*Manuscript*

# *Thromboembolism in patients with congenital afibrinogenemia – long-term observational data and systematic review*

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**Abstract**

*Background:* Frequent arterial and venous thromboembolism in patients with congenital afibrinogenemia (CA) is neither understood nor is a safe and effective treatment established.

*Objectives:* To report on the clinical observations and laboratory data contributing to the understanding of the frequency, physiopathology, prognosis and treatment of CA.

*Patients/Methods:* We observed the long-term clinical course and laboratory data in a cohort of four patients with CA and thromboembolic complications, and conducted a systematic review retrieving all available data.

*Results:* Four patients with CA developed recurrent and extensive arterial and venous thromboembolism (TE) from an age of 25–38 years. In two patients, a treatment strategy targeting at maintaining constantly measurable Fbg levels (≥0.5 g/L) either by regular Fbg replacement or by orthotopic liver transplantation resulted in long-term remissions. Radiological imaging documented resolved arterial thrombi after 6–12 months. In contrast, recurrent thromboembolic events were observed in two other patients with infrequent Fbg replacement. A systematic review of the literature revealed 48 reports of TE in patients with CA (median age at first event 31 years), and a favorable outcome in most patients with frequent application of Fbg, aimed at constant measurable trough levels.

*Conclusions:* Present data suggests that patients with CA are at high risk of arterial and venous thromboembolic events, probably caused by thrombin excess owing to lack of thrombin scavenging by Fbg/fibrin. Regular low-dose Fbg replacement might be a safe and effective treatment option in patients with CA and thromboembolic complications.

**Keywords:**

Afibrinogenemia, venous thromboembolism, thrombosis, aortic disease, arterial occlusive disease, peripheral vascular disease, fibrinogen

## Introduction

Congenital afibrinogenemia (CA) is a rare disorder with a high risk of severe bleeding complications. Paradoxically, thromboembolic (TE) events have also been reported in affected patients. Fibrin and its precursor fibrinogen (Fbg) have a central role in hemostasis. Thrombin is the key procoagulant enzyme [1], converting the soluble glycoprotein Fbg into fibrin monomers, which spontaneously form polymers that are cross-linked by factor XIIIa to form an insoluble and stable fibrin plug. Furthermore, thrombin stimulates inhibitors of fibrinolysis, such as alpha-2-antiplasmin, plasminogen activator inhibitor-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI) [2]. It is difficult to understand how a complete lack of Fbg is consistent with life.

While bleeding problems can be effectively treated with Fbg concentrates, management of thromboembolic events is difficult and recommendations for CA patients are lacking. CA is defined as a total absence of circulating Fbg [3]. In all the CA cases studied to date, homozygous or compound heterozygous mutations have been found within one of the three Fbg genes (*FGA, FGB, FGG*) on chromosome 4q28 encoding the Fbg polypeptide chains (Aα, Bβ, γ) [4]. More than 100 patients with CA have been described and although CA is primarily regarded as a bleeding disorder [3, 5], in a number of cases venous and arterial thromboembolic complications have also been reported. While most authors blame Fbg replacement or the presence of thrombophilic risk factors for these complications, others regard CA itself as a cause of thromboembolism [4].

To contribute to this discussion, we report on the long-term clinical course and laboratory data in a cohort of four CA patients with severe thromboembolic complications. In addition, we conducted a systematic review retrieving all available data on patients with CA and thromboembolic complications.

## Materials and Methods

### *Patients and follow-up*

Four CA patients treated in our institution between 1960 and 2015 were included in this study. Casuistic presentations focus on patients A2, A3 and B1, who were treated predominantly in our

hospital, while the history of patient A1, treated mainly elsewhere, and an additional patient, A4, is discussed only briefly.

The patients were followed in our outpatient unit on a regular basis. The number of visits varied from three times a week in critical situations to once in 6 to 12 months during asymptomatic periods. All patients gave informed consent and approval for the publication of their cases. The study was conducted in accordance with Swiss regulations and the Declaration of Helsinki (1996). Ethical approval was not required.

