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Postoperative deep venous thrombosis in a woman with congenital afibrinogenaemia treated with fibrinogen concentrates

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EDITOR:
Congenital afibrinogenaemia is a rare coagulation disorder with an estimated prevalence of one in one million [1]. The risk of abnormal bleeding during a surgical procedure is high but can be avoided by the administration of fibrinogen concentrates [2,3]. The administration of coagulation proteins in patients deficient in coagulation factors can be complicated by venous or arterial thrombosis [1]. We describe the case of a patient with congenital afibrinogenaemia admitted for enucleation of her right eye whose postoperative course was complicated by a deep venous thrombosis.

Case report

A 30-yr-old Algerian female (height 1.62 m, weight 56 kg), known to have congenital afibrinogenaemia, was referred to the ophthalmology department for the enucleation of her right eye. At birth she had suffered from an umbilical cord haemorrhage. The diagnosis of congenital afibrinogenaemia had been made at the age of 5 yr when she presented with a large musculocutaneous haematoma. The parents were asymptomatic. The patient had seven siblings: one sister died from haemorrhage at birth, two brothers were affected with the same haemorrhagic disease and one brother and three sisters were asymptomatic. In 1986, 1997 and 2006 the patient underwent dental extractions without complication after administration of fresh frozen plasma. She was being treated for menorrhagia with normegestrol and an oral iron preparation for the associated iron-deficiency anaemia. At the age of 5 yr she had suffered trauma to the right eye complicated by intraocular haemorrhage. Since then her vision had been poor and in recent months she had suffered from chronic pain. The ocular pain was not relieved by the usual analgesics and enucleation was suggested and accepted by the patient.

The preoperative haematological tests' results are shown in Table 1. Fibrinogen, determined by a functional assay (von Clauss method), was $<0.30\,g\,L^{-1}$, and the level determined by an immunological assay was $<0.50\,g\,L^{-1}$. The plasma concentrations of the other coagulation factors were normal. Immediately before the surgical procedure, the patient received 4.5 g of fibrinogen (Clottagen®; LFB, Lille, France), the target being a plasma concentration of fibrinogen $\geqslant 1\,g\,L^{-1}$.

The enucleation of the right eye was carried out under general anaesthesia. The eye content was replaced by a polymer-coated hydroxyapatite implant. The surgical procedure was uneventful, without abnormal surgical bleeding. She received a further 1.5 g of fibrinogen on the first and the second postoperative days (Table 1). On the fourth postoperative day, she complained of pain in her left calf. Compression ultrasound examination of the lower limb veins revealed thrombosis of the left fibular veins at the mid-calf extending over 3 cm. Contrary to proximal thrombosis, the therapeutic

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Table 1. Coagulation profile during hospital course.

	16 May 2007	22 May 2007, 12.00a.m.	22 May 2007, 8.00p.m.	23 May 2007, 8.00a.m.	23 May 2007, 6.00p.m.	24 May 2007, 8.00a.m.	25 May 2007, 8.00a.m.	26 May 2007, 8.00a.m.	27 May 2007, 8.00a.m.	28 May 2007, 8.00a.m.	29 May 2007, 8.00a.m.
Prothrombin time (s)	>60	15.8	16.0	16.9	16.7	17.2	16.9			19.2	
Activated partial thromboplastin time (s)	>120 (34)	34 (35)	28 (34)	32.5 (34)	32.8 (35)	36.9 (34)	35.1 (34)			40.4 (34)	
Fibrinogen* ($G\,L^{-1}$)	<0.30	1.30	1.25	1.08	1.58	1.12	1.46	1.08	0.71	0.53	0.38
Platelet ($g\,L^{-1}$)	326	259									
Haemoglobin ($g\,dL^{-1}$)	14.7	13.1									
Fibrinogen infused (Clottagen®)		4.5 g		1.5 g		1.5 g					

*Immunological assay.

approach to distal deep vein thrombosis remains controversial. Distal clots appear to have a much lower thromboembolic potential, so we chose not to administer anticoagulants and treated the patient with compressive stockings. The compression ultrasound examination was repeated on the fourth and seventh postoperative day and showed no extension of the thrombosis. The patient was authorized to mobilize on the seventh postoperative day and left hospital on the ninth postoperative day. After discharge from hospital, the postoperative course was uneventful.

