Haemostatic defects in childhood: Principles of diagnosis and treatment

* The chain reaction leading to prompt inhibition of bleeding and provide circulating liquid in the case of lolod vessel damage.

* Hemostasis

*Hemostasis

Hemostatic correct operation depends on:

1. plasma and platelet coagulation factors
2. state of the vessel wall
3. blood clotting inhibitors

Defects / abnormalities in :

1. Vascular (most common Schoenlein- Henoch disease)
2. Platelets (qualitative/quantitative)
3. Coagulation (deficiency of plasma clotting factors)

*Hemostatic defects

In physical examination:

*bleeding in the skin and mucous membranes

* blood hemorrhage to the muscles and joints

*internal bleeding

*Signs of hemostatic disorder

Signs of hemostatic disorder

* petechiae –not-fading under suppression changes to 2mm
* purpura - the result of confluent petechiae
* bruises (ecchymoses) isolated changes larger than petechiae

Platelets number (below 150 000/mm3 – trombocytopenia)

Prothrombin time

Activated Partial Thromboplastin Time

Fibrinogen consentration

*Basic laboratory tests

Primary trombocytopenia:

- Immune/idiopathic thrombocytopenic purpura (ITP)
- Neontal alloimmune thrombocytopenia
- TAR Syndrome
- Wiskott-Aldrich Syndorme

Primary coagulopathy:

- von Willebranda disease
- Haemophilia
- abnormal platelet function

Hematological causes of bleeding

Secondary thrombocytopenia:

- Canser
- Aplastic anemia
- DIC- Disseminated Intravascular Coagulation, sepsis
- Drug caused trombocytopenia
- HUS- haemolitic-uremic syndrome
- hemangiomas
- hypersplenism
- artificial heart valves
- SLE
- HIV

Secondary coagulopathy:

- DIC
- Antykoagulants drugs
- Vit. K deficiency
- Liver failure
- Renal failure
- Anti convulsant therapy during pregnancy-> vit k deficiency

Hematological causes of bleeding

Platelets disorders

acquired, symptomatic, congenital

Platelets disorders

* Acquired (shortened survival time of platelets) - immunological, in infancy and early childhood
* Symptomatic (abnormal production of megakaryocytes) - in hyperplastic diseases or acquired insufficiency of hematopoietic system
* Congenital (lack of production of megakaryocytes in the bone marrow blood)

Thrombocytopenia

Result of:

decreased platelets production

increased their destruction

sequestration

Immune/idiopathic thrombocytopenic purpura (ITP)

ITP – what is it?

* Affects young children (> 90% of cases)
* Acute in onset, usually self-limiting
* Majority of cases follow vaccinations or viral infections
* ♂ : ♀ = 1:1
* 2-6 years ogf age
* Antibodies (IgG, IgM) connected to the cell membrane of platelets and lead to their destruction
* About 10% fail to recover within 6 months → chronic ITP

*ITP – signs and symptoms

* Acute onset- petechiae, purpura, epistaxis, bleeding gums- 1-4 weeks after viral infection

20,000/µl

* Spontaneous formation of purpura and petechiae
* Epistaxis
* Bleeding gums
* Hematomas in mouth/mucous membranes

<5,000 /µl

* Subarachnoid/intracerebral hemorrhage
* Lower GI bleeding/internal bleeding

Sometimes- adenopathy, hepatosplenomegaly

Elongate bleeding time

*ITP - treatment

* Treatment in most cases when PLT number is less then 30 tys./mm3
* In deep thrombocytpenia:
  - prednizon 2-4mg/kg/24 h for 2 weeks

    or

  - IVIG 1g/kg/ 24 h for 1-2 days

    or

  - concentrate of human gamma globulin anti-D Rh-positive patients

ITP - treatment and prognosis

* splenectomy only for life-threatening bleeding (eg. to CNS)
* at approx. 80% of children spontaneous withdrawal of the disease within six months of diagnosis
* serious bleeding (including intracranial) less than 1% of patients

thrombocytopenia - if it takes 6-12 months = chronic = exclude SLE and HIV infection

dental treatment contraindicated during acute thrombocytopenia; in chronic thrombocytopenia - only in a hospital setting: local prevention- aminocaproic acid, drugs sealing

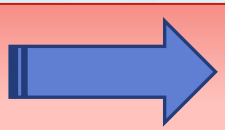
*ITP -prognosis

*Thrombocytopenia caused by reduced production of blood platelets

- Megacariopoetic disorders

Primary megacariopoethic disorders

* TAR syndrome= thrombocytopenia absent radius
* Congenital bone marrow aplasia (Fanconi anemia) – anemia, leucopenia, trombocytopenia
* Wiskott-Aldrich Syndrome



