IN THE NAME of GOD

Rare bleeding disorders

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Rare bleeding disorders (RBDs)

❖ **These conditions may be referred to as:**

- Rare inherited coagulation disorders (RICDs)
- Rare coagulation deficiencies (RCDs)
- Rare bleeding disorders (RBDs)
- Rare congenital bleeding disorders

Rare bleeding disorders (RBDs)

- Fibrinogen (FI) disorders
- Prothrombin (FII) deficiency
- Factor V (FV) deficiency
- Combined deficiency of FV and FVIII
- Factor VII (FVII) deficiency
- Factor X (FX) deficiency
- Factor XI (FXI) deficiency
- Factor XIII (FXIII) deficiency
- Vit K-dependent coagulation factors deficiency
- Glanzmann Thrombasthenia
- Bernard-Soulier syndrome

Rare bleeding disorders (RBDs)

Clotting Protein Disorders	Platelet Defects
Fibrinogen	Glanzmann Thrombasthenia
Prothrombin	
Factor V	Bernard Soulier Syndrome
Factor VII	
Factor X	Storage Pool Disease
Factor XI	
Factor XIII	
Combined Factors V & VIII	Connective Tissue Diseases
Combined Factors II, VII, IX, X	
PAI – 1 Deficiency	Collagen Defects

Inheritance of RBDs

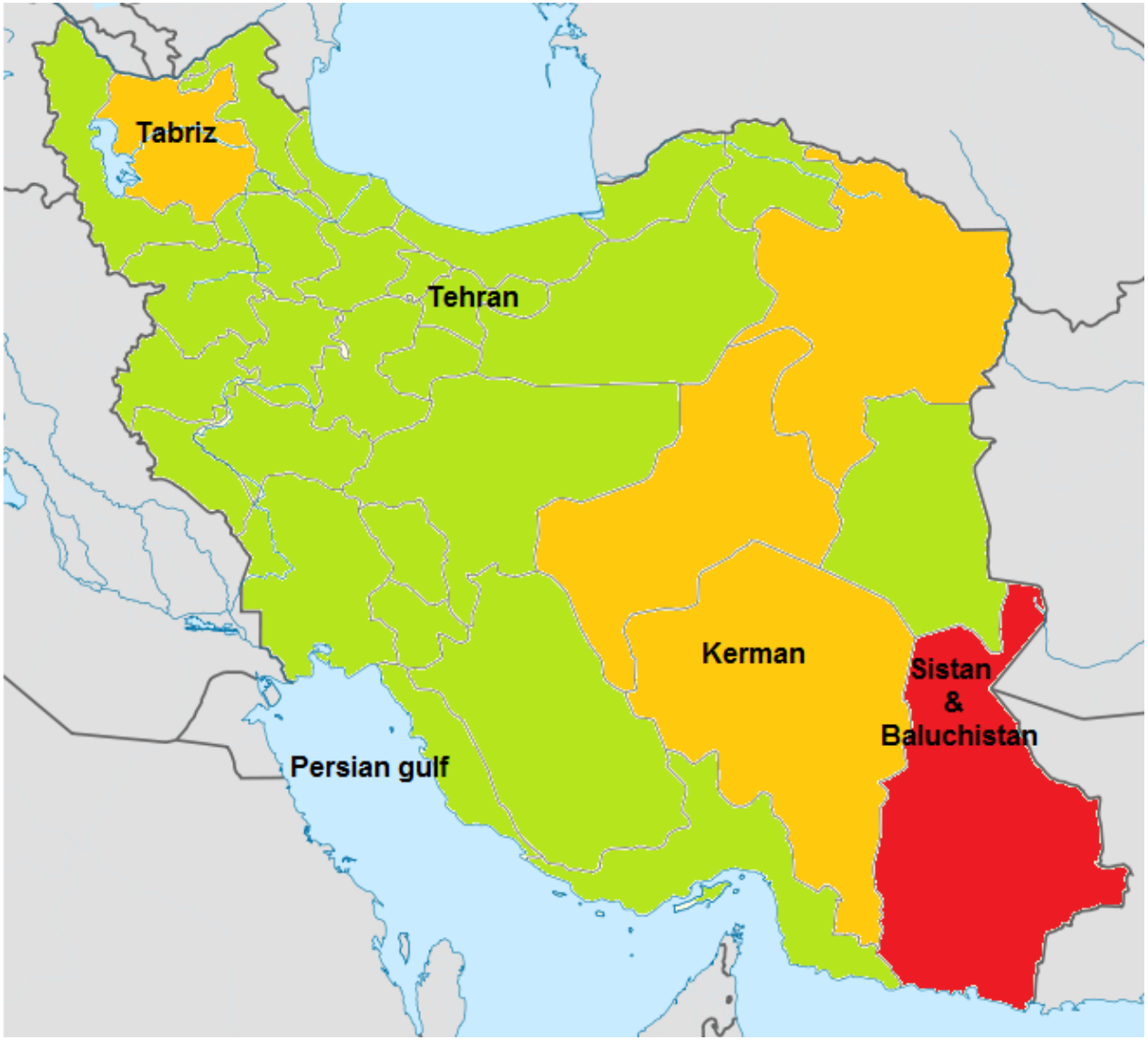
- Most of the RBDs are Autosomal recessive
- Heterozygotes are relatively asymptomatic (trauma, pregnancy)
- Homozygotes or compound heterozygotes manifest the disease.
- Prevalence is higher in populations in which there is a high degree of consanguinity.
- Males and females are affected equally .

