S. N. KOZAREZOV

HEMORRHAGIC DISEASES IN CHILDREN

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С. Н. Козарезов

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HEMORRHAGIC DISEASES IN CHILDREN

Учебно-методическое пособие

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Рецензенты: д-р мед. наук, проф. 1-й каф. детских болезней Белорусского государственного медицинского университета И. А. Козыро; каф. детской онкологии, гематологии и иммунологии Белорусской медицинской академии последипломного образования

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На английском языке

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ABBREVIATIONS

ASH — American Society of Hematology
DIC — disseminated intravascular coagulation
FVIII — factor VIII
FIX — factor IX
FVIII:C — activity of FVIII
FIX:C — activity of FIX
GI — gastrointestinal
HRQoL — health-related quality of life
IgAV — IgA vasculitis
ICH — intracranial hemorrhage
ITP — immune (idiopathic) thrombocytopenic purpura
IVIG — intravenous immunoglobulin
aPTT — activated partial thromboplastin time
PT — prothrombin time
TT — thrombin time

CLASSIFICATION OF HEMORRHAGIC DISEASES

For the adequate functioning of the hemostatic system, it is necessary that its main components work correctly. Respectively all hemorrhagic diseases are caused by one of the three defects:

1. **Vasopathies** are disorders, caused by damage of the vessel wall, which activates the hemostatic system (vasculitis).

2. **Thrombocytopenia and thrombocytopathy** (platelet abnormality) — a quantitative deficiency (immune (idiopathic) thrombocytopenic purpura (ITP)) or functional defect of adhesion and aggregation.

3. **Coagulopathies** are disorders in which a quantitative or functional defect in one or more plasma coagulation proteins (clotting factors) are present (hemophilia).

CHILDHOOD IGA VASCULITIS (HENOCH-SCHONLEIN PURPURA)

Definition, epidemiology and etiology

IgA vasculitis (IgAV) is a non-thrombocytopenic, systemic small-vessel vasculitis, that typically presents acutely, with IgA deposition in vessel walls leading to symptoms involving the skin, joints, intestines and kidneys.

IgAV is the most common form of childhood vasculitis, affecting 8 to 20 children per 100 000 annually. It can present in any age, even during adulthood, but it is much more frequently seen in childhood with peak incidence from 4 to 6 years old. 90 % of cases occur under the age of 10 years. It is extremely rare in infants. In children, it has a slight male predominance (male : female ratio is 3:2) and a decreasing incidence according to increasing age.

Although the cause is unknown, IgAV is often preceded by an acute infectious illness and has a seasonal pattern (nonsummer months), providing strong evidence for an infectious trigger.

In most cases IgAV in children is typically an acute, self-limited illness, and treatment is primarily supportive. However, in part of the patients glomerulonephritis develops, which can lead to end stage renal disease in a small percentage of pediatric patients.

Clinical Manifestations

The diagnosis is made clinically and 100 % of patients will present with a **symmetric purpuric rash** — palpable purpura with a lower limb (legs and buttocks) predominance (Fig. 1) in addition, together **with any from a triad of other systems** (Table 1).

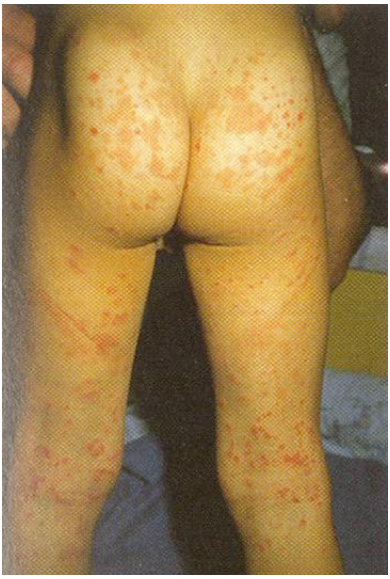

Fig. 1. Typical localization of palpable purpura

Table 1

Most common symptoms associated with IgAV

Symptoms	Affected body area	Average duration	% of affected patients
Palpable purpura	Skin (mainly lower extremities and lower parts of the arm)	3–10 days	100
Arthritis or arthralgia	Joints (knees and ankles)	7–10 days	70–90
GI disturbances (bleeding and colicky abdominal pain)	GI tract	4–8 days	50–70
Glomerulonephritis	Kidney	3–12 days	40–50

Symmetric hemorrhagic palpable purpura preceded non-hemorrhagic erythematous macular or urticarial lesions and papules. It can include areas of bruising, usually with the purpura, and more rarely necrotic lesions or bullae (Fig. 2). Rash also could be located on the upper extremities and the body. Facial involvement is very rare, it can be seen in more severe cases but never in isolation.

