

## Haemophilia A

Haemophilia A or constitutional deficit of factor VIII (FVIII) is an X-linked disease that affects 1 male birth in 5000. It is a 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.

Three forms have been identified:

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

### Symptoms of haemophilia A

**Severe haemophilia:** Is characterised by haemarthrosis and sub-cutaneous haematomas. Episodes of bleeding occur once or twice per week and seem to be spontaneous.

**Moderate haemophilia:** Is associated with haemorrhages that usually occur from slight traumas. Episodes of bleeding occur approximately once per month. Spontaneous haemorrhages are rare.

**Minor haemophilia:** Can go unnoticed. Coagulation problems are seen only in cases of severe injury. There is, nevertheless a risk of prolonged bleeding in surgery or dental extractions. The patient must be informed and educated of the warning signs when symptoms are more insidious.

**Other symptoms:** Haematuria, muscular haemorrhages, CNS haemorrhages.

### Constitutional haemophilia A

#### Severe haemophilia A:

- **Average age of diagnosis:** 1 years old
- **Average age for the first FVIII injection:** 1½ years old

#### Moderate haemophilia A:

- **Average age of diagnosis:** 2 – 3 years old
- **Average age for the first FVIII injection:** 4 – 7 years old

#### Minor haemophilia A:

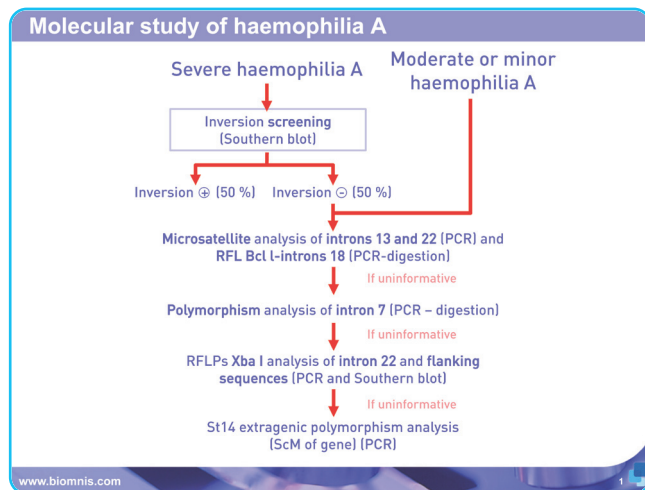
- **Average age of diagnosis:** 7 – 8 years old
- **Average age for the first FVIII injection:** 12 years old, however in 35 to 40% of cases no FVIII is given

### 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. For a differential diagnosis, a family tree is recommended in order to identify if the anomaly is sex linked or not, as it could be 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 confirm the diagnosis, perform prenatal screening and identify the causative factors. The type of molecular anomaly allows us to predict the development of anti-VIII inhibitors.

## Main molecular anomalies

- **Deletions (less than 5% of cases):** Large deletions, small deletions and micro-insertions.
- **Point mutations:** Nonsense mutations (severe forms) and missense mutations (more moderate forms).
- **Point mutations:** An inversion of exon 22 (50% of cases of severe haemophilia A).



## Haemophilia A treatment: plasma and recombinant factor VIII

Treatment – Factor VIII target level		
Haemorrhagic accident and surgical act.	Plasma level of factor VIII*	Injection frequency and the period within which the plasma level must be maintained
Minor haemorrhagic accident: Haematoma, haemarthrosis, epistaxis	15-30 %	At least 1 injection, depending on the severity of the haemorrhage
Serious haemorrhagic accident: muscular haemorrhage, slight cranial trauma,	30-50 %	2 – 4 days or until satisfactory healing.
Haemorrhaging whereby the patient's survival prognosis is at stake: Gastro-intestinal, abdominal, cerebral, or thoracic haemorrhaging, fracture, and cranial trauma.	50-100 %	For 7 days, then following of treatment for 4 – 7 days in order to maintain the factor VIII level at between 30 – 50%

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## The main complications with haemophilia A: Anti-VIII(IgG) allo-antibodies

The main preventative or curative treatment for haemophilia is FVIII injections. In 30% of cases of severe haemophilia A, 15% of moderate haemophilia and in 3% of minor cases of haemophilia A, anti-VIII inhibitors appear during treatment. These anti-FVIII antibodies inhibit exogenous and endogenous FVIII. This can also cause minor haemophilia to develop into

severe haemophilia. If the level of the inhibitor is <5U Bethesda (poor response), the dose of the FVIII injections must be raised. If the inhibitor level is greater (strong response) it is then possible to administer Novoseven® (FVIIa) or Feiba®, which favour another coagulation pathway.

## Female carriers of haemophilia A

Female carriers of haemophilia A can pass on the mutation to their daughters, (who then themselves will become carriers), and they pass on haemophilia on to their sons. Daughters born from a haemophilic father are obligatory carriers. Sisters of a haemophiliac brother or daughters of a female carrier are all possible carriers (1/2). The mothers of a haemophiliac son are probable carriers.

The level of FVIII in carriers is on average 50 – 55%, but it can vary to 22 – 116%. 30% of carriers have a FVIII level of <50% and 2% have a level of <30%. A normal FVIII level does not exclude the possibility of being a carrier and the FVIII level of the carrier does not indicate the severity of the haemophilia A inherited.

The diagnosis of a carrier is derived from the family tree and the FVIII level, and is confirmed by molecular analysis (usually planned in advance).

Female haemophiliacs are rare but they exist. They can be: daughters of a mother carrier and a haemophilic father, women with a majority inactivation of the normal X chromosome, or women with a X/autosome translocation or with Turner syndrome (X/0).

## The haemorrhagic risk of carriers

The majority of carriers are asymptomatic or have a tendency of ecchymosis, menorrhagia, or of evoked haemorrhages. In these women, the haemorrhagic risk is limited to the period of menstruation as the FVIII increases at the end of the cycle and during pregnancy (the FVIII is therefore physiologically increased). It is therefore generally agreed to investigate the FVIII level at 32 – 34 weeks into pregnancy (if the level is >50% there is no problem) and the post-partum haemorrhagic risk at day 5 (as the FVIII values decreases). DDAVP can be administered (not a contraindication during breast feeding). One should be cautious of the notably cerebral haemorrhages in new-borns following the use of forceps or a suction cap.

Carole Emile, from a communication by Laurence Pellegrina, Biomnis Lyon.