Epidemiology of RBDs

- Represents 2–5% of all the inherited deficiencies of clotting factors.
- 95% of inherited coagulation factor defects are due to F VIII, F IX .
- Their frequency ranges from 1:500 000 for FVII deficiency to 1:2 millions for F II and FXIII deficiency in the general population.
- FVII and FXI deficiencies are the most common prevalent RBDs.(28-31% of RBDs)

Epidemiology

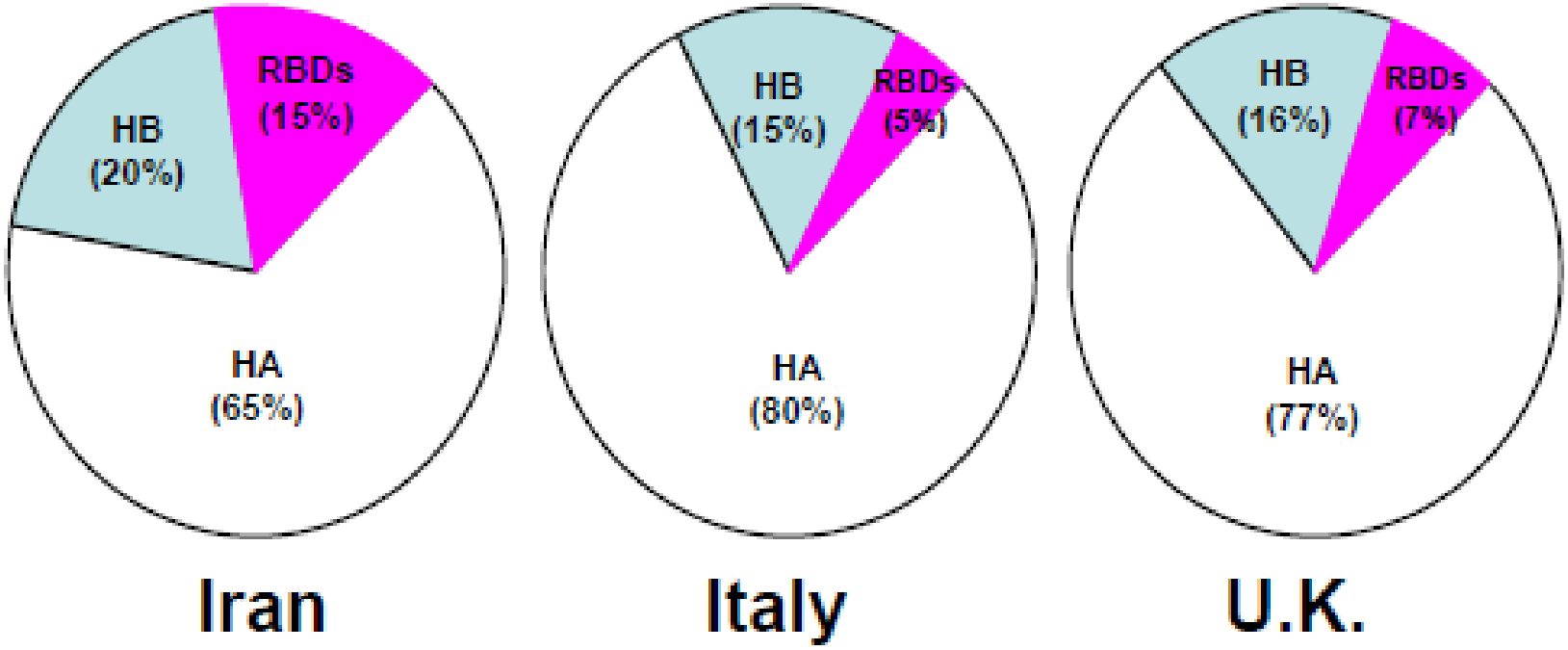
- **F XIII:** More than 600 patients in Sistan & Baluchistan
- The highest prevalence of the disease in the world with an approximate incidence of 200 FXIII deficient patients in 1 million populations.
- City of Khash : highest prevalence


