THE NORTHERN HOSPITAL

FACTOR V - LEIDEN

"My Grandparents, My Parents and I" oil and tempera on zinc, 1936, Frida Kahlo.

The story of Frida Kahlo begins and ends in the same place. From the outside, the house in the corner of Londres and Allende streets looks very like other houses in Coyoacan, an old residential section on the southwestern periphery of Mexico City. A one story stucco structure with bright blue walls enlivened by tall many paned-windows with green

shutters and by the restless shadows of the trees, it bears the name "Museo Frida Kahlo" over the portal. Inside is one of the most extraordinary places in Mexico - a woman's home with all her paintings and belongings, turned into a museum.

The entrance is guarded by two giant papier-mâché Judas figures nearly twenty feet tall, gesticulating at each other as if they were engaged in conversation. Passing them, one enters a garden with tropical plants, fountains, and a small pyramid decked with pre-Columbian idols.

The interior of the house is remarkable for the feeling that its former occupants' presence animates all the objects and paintings on display. Here are Frida Kahlo's palette and brushes, left on her worktable as if she had just put them down. There, near his bed, are Diego Rivera's Stetson hat, his overalls, and his huge miner's shoes. In the large corner bedroom with windows looking out onto Londres and Allende streets is a glassed-doored cabinet enclosing Frida's colourful costume from the region of Tehuantepec. Above the cabinet, these words are painted on the wall: "Aqui nacio Frida Kahlo el dia 7 de Julio de 1910", (Here Frida Kahlo was born on July 7, 1910) They were inscribed four years after the artist's death, when her home became a public museum. Another inscription adorns the bright blue and red patio wall. "Frida y Diego vivieron en esta casa 1929 - 1954" (Frida and Diego lived in this house 1929-1954) Ah! the visitor thinks . How nicely circumscribed! Here are three of the main facts of Frida Kahlo's life - her birth, her marriage, and her death.

The only trouble is that neither inscription is precisely true. In fact, as her birth certificate shows, Frida was born on July 6, in 1907. Claiming perhaps a greater truth than strict fact would allow, she chose as her birth date not the true year, but 1910, the year of the outbreak of the Mexican Revolution. Since she was a child of the revolutionary decade, when the streets of Mexico City were full of chaos and bloodshed, she decided that she and modern Mexico had been born together.

The other inscription in the Frida Kahlo Museum promotes an ideal, sentimental view of the Rivera - Kahlo marriage and home. Once again reality is different. Before 1934, when they returned to Mexico after four years of residence in the United States, Frida and Diego lived only briefly in the Coyoacan house. From 1934- to 1939 they lived in a (conjoined) pair of hours built for them in the nearby residential district of San Angel. After that there were long periods when Diego, preferring the independence of his San Angel studio, did not live with Frida, not to mention the one year when the Riveras separated, divorced and remarried....

Hayden Herrera, "Frida", 1983.

In 1936 Frida Kahlo painted a nostalgic portrait of her birth place, La Casa Azul, or the Blue House, arising out of which we see her family tree. Her father Guillermo Kahlo, a prominent photographer was German. He was born in Baden Baden Germany and was the son of Jakob Heinrich Kahlo, a goldsmith, and Henriette Kaufmann. Guillermo's parents were Hungarian Jews who had emigrated to Germany where they prospered.

Her mother Matilde Calderon was a mestizo, her father Antonio Calderon, a photographer, was of native Indian descent and her mother Isabel Gonzales being of Spanish descent and the daughter of a general

The portraits Frida made of her parents and grandparents were modelled from old photographs. Frida herself appears as a small child, but a disproportionate giant, standing in the courtyard of her place of birth, the Casa Azul, or Blue House, which today is the Frida Kahlo Museum. Above her are the images of her parents, taken from their weeding photograph, taken in 1898. In keeping with Frida's intense early interest in medical science, and reproduction in particular - she had wanted to become a doctor - we see an image of her prenatal existence as a fetus in her mother's womb. But even more than this, she traces her existence back to the very instant it began as a sperm penetrating an ovum. Fertility would become a strong recurring theme in Frida's work throughout her life. This was not only human fertility, but the all encompassing fertility of nature and the cycle of life and death. We see beside the image of the moment of her own conception, the simultaneous pollination of a plant. In a second motif that appears again and again in her works, we see the ribbon of life-inter connectedness. Frida holds a red ribbon in her right hand which rises upwards, like an umbilical cord to her grandparents, whose images float in the sky cushioned in clouds akin to Boticelli angels. Frida was strongly attracted to Renaissance Art. Her German grandparents float above the sea, showing that they were born far away over the seas, were they lived and died. Her Mexican grandparents, who were born in Mexico, float about the land, that sprouts nopal cacti a native plant that in pre-Columbian mythology features in the foundation of Mexico.

