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Although inherited fibrinogen disorders (IFD) are primarily considered to be bleeding disorders, they are associated with a higher thrombotic complication risk than defects in other clotting factors. Managing IFD patients with thrombosis is challenging as anticoagulant treatment may exacerbate the underlying bleeding risk which can be life-threatening. Due to the low prevalence of IFD, there is little information on pathophysiology or optimal treatment of thrombosis in these patients. We searched the literature for cases of thrombosis among IFD patients, and identified a total of 128 patient reports. In approximately half of the cases, thromboses were spontaneous, while in the others trauma, surgery, and parturition contributed to the risk. The true mechanism(s) of thrombosis in IFD patients remain to be elucidated. A variety of anticoagulant treatments have been used in the treatment or prevention of thrombosis, sometimes with concurrent fibrinogen replacement therapy. There is no definite evidence that fibrinogen supplementation increases the risk of thrombosis, and it may potentially be effective in the treatment and prevention of both thrombosis and hemmorhage in IFD patients.

Introduction

Fibrinogen plays a key role in the process of coagulation. It functions not only as the precursor of the fibrin net that gives structure to blood clots, but also as a promoter of platelet aggregation and fibrinolysis. Two types of inherited fibrinogen disorder (IFD) are recognized, both of which are rare: Type I involves reduced quantities of fibrinogen, whilst type II involves qualitative abnormality. Type I IFD includes afibrinogenemia (absence of fibrinogen, plasma level < 0.1 g/l) and hypofibrinogenemia (low plasma levels of fibrinogen, 0.1—1.5 g/l), while type II encompasses dysfibrinogenemia (normal fibrinogen levels (1.5—3.5 g/l) with low functional activity) [1, 2]. A small number of patients have both hypofibrinogenemia and dysfibrinogenemia, and this condition is described as hypodysfibrinogenemia. IFD is considered as rare on the basis that afibrinogenemia and dysfibrinogenemia each have an estimated prevalence of one in 1,000,000 [1--3], although the frequency of hypofibrinogenemia is believed to be higher [1].

Increased bleeding is generally considered as the primary manifestation of IFD, with umbilical cord bleeding affecting as many as 85% of neonates with afibrinogenemia [4]. Patients with hypofibrinogenemia and dysfibrinogenemia have a lower risk of bleeding events, but these individuals are still at higher risk than the general population, for example during surgery or pregnancy [5].

Despite the deficiency of fibrinogen, there is a potential risk of thromboembolic complications among IFD patients [6, 7]. Managing IFD patients with thrombosis is challenging as they may be at risk of life-threatening hemorrhage [8], or require hemostatic support following surgery, trauma, or childbirth [9, 10]. In such situations, clinicians face the difficult task of providing sufficient hemostasis while minimizing the risk of thromboembolism. Due to the low prevalence of IFD, there is little information on pathophysiology or optimal treatment of thrombosis in these patients.

Literature Review

In order to obtain more information about thrombosis in IFD patients, we searched the PubMed database on September 21, 2015 using the terms ‘congenital fibrinogen deficiency’, ‘afibrinogenemia’, ‘dysfibrinogenemia’ or ‘hypofibrinogenemia’ in combination with the terms ‘thrombotic’, ‘thrombosis’ or ‘emboli’ to identify relevant case reports and clinical studies. This yielded a total of 490 results. Based on titles and abstracts, we identified 86 potentially relevant publications. Further full-text examination of these publications identified 62 case reports of patients with IFD experiencing thrombotic symptoms. We also identified 8 clinical studies or case
series (>3 patients) that included reports of thrombosis among IFD patients. However, these publications provide minimal information on the individual patients concerned or the circumstances in which thrombosis occurred, for example using the word ‘thromboembolism’ without providing any additional details.

