Received: 10 April 2022 / Accepted: 24 Jule 2022 / Published online: 31 August 2022

DOI 10.34689/SH.2022.24.4.020

UDC 616-007.17:616-005.1-08

HEMOSTASIS DISORDERS IN HEMATOMESENCHYMAL DYSPLASIA SYNDROME. LITERATURE REVIEW

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Abstract

Relevance: Hematomesenchymal dysplasia (HMD), as a background pathology in recurrent clotting disorders, is reported with a frequency of 54.9% and manifests as combined and concomitant forms in 45.1% of patients, undifferentiated forms in 22.1%, and differentiated forms in 9.8% as Marfan, Ehlers-Danlos, Whrolick-Lobstein, Franceschetti syndrome, etc. Hemorrhagic disorders are one of the obligate syndromes of HMD, characterized by an early onset and recurrent course, and the nosological structure is quite heterogeneous, due to genetic defects in various parts of the hemostatic system. Angiopathies were detected in 12.3% of patients, thrombocytopathies - 25.5%, Willebrand syndrome (disease) - 11.5%, hemophilia - 4.3%, their combinations - 45.1%, 1.3% had latent (asymptomatic) defects.

Aim: To review the literature on disorders of the hemostasis system in hematomesenchymal dysplasia.

Search strategy: Sources were searched in the following databases: UpToDate, BMJ, PubMed, Scopus, Ebscohost, Medline, The Cochrane Library, SpringerLink, Web of Science, Paragraph Medicine, Science Direct. The depth of the search was 10 years: from 2011 to 2021. Thirty-three articles were included in the literature review, which were available in full text and underwent a critical appraisal process.

Algorithm for selecting literary resources → Study of clinical guidelines, monographs reporting the concept of undifferentiated connective tissue dysplasia, mesenchymal dysplasia syndrome, hematomesenchymal dysplasia, joint hypermobility syndrome → Review of articles from journals, academic journals, dissertations → Systematization of the material → Literature analysis and article writing.

This literature review was carried out as part of the PhD Dissertation on "Complex assessment of the hemostasis system and genetic screening in children with hematomesenchymal dysplasia". The study theme was approved by the ethical committee.

Results and conclusions: The problem of hemostasis disorders in HMD is understudied and requires more attention to cover this narrow field of hematology as variants of the clinical picture is various and the most life-threatening complications are both profuse bleeding and thrombophilic manifestations.

Keywords: *hematomesenchymal dysplasia, children, hemostasis system, systemic mesenchymal dysplasia, complications.*

Резюме

НАРУШЕНИЯ СИСТЕМЫ ГЕМОСТАЗА ПРИ СИНДРОМЕ ГЕМАТОМЕЗЕНХИМАЛЬНОЙ ДИСПЛАЗИИ. ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: Гематомезенхимальная дисплазия (ГМД), как фоновая патология при рецидивирующих нарушениях свертывания крови, регистрируется с частотой 54,9% и проявляется как комбинированными и сочетанными вариантами у 45,1% пациентов, недифференцированными формами – у 22,1%, так и дифференцированными - у 9,8% в виде синдромов Марфана, Элерса-Данлоса, Вролика-Лобштейна, Франческетти и др. Геморрагические расстройства являются одним из облигатных синдромов ГМД, характеризуются ранним

дебютом и рецидивирующим течением и по нозологической структуре весьма неоднородны, что обусловлено генетическими дефектами в различных звеньях системы гемостаза. Ангиопатии обнаруживаются у 12,3% пациентов, тромбоцитопатии – 25,5%, синдром (болезнь) Виллебранда – 11,5%, гемофилия – 4,3%, их комбинации – 45,1%, у 1,3% - скрытые (бессимптомные) дефекты.

Цель: обзор литературных ресурсов по нарушениям звеньев системы гемостаза при гематомезенхимальной дисплазии.

Стратегия поиска: Поиск источников проводился в базах: UpToDate, BMJ, PubMed, Scopus, Ebscohost, Medline, The Cochrane Library, SpringerLink, Web of Science, Параграф Медицина, Science Direct. Глубина поиска составила 10 лет: с 2011 по 2021 годы. В обзор литературы были включены 33 статьи, которые были доступны в виде полного текста и прошли критический процесс оценки.