The motif of nature's cycles of life and death featured strongly in Frida Kahlo's work, in symbols of fertility, death. The interconnecting nourishing umbilical cords of vines, roots and ribbons appear everywhere in her oeuvre Towards the tortured end of her life, when she knew she had not much of it left, she would return to the theme of her family tree. Desperately sad that she had not been able to have children of her own, she added the images of her sisters and her nephew and niece. Though she worked on the painting on and off for the last four years of her life she never finished it. There are three unfished faces and it is unknown who these children were meant to be. Perhaps they were the children that Frida had lost in pregnancy. Poignantly, we also see to her left, the image of a tiny unborn fetus.

Frida Kahlo possessed two features which today would not be called attractive in a woman, however she had no issue whatever with these, in fact not only did she portray them over and over in her prolific self-portraits, but even highlighting them to such a degree that they virtually became her personal signatures, and by so doing transformed them into something charming. The first was her faint moustache above her upper lip, the second was her striking eyebrows, so thick and luxuriant were they, they met in the middle of her face above her nose. Frida was fascinated by hereditary. She always said that she looked like both her parents. "I have my father's eyes and my mother's body" she said. And judging from the unsettling penetrating gaze of her father's eyes in photographs, this was certainly true of her father. But she also had some strong traits of her grandparents as well. On close inspection of "My Grandparents, My Parents and I",

it is clear that Frida inherited her eyebrows, only indirectly from her father. In this trait Frida was the legacy of her paternal grandmother.

The interconnectedness of all life on planet Earth is based on a single genetic code. All life forms are the result of this single code. Not a solitary life form has ever been discovered that uses a different one, a profoundly interesting fact that leads us to the conclusion that every living thing on the planet is derived from one original and very ancient primal source. Every life form carries its own unique history of evolution from that original code that in Homo sapiens culminates as a vast incomprehensibly complex biochemistry. Every physical aspect from brain down to eyebrows derives from this inherited code, passed down through untold eons of time. The fact that the whole organism works at all seems like a miracle. Given this cosmic complexity it is unsurprising that occasionally the code goes awry.

"Family Tree" - Unfinished, oil on masonite, 1950-54, Frida Kahlo

FACTOR V - LEIDEN

Introduction

Factor V is a normal protein of the coagulation cascade.

Factor V Leiden (FVL) is a variant (or mutated) form of human **factor V**

The Leiden mutation renders the factor **resistant to binding** by **activated protein** C, an **anti**coagulant protein, whose normal function is to **inhibit** the activity of factor V

Factor V Leiden therefore leads to a hypercoagulable state

History

The **Factor V Leiden** variant is named after the Dutch city of **Leiden**, where it was first identified in 1994 by **Professor R. Bertina.**

The defect was initially termed "**APC resistance**" because the anticoagulant activity of APC was reduced in a modified activated partial thromboplastin time (aPTT) assay.

Epidemiology

Heterozygosity for the FVL mutation is the **most common *inherited* thrombophilia** in unselected Caucasian populations, accounting for 40 - 50 % of cases.

Classification

Heritable thrombophilia conditions include:

1. Anti-thrombin III deficiency
2. Protein C deficiency
3. Protein S deficiency
4. **Factor V Leiden mutation (or Activated Protein C (APC) resistance).**
5. Prothrombin (20210A gene mutation).
6. Increased plasma concentration of fibrinogen or other coagulation factors.
7. Hyper-homocysteinaemia, (may be partly determined by environment).

Pathophysiology

Activated Protein C is a serine protease with potent **anticoagulant** properties, which is formed in blood on the endothelium from an inactive precursor.

During normal haemostasis, APC *limits* clot formation by the proteolytic inactivation of factors Va and VIIIa.

To do this efficiently, the enzyme also needs, a **non-enzymatic cofactor** called Protein S

The defective **Factor V Leiden** therefore leads to a **hypercoagulable state**

See also Appendix 1 below

Genetics:

Factor V Leiden (FVL) results from just a **single** point mutation in the factor V gene (guanine to adenine at nucleotide 1691)

This leads to a **single amino acid** change (replacement of arginine with glutamine at amino acid 506); that results in the defective factor V

FVL is an **autosomal dominant** condition, and 99% of individuals with FVL are **heterozygous** for the mutation

Interestingly only about **5%** of FVL heterozygotes will experience a venous thromboembolism episode during their lifetime.