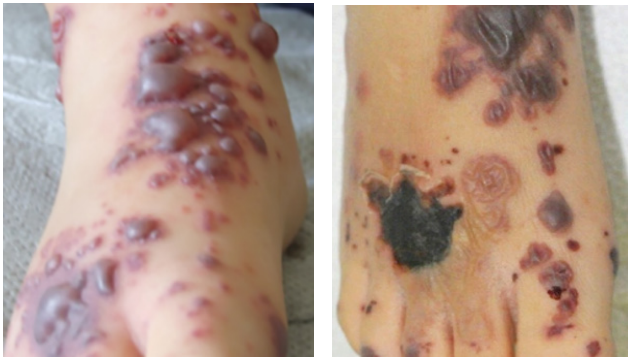

Fig. 2. IgAV: hemorrhagic-bullous and necrotic rash

Musculoskeletal symptoms (70–90 %): arthritis or arthralgia, especially involving the knees and ankles. Arthritis tends to have an oligoarticular pattern (4 or fewer joints). Joint involvement can rarely precede skin involvement. Arthritis is usually transient and does not cause any residual abnormalities such as joint erosions.

GI tract involvement occurs in up to 70 % of patients and usually presents with colicky abdominal pain or acute GI (gastrointestinal) bleeding either manifesting as melena or hematemesis that can be severe and life-threatening. Intussusception can also occur and this is a surgical emergency. GI manifestations may precede

the skin manifestations, by a few days or a week, and this can sometimes lead to clinical confusion until the rash appears.

Renal involvement, termed IgAV nephritis, is usually asymptomatic and thus requires active screening. It is seen in around 40–50 % of patients, most of whom have a mild renal course that self resolves. Microscopic hematuria is the most common finding on urinalysis followed by proteinuria without edema. Macroscopic hematuria or nephrotic syndrome rarely can be seen. Renal involvement is the most serious long-term manifestation accounting for 1–2 % of all childhood end stage renal disease.

Renal monitoring typically relies on regular urinalysis and blood pressure checks. A renal biopsy should be performed if an IgA vasculitis patient has:

– severe (nephrotic) proteinuria (> 2000 mg/g for at least 4 weeks; although shorter duration of severe proteinuria is also a relative indication for biopsy);

– or persistent moderate (1000–2000 mg/g) proteinuria or impaired glomerular filtration rate.

Due to the risk of long-term renal complications, there is consensus agreement that all patients with IgAV should have renal monitoring for at least 6 months after the acute episode, even if the initial urine is normal.

Diagnosis

In 2005, a new European League Against Rheumatism (EULAR)/Pediatric Rheumatology European Society (PReS) classification criterion for all childhood vasculitis including IgAV was proposed based on expert consensus and validated with the support of the Pediatric Rheumatology International Trials Organization (PRINTO). The EULAR/PReS/PRINTO criteria rely on clinical features and include the mandatory presence of a vasculitic purpuric rash together with additional symptoms and signs yielding an excellent sensitivity (100 %) and specificity (87 %) in distinguishing IgAV from other types of vasculitis.

The EULAR/PReS/PRINTO (2005) classification criteria for childhood IgA vasculitis

Mandatory criterion: palpable purpura with lower limb predominance and at least 1 out of 4:

1. Acute onset diffuse abdominal colicky pain (may include intussusception and gastrointestinal bleeding).
2. Histology showing leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposition.
3. Acute onset arthralgia or arthritis.
4. Either proteinuria or hematuria.

Treatment

Most cases of IgAV in children spontaneously improve and do not require any specific treatment. In more severe cases, treatment options in part depend on the type and severity of organ involvement.

Skin involvement is usually self-limiting and doesn't require specific treatment. It may require treatment when the condition presents with a bullous or necrotic rash, but this is rare. Corticosteroids (prednisolone orally 1 mg/kg/day) recommended as the first line treatment and should be started as soon as the bullae or necrotic areas appear.

Management of **musculoskeletal involvement** is usually supportive by providing pain relief usually using non-steroid anti-inflammatory medications, such as ibuprofen. More severe cases have been reported to respond to corticosteroids at a dose similar to that proposed for severe skin disease.