The case reports are summarised in supplemental table 1 (available at http://content.karger.com/ProdukteDB/produkte.asp?doi=452864): 72 patients with thrombotic events were described in the 62 publications. A summary of data from the clinical studies and case series is presented in table 1. A total of 56 patients experiencing at least one thrombotic episode are described. Consequently, the total number of IFD patients with thrombosis is 128. Twenty-five patients were diagnosed with afibrinogenemia, 79 with dysfibrinogenemia, 16 with hypofibrinogenemia, and six with hypodysfibrinogenemia. Venous thrombosis appears to be the most common thrombotic event, having been reported in 74 patients (58%). In 35 of these cases (27% of the overall population), pulmonary embolism was the manifestation. Arterial thrombosis was reported in 31 patients (24%). In a small number of patients (n = 5), combinations of venous and arterial events occurred at the same time. There were also a number of reports of ischemia and necrosis where it could not be clearly established whether the cause was venous or arterial thrombosis. Thromboses occurred in a variety of different locations, including the legs, vena cava, portal system, and pulmonary artery.

In a large European case series of patients with dysfibrinogenemia (n = 101), the age- and sex-adjusted risk of thrombotic events after diagnosis of dysfibrinogenemia was 18.7/1,000 patient-years [7]. The overall risk of thrombotic events did not differ between men and women, and the cumulative incidence of thrombotic events at the age of 50 years was estimated to be 30.1% (95% confidence interval, 20.1% to --43.5%). A large study of Chinese cases included retrospective analysis of clinical manifestations among 102 individuals with dysfibrinogenemia; thrombosis was reported in four of these patients (3.9%) [11].

Risk Factors for Thrombosis

In 22 of the 72 case reports (31%), thrombosis developed after a surgical procedure, parturition, or trauma. This suggests that, as in the general population, such events can precipitate thrombosis among individuals with IFD, including those without previous history of thrombosis. Epidemiological risk factors for thrombosis include smoking, hypertension, obesity, and the use of oral contraceptives [12--14]. Such risk factors were present in nine of the cases that we identified (13%), with some patients having more than one risk factor. Furthermore, in four cases (6%) factor V Leiden mutation was present as a thrombophilic risk. Despite these observations, approximately half of thromboses appear to have occurred in the absence of surgery/trauma or epidemiological risk factors, meaning that IFD itself was the probable cause.

In the large European case series of dysfibrinogenemia patients, the authors examined whether there was a relationship between plasma fibrinogen levels and thrombotic risk [7]. No such relationship was found, with respect to either fibrinogen activity or fibrinogen activity:-antigen ratio where available.

One question of interest is whether fibrinogen substitution constitutes a risk factor for thromboembolism in IFD patients. Of the patients presented in table 1, 44% (32 out of 72) had previously received fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate before thrombosis. However, there are reports of a number of patients who had been receiving fibrinogen for many years without experiencing any thrombotic symptoms [15--
while others showed a different course. Some experienced onset of thrombotic symptoms after more than a year of being off fibrinogen [17] or experienced thrombosis before as well as after receiving fibrinogen [18]. A close temporal relationship between the administration of fibrinogen concentrate and the development of thrombotic events was observed mainly in cases where fibrinogen was administered as perioperative hemostatic management [9, 19, 20]. In one of these cases, the patient had also had a thrombotic stroke prior to surgery and fibrinogen infusion [20]. Thrombotic events also developed postoperatively when cryoprecipitate was used to maintain fibrinogen levels [10, 21]. Given the small number of cases and the broad range of clinical circumstances, it is not possible to conclude from the case reports that any form of fibrinogen replacement increases the risk of thrombotic events.

Pathophysiology of Thrombosis in Inherited Fibrinogen Disorders

IFD, particularly certain forms of dysfibrinogenemia, is associated with increased risk of thrombosis [5]. Such a relationship may appear counterintuitive, considering that fibrinogen serves as a primary substrate of coagulation. One hypothesis for the increased thrombotic risk is that concentrations of circulating thrombin are increased in fibrinogen deficiency [22, 23]. In the past, fibrin has been described as antithrombin I due to its ability to bind thrombin [24]. Thrombin is sequestered by the fibrin clot as it forms, reducing the amount of free thrombin in the circulation [23]. This in vivo clearance mechanism does not occur in patients with afibrinogenemia. Free thrombin remaining unbound to fibrin is not contained locally [25], and its potential effects include platelet activation [23]. It has also been shown that fibrin can down-regulate thrombin generation [22]. Therefore, a reduction or absence of functional fibrinogen could directly increase thrombin activity.