*Data collection*

Clinical and laboratory data were systematically recorded in the hospital database and patient charts; responsible physicians entered health related information on every visit. Magnetic resonance imaging (MRI) and computed tomography (CT) scans obtained over the past 15 years were stored electronically. The following clinical data were pseudonymized and transferred to the study database: number, type, severity and circumstances of bleeding events; number, type, severity and circumstances of thromboembolic (TE) events; dosage, interval and type of treatment (Fbg replacement, anticoagulant treatment, platelet inhibitors, interventions); outcome of treatment. Additionally, we contacted responsible physicians, requested patient reports and asked patients to complete a questionnaire regarding bleeding and TE episodes, treatment and involved physicians and institutions.

*Laboratory analyses*

The following laboratory data were recorded: functional Fbg plasma levels (peak and trough; Clauss method), Fbg antigen levels, D-dimers, prothrombin fragment F1+2, thrombin-antithrombin complexes (TAT), prothrombin time, activated partial thromboplastin time, platelet aggregation and platelet flow cytometry studies. Even though coagulation analyzers, reagents and assay details changed several times between 1960 and 2015, the methodological principles remained the same. All laboratory analyses were performed at the University Clinic of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, Bern, Switzerland, which is accredited by the Swiss Accreditation Service (SAS). Functional Fbg levels were determined by the Clauss method [6]. In plasma samples with a Fbg level < 0.75 g/L, concentration was determined using a manual method. Underlying mutations in *fibrinogen* genes were identified as previously described [7].

*Systematic review*

MEDLINE and EMBASE databases were searched for publications reporting venous and arterial thromboembolic complications in patients with CA. A search strategy was developed (see supplemental data) and tested in a set of 6 index publications (100% sensitivity). The literature search was supplemented by a manual review of the reference lists in identified publications. No restrictions regarding language or publication date nor formal requirements for diagnosis of CA were applied. In case patients were reported more than once, only the most comprehensive publication was included. We did not include a previous publication on patient A2 of our case series [8]. No quality assessment was conducted as quality was expected to be low and an established quality assessment tool for case reports does not exist. The literature search was last updated on May 5$^{th}$ 2015. The following data were extracted: author/year, results of molecular analysis, age at first TE symptoms, type of thromboembolic complication, treatment (type, dose and interval of Fbg replacement and anticoagulation therapy), outcomes and observation period.

## Results

*Patients*

Four patients with CA and TE were treated between 1960 and 2015 in our institution: two brothers *(A1, A2)*, their male cousin *(A3)* and one unrelated female patient *(B1)*. An additional patient (*A4*; brother of *A3*) did not experience TE. All five patients were homozygous for a large 11kb deletion of the *fibrinogen alpha gene (FGA)*, which according to haplotype analysis had occurred on four distinct ancestral alleles [9, 10]. A summary of the clinical characteristics, treatment and outcomes is given in Table 1, details are provided below.

*Patient A2*

The 53-year-old male patient *A2* experienced severe bleeding events already in childhood: multiple skin and gingival bleedings, extensive muscle hematomas, joint bleeding, and a major intracranial hemorrhage. Fbg was replaced weekly. At the age of 38, he suffered a major stroke due to a thromboembolic occlusion of the left middle cerebral artery. A large floating thrombus was documented in the aortic arch and the thoracic aorta (Figure 1). Even though low molecular weight heparin (LMWH) and aspirin 100 mg were given, additional TE events occurred: recurrent splenic and renal infarctions, ischemic necrosis of toes, paralytic ileus, thrombosis of

subclavian vein, and recurrent ischemic strokes. Eventually, liver transplantation was considered the only remaining option and at the age of 44 years, the patient underwent successful orthotopic liver transplantation [8]. The last Fbg replacement was applied before and during surgery (6 g), and since then Fbg plasma levels remained above 2.5 g/L. The aortic thrombus nearly disappeared (Figure 1) and no further TE or bleeding events occurred after the liver transplantation ten years ago.