As most **GI involvement** is mild and short-lived, treatment is not usually required. GI hemorrhage and/or intussusception will necessitate surgical intervention. Abdominal pain that is not tolerable will benefit from treatment with prednisolone orally 1–2 mg/kg/day). Intravenous methylprednisolone could be administered if the condition is life-threatening, oral route is not tolerated or they have failed to respond.

Treatment of renal involvement is important because it is the only organ associated with long term consequences. The Cochrane Systematic Review group concluded that there is no evidence to support the use of corticosteroids in all children with IgAV to prevent the onset of nephritis.

Treatment of established renal inflammation

Oral prednisolone is recommended as first line treatment for mild renal disease (those with a normal renal function and mild/moderate proteinuria).

Oral or intravenous prednisolone for moderate nephritis (< 50 % crescents on biopsy and impaired renal function or severe persisting proteinuria) together with either azathioprine, mycophenolate mofetil or intravenous cyclophosphamide.

In severe nephritis (defined as > 50 % crescents on renal biopsy and impaired renal function or severe persisting proteinuria), intravenous corticosteroids and intravenous cyclophosphamide are recommended to induce remission.

Targeting the coagulation system. Abnormalities in coagulation have been implicated in the renal pathophysiology of IgAV. Using of low molecular weight heparin (administered daily over an 8-week period) alongside immunosuppression treatment demonstrated improvement in the overall outcome with less ESRD and improvement in proteinuria.

Targeting the angiotensin system. Due to their well-recognized role in long-term renal protection, it is consensus opinion that all patients should receive adjunctive ACE inhibitor or angiotensin receptor blocker for persisting proteinuria.

Outcome

Overall the outcome is excellent in the vast majority of children (50 % have spontaneous remission) however relapses can occur and there is a recognized risk of life-long renal complications.

The majority of children will have a self-limiting disease course with symptoms resolving within the first 1 month and more than 90 % of children will make a complete recovery by 2 years.

Recurrent episodes of IgAV occur in around 25 % of patients and there is some suggestion that they may be more common in slightly older children (aged > 8 years) and in those with nephritis.

IMMUNE (IDIOPATHIC) THROMBOCYTOPENIC PURPURA

Definition and Epidemiology

ITP is an acquired autoimmune disorder characterized by a low platelet count resulting from platelet destruction and impaired platelet production.

ITP is the most common cause of thrombocytopenia in children of any age with a peak occurrence between 2 and 5 years of age.

In most children the disease is self-limited, with resolution in 60–80 % of patients within 2–12 weeks (acute) or 3–12 months (persistent) from diagnosis. Approximately 20 % of patients who present with acute ITP have persistent thrombocytopenia for > 12 months and are said to have chronic ITP.

There is a seasonal pattern to ITP with a peak in late winter and early springtime, presumably mimicking the pattern of viral illnesses.

Pathophysiology

Antibody-mediated destruction. Autoantibody-coated platelets are destroyed by activated Fc receptors on reticuloendothelial cells (mostly splenic).

Impaired megakaryopoiesis. Antibody, cellular cytotoxicity, and/or immune-cell-derived cytokines have been implicated in impairment of megakaryocytes. Absolute platelet reticulocyte counts are reduced.

T-cell activity. Antiplatelet autoantibodies are absent in 20–40 % of cases of ITP. But there is an upregulation of genes involved in cell-mediated toxicity.

Clinical Manifestations

Typically, patients are present with petechiae (tiny red dots under the skin that are a result of very small bleeds into the skin), purpura, and non-palpable ecchymoses 1–3 weeks after almost any viral infection or live virus vaccination.

Occasionally patients may present with mucosal bleeding (hematuria, hematochezia, menometrorrhagia or epistaxis).

Most often, bleeding symptoms are mild, but rarely patients may develop severe bleeding including ICH, protracted epistaxis, hematuria, hemoptysis, menometrorrhagia, and GI bleeding.

Characteristic of the skin hemorrhagic syndrome (Fig. 3):

1. ***Polymorphism of the rash.*** Along with ecchymoses of different sizes and shapes there are small petechiae.

2. ***Polychromy.*** As a rule, ecchymoses of different colors are simultaneously found on the skin, depending on the time of their appearance: from bright purple to blue-green and yellow.