Алгоритм отбора литературных ресурсов → Изучение руководств, монографий, отражающих концепцию недифференцированной дисплазии соединительной ткани, синдрома мезенхимальной дисплазии, гематомезенхимальной дисплазии, синдрома гипермобильности суставов → Изучение статей из журналов, научных сборников, диссертаций → Систематизация материала → Анализ литературы и написание статьи.

Данный обзор литературы был выполнен в рамках выполнения PhD диссертации на тему: "Комплексная оценка системы гемостаза и генетический скрининг у детей с гематомезенхимальной дисплазией". Тема исследования была одобрена этическим комитетом.

Результаты и выводы: Проблема гемостазиологических расстройств при ГМД недостаточно изучена и требует большего внимания с целью освещения данной узконаправленной области гематологии, так как варианты клинической картины разнообразны и наиболее жизнеугрожающими осложнениями являются как профузные кровотечения, так и тромбофиллические проявления.

Ключевые слова: *гематомезенхимальная дисплазия, дети, система гемостаза, системная мезенхимальная дисплазия, осложнения.*

Түйіндеме

ГЕМАТОМЕЗЕНХИМАЛЫҚ ДИСПЛАЗИЯ СИНДРОМЫНДАҒЫ ГЕМОСТАЗ ЖҮЙЕСІНІҢ БҰЗЫЛУЫ. ӘДЕБИЕТТІК ШОЛУ.

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Өзектілігі: Гематомезенхимальды дисплазия (ГМД) қайталанатын қан ұюының бұзылуларындағы фондық патология ретінде 54,9% жиілікпен тіркеледі және пациенттердің 45,1%-ында біріктірілген және ілеспе формалар, 22,1%-да бөлінбеген формалар және 9,8% - да сараланған формалар түрінде Марфан, Элерс-Данлос, Вролик-Лобштейн, Франческетти және т.б. геморрагиялық бұзылулар ГМД облигациялық синдромдарының бірі болып табылады. басталу және қайталанатын курс, ал нозологиялық құрылым гетерогенді, бұл гемостаз жүйесінің әртүрлі бөліктеріндегі генетикалық ақауларға байланысты. Ангиопатиялар науқастардың 12,3% - да, тромбоцитопатиялар - 25,5% - да, Виллебранд синдромы (ауру) - 11,5% - да, гемофилия-4,3% - да, олардың комбинациясы - 45,1% - да, 1,3% - да жасырын (асимптоматикалық) ақаулар бар.

Мақсаты: гематомезенхимальды дисплазиядағы гемостаз жүйесінің бұзылуы туралы әдебиеттік шолу.

Іздеу стратегиясы: дереккөздер келесі мәліметтер базасынан табылды: UpToDate, BMJ, PubMed, Scopus, Ebscohost, Medline, Cochrane кітапханасы, SpringerLink, Web of Science, Paragraph Medicine, Science Direct. Іздеу тереңдігі 10 жыл болды: 2011 жылдан 2021 жылға дейін. Әдебиеттерге шолу толық мәтінде қол жетімді және сыни бағалаудан өткен отыз үш мақаланы қамтыды.

Әдеби ресурстарды таңдау алгоритмі → Дәнекер тінінің бөлінбеген дисплазиясы, мезенхималық дисплазия синдромы, гематомезенхималық дисплазия, буындардың гипермобилділік синдромы туралы түсініктерді, монографияларды зерттеу → Журналдардан, ғылыми жинақтардан, диссертациялардан мақалаларды зерттеу → Материалды жүйелеу → Әдебиеттерді талдау және мақала жазу.

"Гемостаз жүйесін кешенді бағалау және гематомезенхималық дисплазиясы бар балалардағы генетикалық скрининг" тақырыбында PhD диссертациясын орындау аясында жасалды. Зерттеу тақырыбын этикалық комитет мақұлдады.

Нәтижелер мен қорытындылар: ГМД гемостазының бұзылуы мәселесі жеткілікті түрде зерттелмеген және гематологияның осы тар аймағын қамтуға көп көңіл бөлуді қажет етеді, өйткені клиникалық көріністің нұсқалары әртүрлі және өмірге қауіпті асқынулар-бұл ауыр қан кету және тромбофильді көріністер.

