the course of TTP show that the main cause of death were most likely small coronary

vessel platelet thrombi and myocardial ischemia as a consequence. Furthermore, other authors have observed that the heart failure may be also associated with infarctions of the sinoatrial (SA) node and the atrioventricular (AV) node as well as hard upon of the cells of the cardiac conduction system [34-35]. However, myocardial infarction in TTP patient, especially in the idiopathic form of that disease might manifest with no angina, MI symptoms or electrocardiograph, laboratory abnormalities. That is why, the myocardial infarction in the course of TTP should be considered in young adults presenting another clinical features from the pentad symptoms [36]. Moreover, it is also crucial due to the different methods of treatment the MI in TTP patient or without, because invasive therapy in the form of cardiac catheterization and percutaneous coronary intervention may be burdened by complications and is forbidden in case of acute kidney injury and severe thrombocytopenia [33]. A systematic review study revealed that the symptomatic cardiac disturbances due to TTP may manifest as angina (54%), syncope (4%) and congestive heart failure (42%). The arrhythmias (complete heart block, supra-, atrial-ventricular, ventricular tachycardia), cardiogenic shock and sudden cardiac death were observed in 15%, 9% and 12% of cases respectively [32, 37-38].

1.6. Digestive abnormalities

Digestive abnormalities usually occur in TTP at an atypical course and the incidence range from 5-13%. Abdominal pain, bloody diarrhea, hematemesis, melena and pancreatitis are observed predominantly [3, 39-40]. It is worth to highlighted that these symptoms may mimic lots of other diseases such as digestive tract infections, inflammatory bowel disease (especially Crohn's disease), hemolytic-uremic syndrome or disseminated intravascular coagulation.

Clinical manifestation	Other diseases that may imitate similar symptoms	Differential symptoms and results of laboratory or imaging tests	References
general symptoms	infections, especially viral (influenza A, adenovirus, cytomegalovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal	symptoms associated with the system occupied by the infection, hypotension, mild anemia (may be microangiopathic) and thrombocytopenia, renal abnormalities	23
hematological disturbances	typical hemolytic-uremic syndrome	commonly affect children < 5 years old, a history of a recent gastrointestinal system infection (EHEC O157:H7, Shigella dysenteriae – Shiga toxin), bloody diarrhea preceding hematological changes, severe thrombocytopenia, predominant symptoms of acute kidney injury, moderate increase in FDP and D-dimer	1, 6-7, 11, 22
	atypical hemolytic-uremic syndrome	may occur in familiar (10-15%, usually in infant and young children, without diarrheal symptoms, severe renal impairment gene mutation of H factor) or acquired form (renal failure of ischemic origin), dysfunction of the complement system, presence of schistocytes, less severe thrombocytopenia, slightly elevated FDP and D-dimer levels	
	disseminated intravascular coagulation	a history of the disease, which could induce (trauma, sepsis, HELLP syndrome, metastatic cancer), prolonged prothrombin time, activated partial thromboplastin time, increased the value of international normalized ratio, elevated FDP and D-dimer level, decreased fibrinogen level, ADAMTS-13 >10 IU/dL	
	immune thrombocytopenic purpura	no schistocytes in blood smear, presence of platelet-bound antibodies	
	pernicious anemia	megaloblastic anemia, vitamin B12 deficiency, atrophic gastritis, presence of antibodies against IF factor, parietal cells or positive result of the Schilling test	
	Evans syndrome	no signs of end-organ ischemia, presence of thrombocytopenia, hemolytic anemia, anti-platelets and anti-erythrocyte antibodies, positive Coombs' antiglobulin reaction	
	thrombotic microangiopathy induced by: calcineurin inhibitors (tacrolimus), chemiotherapy drugs (gemcitabine, anti-VEGF, mitomycin), heparin induced thrombocytopenia (HIT)	hypertension, proteinuria, rarely renal impairment, the important factor is the anamnesis of using drugs which are associated with TMA, in case of HIT: mainly platelet thrombi, usually absence of hemolysis as well as schistocytes	
	disseminated malignancy	local symptoms resulting from the presence of malignancy, positive biopsy of the affected organ or bone marrow, the positive results of imaging tests, some malignancy may be associated with TTP, especially adenocarcinomas	
	preeclampsia, HELLP syndrome	blurred vision, peripheral oedema, abdominal pain, headache, rarely convulsion, hypertension, thrombocytopenia (PLT < 100 000/mm^3), hemolytic anemia (rarely), elevated liver enzymes, acute kidney injury, increase FDP and D-dimer	
neurological disorders	meningitis	positive meningitis symptoms, severe general condition of the patient, fever, no signs of thrombocytopenia or hemolytic anemia	13, 26-29
	ischemic stroke	a history of atherosclerosis, headache, nausea and vomiting, focal deficits (motor, mental, sensory), hypertension, without thrombocytopenia or hemolytic anemia in blood test, early changes in CT or MRI imaging	
renal insufficiency	urosepsis	severe general condition of the patient, increased inflammatory parameters (CRP, PCT), oliguria/anuria, azotemia, hyperkalemia, leukocytosis, leukopenia	16, 30-31
	diabetic non ketotic hyperosmolar acidosis	high blood glucose levels	
	drug-related renal toxicity	anamnesis	
	glomerulonephritis	positive result of kidney biopsy	
cardiac symptoms	myocardial infarction	angina symptoms, shortness of breath, nausea, vomiting, characteristic changes in the ECG	15, 32-38
	malignant hypertension	headache, usually located in the occiput, occurring mainly in the morning, symptoms of hypertensive encephalopathy, hemolytic anemia, sometimes thrombocytopenia, increase in FDP and D-dimer level, no schistocytes in blood smear	
digestive abnormalities	pancreatitis	a history of alcohol abuse and cholelithiasis, symptoms appear suddenly, epigastric pain radiating to the back, nausea, vomiting, elevated activity of amylase and lipase and liver enzymes, increased bilirubin level	39-40
	gastroenteritis	gastrointestinal endoscopy, normocytic anemia without schistocytes	
others symptoms	bone tumor	pathological fractures, change the strokes joints and bones, positive result of biopsy	17, 67
	systemic lupus erythematosus, catastrophic antiphospholipid syndrome, acute scleroderma	historic of obstetric complications, arthritis, skin changes, multi-organ manifestation, presence of antinuclear antibodies, moderate thrombocytopenia, anemia with the presence of reticulocytes, elevated inflammatory markers (CRP)	