*Patient A3*

The clinical course of the currently 50-year-old male patient *A3* is illustrated in Figure 2 [11]. Severe bleeding events occurred already in childhood and prophylactic treatment was initiated (2 g Fbg weekly to monthly). At the age of 25 years, a deep vein thrombosis and extensive pulmonary embolism occurred several days after surgery for a hip fracture despite prophylactic heparin treatment while receiving Fbg replacement. During subsequent years, the patient experienced cerebral vein thrombosis and recurrent pulmonary embolism. A possible TE trigger was identified for some events (postoperative period, infection, Fbg replacement), but not in others. At the age of 43 years, following a mild upper respiratory infection, acute ischemia of digits I to IV of the right hand occurred and a large thrombus in the brachiocephalic trunk and the left subclavian artery was documented (Figure 3). Despite prophylactic LMWH treatment, multiple and recurrent cerebral infarctions developed. An intensified treatment scheme was developed consisting of frequently administered, low-dose Fbg replacement aimed at maintaining measurable Fbg levels with trough values of $\geq 0.5$ g/L and avoiding high peak values. Initially, 1 g was given daily (patient weight 74 kg). Currently the patient administers Fbg every three to four days (1 and 2 g, respectively, weekly dose 3g). Additionally, aspirin 100 mg and prophylactic doses of LMWH was given during the first year. Since implementation of this regimen eight years ago, no further TE or major bleeding events have occurred. MR imaging five months after intensified treatment revealed nearly complete regression of the arterial thrombi (Figure 3).

*Patient B1*

The 48-year-old female patient suffered from mild to moderate bleeding during childhood and adolescence. At the age of 30 years, she experienced massive pulmonary embolism while suffering from pneumonia and following a blunt thoracic trauma, needing Fbg replacement (2 g

daily; body weight 75 kg). Pulmonary embolism reoccurred despite daily application of fresh, frozen plasma supplemented with prophylactic-dose LMWH. However, the patient preferred to remain on Fbg concentrates every two weeks rather than to switch to a frequently administered, low-dose application as used in patient *A3*. A growing thrombus occluding the right main pulmonary artery and extending into the left pulmonary artery with multiple small pulmonary emboli into the left lung were diagnosed in 2015. An intensified treatment aimed at Fbg trough levels of ≥ 0.5 g/L (while avoiding high peak values) and anticoagulation with apixaban (2 x 2.5 mg daily) was initiated.

*Patient A1* was born in 1960. He suffered from a stroke with multifocal cerebral ischemia due to occlusion of the left vertebral artery at the age of 51. While receiving treatment with 1 x 3 g Fbg per week supplemented with 100 mg aspirin (body weight 74 kg), he experienced further thromboembolic events: myocardial infarction, pulmonary embolism and occlusion of the right iliac artery. At present, patient *A1* is not treated in our institution and intensified treatment with twice weekly Fbg replacement was not implemented.

Other causes for TE could not be identified. The father of patient *A3* experienced myocardial infarction at 50 years of age and the mother of *A1/A2* suffered from coronary heart disease.

*Laboratory studies*

In all patients, Fbg plasma concentrations were below the detection limit of the Clauss method and were not measurable immunologically. Prothrombin time and activated partial thromboplastin time were not clottable. No anti-Fbg antibodies have been detected in any of the patients. An extensive panel of thrombophilia markers was negative in all patients except for patient B1, who was found to be a heterozygous carrier of the prothrombin G20210A mutation.

TAT complexes were assessed before Fbg administration on 49 occasions (patients A2, A3 and B1) as well as before and after Fbg administration on 18 occasions, and were increased in 90% of cases (mean 19.5 µg/L; SD 15.9; normal <4.1 µg/L). Administration of Fbg resulted in a decrease of TAT levels in all but two instances ($p = 0.008$; Figure 4A). Without Fbg replacement, D-dimers were < 45 µg/L (detection limit) at all-time points. After treatment, D-dimers increased to normal values (Figure 4B). Changes of hemostatic parameters upon Fbg replacement for patient A3 (most complete records) are shown in Table 2.

*Systematic review*

The literature search yielded 599 records including 5 publications identified by manual review (see PRISMA flow chart, Figure S1 supplemental data). After removal of duplicates, titles and abstracts of 537 records were screened, and 94 publications were selected for full-text review. Finally, we included 46 studies reporting on 48 patients with CA and TE complications. Details of the patients are reported in Table 3. A wide range of venous and arterial TE complications were reported, covering not only common (such as pulmonary embolism) but also rare manifestations (spinal cord infarction). A cluster of aortic thrombi and ischemic necrosis of toes and fingers is discernable. At the time of the first TE event, patients were at young age (median 31 years, range 0 to 48, mean 29.6). Treatment strategies varied widely though details of dosage and timing were often not provided. In addition, the effects of treatment are difficult to appraise because the observation period was usually short. However, treatment comprised frequent applications of Fbg aimed at maintaining Fbg levels above a certain threshold in 11 patients [12-22]. The reported outcome was favorable in all but one [21] of these patients.