Tabriz
Tehran
Kerman
Sistan
&
Baluchistan
Persian gulf


Zabol
Zahedan
Khash
Saravan
Iranshahr
Nikshahr
Chah bahar

Deficiency	Frequency	Chromosome
Fibrinogen	1:1 milion	4
Prothrombin (FII)	1:2 milion	11
FV	1:1 milion	1
FV+FVIII	1:1 milion	LMAN1:18 MCFD2: 2
FVII	1:500,000	13
FX	1:1 milion	13
FXI	1:1 milion	4
FXIII	1:2 milion	A subunit: 6 B subunit: 1

RBDs in Iran, UK and Italy



Clinical Manifestations

The European Network of RBDs classifies bleedings as follows:

Clinical bleeding severity	Definition
Asymptomatic	No bleeding
Grade I	Bleeding after trauma or antitrombotic therapy
Grade II	***Spontaneous minor bleeding:*** bruising, ecchymosis, oral cavity bleeding, epistaxis and menorrhagia
Grade III	***Spontaneous major bleeding:*** Intramuscular, joint, CNS, GI, and umbilical cord bleeding

- Bleeding is the predominant manifestation of RBDs.
- Impaired wound healing and early pregnancy loss are seen with some of the RBDs.
- Genotype-phenotype relationships for RBDs are not well established.

- RBDs have a wide spectrum of clinical presentations that vary from a mild or moderate bleeding tendency, to potentially serious or life-threatening haemorrhages

- There was a strong association between coagulation factor activity level and clinical bleeding severity for fibrinogen, FX, FXIII, and combined FV and FVIII deficiencies .

- A weaker association was present for FV and FVII deficiencies.

- There was no association between coagulation factor activity level and clinical bleeding severity for FXI.

- However these disorders appear generally less severe than haemophilia A and B, as life- and limb-threatening symptoms as CNS, GI tract bleeding, haemarthroses and haematomas are definitely less frequent.
- An unexplained common feature of these disorders is frequent mucosal bleeding, relatively uncommon in the haemophilias.

- The most severe bleeding symptoms are found in patients with afibrinogenemia, factor X and II deficiency, with a relatively high frequency of joint and muscle bleeding.

- CNS bleeding is a frequent symptom in FXIII, FI, FVII, FX deficiency.

- Umbilical cord bleeding is prevalent in afibrinogenemia, FXIII and FX deficiency, but it may also occur in F II deficiency.
- GI bleeding occurs mainly in FX deficiency.
- Menorrhagia occurs in about 50% of women with RBDs, with no difference among each bleeding disorder.
- Recurrent miscarriages: FI, FXIII and F X deficiency.
- Thrombotic episodes: FI, FVII, F XI, F V and F XII deficiency
- Impaired wound healing: F I and F XIII.

- Hemarthroses are mostly present in severe afibrinogenemia, FII, FX, FXI, FXIII deficiencies.

- Soft tissue hematoma occur with highest frequency in FI, FII, FX deficiency.

- RBDs do not appear to be protective against arterial thrombosis such as acute coronary syndromes.