Table 1. *Possible clinical manifestation of acute idiopathic TTP and other diseases, which should be taken into consideration as the first step in the differential diagnosis*

2. Diagnostic strategies

The diagnosis of TTP may be a huge challenge due to diversified symptoms deriving from multiple organs. However, it is considered that the initial suspicion of TTP, indispensable for the prompt implementation of treatment, should be based on medical history, clinical features as well as microangiopathic hemolytic anemia and thrombocytopenia without any other obvious reason, confirmed in laboratory tests [8].

The blood examination of TTP patient usually revealed the normocytic anemia with decreased hemoglobin (<10g/dL), hematocrit and significantly lower or undetectable level of haptoglobin, elevated lactate dehydrogenase (LDH) activity and indirect bilirubin level. The meaningful changes observed in the blood smear is the presence of schistocytes as a consequence of mechanical destruction of erythrocytes flowing among the large conglomerates of platelet binding to vWF and reticulocytes. According to scientific reports, the percentage of schistocytes >1-3% seems to be suggestive of TTP [20,41]. However, it should be noted that the level of these small form of red blood cells amounting >4%, requires the differential diagnosis with other thrombotic microangiopathies induced by whole body irradiation, hematopoetic stem cells transplantation or chemotherapy. Furthermore, the negative result of Coombs' antiglobulin reaction is a useful tool to differentiate MAHA in the course of TTP with other hemolytic anemias (e.g. Evans syndrome) [7].

TTP patient blood specimen examination commonly indicate the severe thrombocytopenia with the platelet level < 30 G/L. The parameters determining the function of coagulation system such as prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR) generally do not deviate from the norm in contrast to another thrombotic microangiopathy as disseminated intravascular coagulation. Moreover, DIC, typical hemolytic-uremic syndrome and pregnancy associated condition such as preeclampsia or HELLP syndrome manifest by the increase of fibrinogen degradation products (FDP) and D-dimer level in the blood, which have not been observed in the course of TTP [11].

The parameters evidence of the kidney injury are not too common and may manifest as elevated creatinine (usually <200 μmol/L) and potassium level in the serum, decreased estimated glomerular filtration rate (eGFR), proteinuria, hematuria, malignant hypertension as well as azotemia [10].