## Discussion

*Key findings*

Extensive venous and arterial thromboembolism was observed frequently in patients with CA, both in our cohort of four patients and also in published reports. Frequent Fbg replacement with target trough levels of ≥0.5g/L or orthotopic liver transplantation permitted anticoagulant and/or antiplatelet therapy supporting resolution of arterial and venous thrombi, and effectively prevented further TE events, which in contrast, were not prevented in patients with infrequent and sporadic Fbg replacement. It seems likely that regulation of generated thrombin is enhanced by the permanent presence of Fbg as reflected by decreased TAT-levels upon Fbg replacement (Figure 4). Systematic review identified 48 reports of patients with CA and often severe TE, which occurred at young age. Treatment schemes aimed to maintain Fbg levels above a certain threshold resulted in favorable outcomes in all but one of 11 patients.

*Comparison with other studies*

The present investigation expands previous case reports and laboratory studies, which are essentially in line with our results. TE complications in CA patients reported in the literature

were identified by the systematic review [5, 12-55]. Even though many details of treatment schemes and outcomes were not described, frequent Fbg administration aiming at maintaining trough Fbg levels above a certain threshold were apparently successful in 10 patients [12-20, 22]. Several authors observed elevated markers of thrombin formation in CA patients' plasma, as we did: TAT complexes [31, 53], thrombin generation [31, 56] and prothrombin fragments F1+2 [31, 57] were often increased. Following Fbg replacement, these markers usually decreased. Reduced levels of D-dimers were also observed in a study by Korte et al. [57] and were corrected by Fbg replacement.

*Strengths and limitations*

Our investigation has limitations. As is typical for ultra-rare diseases we are restricted to a case series rather than to a prospective cohort study or a randomized controlled trial. However, four out of our five patients experienced severe and recurrent arterial and venous TE events from a young age. In addition, we identified 48 patients with TE complications through a systematic review of the literature further supporting an association between CA and TE risk. Similarly, treatment effects have not been studied in a randomized controlled trial applying standardized interventions and pre-specified outcome definitions. Again, given the rarity of the disease, this is unlikely to be possible in the near future. The clinical course of our four patients as well as the reports identified in the literature suggest that TE events re-occur frequently in inadequately substituted patients. In contrast, in our two patients (A2 and A3) after establishing Fbg trough levels $\geq 0.5$g/L, no further TE events occurred during subsequent follow-up of 7 and 9 years, respectively, which is in line with a number of reports successfully employing similar replacement schemes.

As another limitation, we are not able to draw conclusions on two important questions: (1) is there an association between Fbg replacement and the occurrence of TE events, and (2) how shall we treat TE events initially. Patients showed up several hours or even days after the onset of symptoms and Fbg plasma levels were not systematically determined. Some events occurred in the course of an intensified treatment (eg. postoperatively, or after hemorrhage) suggesting Fbg replacement to be a potential contributor. However, other events occurred several days or even weeks after last Fbg application when plasma levels were already below detection limit, suggesting other triggers as well. The same holds for the initial treatment of TE. We treated the

patients over a time-period of several decades. The dosage and time-interval of Fbg concentrates as well as anticoagulants and platelet inhibitors varied widely and depended on a large number of factors, the presence of bleeding complications in particular.

The strength of our report is that we treated several patients and observed their long-term outcomes over many years.

*Implications for clinical practice*

We believe that CA must not only be perceived as a bleeding disorder but as a major thromboembolic risk factor, in particular with increasing patient age. Medical care should not only focus on treatment and prevention of bleeding complications, but also on the prevention of (recurrent) TE events, especially as patients get older. Even though many events occur without triggers, the risk appears to be higher in situations with coagulation activation, such as infections, interventions or trauma. Frequently administered, low-dose Fbg replacement to maintain Fbg levels of at least 0.5 g/L is a promising strategy for the treatment and prevention of TE complications.

