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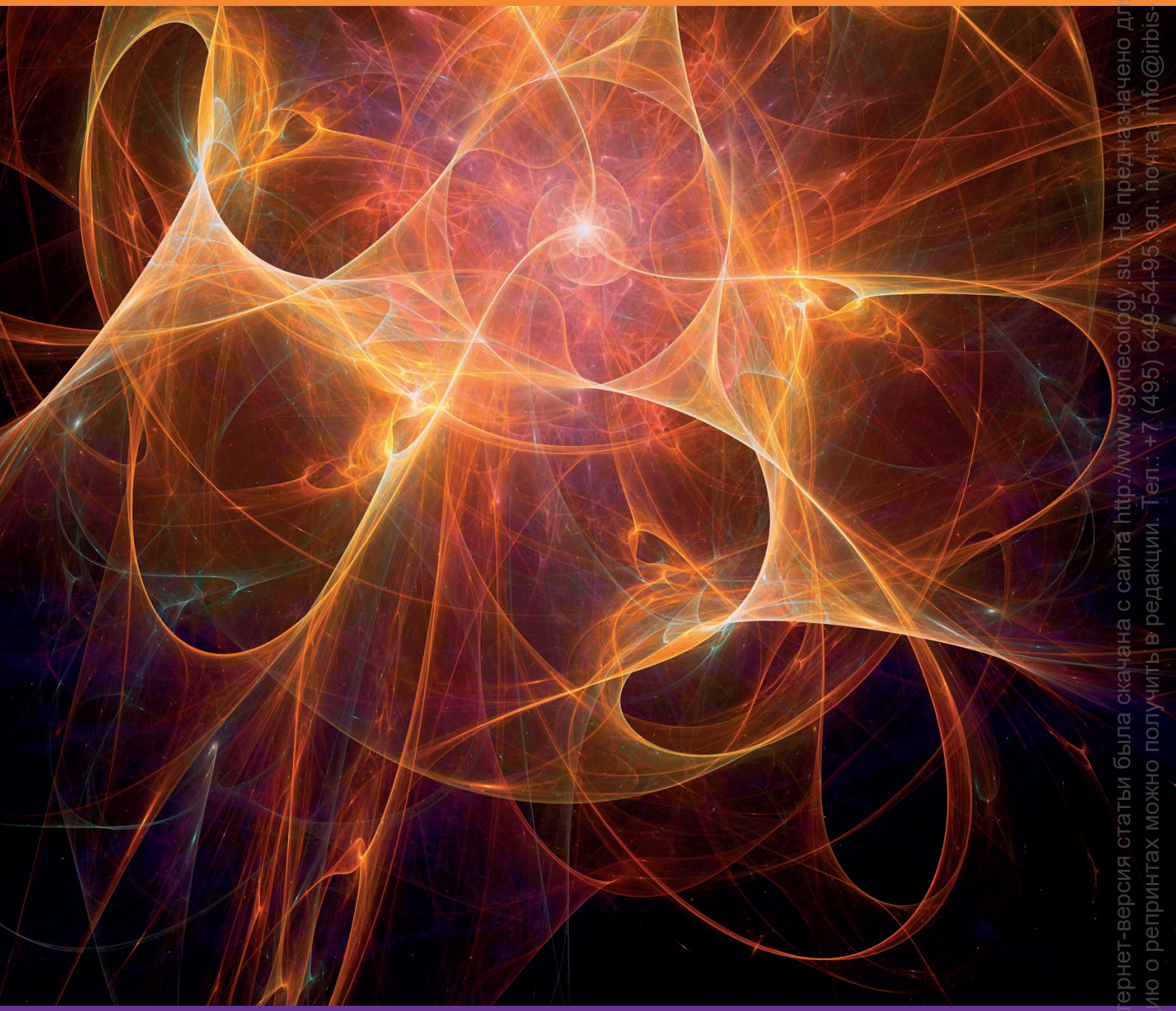

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Prognostic value of von Willebrand factor in clinical practice

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Abstract

The von Willebrand factor (vWF) is a multimeric plasma glycoprotein, which quantification has important prognostic value. The current literature review demonstrates a relationship between the disease severity and vWF level. For example, von Willebrand disease is characterized by a quantitative/qualitative genetic vWF deficiency resulting in potentially developed massive bleeding, which knowledge can prevent development of formidable complications. We should also not forget about an opportunity of developing acquired Willebrand syndrome most often occurring in response to autoimmune diseases. A marked vWF increase during pregnancy may evidence about developing preeclampsia, whereas in newborns exposed to additional risk factors, it can lead to thrombosis. In cancer patients, a substantially elevated vWF level correlates with low survival, especially in those with ovarian cancer, glioblastomas, esophageal and lung cancer. The emergence of a novel coronavirus infection COVID-19 allowed us to take a fresh look at prognostic value of vWF, because numerous studies show that increased blood plasma vWF:Ag is associated with more adverse outcome in patients with COVID-19. Here, we demonstrate an importance of determining vWF level, because early diagnostics and treatment can improve the outcomes of all such patients.

