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Hypofibrinogenaemia: A Case of Spontaneous Bleeding and Central Venous Thrombosis in the Same Lifetime

Adriana Watts Soares[1], Maria Maia[1], João Espirito Santo[1], Ana Palricas Costa[2], Artur Pereira[2], Cristina Catarino[2]

[1]Internal Medicine Department , Hospital Beatriz Ângelo, Loures, Portugal

[2] Immunohemotherapy Department, Hospital Santa Maria, Lisbon, Portugal

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ABSTRACT

The authors present the case of a 27-year-old patient who suffered from spontaneous bleeding during infancy and from a severe and central venous thrombosis in adult years. The patient underwent a thorough laboratory work-up on both occasions and was diagnosed with hypofibrinogenaemia as well as protein S deficiency, 2 diseases that contrast in their intrinsic bleeding/thrombotic risk. The patient´s high-risk pregnancy was carried out up to a successful full-term eutocic delivery which required fibrinogen concentrate to reduce life-threatening bleeding. The patient´s child was also diagnosed with hypofibrinogenaemia, later on confirmed with the pathogenic mutation Fibrinogen Marseilles II. This case was used to conduct a literature review of congenital fibrinogen disorders, rare entities that require more awareness for early diagnosis and accurate management.

LEARNING POINTS

- Fibrinogen disorders are uncommon causes of either bleeding or thrombotic events and may be acquired or inherited in a recessive or dominant autosomal manner.
- Congenital fibrinogen deficiencies are rare but should be investigated when undergoing diagnostic work-up for thrombotic or haemorrhagic events in adult years.
- Determination of molecular defects is important for confirmation and to elaborate a treatment strategy according to the inherent risk for either thrombotic or haemorrhagic events.

KEYWORDS

Thrombosis, hypofibrinogenaemia, protein S deficiency, spontaneous bleeding, congenital coagulopathies

CASE REPORT

The authors present a rare case of a 27-year-old Caucasian patient who had both bleeding and thrombosis symptoms of a genetically determined thrombophilia.

The patient mentioned a previous hospital admission at paediatric age due to spontaneous digestive tract bleeding. The inpatient differential diagnostic work-up included a normal upper and lower endoscopic examination of the digestive tract, acute bowel infection exclusion and negative autoimmune disease screening. Exhaustive laboratory testing for bleeding disorders was also performed, revealing a fibrinogen deficiency. No specific medication was prescribed due to spontaneous resolution and she was eventually discharged from outpatient management owing to asymptomatic but persistently low fibrinogen levels.

European Journal of Case Reports in Internal Medicine

At 27 years of age, the patient attended the emergency department due to complaints of a spontaneous, atraumatic acute and intense pain on the right calf associated with homolateral limb swelling that rendered her unable to walk. Venous ultrasound with Doppler imaging revealed a completely occlusive recent thrombosis involving the right popliteal, superficial femoral, common femoral and external iliac veins. Regarding the aetiology, two important aspects were noted: the patient's daily medication was an oestrogen-based oral anticontraceptive with the intent of family planning and menstrual flow control due to metrorrhagia secondary to hypofibrinogenaemia. Thrombophilia laboratory work-up was remarkable for, as was expected from the past medical history, low levels of fibrinogen (<80 mg/dl) and, new and concomitant, deficient levels of functional protein S activity (21%). Six months later, after enoxaparin interruption, thrombophilia work-up was repeated and the results persisted: low fibrinogen levels, protein S with a normal quantitative value (74%), albeit with a diminished activity (32%). Autoimmune systemic disease, a subjacent neoplastic disorder and other thrombophilia diagnoses were excluded.

However, regarding the fibrinogen disorder, the assisting physicians attempted to rule out an even rarer mutation defect that would explain the past spontaneous haemorrhage and the present thrombotic event, namely hypodysfibrinogenaemia, as opposed to the co-existing and "contradictory" coagulation disorders: hypofibrinogenaemia and deficient protein S activity. Hence, further diagnostic tests were performed that were favourable to hypofibrinogenaemia solely. The tests revealed a normal reptilase time (reference value under 22 seconds), low levels of functional fibrinogen (reference values: 180–360 mg/dl) and immunological antigenic fibrinogen (reference values: >80 mg/dl) of 87 mg/dl and 68 mg/dl, respectively, and a normal calculated functional antigenic fibrinogen ratio.

The vitamin K inhibitor warfarin was prescribed with a target INR of 2–3 being sought and successfully attained. This medication was substituted for parenteral low molecular weight heparin during the patient´s pregnancy. At the due labour date, the patient had an eutocic delivery, with 1 g of fibrinogen concentrate being given throughout to avoid unexpected major bleeding.