*Pathophysiology of thrombus formation in CA patients*

It is still unclear how patients with CA form thrombi. We observed increased levels of TAT complexes, which were normalized following Fbg administration. This observation is in line with studies demonstrating increased thrombin generation in patients with CA [31, 53, 56, 57]. The most likely reason for increased thrombin generation is impaired clearance and sequestration of thrombin by missing Fbg/fibrin [4, 56, 58] which was shown to have an antithrombin activity *(formed fibrin: Antithrombin I* [56, 58]*).* Excess thrombin might not only activate endothelial cells [59] but also platelets that may aggregate in the presence of von Willebrand factor even in the absence of Fbg [60]. Indeed, in fibrinogen knockout mice, platelet deposition upon vessel wall injury was similar to wild-type mice and thrombi grew very efficiently; the formed thrombi, however, were not stable, often ripped off the vessel wall leading to the downstream vessel occlusions [61]. Enlarged and loosely packed thrombi were also observed in the blood of CA patients under flow conditions in vitro [62].

*Conclusions*

In conclusion, our data indicate that patients with CA are at high risk of arterial and venous thromboembolic events. Our data provide further evidence of an antithrombotic effect of Fbg/fibrin *in-vivo* and suggests frequent, low-dose Fbg replacement therapy to be a safe and effective treatment option in CA patients with thromboembolic complications.

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## Authorship contributions

MN retrieved all data, conducted the literature research and wrote the manuscript. JKH, KPS, DL, LA and BL developed the treatment protocol, and reviewed the manuscript. LA conducted the laboratory analysis and reviewed the manuscript. HVT analyzed the imaging results and reviewed the manuscript. MNA conducted the genetic analyses and reviewed the manuscript. All authors approved the final version of the manuscript.

## Disclosure of Conflict of Interest

MN has received research grants or lecture fees from Bayer and CSL Behring. BL has received travel and accommodation support for participation at scientific congresses or meetings from Baxalta, Siemens, Alexion and lecture fee from Siemens. He is chairman of the Data Safety Monitoring Board in the BAX 930 study (rADAMTS13 in patients with hereditary thrombotic thrombocytopenic purpura) and holds a patent on ADAMTS13. All other authors declare no conflict of interest.

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## Tables

**Table 1:** Characteristics of four patients with congenital afibrinogenemia and thromboembolic events

| Patient | Sex | Year of birth | Age at first TE symptoms | Thromboembolic complications | Bleeding events | Long-term treatment | Outcomes *(observation period)* |
|---|---|---|---|---|---|---|---|
| **A1** | male | 1960 | 51 | Recurrent ischemic stroke<br>Major myocardial infarction<br>Bilateral pulmonary embolism<br>Peripheral artery disease | Joint bleedings<br>Extensive muscle bleedings | 1x3 g Fbg / week | Recurrent TE events |
| **A2** | male | 1962 | 38 | Amaurosis fugax<br>Major thrombus aortic arch<br>Recurrent ischemic stroke<br>Recurrent splenic infarction<br>Renal infarction<br>Upper extremity deep vein thrombosis<br>Superficial vein thrombosis<br>Ischemic necrosis of toes | Recurrent intracranial hemorrhage<br>Extensive muscle bleedings<br>Multiple hematomas<br>Gingival bleedings<br>Ankle joint bleeding | Orthotopic liver transplantation (OLT) | No TE in the 9 years following OLT |
| **A3** | male | 1965 | 25 | Recurrent pulmonary embolism<br>Deep vein thrombosis<br>Cerebral vein thrombosis<br>Recurrent ischemic stroke<br>Arterial occlusion right hand<br>Thrombosis subclavian artery<br>Ischemic necrosis of toes and fingers | Umbilical cord bleeding<br>Subdural hematoma<br>Intracerebral hemorrhage<br>Joint bleedings<br>Extensive muscle hematomas<br>Multiple skin bleedings | 1x2g, 1x1g Fbg / week<br>Aspirin 100mg/d | No TE event recorded in 7 years |
| **B1** | female | 1967 | 30 | Massive, recurrent pulmonary embolism<br>Extensive thromboembolism of both pulmonary arteries<br>Perfusion disorder of fingers and toes | Umbilical cord bleeding<br>Joint bleedings<br>Recurrent hemoptysis<br>Extensive pleural bleedings<br>Gingival bleedings<br>Extensive muscle bleedings<br>Menorrhagia | 2x2 g Fbg / week<br>Apixaban 2.5mg 2x/d | No recurrent event since Fbg/apixaban 9 months ago |