Түйінді сөздер: *гематомезенхималық дисплазия, балалар, гемостаз жүйесі, жүйелік мезенхималық дисплазия, асқынулар.*

Библиографическая ссылка:

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Relevance

HMD is a clinical variant of undifferentiated systemic mesenchymal dysplasia (SMD) with hemorrhagic symptoms. The doctrine (the concept of SMD) created by Prof. Barkagan Z.S., Corresponding Member of RAMS (1998-2006), further the pupils [Sukhanova G.A., 2004; Suvorova A.V., 2000 and others] studied the hemorrhagic and thrombotic conditions on the background of connective tissue dysplasia.

However, the character of manifestations of bleeding in children with hemorrhagic mesenchymal dysplasias in the literature is insufficiently analyzed [Sukhanova G.A., 2004; Andreeva N.N., 2005; Sturov V.G., 2008].

Connective tissue abnormalities are mostly of hereditary origin, represented by connective tissue dysplasia syndrome. This syndrome, in itself, manifests as differentiated and undifferentiated variants. The pathogenetic basis of connective tissue dysplasia is a genetically determined defect in the structure of collagen proteins, which results in abnormal hemostasis. This feature had confirmed by many research groups focusing on the hemorrhagic syndrome in complex with platelet dysfunction, coagulation, and plasma hemostasis disorders, HMD, Ehlers-Danlos syndrome. "According to Gladkih N.N. et al., in hematomesenchymal dysplasia, genetically predetermined defects in maturation and differentiation of mesenchymal progenitors affect the structure and functional integrity of cell membranes, causing dysfunction of platelets and endothelium"[9].

Moreover, as reported by Ben Salha M., et al, “In Russia, an Expert Council was established in 2008 to develop criteria for the diagnosis of uCTD, and the Russian guidelines 'Hereditary disorders of connective tissue structure and function' were drawn up. Differentiated CTDs include connective tissue diseases with a specific type of inheritance and clear symptomatology. Undifferentiated CTD includes many variants of CT abnormalities without clearly defined symptomatology. In the literature there are various synonyms of uCTD - "mesenchymal dysplasia", "connective tissue dysfunction", "connective tissue weakness", "connective tissue dysplasia syndrome", "unclassified forms of connective tissue dysplasia"” [2].

In addition, the pathogenetic components of hematological disorders can be varied, i.e., defects are found both, in the symbiosis of clotting factors with connective tissue and in the hemostasis system itself, particularly in platelets, vascular endothelium, and particular factor. Pathological conditions have manifested with hemorrhages and thromboses and may affect various hemostasis reactions, but the predominant prevalence of primary blood clotting diseases. Clinically, microcirculatory bleeding is more common than the combined type. It is crucial to recognize hemorrhagic syndrome due to CTD at the onset of symptoms. First of all, treatment should be preventive and be part of a comprehensive treatment plan for children with connective tissue dysplasia [2,23,25,29].

According to Siegel C.H., et al, the term 'undifferentiated connective tissue disease' was first introduced in the 1980s and was used to diagnose patients who were in the early stages of the disease, but the clinical data did not meet the basic criteria of distinct connective tissue diseases. Most patients remained in the same undifferentiated state, or entered remission without progressing to definite connective tissue disease. Examples of early-stage diagnoses were "latent lupus" and "incomplete lupus erythematosus". In addition, many patients suffering from UCTD had clinical features similar to lupus, the remaining patients had symptoms of another definite rheumatological nosology, so it is legitimate to apply the definition of "UCTD". According to recent data, persistent variant UCTD appears as an independent disease rather than as a precursor to an overt rheumatological nosology. Indeed, the etiopathogenesis of UCTD and most other connective tissue diseases remains poorly understood. UCTD is difficult to investigate due to the fact that it affects patients with different clinical symptoms and blood counts. One hypothesis is that certain individuals have a hereditary predisposition or risk of developing rheumatological pathology and, under the influence of an infectious environmental factor, the immune system begins to work against its own body. What mechanisms are involved in the development of UCTD remains unclear and unexplored. Certainly, UCTD and other connective tissue diseases are not infectious [30].