3. ***Asymmetry.*** There is no favorite localization of skin hemorrhagic syndrome.

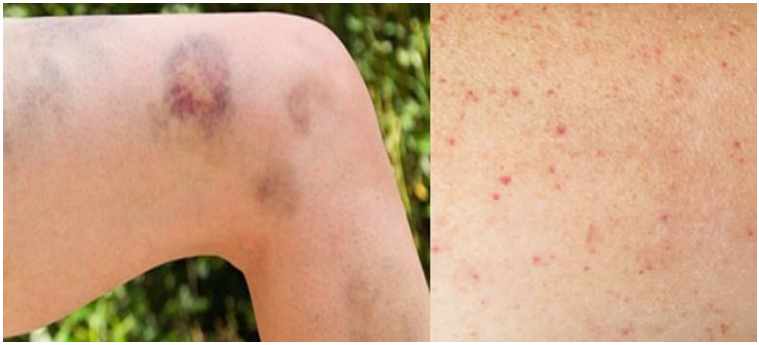

Fig. 3. Typical skin hemorrhagic syndrome in ITP

With the exception of hemorrhagic manifestations, the physical examination is normal. Pallor is usually absent unless there has been significant bleeding.

Spleen tip is palpable in fewer than 10 % of patients. The finding of splenomegaly suggests the probability of leukemia, systemic lupus erythematosus, infectious mononucleosis, or hypersplenism.

Cervical lymphadenopathy is not present unless the precipitating factor is a viral illness.

There are no congenital anomalies suggestive of an inherited bone marrow failure syndrome.

Intracranial hemorrhage (ICH) incidence is 0,2–0,8 %, Platelet count ($< 20 \cdot 10^9$/L in 90 % of cases and $< 10 \cdot 10^9$/L in 75 % of cases).

Identifiable risk factors for ICH include:

1. Head injuries (33 % vs 1 % in ITP without ICH).
2. Hematuria (22 % vs 0 % in ITP without ICH).
3. Hemorrhage more than petechiae and bruises (63 % vs 44 % in ITP without ICH).
4. Aspirin treatment.

Diagnosis

The diagnosis of ITP remains almost entirely one of exclusion. That is why other possibilities with secondary ITP must be excluded (inherited thrombocytopenia, lymphoproliferative disease, chronic infection with human immunodeficiency virus, hepatitis C, Helicobacter pylori, and cytomegalovirus, immunodeficiency, Evans syndrome, drug-dependent antibody-mediated immune thrombocytopenia).

Severe thrombocytopenia (platelet count $< 20 \cdot 10^9$/L) is common, and platelet size is normal or increased, reflective of increased platelet turnover. Demonstrating antiplatelet autoantibodies has not been shown to be of diagnostic or prognostic importance since antiplatelet autoantibodies are only present in approximately 60–80 % of cases.

Diagnostic criteria of ITP:

1. Isolated thrombocytopenia with otherwise completely normal CBC and blood smear.
2. Absence of hepatosplenomegaly, lymphadenopathy, and congenital anomalies such as radial ray anomaly.
3. Platelet response to ITP therapy (especially intravenous immunoglobulin (IVIG) or anti-D, possibly steroids) is the only finding that helps to positively support the diagnosis of ITP (including secondary ITP).

Treatment

The goal of therapy in ITP is to increase the platelet count enough to prevent serious hemorrhage. Treatment decisions should be based on the potential for bleeding including the physical activity level, patient's history of bleeding, current platelet count, signs and symptoms.

In 2019 American Society of Hematology (ASH) formed guidelines for ITP:

1. In children with newly diagnosed ITP and a platelet count of $< 20 \cdot 10^9$/L (Recommendation 10a) or $\geq 20 \cdot 10^9$/L (Recommendation 10b) who have no or

mild bleeding (only skin manifestations), the ASH guideline panel suggests against admission to the hospital and in favor of management as an outpatient.

Remark: For patients with uncertainty about the diagnosis, those with social concerns, those who live far from the hospital, and those for whom follow-up cannot be guaranteed, admission to the hospital may be preferable.

2. Treatment vs Observation. In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel suggests observation rather than corticosteroids (Recommendation 11), IVIG (Recommendation 12) or anti-D immunoglobulin (Recommendation 13).

3. Corticosteroid duration. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life (HRQoL), the ASH guideline panel recommends against courses of corticosteroids longer than 7 days and in favor of courses 7 days or shorter (Recommendation 14).

4. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests:

– Prednisolone (2–4 mg/kg per day; maximum, 120 mg daily, for 5–7 days) rather than dexamethasone (Recommendation 15).

– Corticosteroids rather than anti-D immunoglobulin (Recommendation 16). Because treatment with Anti-D immunoglobulin was associated with rare but serious side effects (fatal intravascular hemolysis) against the common but milder side effects associated with a short course of corticosteroids. The use of corticosteroids is substantially less expensive than anti-D immunoglobulin. Anti-D immunoglobulin availability is also limited in many places and requires that a patient be Rh+ with an intact spleen to be effective.

5. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished HRQoL, the ASH guideline panel suggests:

– Either anti-D immunoglobulin or IVIG (Recommendation 17). Both agents were thought to have similar benefits. In consideration of harms, both treatments are associated with rare but potentially serious events and require careful monitoring during use.

– Corticosteroids rather than IVIG (Recommendation 18). A short course of corticosteroids is associated with some mild side effects in the majority of patients. IVIG, however, is associated with the risk of thrombosis and renal failure. Furthermore, the side effect of IVIG-associated headache can be significant and lead to additional medical interventions, such as computed tomography scans of the brain evaluating for ICH.

IVIG has high costs compared with a short course of corticosteroids. IVIG may also not be widely available, whereas corticosteroids represent a universally available treatment.

6. In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests:

– The use of thrombopoietin-receptor agonists (TPO-Ras) rather than rituximab (Recommendation 19) or splenectomy (Recommendation 20).

– Rituximab rather than splenectomy (Recommendation 21).

Prolonged use of corticosteroids in ITP is undesirable. Large doses or prolonged usage may depress platelet production. It also leads to side effects including gastritis, ulcers, weight gain, hyperglycemia, hypertension, growth retardation, cushingoid facies and others.

Mechanism of action of steroids:

1. Inhibit platelet antibody production and the phagocytosis of antibody-coated platelets.

2. Suppress activation of T-cells driving the autoimmune response.

Mechanism of action of IVIG (Fig. 4):

1. Inhibits clearance of Ig-coated platelets.

2. Upregulates the inhibitor of FcγR on phagocytes.

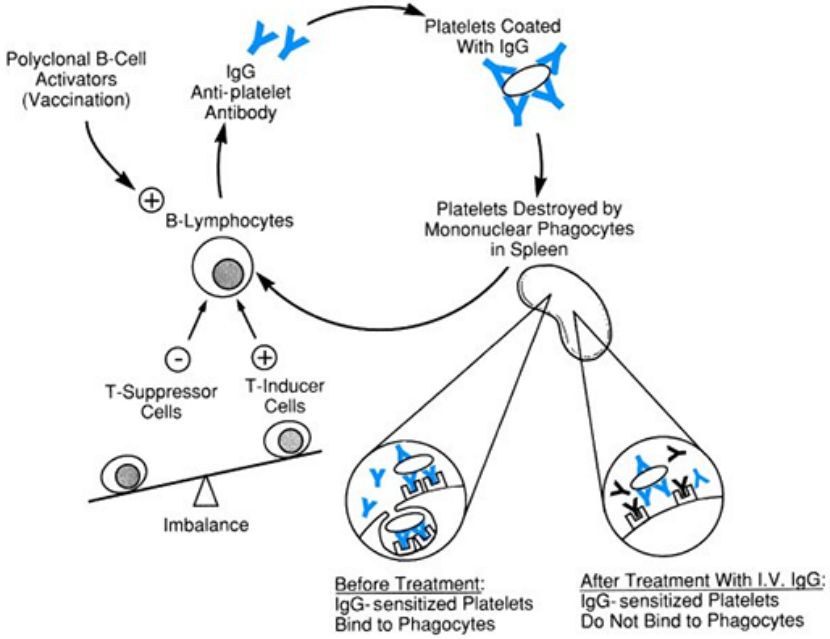

Fig. 4. Mechanism of action of IVIG

IVIG can be administered in a dose of 0.4–1 g/kg/day for 1–5 days for initial therapy or for relapsed disease.

Some studies conclude that treatment with IVIG is preferred over steroids in children less than 2 years of age because they tend to have lower response rate to steroids and more challenging behavioral risk factors for bleeding.