	FI	FII	FV	FV+FVIII	FVII	FX	FXI	FXIII
Nosebleed	common	common	common	occasional	common	common	common	common
Cutaneous	common	na	common	common	common	common	common	common
Menorrhagia	common	common	common	common	common	occasional	common	occasional
Haematuria	absent	rare	absent	absent	rare	occasional	absent	occasional
GI bleeding	occasional	occasional	occasional	absent	occasional	common	occasional	occasional
Joint bleeding	common	common	rare	rare	occasional	common	common	common
Muscle bleeding	common	common	occasional	occasional	occasional	common	rare	occasional
Umbilical cord bleeding	common	occasional	absent	absent	rare	common	absent	common
CNS bleeding	occasional	rare	rare	absent	occasional	occasional	absent	common
Oral cavity bleeding	common	common	common	common	common	common	occasional	common
Pregnancy/delivery#	absent	na	absent	absent	occasional	absent **	absent	absent **
Major surgery* #	occasional	occasional	occasional	common	occasional	common	common	absent
Minor surgery*	common	occasional	occasional	common	common	common	common	common
Other	rare	na	rare	occasional	absent	occasional	rare	absent
None	absent	absent	absent	absent	absent	absent	occasional	absent

Clinical manifestations of RBD$_s$ in Iran

Deficiency	Clinical symptoms
Fibrinogen	Umbilical cord and mucosal tract bleeding (teeth and gum bleeding, epistaxis), menorrhagia
Prothrombin	Umbilical cord, joint and mucosal tract bleeding
V	Epistaxis and mucosal tract bleeding
VII	Umbilical card and joint bleeding (hematuria, ICH, GI bleeding)
X	Umbilical card and joint bleeding, post circumcision bleeding, menorrhagia
XI	Post traumatic bleeding
XIII	Umbilical cord, intracranial and mucosal tract bleeding, recurrent miscarriages , menorrhagia
V + VIII	Mucosal tract and post circumcision bleeding

F XIII Classification

FXIII-A deficiency:

>95% of all cases, severe hemorrhagic diathesis

FXIII-B deficiency:

Rare, mild bleeding symptom

- Patients with severe FXIII deficiency usually present with less than 1% of plasma FXIII activity level, and therefore have a potentially severe bleeding tendency.

- **Clinical manifestations:**

❖ Delayed wound healing
❖ Umbilical bleeding
❖ Recurrent spontaneous miscarriage
❖ Severe bleeding
❖ Menorrhagia
❖ Spontaneous intracranial hemorrhage
❖ Superficial bruising and hematomas
❖ Hemarthrosis
❖ Mucosal tract bleeding
❖ Epistaxis
❖ Postsurgical bleeding
❖ Delayed bleeding after trauma
❖ GI bleeding
❖ Hematuria
❖ ICH

- In affected individuals, the most common manifestation is bleeding from the umbilical cord after birth.

- Up to 50% of severely affected pregnant women may miscarry without appropriate treatment.

- Treatment of an acute bleeding episode requires the administration of FXIII concentrate at a dose of 10-20 units/ kg .

Intracranial hemorrhage(**ICH**)is a common(25-30%)and life-threatening clinical manifestation of severe FXIII deficiency that requires regular care with a **prophylactic treatment** because it is a significant cause of mortality and morbidity in these patients..

The coagulation factor activity levels that were necessary for patients to remain asymptomatic were:

- **Fibrinogen > 100 mg dL**
- **FV, 12 U/dL**
- **Combined FV + VIII ,43 U/ dL**
- **FVII, 25 U /dL**
- **FX, 56 U/dL**
- **FXI, 26 U /dL**
- **FXIII, 31 U/dL**

Diagnostic evaluation

- **History:** dental procedures, surgery, trauma, menstruation, childbirth, bleeding manifestations, antiplatelet medications, ethnic background, consanguineous marriage, family history of factor deficiency,

- **Laboratory evaluation:** PT, aPTT, TT, factor assay

- **Genetic testing**

Diagnosis

- **Screening test**

➢ PT, PTT, TT

➢ The combined use of the global coagulation tests (PT) and (APTT) is usually used to identify RBDs of clinically significant severity, but not FXIII deficiency