Discussion

Fibrinogen is a plasma glycoprotein with a central role in the haemostatic process both as an adhesion protein essential to platelet aggregation and as a precursor of insoluble fibrin that forms the haemostatic clot. Fibrinogen is produced in the liver and its half-life is about 4–5 days. Fibrinogen is composed of six polypeptide chains ($\alpha_2/\beta_2/\gamma_2$) and is encoded by three separate genes (FGA, FGB and FGG) located on chromosome 4 [4]. A number of different mutations have been detected in all three genes in association with afibrinogenaemia, although the majority involve truncations of Aα chain. Patients can be homozygotes with the complete absence of endogenous fibrinogen or heterozygotes with mild-to-moderate hypofibrinogenaemia. Congenital afibrinogenaemia is inherited as an autosomal recessive disorder. Patients are usually offsprings of a consanguineous marriage and are very rare among European populations. A large series of 55 afibrinogenaemic patients has been reported from Iran [1].

The bleeding manifestations in congenital afibrinogenaemia are different from and less severe than that in haemophilia A and B. The severity of bleeding varies from patient to patient. Afibrinogenaemia is in general not characterized by profuse spontaneous bleeding. It is thought that the presence of functional von Willebrand factor allows for platelet aggregation and adhesion to form loose thrombi. Umbilical cord haemorrhage (unusual in haemophilia) is often the first bleeding episode in afibrinogenaemic patients, whereas spontaneous haemarthroses, muscular haematomas and mucosal bleeding occur with a varying severity. Bleeding in the central nervous system is relatively rare but can be life-threatening. The mucosal-type haemorrhages such as nose bleeding and menorrhagia are relatively frequent. Recurrent miscarriages are not uncommon. Management of haemorrhage in afibrinogenaemic patients is based on the administration of fibrinogen concentrates, if available, or of

cryoprecipitates [2,3]. Inactivated plasma-derived concentrates of fibrinogen are available in France (Clottagen®; LFB, Lille, France) and Germany (Haemocomplettan® P; ZLB Berhring, Marburg, Germany). The target fibrinogen plasma levels considered adequate to control bleeding are not well defined. Recent guidelines support recommended target fibrinogen levels of approximately $1\,g\,L^{-1}$ in the perioperative period, and $2\,g\,L^{-1}$ during labour [5].

Arterial or venous thrombosis have been reported to occur spontaneously or after infusion of fibrinogen-containing preparations [1,5,6]. The puzzling association of a severe coagulation defect such as afibrinogenaemia and thrombosis has no definitive explanation. It has been suggested that thrombotic events are related to thrombin-induced platelet aggregation *in vivo* due to poor neutralization of this enzyme, in turn due to lack of its adsorption on fibrin. Aggregation of platelets is induced by thrombin in patients with afibrinogenaemia. During the activation of the coagulation cascade, the relative absence of fibrinogen results in an increase in 'free' thrombin as a result of the lack of the antithrombin activity of fibrin. Because fibrin inactivates thrombin, patients with a lack of fibrinogen may be at risk for thrombosis because of the constant presence of thrombin. Abnormal elevated thrombin generation was described in a case report by Dupuy and colleagues [7]. In that case, the thrombin–antithrombin complexes as a measure of thrombin generation only normalized with fibrinogen replacement.

Fibrinogen replacement therapy is considered to be one of the risk factors for thrombosis in afibrinogenaemic patients. It has been proposed that in the absence of fibrinogen, the small traces of thrombin usually formed, remain longer in the circulation as no absorption on circulating fibrinogen occurs. Such traces of circulating thrombin could clot some fraction of the infused fibrinogen [6]. Indeed, several reports have suggested a possible link between the infusion of fibrinogen-containing preparations and the development of thrombosis [5]. However, it is also apparent that in the majority of patients no known risk factors including the infusion of fibrinogen are present. In a recent review of all reported cases of thrombosis, both arterial and venous, which occurred in rare congenital bleeding disorders, 16 (20%) out of 81 patients had afibrinogenaemia. Among those 16 patients with afibrinogenaemia associated with thrombosis, only seven had possible link with the infusion of fibrinogen-containing preparations [6]. In our patient, the maximum level of fibrinogen after infusion was $1.58\,g\,L^{-1}$, and we chose to repeat the infusion of fibrinogen due to the high risk of bleeding immediately after the right eye enucleation.

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