Meta-analysis has shown a more rapid response to IVIG in children compared to corticosteroids. In addition, there may be a lower rate of chronic disease in patients initially treated with IVIG compared to those treated with prednisolone.

Splenectomy is rarely indicated because of the increasing number of effective medical therapies that have been developed combined with the favorable natural history of ITP in children. ASH 2019 guidelines conclude that the risks associated with non-surgical treatment are low and the potential benefits high. The panel also placed high value on **avoiding splenectomy in the pediatric population**, especially given that many children are likely to undergo spontaneous remission.

Platelet transfusion. Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus, platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Platelet transfusions may be transiently effective and required for rare emergency situations including ICH, internal bleeding, and emergency surgery. Some short-term hemostatic activity is usually obtained.

HEMOPHILIA

Definition

Hemophilia is one of the most common inherited bleeding disorder and the most common and serious congenital coagulation factor deficiency.

Conventionally, hemophilia refers to deficiencies of the coagulation proteins, factor VIII (FVIII) and factor IX (FIX). FVIII deficiency is known as hemophilia A or classic hemophilia. FIX deficiency is known as hemophilia B or Christmas disease.

Genetics

The X and Y chromosomes are called sex chromosomes. The gene for hemophilia is carried on the X chromosome. Hemophilia is inherited in an X-linked recessive manner (Fig. 5). Females inherit two X chromosomes, one from their mother and one from their father (XX). Males inherit an X chromosome from their mother and a Y chromosome from their father (XY).

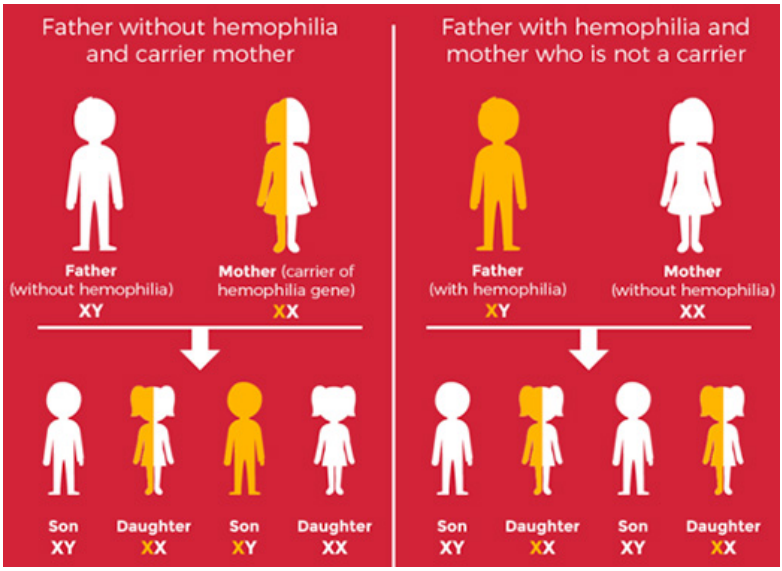

Fig. 5. Hemophilia inheritance patterns

If a male with hemophilia has children, all the daughters will be carriers and no son will be affected. If a female hemophilia carrier has children, there will be a 50 % chance that each male child will have hemophilia and a 50 % chance of a female child being a carrier.

It should be noted that female carriers of severe hemophilia mutations frequently have reduced FVIII:C or FIX:C levels. Rarely, females who are carriers of hemophilia mutations may have levels as low as affected males within the family due to inactivation of the X chromosome, inheritance of a mutated FVIII gene from both maternal and paternal chromosomes, or Turner syndrome.

Etiology and epidemiology

Hemophilia A and B affect approximately 1 in 5000 and 1 in 30 000 live births, respectively, and are equally common in all ethnic groups.

The vast majority of patients are male, but hemophilia can occur very rarely in females. The reason for the relatively high incidence of FVIII deficiency is partly due to the high mutation rate.

In approximately one-third to half of newly diagnosed infants with hemophilia A there is no family history of the disorder and the hemophilia has resulted from spontaneous (de novo) mutations.

Pathophysiology

FVIII and FIX are the two components of the intrinsic tenase. Consequently, their absence causes virtually identical patterns of bleeding. Combined with the fact that they are both encoded on the long arm of the X chromosome, they present almost indistinguishable sex-linked clinical syndromes and specific assays are required to determine which is present. In both cases, failure to form the intrinsic tenase complex results in failure to produce the thrombin and fibrin.

