

Physiological and pathological variations in factor VIII

Factor VIII is a plasma glycoprotein that plays an essential role as a cofactor of factor IX within the coagulation cascade.

Factor VIII physiology

Factor VIII (FVIII) is produced mainly by the liver via intracellular transport via chaperone proteins such as Bip and LMAN-1. Once secreted into the plasma circulatory system, it immediately binds with its transport protein; the von Willebrand factor (vWF). This transport protein protects factor VIII. This is seen by the difference in half-life: FVIII without vWF = half-life of 2 hours versus FVIII with vWF = half-life of 12 hours.

Once factor VIII has been activated by thrombin it detaches itself from vWF in order to bind with factor IX, where it can now play the role of cofactor in the coagulation cascade. FVIIIa is then destroyed by the PC/PS inhibitor system.

The main determining factors of factor VIII levels in plasma

Environmental determining factors:

- **Physiological:** age, hormonal status (pregnancy), stress, and exercise.
- **Pathological:** inflammation, liver conditions, raised body mass index, and metabolic disorders.
- **Iatrogenic:** vasopressin, β -blockers, and oestrogen progesterone combined oral contraceptive pill.

Genetic determining factors:

- **Gender:** FVIII levels are higher in women than in men.
- **Ethnic group:** FVIII levels are higher in Afro-Caribbeans than Caucasians.
- **FVIII gene (Xq28) and Willebrand factor gene (12p13.3).**
- **Blood group:** FVIII levels are lower in individuals with blood group O compared to those of other blood groups (A, B, AB).
- **Others:** ADAMTS13 protease, Bip and LMAN 1 chaperone proteins, LRP receptor etc.

Physiological decrease in factor VIII

This mainly concerns those of blood group O, who have low stoichiometric blocking of the Willebrand molecule along with facilitated and accelerated degradation by ADAMTS 13 protease.

As a result the half-life is reduced and the plasma levels of vWF are lowered. Contrarily, for the other blood groups, the stoichiometric environment of the Willebrand molecule is considerable and degradation by ADAMTS 13 is slowed, resulting in a longer vWF half-life and raised vWF plasma levels. The levels of FVIII follow suit due to their correlation with the vWF levels.

Isolated occurrence of a pathological decrease of factor VIII

A. Constitutional haemophilia A (See Focus on haemophilia A)

Haemophilia A is an X-linked disease that affects 1 male birth in 5000. It is an hereditary disease usually accompanied by a family history of haemorrhages in boys from the mother's side of the family. In 1 case out of 3 it is a de novo mutation, with no previous family history. However the anomaly would then continue to be transferred through the patients descendants. Within the same family, the severity of the deficit remains the same from one family member to another which cannot be said for Willebrand disease.

Three types have been distinguished:

- **Major:** FVIII < 1 % (45 % of cases)
- **Moderate:** FVIII 1 - 5 % (20 %)
- **Minor:** FVIII 6 - 30 % (35 %)

Clinical profile

For a patient suffering from haemophilia A, we find the following: a long if not very long partial thromboplastin time (PTT), normal PT and fibrinogen levels, along with normal bleeding time (BT) and closure time (CT) results on the PFA-100®. FVIII is decreased in an isolated fashion (see 3 types). For a differential diagnosis, a genetic tree (family studies) is recommended in order to identify if the anomaly is sex linked or not, as it could be a type 2N Willebrand disease. It is also recommended to screen for other causes of FVIII decrease (Willebrand disease; combined deficiency of factor VIII and V) and in particular one should perform molecular testing to identify the anomaly and its causative factors and consider a prenatal diagnosis screen for severe forms.

B. Causative factors of constitutional haemophilia A (See Focus on haemophilia A)

Levels of FVIII in the carrier are on average 50 %; however in function to the degree of inactivation (lyonisation) of affected

chromosome X, the levels can be higher or lower. Please note that very rare cases of real female haemophilia do exist with FVIII results of < 30 %.

C. Acquired haemophilia A

A rare disease, seen in 1.48 cases/1,000,000 up to 15/1,000,000 after 65 years of age.