Aim: To review the literature concerning disorders of the hemostasis system in hematomesenchymal dysplasia.

The search strategy: Sources had searched in the following databases: UpToDate, BMJ, Pub Med, Scopus, Ebscohost, Medline, The Cochrane Library, SpringerLink, Web of Science, Paragraph Medicine, Science Direct. The depth of the search was seventeen years: from 2011 to 2021. The literature review included 33 articles available in full text and reviewed via a critical appraisal process.

An algorithm for selecting literary resources → Study of clinical guidelines, monographs reporting the concept of undifferentiated connective tissue dysplasia, mesenchymal dysplasia syndrome, hematomesenchymal dysplasia, joint hypermobility syndrome → Review of articles from journals,

academic journals, dissertations → Systematization of the material → Literature analysis and article writing.

This literature review was carried out as part of the PhD Dissertation on "Complex assessment of the hemostasis system and genetic screening in children with hematomesenchymal dysplasia". The study theme was approved by the ethical committee.

The results of the search and discussion section.

Prevalence of mesenchymal dysplasia syndrome.

Systemic mesenchymal dysplasia (SMD), as a background pathology in relapsing bleeding disorders, has a frequency of 54.9% and manifests as combined and concomitant forms in 45.1% of patients, undifferentiated in 31.9%, unidentifiable in 13.3% and differentiated in 9.7% as Marfan, Ehlers-Danlos, Vrolik-Lobstein, Franceschetti syndrome, and others. Hemorrhagic disorders are one of the obligate syndromes of SMD, characterized by an early onset and relapsing course, and have a heterogeneous nosological structure due to genetic defects in various parts of the hemostasis system. Angiopathies were detected in 12.3% of patients, thrombocytopathies in 25.5%, Willebrand syndrome in 11.5%, hemophilia in 4.3%, their combinations in 45.1%, and 1.3% had latent (asymptomatic) defects. The clinical equivalents of these diseases are recurrent hemorrhagic manifestations in 88.5% of cases and thrombotic analogs in 10.2%. Their frequency, localization, severity, and time of onset largely depend on the clinical and pathogenetic form of SMD [11].

As claimed by Ben Salha M., et al, “DCT has recently been of significant interest to practitioners due to the increasing detection rate of patients with this pathology. The incidence of DCT is quite high, ranging from 26% to 80% depending on the study group. Undifferentiated connective tissue dysplasia (uCTD) is understood as a nosologically independent syndrome of multifactorial nature, manifested by external phenotypic signs of connective tissue dysplasia and clinically significant dysfunction of one or more internal organs. This syndrome is mostly diagnosed at the physical examination stage with a comprehensive assessment of phenotypic markers. There are no strictly accepted morphological and genetic criteria for this syndrome. A critical number of external phenotypic markers for a diagnosis of uCTD has been suggested by various authors to indicate mild uCTD when a patient scores 3 to 6; when a patient scores 7 to 11, the diagnosis is made as moderate uCTD; when a patient scores over 11, the diagnosis is made as severe uCTD” [2].

Moreover, prophylactic treatment is the first choice because microcirculatory bleeding associated with CTD has its characteristics, most notably, the intensity of the hemorrhagic syndrome at the time of and right after medical manipulations: tooth extraction, adenotomy, tongue frenum excision, increased contact injury to mucous membranes on fibrogastroscopy, cystoscopy, and other procedures [8,25].

Manifestations of hemorrhagic syndrome - recurrent epistaxis, heavy menstrual bleeding, easy bruising, excessive gingival bleeding, prolonged bleeding after skin incisions and tooth extraction - were noted in 62.5% of those with mitral valve prolapse [5,15,18].

A study by Trutnev et al. presented that hemorrhagic syndrome is often a comorbidity of chronic gastroduodenitis in children, with nasal bleeding present in 57.7% and a tendency to mild ecchymosis in 43.1% of cases. This syndrome results from mesenchymal dysplasia, characterized by impaired platelet aggregation, Willebrand factor activity, and clotting final stage, and is associated with a predisposition to excessive bleeding in CTD [13].