Soluble fibrinogen competitively inhibits normal platelet adhesion to immobilized fibrinogen [26]. Accordingly, experiments suggest that adhesion of normal platelets suspended in afibrinogenemic plasma to immobilized fibrinogen is high, and that this can be reversed by soluble fibrinogen [26]. The addition of von Willebrand factor (vWF) to afibrinogenemic platelet-rich plasma supports platelet aggregation induced by adenosine diphosphate (ADP) [27]. This suggests that vWF may potentially play a compensatory role in the absence of fibrinogen.

Thrombus formation has been shown to occur in mice lacking fibrinogen and vWF. The thrombi that formed in this model were unstable and, as a consequence, detached from the subendothelium of the arterioles where they formed [28]. Translocation and embolization of the thrombi led to downstream occlusion of blood vessels.

The mechanisms above suggest that the absence of fibrinogen may lead to increased levels of other procoagulants, and this could increase patients’ prothrombotic tendency. Fibrinogen substitution aimed at normalizing fibrinogen levels may, potentially, reverse the compensatory adjustments and reduce prothrombotic tendency.

In patients with dysfibrinogenemia, thrombosis may be caused by pre-existing risk factors such as antiphospholipid antibody syndrome, or by certain mutations in the fibrinogen gene. For example, in Dusart syndrome the mutation A-α-554 arginine → cysteine increases the brittleness of blood clots so that they break easily and cause embolism [29]. Another mutation, BβAla98(68)Thr, prevents thrombin from binding to fibrin, leading to an increase in the level of free thrombin in the blood [11]. A variety of alterations in the strength, structure, or stability of the fibrin clot may potentially lead to the occurrence of thrombosis [7, 30].

Overall, despite the identification of several factors which may contribute to thrombosis in patients with IFD, the exact mechanism(s) behind each clinical occurrence are yet to be elucidated.
Prevention of Thrombosis

The key to optimal management of patients with IFD is to achieve an appropriate balance between pro- and anticoagulant interventions based on the individual patient’s laboratory results and clinical presentation. This should enable effective prevention of thrombosis while also maintaining a low risk of hemorrhage. The literature suggests that thromboembolic events are not always preventable, but it should be possible to minimize their occurrence and successfully treat the few cases that still occur. IFD patients with underlying thrombotic risk(s) may potentially be susceptible to thrombotic complications when hemostasis is normalized by replacement therapy.

A number of therapeutic options have been explored for the prevention of thrombosis in patients with IFD. The principal options are briefly reviewed below.

Anticoagulant Therapy

Administration of low-molecular-weight heparin (LMWH, enoxaparin) has been advocated in advance of surgery for IFD patients with a thrombotic phenotype [1, 31]. In afibrinogenemia, LMWH (15,000 anti-factor Xa activity units twice-daily) has been used to prevent thromboembolism [32]. LMWH thromboprophylaxis has also been pursued in dysfibrinogenemia [33]. Some authors have suggested administering small doses of heparin alongside fibrinogen therapy [1, 2].

Other anticoagulant drugs have also been used, including vitamin K antagonists, factor Xa inhibitors, and aspirin. Supplemental table 1 (available at http://content.karger.com/ProdukteDB/produkte.asp?doi=452864) provides an indication of the extent to which these treatments have been used in patients experiencing thrombosis.