- X-linked recessive disease
- eczema, immune deficiency- hipogammaglobulinemia, T cells dysfunction, thrombocytopenia-> caused by molecular defect
- In peripheral smear- small platelets
- abnormal production of megakaryocytes in the bone marrow and abnormal platelets function
- causal treatment: transplantation of hematopoietic stem cells

*Wiskott-Aldrich Syndrome

Secondary megacariopoetic disorders

- pancytopenia in bone marrow failure - infiltration of bone marrow by cancer cells or aplastic process
- some chemotherapeutic agents can selectively destroy megakaryocytes
- cyanotic congenital heart defects with polycythaemia and thrombocytopenia
- congenital viral infection (TORCH)
- acquired viral infections (HIV, EBV, measles virus)
- some drugs (antiepileptic, antibiotics, heparin, quinidine) can cause thrombocytopenia

*Thrombocytopenia caused by peripheral platelets destruction

- Immunological mechanisms
- destruction of antibody-coated platelets by cells of the reticuloendothelial system- macrophages

Neontal alloimmune thrombocytopenia

* due to the sensitization mother to fetus platelet antigens
* antibodies across the placenta and attack fetal blood platelets
* maternal ITP may have passive transfer of anti-platelet antibodies, which bind to fetal platelet antigens, resulting in their destruction in the spleen
* risk of intracranial bleeding in utero and at birth
* IVIG supply before birth increases the number of platelets in the fetus
* indicated giving birth by CC
* neonates with thrombocytopenia <20 tys./mm3 may receive IVIG or corticosteroids or get washed maternal platelets

*Other diseases

Thrombotic thrombocytopenic purpura(TTP)

- thrombocytopenia, microangiopathic hemolytic anemia, neurological disorders, changes in urine
- Symptoms resulting from the formation of blood clots in the terminal parts of the arterioles and capillaries
- Causes:
- congenital or acquired deficiency of metalloproteinase (ADAMTS13) cleaving von Willebrand factor, or
- the appearance of antibodies to inactivate the enzyme

*TTP

Thrombotic thrombocytopenic purpura(TTP)

- petechiae and bruising, retinal haemorrhages, bleeding from the gastrointestinal tract; haemolytic anemia
- headaches, confusion, hemiplegia, cranial nerve damage, convulsions
- anemia, increased reticulocytes, fragmentocytes
- elevated serum LDH and bilirubin
- reduced platelet count
- proteinuria, renal impairment
- treatment - plasmapheresis, FFP- fresh frozen plasma

*TTP

Platelets dysfunction

* Secondary - exposure to toxins and drugs:
  * uremic toxins
  * valproic acid
  * acetylsalicylic acid
  * other NSAIDs
  * infection

Primary - cell membrane receptors responsible for platelets adhesion:

Bernard-Soulier syndrome

Glanzmann's thrombasthenia

*Serum coagulation disorders

- Congenital and acquired

Factor	Name	Disease name
I	Fibrinogen	A/hipofibrinogenemia
II	Prothrombin	hipoprothrombinemia
III	Tissue factor/ thromboplastin	No disease
IV	Calcium	No disease
V	Proaccerin	Hipoproaccerinemia
VII	Proconvertin	hipoproconvertinemia
VIII	antihemophilic factor	hemophilia A
IX	Christmas factor	hemophilia B
X	Stuart factor	hipostuartemia
XI	plasma trombofactplastin antecedent	hemophilia C
XII	Hagemna's factor	Hageman's defect
XIII	Fibrin stabilizing factor	Congenital XIII factor deficiency

Deficiency of clotting factors

* Deficiency of clotting factors 8 and 9- severe bleeding disorders (recessive X-linked disorders)

* von Willebrand disease – the most common congenital bleeding disorder

*Hemophilia

- Hemophilia A (factor VIII deficiency) - 1:5000 men
- Hemophilia B (factor IX deficiency) - 1:25 000
- delayed thrombin creation
- The course of disease depends of degree of clotting factor deficiency
- different ways of treatment course depends on the degree of deficiency of clotting factor
- lab. tests: normal bleeding time, normal prothrombin time, normal thrombin time, but prolonged partial thromboplastin time (APTT)

Hemophilia - signs

* Concentration VIII and IX factors
* < 1% of normal range (severe hemophilia) – spontaneous bleeding or after mild injuries to the muscles and joints
* 1-5% normal range (moderate hemophilia) – signs after stronger trauma
* > 5% normal range (mild hemophilia) – very strong trauma can cause bleeding ; there are no spontaneous bleeding

Hemophilia -treatment

- replacement therapy (recombinant coagulation factors); symptomatic and supportive treatment
- treatment of acute bleeding episodes
- prevention of bleeding complicating during surgery or tooth extraction