Three months after birth, the patient's child underwent screening tests that showed even lower levels in a functional fibrinogen assay (52%) and in an immunological antigenic assay (47 mg/dl). Genetic testing was finally carried out on our patient, unveiling a pathogenic heterozygous mutation in the FGA gene, c.191G>A, p.Cys64Tyr (Fibrinogen Marseilles II). This is already described as a pathogenic variant of hypofibrinogenaemia and leads to alteration of the protein conformation and secretion.

DISCUSSION

Fibrinogen, or coagulation factor I, is a soluble 340 kDa hexameric plasma glycoprotein synthesized in the liver, encoded by three genes – FGA, FGB and FGG – clustered on chromosome 4q. Once secreted into the circulation, it is intimately involved in health and disease through its pivotal roles in blood coagulation (fibrin clot formation, non-substrate thrombin binding, fibrinolysis).

Fibrinogen disorders are uncommon causes of either bleeding or thrombotic events and may be acquired or inherited in a recessive or dominant autosomal manner.

Congenital fibrinogen deficiencies are very rare, constituting 0.6% of all inherited coagulation factor disorders. The causative mutations, more frequently to the FGA gene than FGB and FGG, can be divided into main two classes: null mutations where no protein is produced or missense mutations where an abnormal protein is produced and retained inside the cell (in this case, the hepatocyte)[1].

It is difficult to establish a genotype-phenotype correlation in congenital fibrinogen deficiencies. The severity of bleeding risk is highly variable amongst patients that carry the same genotype and factors that explain such clinical variability are yet to be described. Possible explanations include the heterozygous trait of hypofibrinogenemia that might contribute to modifying genes/alleles and the presence of common variants predisposing to thrombophilia (e.g. factor V Leiden or protein-S deficiency, as is the described case)[2].

Categorization is traditionally based on plasma concentrations. Quantitative or type I deficiencies have absent or low plasma fibrinogen activity levels (afibrinogenaemia with levels <0.5 g/l and hypofibrinogenaemia with levels between 0.5–1.17 g/l) that may result from mutations affecting fibrinogen synthesis, assembly, intracellular processing, domain stability and protein secretion. Qualitative or type II deficiencies, including dysfibrinogenaemia or hypodysfibrinogenaemia, show normal or reduced antigen levels but disproportionately low functional activity and are caused by mutations affecting the functional properties of fibrinogen, including the absence or delayed release of fibrinopeptides from the α and β chains, delayed or enhanced polymerization, defective cross-linking, decreased thrombin binding and defective assembly of the fibrinolytic system[3,4].

The clinical presentation of patients with congenital hypofibrinogenaemia is heterogeneous. It varies from asymptomatic, to moderate bleeding (for example, umbilical cord bleeding at birth, cutaneous bleeding, gastrointestinal bleeding, increased tendency for epistaxis and menorrhagia in women) to catastrophic life-threatening bleeds (such as intracerebral bleeding). This disorder can also be responsible for venous thrombotic events, albeit a rare cause, as described in case series reports, and is usually associated with epidemiological risk factors such as smoking, hypertension, obesity and the use of oral contraceptives[2,5].

Diagnosis of hypofibrinogenemia is suggested when coagulation tests that depend on fibrin formation, Prothrombin Time (PT), activated partial thromboplastin time (aPTT) and Thrombin Time (TT) are prolonged. The extent to which these results are prolonged vary according to the level of functional fibrinogen present.

Confirmation is established when there is a proportional decrease in both functional and immunoreactive fibrinogen and certainty is given by genetic testing [2,5,6]. Evaluation of liver function, including invasive measurements such as liver biopsy, is necessary in case of suspected hepatic storage disease[1].

Even though genotype–phenotype correlations are not easy to establish, determination of the molecular defects is important, because not only does this provide confirmation and prenatal diagnosis but it also allows assessment of the inherent risk of thrombotic or haemorrhagic events[2].

Due to the low prevalence of IFD, there is little information on the pathophysiology or optimal treatment of thrombosis in these patients[5]. Managing congenital fibrinogen disorder patients with thrombosis, as in the presented case, is challenging, since anticoagulant treatment may exacerbate the underlying bleeding risk. When fibrinogen levels are very low or absent, or there is a past medical history of bleeding events, replacement therapy should be employed to prevent life-threatening haemorrhage in specific scenarios, such as surgery or labour/caesarean delivery[7].

CONCLUSION

In conclusion, the authors present the case of a young patient with a history of spontaneous bleeding caused by congenital hypofibrinogenaemia due to Fibrinogen Marseilles II mutation and, later, an episode of central venous thrombosis due to deficient protein S activity and use of oral contraceptives. Interestingly, the hereditary nature of this congenital fibrinogen deficiency was shown not only through genetic confirmation but with consistent and similar screening tests performed on the child. Medical management is quite challenging due to the need for in aeternum anticoagulation therapy and the heightened risk of clinically significant haemorrhage that such therapy imposes on an underlying congenital condition with a tendency for bleeding.

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