It is essential to emphasize that the renal insufficiency, especially in the severe form as acute kidney injury in combination with the less severe thrombocytopenia, is deemed sufficient to give a diagnosis of hemolytic-uremic syndrome rather than TTP (Figure 1.) [16].

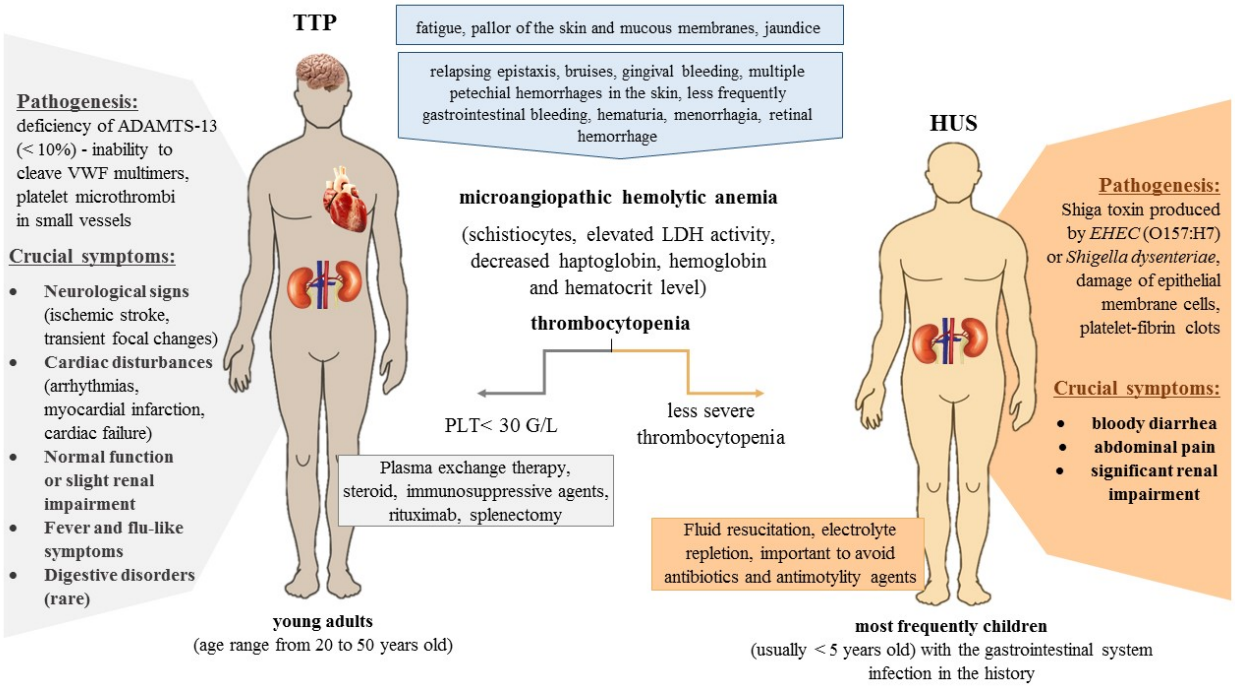

Figure 1. *The differential diagnosis between thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome.*

The patient presenting neurological abnormalities are diagnosed by imaging examinations, however, lots of authors described the cases of symptomatic ischemic stroke without any signs of cerebral injury in the magnetic resonance imaging (MRI) of the head. The further observations suggest that it may be associated with the early period of disease development when the neurological condition is caused by disturbances in microcirculation [28]. Thrombotic changes in the course of TTP usually affect small cerebral vessels, however, cases of cerebral infarction caused by the closure of large cerebral arteries manifesting in extensive symptoms, leaving permanent neurological deficits have been also described [42]. MRI reveals the diverse group of cerebral injury, from moderate and transient such as multifocal cortical, lacunar or be localized in the periventricular region. Moreover, the single photon emission tomography (SPET) performed during the acute phase of the disease showed the reduction in cerebral blood flow, but it was not sufficient to achieve a permanent brain damage [29].