*Hemophilia - treatment

in the case of life- threatening bleeding, the concentration VIII or IX factors should reach 80-100 % of normal range

for mild to moderate bleeding the sufficient range is a concentration of :

factor VIII- 40% normal range,

factor IX 30-40% normal range

8 factor → 1 j.m./kg body mass
increases the 8 factor concentration about 2 %

9 factor → 1,5 j.m./kg body mass
increases the 8 factor concentration about 1%

*Hemophilia - treatment

Factor 8 dose=

Target concentration [%] x body mass [kg] x 0,5

Factor 9 dose=

Target concentration [%] x body mass [kg] x 1,5

*Hemophilia - treatment

- is a synthetic analog of vasopressin
- Patients with mild to moderate hemophilia A
- It has no effect on the concentration factor 9

*Desmopressin acetate

- fibrinolysis inhibitor
- It may be useful in controlling bleeding in the mouth
- contraindicated in strokes of blood to the internal organs, hematuria and bleeding to CNS

*Aminocaproic acid

*Inhibitors

- IgG antibodies directed against infused factor 8 and 9 in patients with their congenital deficiency .

Inhibitors

- inhibitor is created in 15 % of patients with factor 8 severe deficiency (less common in patients with factor 9 deficiency)
- with low concentration of inhibitor -> continuous infusion of factor 8

*Inhibitors

- In case of patients with high range of inhibitor it is neccesery to supply the product which passes the blocade

- Recommended drug is recombined 7a factor

It may be advantageous – the attempt of immunological tolerance induction by repeated infusions of missing factor with or without immunosuppression.

*Inhibitors

Treatment during teeth extraction

* Prior to surgery (15-30min) patient has to receive factor 8 or 9
* Antifibrinolytic agents : Exacyl 2 hours before surgery , then for 7 days until adequate gum healing
* The alveolus fill with spongostan with thrombin and pressure with gauze
* Diet- liquid- mushy during the healing of the alveolar

von Willebrand disease

* the presence of 1 % of the population
* inheritance : AD or AR
* vWF is a protein adhesive : running as a bridge between collagen and platelets and combining with the circulated factor 8 protecting it before removal from plasma

von Willebrand disease

* approx. 80% of patients have a form of classical (Type 1 - mild or moderate deficiency of vWF)
* symptoms: mucocutaneous bleeding, bleeding from the nose, gums, bruises, heavy menstrual periods

von Willebrand disease

* Laboratory tests
* measurement of protein concentration - vWF
* antigen vWF activity (functional test with ristocetin)

von Willebrand disease

Treatment:

- desmopressin
- concentrate containing vWF
- Not use crioprecipitat (the risk for viral infection)
- avoid ASA !

- Epsilon-aminocaproic acid
- Tranexamic acid
- Spongostan (sponge fibrin) + thrombin
- The tissue adhesive (fibrinogen with factor XIII and thrombin with Ca ion)

* Symptomatic treatment of congenital hemorrhagic diathesis- bleeding disorders

*Vascular coagulation disorders

Allergic purpura

* Allergic purpura (Schoenlein –Henoch disease)

- disease of the small vessels on immune background - increased vascular permeability
- usually after bacterial infections of the throat, often streptococcal
- during chronic infections
- hypersensitivity to milk, fish, crabs

Schoenlein - Henoch disease - signs

- Skin changes : maculopapular rash, often bleeding around the hocks, on the extensor parts of the lower legs, thighs, buttocks
- pain and swelling of joints (ankle , knee)
- abdominal pain, bleeding from thegastrointestinal tract
- proteinuria, hematuria (glomerular involvement)

Schoenlein - Henoch disease - signs

- intestinal motility disorders - possibly intestinal intussusception - obstruction of the gastrointestinal tract
- no evidence of abnormalities in coagulation tests

Schoenlein- Henoch disease - course

* course is usually mild
* 1 % of the renal lesions may cause damage and renal disease (immune complex deposition IgA)
* Relapses

Schoenlein - Henoch disease - treatment

* medication sealing vessels (Cyclonamine , Rutinoscorbin , calcium)
* Bed rest in the acute phase of the disease
* in cases of more severe corticosteroids p.o. or i.v. 1-2 weeks (parenteral nutrition)
* The maintaining changes in the kidney are an indication for renal biopsy

Lectures and references

* 1. Nelson, Pediatria, wyd. I polskie
* 2. K.Kubicka, W.Kawalec, Pediatria, PZWL, wyd.III
* 3. Pediatria dla stomatolgów pod red. R.Rokickiej-Milewskiej, wyd.IV