Acquired haemophilia presents acutely in patients with no prior history of haemorrhaging. It requires urgent treatment. FVIII is lowered due to the presence of an auto-anti-factor VIII antibody (IgG, M, A). In 80 % of cases the disease is severe, with a mortality rate of 20 %. It occurs more in the older generation, in those suffering from tumours or those with impaired immunity diseases, but also occurs in young women during the puerperium (secondary acquired haemophilia A). The disease remains unexplained in 50 % of cases (primary acquired haemophilia A).

Clinical profile:

The PTT is long with normal PT and fibrinogen results. The BT and CT are normal. The FVIII is significantly lowered (typically 0 – 10 %), occasionally with a sub normal level (30-49 %) which does not normalize on dilution. The circulating anticoagulant screen is positive and the anti phospholipid confirmation tests are negative: it is an anti-factor type circulating anticoagulant screen result.

D. Type 2N Willebrand disease

This is an autosomal recessive disease characterised by a history of haemorrhages that are different from haemophilia A. They are different due to the absence of previous family history (the parents are heterozygous 'healthy carriers'), also the disease affects men and women equally.

The clinical profile associated with this disease is a raised PTT, with normal values for PT, fibrinogen, BT and CT. The vWF level is normal with a lowered FVIII level: 5 – 35 % (typically 10 – 15 %, but can reach 50 %). The differential diagnosis should be moderate or minor haemophilia (rarely severe). Only tests of the vWF-FVIII binding liaison can be used to further determine the diagnosis: **Haemophilia A:** Normal linkage
2N: Lowered linkage

Pathological decrease in factor VIII associated with other anomalies

A. Type 1, 2 (not 2N), and 3 Willebrand disease

The FVIII level is dependent upon the vWF antigen level.

B. Factors V and VIII combined deficit (F5F8D)

An autosomal recessive disease (1 case/ 1,000,000, i.e. 3 % of rare haemorrhagic syndromes in France) caused by a single mutation in the coding gene for LMAN-1, which causes a combined decrease in FVIII and FV. Clinically speaking this deficit is tolerated quite well with moderate cutaneous and mucosal haemorrhages, and rarely haemarthrosis.

The clinical profile: PT is lowered and PTT is raised. Fibrinogen is normal; FV and FVIII levels are typically between 5 – 30 %. Formal diagnosis relies on genetic studies and mutation screens (mutation LMAN-1 with normal F8 and F5 genes). Treatment use: DDAVP (↗ FVIII) and/or freshly frozen plasma (↗ FV). The thresholds used in case of surgery or childbirth are: FVIII > 50 % and FV > 15 %.

Guidance on factor VIII levels

(To be interpreted in light of treatment and hormonal or inflammatory context)

A. Factor VIII < 5 %

- Severe or moderate constitutional haemophilia A
- Acquired haemophilia A
- Type 3 Willebrand

B. Factor VIII 6 – 30 %

- Minor haemophilia A
- 2N Willebrand disease
- Type 1 or 2 Willebrand disease (3 if FVIII is 5-8 %)
- Combined deficit of FV+FVIII

C. Factor VIII 30 – 50 %

- Minor haemophilia with inflammation
- 2N Willebrand disease
- Heterozygous carrier of the 2N mutation
- Type 1 or 2 Willebrand disease (not 3)
- Carrier of haemophilia A

Physiological increase in factor VIII

Age, pregnancy, stress and physical exercise.

Pathological increase in reactive factor VIII

This is caused by a secondary increase in factor VIII within a context of inflammation, liver disease (cirrhosis, hepatocellular failure), diabetes, obesity or dysthyroidism.

A primary isolated increase in factor VIII

Several publications have shown that an isolated increase in FVIII (> 150 %) which persists over time is a thrombosis risk factor. The prevalence of this increase occurs in 11 % of the general population compared to 25 % in the thrombophilia population. The relative risk of getting thrombosis has been evaluated at a factor of 4.8 in patients with a level of factor FVIII >150 % versus those with a level of <100 % (Koster et al, Lancet 1995;345:152-5). The increase in FVIII would be a dose dependant risk factor of thromboembolic disease as well as a risk factor of reoccurring or spontaneous miscarriages.

However, according to the recent recommendations of GEHT, the role of increased FVIII levels as a thrombosis risk factor remains uncertain. Its measurement is therefore not recommended in a preliminary thrombosis profile.

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