The accurately diagnosis of patient presenting angina symptoms seems to be crucial, due to the fact that the myocardial infarction is one of the most common causes of death in that disease. The electrocardiograph demonstrate changes including rapid atrial fibrillation, ST-elevation or complete heart block, supra-, atrial-ventricular, ventricular tachycardia. However, the MI without any specific abnormalities in ECG was described [33,43]. The routine cardiac enzyme (including troponin T, I and CKMB) should be examined in all patients presenting TTP symptoms to prevent the sudden cardiac death and to document the frequency of heart injury, because nowadays the data has been limited. The echocardiography may also revealed the reduced left ventricular ejection fraction or it dysfunction, pericardial effusions and even cardiac tamponade [32].

A key laboratory parameter, which strongly indicate the pathogenesis of above mentioned symptoms is a plasma ADAMTS-13 activity - it reduction <10% IU/dL seems to be characterized as a high level of sensitivity and specificity (100% and 99%, respectively) [44]. Nowadays, the gold standard of measuring ADAMTS-13 activity is based on fluorescence resonance energy transfer (FRET) assay, which may give a result within nearly 2 hours [45]. However, there are some factors, which can disturbance the results of this measurements including recent plasma exchange, transfusion and other disorders involving systemic lupus erythematosus, antiphospholipid syndrome, hypergammaglobulinemia [46]. The ADAMTS-13 antigen and neutralizing or non-neutralizing anti-ADAMTS-13 autoantibodies measurements can provide more clues, especially in doubtful cases [3, 47].

3. Current and novel methods of TTP treatment

In the case of patients presenting symptoms, which strongly suggest the diagnosis of TTP, an immediate implementation of appropriate treatment seems to be crucial to significantly improve the patient prognosis in terms of survival, as well as the risk of recurrence in the future.Since the introduction of the plasma exchange therapy (TPE) in 1991, based on the randomized clinical trial by the Canadian Apheresis Group, the mortality rate has drastically decreased from around 80-90% to even 10-20%. For many years, TPE, immunosuppressive drugs, splenectomy as well as rituximab were the cornerstones of the treatment of that disease [48-49,6].However, studies of recent years have led to significant progress in the therapeutic approach to TTP, especially its relapsing and refractory forms, mainly due to a more profound understanding of TTP pathogenesis. Numerous studies prove that bortezomib, caplacizumab, N-acetylcysteine, eculizumab, ofatumumab, recombinant

thrombomodulin, as well as recombinant ADAMTS13 protease or gene therapy with the use of viral and nonviral vectors appear to be extremely potential, promising therapeutic options of thrombotic thrombocytopenic purpura [50-51].

3.1. Plasma exchange therapy (TPE) and platelet infusion

The therapeutic plasma exchange (TPE) remains the basis and the first-line strategy of thrombotic thrombocytopenic purpura management. During TPE procedure, an extracorporeal separation of patient's blood plasma from the blood is performed and then the patient's plasma is supplemented with a fresh frozen plasma (FFP) or cryosupernatant as a replacement fluid. This procedure results in the purification of blood plasma from circulating multimers of von Willebrand factor bound to platelets, autoantibodies to ADAMTS13 enzyme and moreover it complements the deficiency of ADAMTS13 protease [20, 22].However, there is still an absence of consensus in the scientific literature on the requiring number of plasmapheresis cycles and doses of FFP administered to patients with TTP. According to guidelines of the American Society of Apheresis, an optimal first-line therapy should be based on twice-daily plasmaferesis in an amount of 1-1.5 times of plasma volume exchanged per day (about 40-60 mL/kg in case of acquired TTP and about 10-15 mL/kg in the congenital form of TTP). This management should be continued until remission of neurological symptoms, normalization of blood parameters in the form of an increase in platelet count to 150 x 10^9/L or above, stabilization of serum lactate dehydrogenase (LDH) activity, and then for at least 48 to 72 hours, although it is usually required to implement this therapy from four to seven day cycles [9,52]. A retrospective multicenter study on the group of 163 patients revealed that TPE is an effective method of TTP treatment with a high complete response rate ranging about 85-87% both in the primary and secondary TTP. [53]. However, this therapy is not free of the risk of side effects, mainly manifesting as disturbances in water and electrolyte balance, hypotension as well as local infections, venous thrombosis, pneumothorax, anaphylaxis and hemorrhage, weakness, headache and dizziness, fever, nausea, vomiting [54]. It is also worth emphasizing that the effectiveness of treatment and further prognosis for the patient correlates closely with the time elapsed from the first symptoms to the moment of implementation therapy with TPE (preferably within 4-8 hours), and the benefits of this method far outweigh the risk of complications associated with it. The alternative for TPE, reserved only to the situation in which we do not have the ability to perform therapeutical plasmapheresis within 24 hours from the onset of symptoms and diagnosis of TTP, is infusion of fresh frozen plasma

(FFP) at a dose of≥ 25 mL/kg/day. However, this method has a much lower percentage of effectiveness, mainly due to the fact that it does not remove from the patient's circulatory autoantibodies to ADAMTS13 [10].