Changes in the hemostasis system in patients with UCTD manifest predominantly as a clinical syndrome of hemorrhagic mesenchymal dysplasia, rarely as thrombophilia and erythrocytosis. The majority of patients with UCTD syndrome have changes in the coagulation, fibrinolytic and platelet-forming components of hemostasis. Patients with HMD syndrome have most characterized by delayed clotting in basic coagulation tests, activation of the fibrinolytic system, and platelet dysfunction. Changes in the hemostasis system in thrombophilia had characterized by signs of coagulation activation, hypercoagulation, and delayed fibrinolysis, forming the hypercoagulation status of these patients and thromboembolic complications [6,16,21].

Patients with juvenile rheumatoid arthritis combined with connective tissue dysplasia; patients with systemic lupus erythematosus with lupus anticoagulant should have considered at risk for severe hemostasis and fibrinolysis. Prognostically unfavorable criteria for thrombohemorrhagic disorders in patients with systemic connective tissue diseases are the presence of high thrombinemia (over 150 μg/ml), inhibition of XIIa-dependent euglobulin lysis, defects of final stage kinetics of blood clotting and reduced levels of physiological anticoagulants. Thrombinemia and final-stage clotting values can serve as objective criteria for determining the severity of systemic disease and predicting the probability of intravascular clotting. Pathology of hemostasis in patients with rheumatoid arthritis combined with connective tissue dysplasia is due to the following factors: thrombocytopathy, hypofibrinogenemia, thrombinemia, and delayed rate of inhibitory fibrin monomer polymerization. The course of the systemic disease had distinguished by polymorphism of clinical manifestations and the severity of the hemorrhagic syndrome. Hypercoagulation, thrombinemia, increased fibrinogen levels, inhibition of fibrinolysis, and accelerated fibrin monomer polymerization is been noticed in patients with renal damage, serositis, capillaritis, hemorrhagic rash. Thrombocytopathy, hypocoagulation, delayed polymerization of fibrin monomers manifested by a recurrent petechial rash. The antiphospholipid syndrome has clinically characterized by vascular thrombosis and neurological disorders [10].

The correlation between the indicators of endothelial-platelet function and a range of CTD characteristics was established and possible for diagnostics, differential diagnosis, and estimation of the risk of hemostasiological and vascular complications development in patients with various forms connective tissue dysplasia. The presence of subclinical endothelial-platelet dysfunction in patients with differentiated and undifferentiated dysplasia with more than five external stigmas, myxomatous degeneration of mitral valve prolapse, three micro anomalies of the cardiovascular system help the early diagnosis of endothelial-platelet dysfunction. The presence of anthropometric features in patients with undifferentiated CTD in the form of decreased body weight and Kettle index and decreased collagen-induced platelet aggregation and increased index can be

used as one of the risk criteria for the hemorrhagic syndrome [7,19,26,27].

All patients with renal damage in systemic connective tissue diseases should have a comprehensive study of the vascular-platelet, and coagulation hemostasis and fibrinolysis on admission and at dynamics and a screening examination of antiphospholipid syndrome. It is appropriate to use the lebetox-echitoxin index to diagnose secondary antiphospholipid syndrome in children, as the sensitivity is 100%, specificity 83.3%, and prognostic value 85.7% [3,24,31].

Based on the application of poison diagnostics and methods of evaluation of auto- and heteropolymerization reactions of fibrin monomers. It was established one of the mechanisms of hemorrhagic disorders development in children with connective tissue dysplasia is qualitative defects of fibrinogen molecules. A comparative study of the dynamics of the parameters of the poison coagulation tests has revealed a high informative value of the echitox test in recognition of hidden hypercoagulation in patients with acute (subacute) disseminated intravascular coagulation syndrome [4].

Consequently, disorders of the hemostasis system in HMD syndrome are the majority cases, hemorrhagic, less frequent thrombotic, and dysfibrinogenemia. The diagnosis of HMD requires not only laboratory confirmation of disaggregated thrombocytopathy, dysfibrinogenemia, and decreased activity of certain blood factors, but also the presence of signs of dysmorphogenesis.