The reasons for the **highly variable phenotype** are incompletely understood; it may be explained in part by the coexistence of other inherited thrombophilias or other genetic modifiers that can alter thrombosis risk. There is evidence for example of a higher prevalence of protein S and protein C deficiencies in individuals with FVL who have had a VTE compared with individuals with FVL who have not had a VTE.

The risk of VTE is greater in the setting of homozygosity for FVL or compound heterozygosity for FVL **and** another inherited thrombophilia.

Other causes of APC resistance:

In **rare** cases, inherited mutations in factor V other than the FVL mutation (Arg506 replaced with glutamine) can produce the APC resistance phenotype.

Examples include:

- Factor V Cambridge (replacement of Arg306 with threonine)
- Factor V Nara (replacement of Trp1920 with arginine)
- Factor V Liverpool (replacement of Ile359 with threonine)
- Factor V Bonn (replacement of Ala512 with valine)

Clinical features

The major clinical manifestation of the heterozygous FVL mutation is **venous** thromboembolism.

However, only a small percentage of individuals with FVL (around 5 %) will develop in venous thromboembolism in their lifetime.

The role of FVL mutation in **arterial** thromboembolism (hence **myocardial infarction** or **stroke**) is unclear, but the risk appears to be far less compared to **venous** thromboembolism.

The FVL mutation also may play a role in some cases of **unexplained recurrent late pregnancy loss**, presumably due to thrombosis of placental vessels

The most common site of VTE in individuals with the FVL mutation are:

1. **DVT**
2. **PE**
    - Some individuals present with isolated PE (i.e without evidence of DVT).

Less commonly:

3. Cerebral venous thrombosis
4. Mesenteric venous thrombosis
5. Portal vein venous thrombosis

Virtually any venous system however may affected.

Superficial vein thrombosis within the limbs may also occur.

Investigations

Tests for **heritable** thrombophilia are often used inappropriately and non-selectively.

For patients suspected of having a thrombophilia condition consider the following tests:

1. FBE
2. Clotting profile
    - INR
    - APPT

3. Fibrinogen

4. Anti-phospholipid syndrome (often an acquired condition) tests include:

    - Lupus anticoagulant
    - Anti-cardiolipin antibodies

When considering a hereditary cause the following thrombophilia screen should be done:

5. Factor VIII levels

6. **Factor V (Leiden factor) mutation:**

7. Protein C.

8. Protein S.

9. Anti-thrombin activity.

Further test that may be specifically requested include:

10. Prothrombin gene G20210A

11. Methylene tetrahydrofolate reductase.

12 Homocysteine

As a general rule for patients above 45 years of age *routine* thrombophilia screening is not necessary.

Below the age of 45 it should be done.

Genetic testing for FVL:

FVL can be detected by DNA testing.

For individuals with a family history of FVL who require testing, **genetic** testing is preferable because it provides **definitive** evidence of the mutation.

For individuals with antiphospholipid syndrome or those who require testing **while receiving an anticoagulant** that might interfere with the results (e.g., direct thrombin inhibitor, direct factor Xa inhibitor), genetic testing can circumvent these potential sources of test interference.

For individuals who have a positive functional assay for APC resistance, genetic testing should be performed to **confirm** the diagnosis, allow family screening if appropriate, and determine if the patient is homozygous or heterozygous for the FVL mutation.

The FVL mutation can be detected directly by analyzing genomic DNA from peripheral blood cells. Since only a single mutation is involved, this testing is straightforward and relatively inexpensive to perform.

Situations in which testing of **relatives** may be appropriate include:

- First degree relatives of affected individuals in families with FVL mutation and a history of VTE in individuals < 50 years of age
- Individuals with VTE in an unusual location,
- Individuals with severe, life-threatening VTE.
- Daughters of parents with FVL, in the setting of contraceptive counselling
- Siblings of individuals who are **homozygous** for the FVL mutation or heterozygous for FVL and another inherited thrombophilia.

Management

The *initial* treatment of venous thromboembolism in individuals with the FVL mutation is the **same** as that of the general population.

The presence of the FVL mutation does not influence the decision of whether to use warfarin or a direct oral anticoagulant (DOAC).

The duration of anticoagulation depends on the risk of recurrent VTE, which is similar in FVL heterozygotes to VTE recurrence risk in the general population

As for the general population, the duration of anticoagulation in these individuals is an individualized decision.

Indefinite anticoagulation therefore should be for those:

- Whose VTE is unprovoked
- With a life-threatening VTE
- Who have a VTE at an unusual site such as the mesenteric or portal vein
- With more than one episode of VTE.