The consequent failure to consolidate the primary (platelet) hemostatic plug results in the characteristic bleeding pattern of hemophilia, which is both delayed after trauma and much prolonged.

Clinical classification

Hemophilia is classified as mild, moderate, and severe on the basis of the patient's residual FVIII and FIX blood concentrations (1IU/dL = 1 %):

– < 1 % Severe: frequent spontaneous bleeding into joints, muscles and internal organs (relative incidence — 50 %);

– 1–5 % Moderate: some spontaneous bleeds, bleeding after minor trauma (relative incidence — 30 %);

– > 5–45 % Mild: bleeding only after significant trauma, surgery (relative incidence — 20 %).

A woman with a clotting factor of < 45 % should be treated the same as a man with similar levels (she has hemophilia). Women with factor levels > 45 % and who show bleeding symptoms are now classified as symptomatic carriers.

Clinical features

Hemarthrosis, bleeding within the joint space, occurs spontaneously or after minor trauma. The frequency and age of onset of joint bleeding depends upon the severity of deficiency. In severe deficiency, joint bleeds typically begin between age 6 months and 6 years and can occur several times a month. Repeated bleeding (four bleeds into the same joint) in a 6-month period is considered a «target joint». The repeated bleeding initiates synovitis and ultimately progression to hemophilic arthropathy.

Muscle bleeding is the second most frequent type of bleeding in patients with hemophilia. Intramuscular hemorrhages within a closed compartment such as the volar aspect of the wrist, deep palmer compartments of the hand, anterior or posterior tibial compartments, and inguinal region cause significant morbidity due to compression of neurovascular bundles (compartment syndrome).

Clinical manifestations with different severities of hemophilia A and B presented in the Table 2.

Table 2

Clinical manifestations with different severities of hemophilia A and B

Type of bleeding	Severe	Moderate	Mild
Age of onset	< 1 year	< 2 years	> 2 years
Hemarthrosis: Spontaneous Following minor trauma	 ++++ ++++	 ++ +++	 – –
Muscle hematoma	++++	++	–
ICH	++	+	–
Hematuria	++++	++	–
Surgery	++++	+++	++
Dental extraction	++++	+++	++
Trauma to soft tissue: Mild Significant	 ++++ ++++	 ++ +++	 – +

Diagnostics

FVIII and FIX deficiency are associated with prolongation of the aPTT. Platelet count, PT and TT are normal.

The diagnosis is made on specific clotting assays that assess the activity of FVIII (FVIII:C) or FIX (FIX:C). These assays should be repeated on separate occasions to confirm the diagnosis.

Genetic testing: investigation of FVIII and FIX gene defects (linkage analysis and direct mutation analysis).

Prophylaxis

Identification of carrier status include family pedigree, measurement of FVIII:C and FIX:C levels, linkage analysis and direct mutation analysis.

A detailed family pedigree may identify obligate carriers. Daughters of men with hemophilia are obligate carriers, as are women with two children with hemophilia, or one child with hemophilia and another maternal relative with hemophilia.

With recent advances in molecular laboratory techniques, it is now possible to give each patient very reliable genetic information. To enable these genetic data to be used for the benefit of the patient with hemophilia or to influence reproductive choices, genetic counseling should be initiated as early as possible.

Factor replacement therapies. Replacement of deficient coagulation factors by administration of exogenous factor concentrates is the primary treatment for patients with hemophilia. These clotting factor concentrates are either derived from plasma fractionation or recombinant technology.

The commonly used treatment regimens fall into one of five categories:

1. Primary prophylaxis: the regular and long-term administration of clotting factor concentrates to prevent bleeding is the current standard of care. This has been shown to prevent recurrent joint bleeds and preserve joint function into adulthood. It is typically started before the age of 2 years and after the first joint bleed.

2. Secondary prophylaxis: regular continuous treatment started after two or more large joint bleeds but before the onset of joint disease.

3. Tertiary prophylaxis: regular continuous treatment started after the onset of joint disease to prevent further joint damage.

4. Intermittent prophylaxis: treatment is given to prevent bleeding for a short period of time, such as during and after surgery.

5. Episodic (on demand) treatment: treatment is given at the time of bleeding.

The choice of treatment regimen depends upon: severity of hemophilia, frequency of bleeding and severity of the bleeding event.