3.2. Immunosuppressive agents

The effectiveness of TTP treatment with immunosuppressive drugs such as steroids, vincristine, cyclosporine A, cyclophosphamide has not been confirmed in randomized controlled studies yet and their use is currently limited mainly to specific cases of acquired TTP, in which the most likely cause of ADAMTS13 deficiency is the autoimmune process. The results of scientific research show that the best results were achieved through the inclusion of steroids as adjunctive therapy in combination with TPE. Based on these studies, methylprednisolone at a dose of 1-2 mg/kg body weight daily until the time of remission or 1g per day by 3 days, was the most frequent drug administered intravenously [55]. Another study revealed that the high-dose instead of standard-dose steroids reduces the percentage of patients who did not achieve remission (23,3% and 53,3% respectively) or presented early relapses. The authors recommended the administration methylprednisolone at a dose of 10 mg/kg body weight/day for 3 days followed by 2 mg/kg body weight/day [56]. Scientific reports also suggest the treatment of TTP with the use of prednisone (200 mg/day) alone or in the combination with TPE. Study on the group of 54 patients treated with steroids alone revealed that only in case of two patients relapses was reported, but interpretation of this study was complicated because 24 patients presented no reaction to treatment and were switched to TPE plus corticosteroids group. However, it is worth to underline that immunosuppressive therapy in the treatment of TPE can help patients to achieve reemission, especially when administered in the acute phase of that disease and moreover, may be useful in the cases of relapses form of TTP or unresponsive to standard treatment [57].

3.3. Rituximab

Rituximab (RTX) is an anti-CD20 monoclonal chimeric mouse/human antibody, which is used to treat a wide range of autoimmune diseases, as well as hematological malignancies such as non-Hodgkin's lymphomas and chronic lymphocytic leukemia [58]. It is worth to mention that the introduction of RTX to the treatment of TTP has been a second,

after TPE procedure, major milestone in TTP management. The main mechanism of therapeutic action of rituximab is based on depletion the peripheral B-cell count, which consequently leads to decrease the level of autoantibodies against ADAMTS13 protease. Currently, rituximab is a treatment of choice in case of refractory/relapsed TTP and with suboptimal response to standard, first-line treatment [59-60]. Moreover, studies revealed that preemptively administrated RTX could forcibly prevent long-term relapses (after a median of 17 months, the relapse incidence decreased from 0.57 episodes/year to 0 episodes/year) [61]. However, the retrospective review of a single center study showed that the recurrence rate after application of RTX in combination with TPE was around 33%, but the authors underline that the further prospective randomized studies are needed [62]. The dosages of rituximab have not been clarified yet, but the numerous studies suggest the administration of the four 375 mg/m^2 infusions within a short period of time (day 1–4–8–15) rather than with a weekly schedule, mainly in order to prevent reducing drug efficacy, by removing it by TPE [63]. Several trials demonstrated that low-dose rituximab (100 mg/dose/week for 4 consecutive weeks and TPE) are effective as front-line treatment for acute TTP likewise [64-65]. Recently, reports on the use of peripheral B-cells count monitoring in the setting of RTX dosing schedules have been published, regarding the fact that the level of these cells, at the acute phase of TTP, strongly correlates with an effective decrease in anti-ADAMTS13 concentrations and clinical response [66].

Conlusions

TTP is a non-common, potentially fatal disease with multiple-organ manifestation and wherefore it is an enormous diagnostic challenge for contemporary medicine. The one of breath through in the management of that disease was introduction the therapeutic plasma exchange as the first-line treatment. However, the mortality rate was dramatically reduced from about 80-90% to about 10-20%, the high percentage of relapses and recurrences remains a huge problem demanding searching for novel therapeutic strategies such as monoclonal antibodies. To conclude, it is worth to emphasize the importance of thorough differential diagnosis of hematological patients presenting clinical symptoms of thrombocytopenia, anemia associated with multi-organ dysfunction, especially when we suspect an autoimmune background of a given disease.

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