It is unclear whether individuals diagnosed with the FVL mutation from random population screening or genomic sequencing of healthy individuals without a clinical

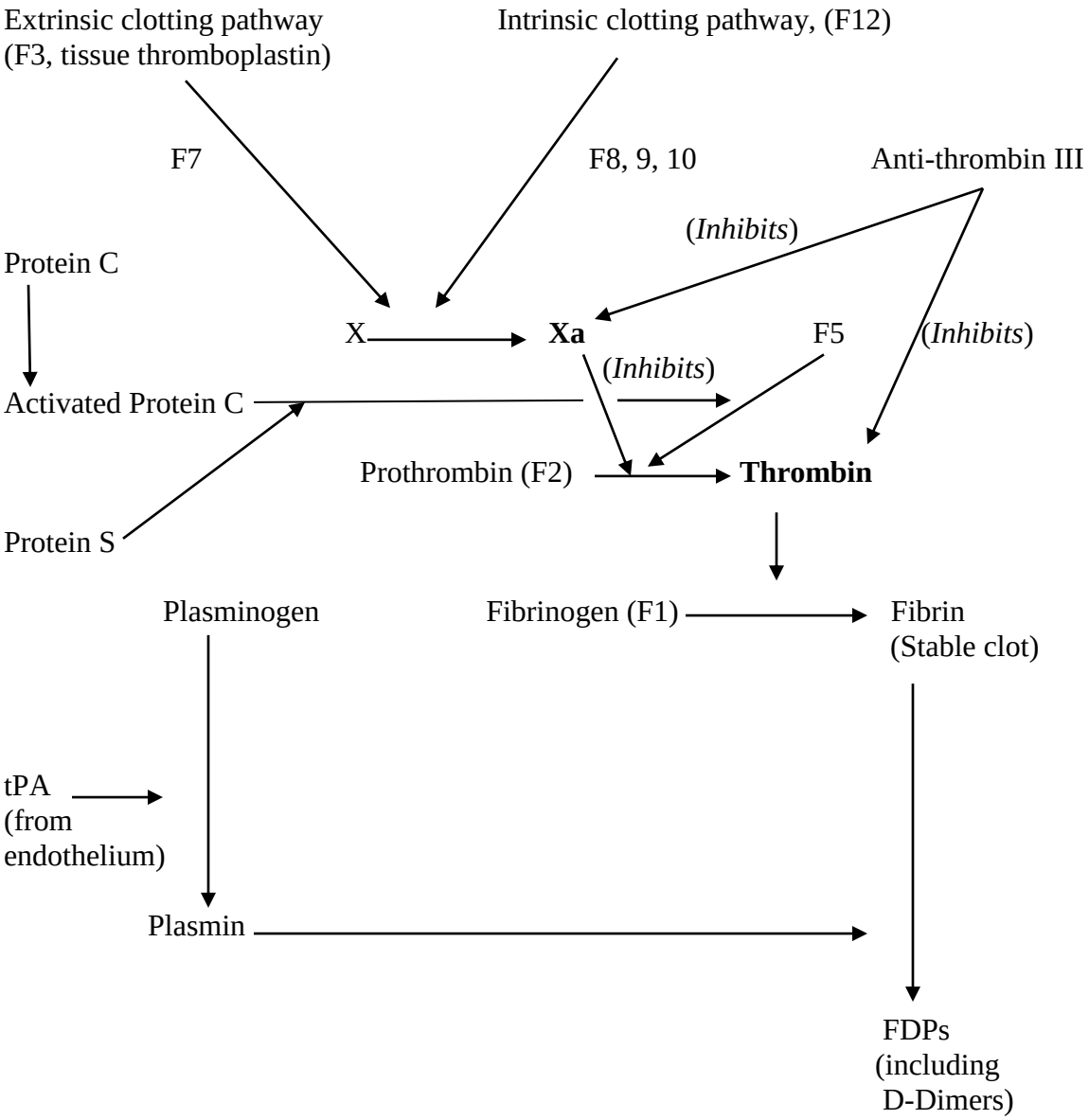
suspicion of thrombophilia should be managed any differently than the general population.

Disposition:

All patients who have or who are suspected to have FVL and have suffered a VTE event should be referred to e Clinical Haematologist.

Appendix 1

The coagulation cascade and fibrinolytic system:



Frida Kahlo working on portrait of her family tree, c. 1950 - 54.

References

1. Kenneth A Bauer, Factor V Leiden and activated protein C resistance in Up to Date Website, December 2018.

Dr. J. Hayes
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