Fibrinogen Replacement Therapy

Fibrinogen replacement therapy is often employed for the treatment or prevention of bleeding in patients with IFD. Despite the focus on bleeding, fibrinogen replacement therapy can also affect the risk of thrombosis. It has previously been suggested that increased risk of thrombotic complications may be an inherent risk of fibrinogen replacement therapy [34]. Thus, a degree of caution is warranted when treating IFD patients with fibrinogen. However, as described above, it is possible that such treatment may reverse procoagulant mechanisms that compensate for fibrinogen deficiency, thereby reducing the pre-existing risk of thrombosis in IFD patients. This perspective was reflected in the conclusions of a recent review of thromboembolism in afibrinogenemia: frequent, low-dose fibrinogen replacement was suggested to be a ‘safe and effective’ treatment [35]. The options for fibrinogen supplementation include fibrinogen concentrate, cryoprecipitate, and fresh frozen plasma. Fibrinogen concentrate may reduce the risk of thrombosis in IFD patients compared with cryoprecipitate because, unlike cryoprecipitate and plasma, it does not contain coagulation factors other than fibrinogen (e.g. factor VIII, von Willebrand factorvWF) [5, 32, 36]. In afibrinogenemia with elevated prothrombin activation, fibrinogen concentrate has been shown to reduce the level of prothrombin activation [37]. Compared with therapeutic plasma, cryoprecipitate and fibrinogen concentrate may be considered as preferable because of reduced infusion volumes [5].

For severe bleeding or major surgery, a target plasma fibrinogen level of >1.0 g/l is recommended, which may be achieved with a fibrinogen dose of 50—100 mg/kg followed by smaller doses every 2—4 days [1, 33]. Long periods without symptoms are common [1] and, as a result, it is common for IFD patients to receive fibrinogen replacement therapy only in response to bleeding episodes. However, for patients with a personal or family history of severe bleeding, long-term prophylaxis
may be considered. In this context, administration of fibrinogen is recommended every 7—14 days, with dose adjustment to maintain the plasma fibrinogen concentration above 0.5 g/l [1, 4, 33]. In pregnant women with IFD and a history of adverse pregnancy outcomes, fibrinogen supplementation twice per week throughout pregnancy should be considered [4, 33]. Treatment to achieve a higher plasma fibrinogen level (ideally >2.0 g/l) is recommended during labor [4].

Treatment of Thrombosis

Supplemental table 1 (available at http://content.karger.com/ProdukteDB/produkte.asp?doi=452864) shows that a broad array pharmacotherapeutic options that have has been used for the treatment of thrombosis in IFD patients. Reported therapies include anticoagulant, antiplatelet or vasodilatory drugs such as LMWH, rivaroxaban, warfarin, aspirin, clopidogrel, urokinase, phenprocoumon, streptokinase, pentoxifylline, nifedipine, and nafamostat [15, 16, 18, 38--44]. Concomitant fibrinogen replacement therapy may be administered to reduce the risk of severe hemorrhage [16, 17, 38]. The choice for of specific drugs and whether to initiate concomitant fibrinogen replacement will depend on the specific clinical situation and patient history. In the large case series of patients with dysfibrinogenemia, all patients with venous thromboembolism were treated with anticoagulant therapy for up to 1 year, and antiplatelet medication was given to patients with arterial events [7].

In some instances, pharmacological interventions alone may not be sufficient. Surgical interventions, including thrombus removal, resection and inferior vena cava filter placement, may be considered. Favorable outcomes have been reported with both pharmacotherapy and surgery in the majority of patients [19, 41, 42]. In seven 7 cases (10%), the thrombotic event was fatal, while the rest made a full recovery.

Conclusion

Although thrombosis in IFD patients is uncommon, it is well reported in the literature. Known risk factors such as surgery, trauma, and parturition increase the likelihood of thrombosis, whilst in approximately half of the cases the thrombotic event was spontaneous. The true mechanism(s) of thrombosis in IFD patients remain to be elucidated. Although it has been suggested that fibrinogen treatment may be a risk factor for thrombosis, the published data do not support this notion. Compensatory regulation of other clotting factors among IFD patients may be reversed by fibrinogen replacement therapy, potentially decreasing the risk of thrombosis. Managing thrombosis in IFD patients is challenging because of the need to balance the need for anticoagulation with the risk of hemorrhage. Fibrinogen supplementation may be effective for the treatment and prevention of both thrombosis and hemorrhage in IFD patients.

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