Interpretation of screening tests for RBDs

APTT	PT	TT	Possible diagnosis
Abnormal	Normal	Normal	FXI deficiency
Normal	Abnormal	Normal	FVII deficiency
Abnormal	Abnormal	Normal	FV, FX, FII Combined V+VIII deficiencies
Abnormal	Abnormal	Abnormal	Afibrinogenemia or Dysfibrinogenemia

- **F XII:** PT normal, aPTT prolonged(not associated with clinical bleeding)

- **FVIII, F IX, some form of VWD:** PT normal, aPTT prolonged

- **Combined vitamin K dependent factor deficiency:** PT and aPTT both prolonged

- Patients with mild deficiency may have normal PT and aPTT (factor level <20% prolong the coagulation times in vitro)

- Specific assays for each different coagulation factor are necessary to determine the level of deficiency

- Immunoassays to measure the conserved antigen levels are not strictly necessary for diagnosis and treatment

- But are necessary to distinguish type I from type II deficiencies

- Most RBDs are expressed phenotypically by a parallel reduction of plasma factors measured by functional and immuno-assays (so-called type I deficiencies).

- Qualitative defects, characterized by normal, slightly reduced, or increased levels of antigen levels contrasting with much lower or undetectable functional activity (type II), are less frequent .

F XIII: Lab tests

- **PT, PTT, TT, BT and platelet count are normal.**

- Early diagnosis of the disease in these patients is based on clot solubility test in 5 M urea or 1% monochloroacetic acid environments.

- Inherited deficiency of FXIII is due to mutations of subunit A or B genes, although disorders of subunit A are more common.

Deficient factor	Hemostatic levels	Plasma half-life
Fibrinogen	50 mg/dL	2-4 d
Prothrombin	20%-30%	3-4 d
V	15%-20%	36 h
VII	15%-20%	4-6 h
X	15%-20%	40-60 h
XI	15%-20%	40-70 h
XIII	2%-5%	11-14 d
V + VIII	15%-20%	36 h for factor V and 10-14 h for factor VIII
Vitamin K—dependent, multiple deficiency	15%-20%	See corresponding factors


Thank You..

Glanzmann Thrombasthenia

- **The disorder is named after Dr. Eduard Glanzmann, who first descrbied it in 1918.**
- **AR (17q21)**
- **Rare cases of acquired GT**
- **Rare: 1: 1 million**
- **Primary hemostatic defect**
- **Abnormality in GP IIb/IIIa(PLT fibrinogen receptor)**
- **Normal platelet count**
- **PLT size is normal**

Clinical manifestations

- **Epistaxis: prevalent in children**
- **Mucocutaneous bleeding**
- **Gingival bleeding**
- **GI bleeding**
- **Petechiae, purpura, ecchymoses**
- **Menorrhagia**