Primary prophylaxis (with standard factor replacement products), typically 25–50 IU/kg administered three times per week to every other day, is now the standard of care for patients with severe hemophilia A and twice a week for severe hemophilia B. This has been demonstrated to prevent joint bleeds and subsequent arthropathy.

Modified recombinant factor products, which extend the half-life in the plasma, could be prescribed every 3–5 days for patients with hemophilia A and every 7–14 days for patients with hemophilia B.

More recently a substitution therapy has been developed that may revolutionize the treatment of hemophilia. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody, restores the function of missing activated factor FVIII by bridging FIXa and FX to facilitate effective hemostasis in patients with hemophilia A. It has no structural homology to FVIII, therefore, it would not be expected to induce FVIII inhibitors or be affected by the presence of FVIII inhibitors. Subcutaneous emicizumab is approved in the USA, EU and Japan for the routine prophylaxis of bleeding episodes in patients with hemophilia A with or without FVIII inhibitors.

Emicizumab prophylaxis significantly prevented or substantially reduced bleeding in children with hemophilia A with or without inhibitors. Emicizumab was also associated with beneficial effects on HRQoL and health status, and was generally well tolerated. In view of its convenient route of administration and

versatile dosage regimens (maintenance dose of once every 1, 2 or 4 weeks), emicizumab provides an effective and generally well-tolerated alternative to conventional FVIII replacement products for the prophylaxis of bleeding episodes in patients with hemophilia A, regardless of the presence or absence of inhibitors.

Treatment for acute bleeding

In the event of an acute bleeding episode, it is critical to raise the levels of FVIII or FIX to the hemostatic range. The intensity and duration of factor replacement therapy depend upon the severity of the bleeding:

1. ***Minor bleeding episodes:*** it is recommended to raise the factor level up to at least 30–50 %.

2. ***Major bleeding episodes*** (e.g., CNS bleeds): factor levels should be raised up to 80–100 % until the bleeding is arrested. Subsequent maintenance of hemostatic levels will depend upon the severity of bleeding episode and its response to treatment and could be achieved by maintaining factor level in the range of 50–100 % during 1–3 weeks.

Adjuvant therapies

Progression of hemophilic arthropathy leads to loss of joint function. Prophylaxis treatment regimens prevent the progression of hemophilic arthropathy by reducing the frequency of joint bleeds, but do not necessarily reverse the joint damage. Immobilization and treatment with glucocorticosteroids are used to reduce the severity of joint damage. Surgical or synovectomy and in some cases synovial embolization can be performed to reduce the bleeding tendency. Joint replacement surgeries are frequently required in adult hemophilia patients.

Desmopressin is a synthetic version of antidiuretic hormone that causes release of von Willebrand factor from storage sites within endothelial cells. This agent also results in a parallel increase in plasma FVIII levels. It's particularly useful in patients with mild hemophilia A and may obviate the need for factor replacement therapy with minor bleeds.

Other adjuvant therapies such as antifibrinolytic medications (aminocaproic acid, tranexamic acid) and topical hemostatic agents (thrombin, fibrin sealant) may also be used even in severe hemophilia along with specific factor replacement therapy.

Inhibitors of coagulation factor VIII and factor IX

Alloantibodies developed against exogenously administered factors that interfere with their procoagulant functions are conventionally known as «inhibitors». Up to 30% of patients with severe hemophilia A develop inhibitors to exogenously administered FVIII, while 3–5 % of patients with severe hemophilia B develop inhibitors against exogenously administered FIX. These antibodies are typically directed against functional epitopes on FVIII or FIX, so they neutralize the functional activity of exogenously administered clotting factor making the treatment ineffective.

Patients with inhibitors typically present with bleeding manifestations despite adequate prophylaxis or failure to achieve hemostasis with replacement therapy in the context of an acute bleed.

Treatment of an acute bleeding episode includes the use of «bypassing agents» such as activated prothrombin complex concentrates (contain multiple activated serine protease molecules such as activated forms of factor X and prothrombin to drive hemostasis without FVIII or FIX) or recombinant factor VIIa (is able to directly activate factor X and increase thrombin production in the absence of FVIII or FIX). Antifibrinolytics may also be used as adjunct therapy.

Immune tolerance induction regimens are used to eradicate the inhibitor. These regimens include frequent, often daily, infusions of high doses of factor concentrates with or without immunosuppressive agents.

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