Keywords: von Willebrand factor, vWF, ADAMTS-13 metalloprotease, vWF/ADAMTS-13, von Willebrand disease, hemostasis

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Прогностическое значение фактора фон Виллебранда в клинической практике

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Резюме

Фактор фон Виллебранда (англ. von Willebrand factor, vWF) является мультимерным гликопротеином плазмы, определение которого имеет важное прогностическое значение. В данном литературном обзоре показана взаимосвязь между тяжестью заболеваний и уровнем vWF. Так, например, болезнь Виллебранда характеризуется количественным/качественным генетическим дефицитом vWF, вследствие чего может развиться массивное кровотечение, и знание этого может предупредить развитие грозных осложнений. Не стоит также забывать о возможности развития приобретенного синдрома Виллебранда, который чаще всего возникает в ответ на аутоиммунные заболевания. Существенное повышение уровня vWF в крови во время беременности может свидетельствовать о развитии преэклампсии, а у новорожденных при воздействии дополнительных факторов риска может приводить к тромбозам. У онкологических больных значительное повышение уровня vWF коррелирует с низкой выживаемостью, особенно у пациентов с раком яичников, глиобластомами, раком пищевода и легких. Возникновение новой коронавирусной инфекции COVID-19 позволило по-новому взглянуть на прогностическое значение vWF: так, многочисленные исследования показывают, что повышение в плазме крови vWF:Ag связано с более неблагоприятными исходами у пациентов с COVID-19. В данной статье показана значимость определения уровня vWF, так как ранняя диагностика и лечение смогут улучшить исходы всех этих пациентов.

Ключевые слова: фактор фон Виллебранда, vWF, металлопротеаза ADAMTS-13, vWF/ADAMTS-13, болезнь Виллебранда, система гемостаза

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Highlights

What is already known about this subject?

- The von Willebrand factor (vWF) is a plasma glycoprotein produced by endothelial cells in the form of ultra-large multimers and stored in specialized organelles known as Weibel-Palade bodies.

What are the new findings?

- The data on the prognostic role for increased vWF level in various populational cohorts are systematized.
- The study of vWF activity is an important prognostic criterion in patients with a high risk of thrombotic complications.

How might it impact on clinical practice in the foreseeable future?

- vWF monitoring should become a routine practice and to be conducted for all patients with preeclampsia, ischemic stroke, oncology, COVID-19, because early diagnostics and timely treatment can improve an outcome of such conditions.

Основные моменты

Что уже известно об этой теме?

- Фактор фон Виллебранда (vWF) – это гликопротеин плазмы, который производится клетками эндотелия в виде ультракрупных мультимеров и хранится в специализированных органеллах, известных как тельца Вейбеля-Паладе.

Что нового дает статья?

- Систематизированы данные о прогностической роли повышения уровня vWF у различных слоев населения.
- Исследование активности vWF является важным прогностическим критерием у больных с высоким риском развития тромботических осложнений.

Как это может повлиять на клиническую практику в обозримом будущем?

- Мониторинг vWF должен войти в рутинную практику и проводиться всем пациентам с преэклампсией, ишемическим инсультом, онкологией, COVID-19, поскольку ранняя диагностика и вовремя начатое лечение смогут улучшить исходы данных состояний.