Laboratory evaluation

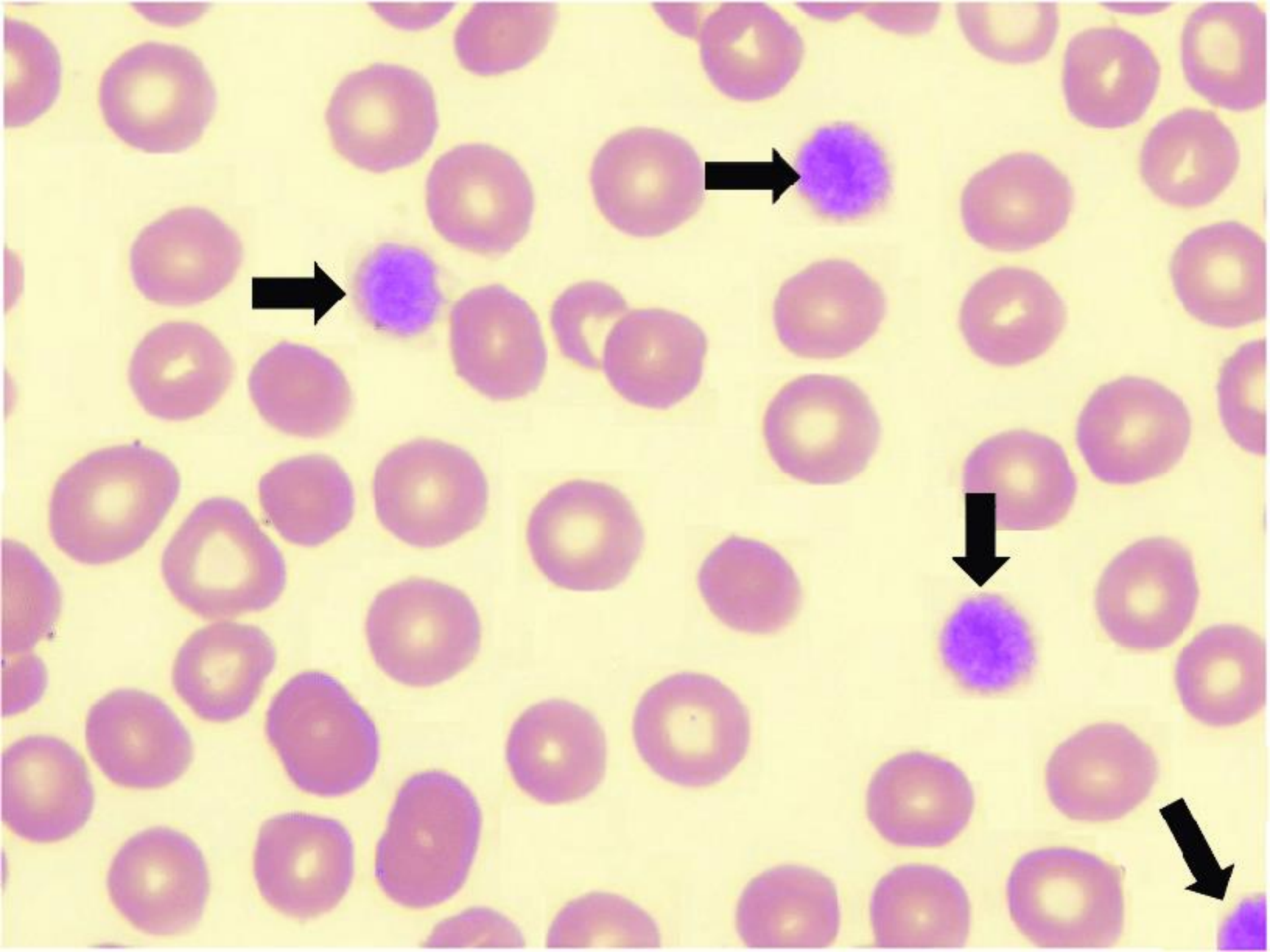
- **CBC**
- **PBS**
- **BT**
- **PLT aggregometry**
- **PFA-100**
- **Flowcytometry: CD41, CD61**
- **PT , PTT: NL**
- **Genetic test**

Treatment

- **Local measures**
- **Platelet transfusion, Apheresis**
- **Antifibrinolytic agents: tranexamic acid**
- **Hormone supplementation**
- **rFVIIa**
- **HSCT**

Bernard-Soulier Syndrome

- **BSS was first described in 1948**
- **AR**
- **Rare: 1: 1 million**
- **Primary hemostatic defect**
- **Abnormality in GP Ib/IX/V complex (VWF receptor)**
- **Giant platelets**
- **Thrombocytopenia**



Laboratory evaluation

- **CBC**
- **PBS**
- **BT**
- **PLT aggregometry**
- **PFA-100**
- **Flowcytometry: CD 42b**
- **PT, PTT: NL**

Clinical manifestations

- **Epistaxis (most common)**
- **Mucocutaneous bleeding, Easy bruising**
- **Gingival bleeding**
- **GI bleeding (occasional)**
- **Petechiae, purpura, ecchymoses**
- **Menorrhagia**

Differential diagnosis

- **ITP**
- **Glanzmann Thrombasthenia**
- **VWD**
- **May-Hegglin Anomaly**
- **Medication effect**
- **Other inherited PLT disorders: familial macro thrombocytopenia, gray PLT syndrome**

Treatment

- **Local measures**
- **Platelet transfusion, Apheresis**
- **Antifibrinolytic agents: tranexamic acid**
- **rFVIIa**
- **DDAVP**
- **HSCT**

Thank you for attention