A specific feature of thrombohemorrhagic syndrome in HMD is its unusual high intensity, which is unexpected in the medical interventions and its recurrent course.

HMD associated with hemorrhagic and thrombophilic syndrome.

Hemorrhagic hematomesenchymal dysplasia (HMD) is a group of hereditary hemorrhagic diatheses based on connective tissue development and structure disorders and related hemostatic disorders. These include Ehlers-Danlos syndrome, Marfan syndrome and juvenile kyphoscoliosis, Quique syndrome (association of telangiectasia and Willebrand factor deficiency), radial absence syndrome, thrombocytopathies and clotting factor X deficiency, Hermansky-Pudlak disease (pigmented and mesenchymal disorders combined with lack of dense granules in platelets), and others. Hemostatic disorders might manifest as thrombophilia, dysfibrinogenemia, coagulopathy with decreased levels of various clotting factors, thrombocytopathy either with decreased aggregation or hyper aggregation of the platelets, and clinically expressed as increased bleeding, but also as the development of thrombosis [14].

The variety of hemostasis disorders characteristic of hematomesenchymal dysplasia, the concept of which was founded by Barkagan Z. S. in the 1980s in our country, requires further versatile research, including that in patients with connective tissue dysplasia. The high incidence of co-morbidity of angiodysplasia and hereditary thrombophilias, and the combination of thrombophilias and thrombocytopathies characteristic of CTD, dictate that the individual hemostasiology profile of each patient should have studied to prescribe adequate correction. The check-up plan consists of a complete blood count and coagulogram. The screening test for thrombocytopathies is bleeding time and should consider prolonged if the indication is more than 5 minutes. Specific tests are platelet aggregation on microscope glass (sec) or aggregometer (%) with different aggregation inductors (ADP, collagen, adrenaline, ristomycin) [8,22].

Mesenchymal dysplasia (MD) often combines with microcirculatory, less commonly hematomas bleeding. Based on clinical and laboratory examination of patients with HMD, the classification features of hemostasis disorders in this pathology were determined, including five main types of abnormalities: hemorrhagic telangiectasia (24.3%), platelet dysfunction (42.8%), Willebrand syndrome (25.1%), coagulation hemostasis disorders, mainly fibrin polymerization disorders (40.7%) and a combination of these disorders. In complex disorders of hemostasis, Ehlers-like and MABB-like syndromes are more common. The pattern of hemostatic abnormalities in these syndromes is similar. MD is frequent (54.7% of cases), although not always diagnosed in hemophilia. In these cases, the hematomas type of hemorrhage superimposes on the microcirculatory (bruise-petechial) one, and platelet dysfunction is detected. Mesenchymal dysplasia had identified in 43.4% of cases with the early development of blood vessel thrombosis and organ ischemia, which is 2.7 times more often in those without MD ($p<0.001$). These thromboses are associated with hematogenous thrombophilias in 72.4% of cases: disorders of the protein C system, hyperhomocysteinemia, antiphospholipid syndrome, and sticky platelet syndrome. In 75% of patients with early ischemic stroke, MD had associated with thrombophilic conditions with factor Va resistance to activated protein C, hyperhomocysteinemia, and hyper aggregation of platelets [12].

Study of Jackson S.C., et al. reported that “Disorders of collagen are associated with a mild bleeding tendency because of the potential abnormal interaction of collagen, von Willebrand factor (VWF) and platelets required during primary hemostasis and due to generalized soft tissue fragility. Abnormal collagen may contribute to bleeding in existing mucocutaneous bleeding disorders, but the prevalence in this setting is unknown. Generalized symptomatic joint hypermobility (SJH) is common in collagen disorders and may be objectively measured. To assess the association between symptomatic joint hypermobility and mucocutaneous bleeding disorders, was performed a case-control study in which case subjects were 55 consecutive individuals who had visited bleeding disorder clinic with a diagnosis of von Willebrand disease, low von Willebrand factor levels, mild platelet function disorder or undefined bleeding disorder. Symptomatic joint hypermobility was associated with increased odds of an underlying mucocutaneous bleeding disorder. These findings suggest that a collagen disorder is common and often unrecognized in the bleeding disorder clinic as a potential contributor to the bleeding symptoms. Collagen disorders are common and may be unrecognized in the bleeding disorder clinic whether detected by revised Brighton criteria or by specific probing on history. The degree of contribution to the bleeding symptoms is difficult to determine in this population with existing disorders of primary hemostasis. Asymptomatic joint hypermobility is

common in this predominately female population and not an adequate screening tool for a potential collagen disorder. Further study to confirm the suspected diagnosis using biochemical or genetic endpoints would be ideal" [20].