Introduction / Введение

The von Willebrand factor (vWF) is a plasma glycoprotein produced by endothelial cells as ultra-large multimers consisting of repeating up to 40,000 kDa-long monomeric units stored in specialized organelles called Weibel-Palade bodies [1]. Endothelial storage organelles (Weibel-Palade bodies) contain several pro-inflammatory and hemostatic proteins, including P-selectin, pro-inflammatory cytokines, vascular tone control agents, and vWF [2, 3]. vWF plays two main roles in human hemostasis: i) "attracting" and binding platelets at the site of vascular injury, thereby promoting platelet aggregation, ii) vWF acting as a protective carrier molecule for procoagulant factor (F) VIII (FVIII), which is critical for maintaining normal circulating FVIII [4]. Studies based on high-resolution microscopy have demonstrated that in the absence of vessel wall injury and under low shear conditions, circulating multimeric vWF exists in a globular or folded form allowing no platelet adhesion. However, at high shear rates (forces) or when the endothelial wall is damaged, the globular vWF rapidly unwinds and elongates, turning into a highly active interface for platelet adhesion. In this unfolded state, vWF serves as a substrate for metalloprotease ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) whose main function is to cleave vWF giant multimers [5]. Modulating vWF plasma antigen (vWF:Ag) levels through regulated secretion pathways and ADAMTS-13-mediated proteolysis is essential to control vWF multimeric distribution and hemostatic activity. Elevated plasma levels of vWF:Ag is associated with an increased risk of venous thromboembolism, venous thrombosis, stroke, and coronary heart disease [6, 7], whereas low levels of von Willebrand factor/von Willebrand disease (WD) is the most common bleeding disorder accompanied by profuse bleeding occurring in 0.1–1.0 % people [8].

Von Willebrand disease / Болезнь Виллебранда

The first report on WD was published in 1926 by the Finnish general practitioner Erik Adolf von Willebrand (**Fig. 1**). In 1925, he was asked to examine a five-year-old girl; when collecting an anamnesis, it turned out that at early age out of the 11 siblings of the girl, four died from bleeding. Later, the researcher found that many relatives on the part of the mother and father tended to bleed from the skin and mucous membranes, and menorrhagia was noted in women. Erik von Willebrand distinguished this condition from classical hemophilia based on the nature of the inheritance and called it a pseudohemophilia. However, the lack of specific and reliable diagnostic tests and evidence of concomitant factor VIII depletion has led to diagnostic confusion between these conditions. In the 1950s, plasma from patients with severe hemophilia could correct von Willebrand's disease, leading to a distinction between the two diseases. In the decades thereafter, a significant progress was made in the immunological distinction between vWF and FVIII, purification of vWF, and vWF gene sequencing leading to our current understanding of vWF as well as the molecular mechanisms underlying von Willebrand's disease. WD is currently subdivided into three categories based on quantitative and qualitative vWF deficiency [9–11] (**Table 1**). It is also important to remember it may develop as an acquired von Willebrand syndrome. In the latter, people have no genetic disorder affecting vWF level. One example of developing acquired von Willebrand syndrome is an autoimmune disease, such as systemic lupus erythematosus, in which the body produces antibodies against normal tissues, sometimes including those directed against vWF. Antibodies bind to the circulating vWF, resulting in insufficient vWF level in the bloodstream.

Von Willebrand disease in women of reproductive age / Болезнь Виллебранда у женщин репродуктивного возраста

Women and men are equally susceptible to WD. However, in women, bleeding symptoms are more common and are associated mainly with a high frequency of heavy menstrual bleeding (HMB). Research data show

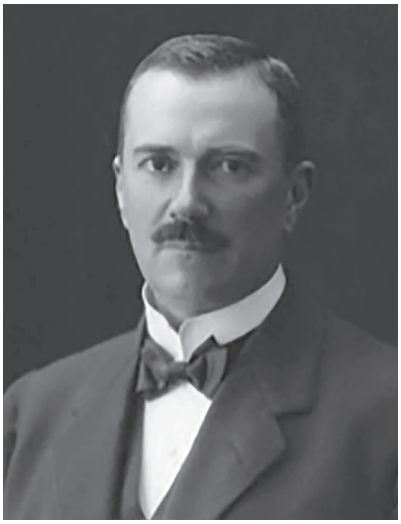

Figure 1. Erik Adolf von Willebrand (1870–1949).

Рисунок 1. Эрик Адольф фон Виллебранд (1870–1949).

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Table 1. Classification of von Willebrand disease [modified by the authors according to 12].

Таблица 1. Классификация болезни Виллебранда [модифицировано авторами по 12].

Type of von Willebrand disease Тип болезни Виллебранда	Characteristics Характеристика
Type 1 / Тип 1	Partial (quantitative) deficiency of von Willebrand factor (vWF) Частичный (количественный) дефицит фактора фон Виллебранда (vWF)
Type 2 / Тип 2:	Qualitative vWF deficiency: Качественные дефекты vWF:
2A	lowered production of might-molecular weight multimers and elevated vWF proteolysis; снижение синтеза высокомолекулярных мультимеров и повышение протеолиза vWF;
2B	increased affinity of vWF to surface platelet receptor – glycoprotein 1b (excessive binding of vWF to platelets); повышенное сродство vWF к рецептору на мембране тромбоцитов – гликопротеину 1b (избыточное связывание vWF с тромбоцитами);
2M	characterized by impaired vWF receptor binding- glycoprotein 1b on the platelet membrane; характеризуется нарушением связи vWF с рецентором – гликопротеином 1b на мембране тромбоцитов;
2N	characterized by normal vWF level and low procoagulant activity due to altered binding between factor VIII and vWF характеризуется нормальным уровнем vWF и низкой прокоагулянтной активностью, что обусловлено нарушением связи фактора VIII и vWF
Type 3 / Тип 3	Characterized by the almost complete lack of plasma, platelet and vascular wall vWF Характеризуется практически полным отсутствием vWF в плазме, тромбоцитах и сосудистой стенке

that from 5 % to 24 % of women with HMB have any WD type. Moreover, studies of women with WD show that 50–92 % of women experience heavy menstrual blood loss, with an average diagnosis of approximately 16 years. However, HMB is not the only problem for women with WD [13–15].

Pregnancy and childbirth are major tests of hemostasis system for many women. Despite significant advances in obstetrics, approximately 2–5 % of all births are complicated by postpartum hemorrhage. Usually, to reduce the risk of bleeding during pregnancy, physiological changes occur, including an increase in the levels of vWF and factor VIII in plasma [16]. However, these physiological changes are blunted or absent in women with WD. The rate of plasma vWF increase in women with its initial low levels before pregnancy will be similar to healthy peers, increasing from the first trimester and increasing to the normal reference range for non-pregnant women [17]. However, in healthy pregnant peers at all pregnancy stages, plasma vWF levels will remain lower; therefore, in this context the term "normalization" can be misleading. Thus, a physiological increase in plasma vWF levels a clear problem while examining women with a family history of WD type 1 who see a doctor for the first time during pregnancy since plasma levels of vWF in the normal range cannot rule out the disease.

Numerous studies have found an increased risk of both primary and secondary postpartum hemorrhage in women with WD, with primary and secondary postpartum hemorrhage rates ranging from 0 to 59 % and from 2 to 32 %, respectively. For example, A.H. James et al. have shown that women with WD have a 1.5-fold increased risk of postpartum hemorrhage after childbirth, a 5-fold increased risk of blood transfusion, and higher maternal mortality rates [18]. Sometimes postpartum hemorrhage triggers the WD, with detection rate 49 % of women with a history of severe postpartum hemorrhage [19]. Thus, an essential step in WD is the timely diagnosis, which will avoid the development of massive blood loss during proper replacement therapy.

ADAMTS-13 and von Willebrand factor / ADAMTS-13 и фактор фон Виллебранда

ADAMTS-13 is a zinc metalloproteinase that cleaves extra-large vWF multimers into Y1605 and M1606 subunits (**Fig. 2**). The cleavage process of vWF by ADAMTS-13 is triggered by vascular injury when extra-large vWF multimers are released from Weibel-Palade bodies. ADAMTS-13 can cleave the vWF only if it is in the "open" state, thereby preventing the formation of super-large multimers that can reach several millimeters in length if they are not controlled [20, 21]. However,

ADAMTS-13 can also bind to vWF while it is in globular form, which leads to the circulation of vWF–ADAMTS-13 complexes in the bloodstream [22].

In patients who have developed venous thromboembolism, the average level of vWF is significantly higher. However, most often, this occurs due to a decrease in the ADAMTS-13 activity [23]. Deficiency of ADAMTS-13 leads to accumulation of large vWF molecules and further thrombocytopenia consumption and microvascular thrombosis [24]. Thus, a decrease in ADAMTS-13 below 50 % can be observed in liver cirrhosis, disseminated tumors, and inflammatory diseases. Patients with hereditary thrombotic thrombocytopenic purpura are characterized by lacked or deficient ADAMTS-13 protease, resulting in much higher vWF level. But in the case of massive damage to the endothelium, a significant release of vWF from the granules occurs; and a relative insufficiency of metalloprotease, in this case, emerges [25].

Elevated serum von Willebrand factor level in pregnancy / Повышение уровня фактора фон Виллебранда в плазме крови во время беременности

Preeclampsia (PE) is a severe condition that complicates many pregnancies and is one of the leading causes of maternal death. According to one theory, PE occurs as a result of endothelial dysfunction, as a result of which a large amount of vWF is released [27]. Numerous patient studies have demonstrated that vWF level was significantly higher in pregnant women with PE than in women with normal pregnancies or non-pregnant [27–30]. A significant increase of vWF level in patients with PE is also associated with a decrease in ADAMTS-13 activity, which leads to the fact that active vWF extra-large multimers circulate in plasma.