As stated in Ben Salha M, et al, "The genetic markers associated with the development of complications in patients with high and moderate severity of UCTD are the following genotypes: C/C of IL6 gene: 174 C>G, G/C of VEGFA gene: -634 G>C, 6A/6A of MMP3 gene: 1171 5A>6A, A/A of MMP9: 855 A>G. The identified associations of gene polymorphisms in patients with UCTD made it possible to clarify certain links in the pathogenesis of this pathology. The application of modern statistical analysis methods made it possible to develop highly specific models for predicting the risk of gynecological, obstetric and neonatal complications. The use of these models in clinical practice will increase the efficiency of complication prediction and improve their outcomes" [2].

Furthermore, according to Kendel N.E., et al. "Patients with hereditary connective tissue disorders may experience significant bleeding symptoms throughout their lifetime, including easy bruising, mucosal bleeding, and heavy menstrual bleeding. While this association is well recognized in the more severe connective tissue disorders, it is perhaps not as diagnostically obvious to healthcare providers seeing patients with milder forms such as generalized hypermobility spectrum disorder (G-HSD) and hypermobile Ehlers–Danlos syndrome (hEDS). The diagnosis of hEDS requires patients to meet specific criteria evaluating joint hypermobility, associated systemic manifestations of connective tissue dysfunction, family history, and musculoskeletal pain symptoms. Most patients with generalized joint hypermobility do not meet these diagnostic criteria, but they can still have significant associated symptoms that place them in the spectrum of disorders known as G-HSD. Given these subtle findings, these patients may present to a hematologist for evaluation and treatment of bleeding symptoms before receiving a diagnosis of G-HSD/hEDS. The diagnosis of these conditions also requires the provider to understand and assess a Beighton score. The Beighton score is a validated and reproducible nine-point assessment of joint mobility that evaluates dorsiflexion of the fifth digits, apposition of the thumbs to the flexor surface of the forearms, hyperextension of the elbows, hyperextension of the knees and forward flexion of the trunk. Recent studies show that Beighton scores can vary significantly with age, sex, and ethnicity, indicating that different thresholds may be necessary for diagnosis. The updated 2017 hEDS diagnostic criteria utilizes the Beighton score as one of its measures, with different thresholds specified for different ages" [22].

A validated bleeding assessment tool has been used currently to effectively assess the frequency and severity of bleeding syndrome in hemostasis disorders, which facilitates proper diagnosis and appropriate treatment. "The study by Hickey S.E. et al. screened patients with bleeding symptoms in Ehlers-Danlos benign joint hypermobility syndrome using a bleeding assessment tool with the results were positive in 56% of cases with no apparent hemostasis defect. In addition, researchers believe that the use of genetic assessment tools had simultaneously needed for a comprehensive understanding of the mechanisms underlying hemorrhagic syndrome" [5,14,16,26,29,30].

Conclusion

Therefore, this literature review highlights the importance of alertness to hereditary coagulopathies that lead to life-threatening complications. Timely diagnosis for patients with severe hemostasis associated with HMD remains an urgent problem in pediatric hematology due to the constant high risk of life-threatening bleeding. Thus, one of the most advanced branches of modern hemostasis diagnostics can serve as a preventive method of examining genetic material to detect the clinical and laboratory correlation of the hallmarks of hemostasis pathology studied in the HMD syndrome.

Authors' contribution

This work had carried out as part of a PhD Dissertation on "Complex assessment of the hemostasis system and genetic screening in children with hematomesenchymal dysplasia".

All authors were equally involved in the search and analysis of the literature and writing the sections of the article.

Conflict of interest: *The authors declare that they have no conflict of interest.*

The authors state that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

Financing: *During this work, there was no funding from outside organizations and medical missions.*

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