In a recent study, G. Elvira et al. demonstrated that in pregnant women with COVID-19, the ratio vWF/ADAMTS-13 increased, which significantly and independently leads to the development of preterm labor since the risk doubles with each increase in the ratio by one unit [31].

Elevated neonatal serum von Willebrand factor level / Повышение уровня фактора фон Виллебранда в плазме крови новорожденных

There are significant differences in the coagulation system of newborns and older children. While studying the hemostatic system of newborns vs. adults,

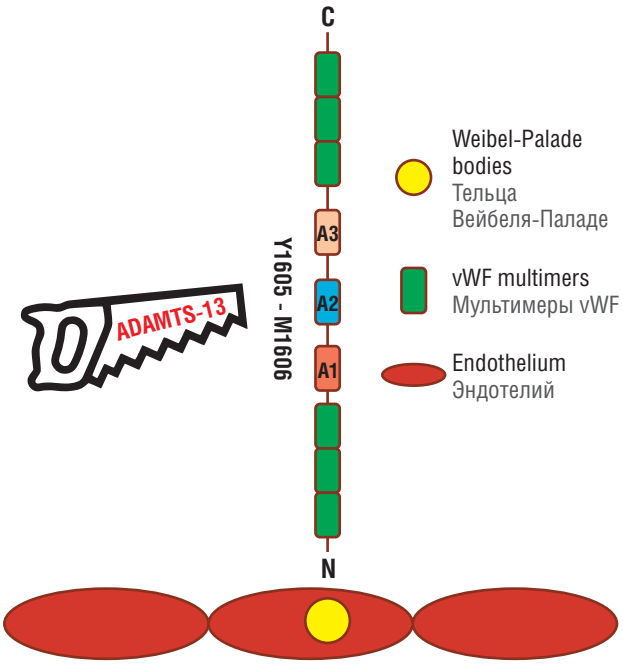

Figure 2. ADAMTS-13-mediated von Willebrand factor cleavage (adapted from [25]).

Рисунок 2. Нарезка фактора фон Виллебранда (vWF) металлопротеазой ADAMTS-13 (адаптировано из [25]).

most researchers concluded that in this period, the ADAMTS-13 activity was lower and much higher vWF level was observed. However, vWF gradually declines, reaching adult levels by about the age of six months. On the other hand, neonatal ADAMTS-13 levels are significantly lower compared to adult levels [32]. It is not entirely clear why neonates have higher vWF levels and lower ADAMTS-13 activity; presumably, this is a physiological reaction that occurs in preparation for childbirth or as a reaction to stress after birth. Usually, in healthy newborns, the abnormality of vWF/ADAMTS-13 ratio leads to no thrombosis. However, it can increase the chances of developing thrombosis when exposed to additional risk factors, such as hypoxia, sepsis, and long-term administration of intravenous devices [33].

Von Willebrand factor in oncology / Фактор фон Виллебранда в онкологии

The connection between cancer and activation of coagulation was established as early as 1865 when Armand Trousseau reported about the development of complications in the form of venous thromboembolism (VTE) in oncology patients. VTE occurs in 20 % of cancer patients and is one of the leading causes of death [34]. In a recent study, A.L. Palacios-Acedo et al. demonstrated that cancer cells directly interact with clotting factors and platelets to promote tumor growth and metastasis

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[35]. In addition, new evidence suggests that vWF can modulate angiogenesis and cell proliferation, leading to cancer progression [36, 37]. Several studies have shown the independent predictive value of vWF:Ag, with higher vWF levels correlated with lower survival in patients with ovarian, glioblastoma, esophageal, and lung cancers [38–40]. In addition, plasma proteomic analysis has identified vWF as a biomarker for the early detection of colon cancer [41].

Some tumor cells can produce vWF; moreover, vWF expression in tumor cells induces the formation of endothelial Weibel-Palade-like organelles called Weibel-Palade pseudo bodies [42]. Also, tumor cells derived from lung tissue (A549), prostate cells (PC3), urothelial carcinoma cells (RT4), colon cancer cells (HT-29), and melanoma cells (MV3, BLM) were able to stimulate vWF secretion from primary human endothelial cells *in vitro* [43–45]. Thus, tumor-mediated secretion of vWF from endothelial cells probably contributes to elevated plasma levels of vWF.

The von Willebrand factor may also promote cancer metastasis and can directly bind to various tumor cells through several integrin receptors [46]. In addition, studies have shown that some cancer cells can express pseudo-GPIbα receptors for direct adhesion of vWF. In particular, C.M. Suter et al. reported surface expression of GPIbα on several cultured breast tumor cells and positive GPIbα staining in primary breast tumor tissues [47]. The effect of vWF on such GPIbα-positive breast tumor cells leads to increased spread of tumor cells through cytoskeletal rearrangement and tumor migration *in vitro*. Consistent with this, an experimental metastasis study showed that anti-vWF (desmopressin) treatment inhibited lung metastasis by 64 % for disseminated colon carcinoma cells as well as for melanoma and Lewis bladder cancer cell lines by 45 and 46%, respectively.

Similarly, gastric vWF-expressing cancer cells significantly reduced lung metastasis in anti-vWF-treated mice [42, 48]. It is important to note that the contribution of vWF to the spread of cancer appears to be specific to blood metastasis and not lymphatic metastasis [49]. The mechanism underlying vWF role in promoting tumor cell seeding in distal tissue remains unclear. However, L. Goertz et al. reported the presence of intraluminal vWF multimers in mouse melanoma model, which was present not only in the primary tumor microvasculature but also in distal tumor-free organs, including the liver, brain, and lungs [49]. These data suggest that even at disease early stage, tumors can induce vWF systemic secretion from endothelial cells at sites where tumors often metastasize.

Von Willebrand factor and ischemic stroke / Фактор фон Виллебранда и ишемический инсульт

An increasing number of studies show that vWF plays a vital role in the formation of blood clots in venous and arterial thromboses [50, 51]. In ischemic stroke (IS), platelet-derived von Willebrand factor contributes significantly to thromboinflammation [52].

In particular a recent meta-analysis of 1567 cases found a positive association between high vWF level and IS, also observing an association between high vWF level and death from IS [53]. Studies by D.J. McCabe et al. [54] and K.D. Kovacevic et al. [55] also demonstrated that high plasma vWF level and IS are closely related. However, it is essential to understand that it is not due to increased vWF that causes IS but rather inverse when IS results in elevated vWF.

Case-control clinical studies have shown an association between elevated vWF level and a decrease in ADAMTS-13 at admission and follow-up with severity and risk of relapse [56, 57]. However, there is still no consensus on whether any marker of hemostasis can be used to predict clinical outcomes after stroke [58].

Von Willebrand factor and COVID-19 / Фактор фон Виллебранда и COVID-19

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected dozens of millions of families worldwide [59, 60]. The main problem of COVID-19 is thrombotic and microvascular complications, especially in patients with severe disease and death, despite standard thromboprophylaxis and therapeutic doses of anticoagulants used [61, 62]. It is well known that deaths are mainly associated with impaired lung function due to local pulmonary thrombosis [63]. However, it should not be forgotten that in COVID-19 patients, a phenomenon of inflammatory vascular damage without microthrombosis as such may occur [64]. In severe respiratory syndrome 2, increased thrombin generation, intravascular blood coagulation in capillaries, extensive endothelial damage, macrophage/monocyte activation, release of excessive amounts of pro-inflammatory cytokines, and activation of the complement system occur [65]. R. Seth et al. have shown that during coronavirus infection, there is a significant vWF increase and ADAMTS-13 decrease in severe patients [66]. E.J. Favaloro et al. came to the same conclusion [67]. In 2022, the Thrombosis Research published a meta-analysis involving 3764 patients

of X. Xu et al. demonstrating that increased plasma vWF:Ag level is associated with poor outcomes in COVID-19 patients [68]. V.O. Bitsadze et al. in a single-center retrospective observational study involving 129 patients with severe COVID-19 showed that assessing blood MPO has a prognostic value in patients with severe COVID-19, and the concentrations of MPO and vWF:Ag are independent predictors of death in patients on mechanical lung ventilation [69].

Hypothetically, restoring ADAMTS-13 level and reducing vWF extra-large multimers level could improve patient prognosis. However, to date, no experimental or clinical evidence supports this assumption.

Conclusion / Заключение

The vWF is an essential marker of many conditions. A decrease or increase of vWF level should be monitored in patients with von Willebrand's disease, preeclampsia, ischemic stroke, oncology, and COVID-19 since early diagnosis and timely treatment can improve the outcomes of these conditions.

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