**Table 2:** Hemostatic parameters before and after replacement of 2g fibrinogen concentrate (patient A3; body weight 74 kg)

| Parameter | Before treatment* | Effects of prophylactic treatment† |
|---|---|---|
| Prothrombin time (%) | incoagulable | 30 to 50* |
| Activated partial thromboplastin time (s) | incoagulable | 35 to 40*# |
| Plasma fibrinogen level (g/L) ‡ | not detectable | 0.5 to 0.7* |
| D-dimer levels (µg/L) | < 45* | 100 to 200* |
| Thrombin-antithrombin complex (µg/L) | 19.5 (15.9)§ | 1.5 to 5.0* |

* approximate values; † peak-level; ‡ Clauss' method; § mean (SD)

**Table 3:** Reports of afibrinogenemia patients with thromboembolic events, treatment and outcome – a systematic review.

| Author, year | Age* | Sex | Molecular analysis | Type of complication | Treatment | Outcomes *(observation period)* |
|---|---|---|---|---|---|---|
| Bas 2009 [23] | 22 | Female | - | Spinal cord infarction | Fibrinogen replacement | Neurological improvement (4 months) |
| Berkouk-Redjimi 2014 [24] *(two patients)* † | - | - | - | Type of TE not stated | - | - |
| Bornikova 2011 [25] | - | - | Heterozygous mutation in *FGG* gene | Type of TE not stated | - | - |
| Boukhris 2014 [26] | - | - | - | Digital necrosis | - | - |
| Casini 2014 [63] | 30 | Male | Homozygous mutation in *FGB* gene | Pulmonary embolism | Low molecular weight heparin | Symptomatic pulmonary hypertension |
| Castaman 2009 [12] | 35 | Female | Homozygous mutation in *FGG* gene | Renal artery occlusion | 2 g fibrinogen every second day | Partial lysis of thrombus (10 days) |
| Chapin 2013 [13] | 33 | Female | Homozygous mutation in *FGA* gene | Pulmonary embolism<br>Catheter-related thrombosis | Bi-weekly fibrinogen replacement<br>LMWH | Resolution of PE (4 month) |
| Chevalier 2011 [27] | 37 | Male | Compound heterozygous mutation in *FGA* gene | Recurrent deep vein thrombosis<br>Cerebral vein thrombosis<br>Pulmonary embolism<br>Inferior vena cava thrombosis | Changing doses of fibrinogen, LMWH/ UFH | Death |
| Chun 2005 [14] | 22 | Male | - | Internal carotid artery occlusion (cerebral infarction)<br>Myocardial infarction<br>Catheter thrombosis | Fibrinogen (target 0.8 to 1.5 g/L) | Improvement (3 weeks) |
| Dear 2006 [29] | 34 | Male | Homozygous intronic mutation in *FGB* gene | Cerebral infarction<br>Myocardial infarction | - | - |
| Dupuy 2001 [31] | 30 | Male | - | Ischemic lesions of toes<br>Stenosis of iliac artery | Bypass operation, fibrinogen, LMWH, Aspirin | Clinical improvement, bypass occlusion (three weeks) |
| Erlacher 2009 [15] | 20 | Male | Homozygous mutation in *FGA* gene | Digital ischemic necrosis | Fibrinogen replacement for 7 weeks (initially daily) | Clinical improvement (7 weeks) |
| Falsoleiman 2012 [32] | 30 | Female | - | Myocardial infarction | Antiplatelet therapy, angioplasty, bare metal stent | Recurrent event (one year) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Fuchs 2007 [33] | 20 | Female | Homozygous mutation in *FGG* gene | Budd-Chiari syndrome<br>Inferior vena cava thrombosis, ommon iliac vein thrombosis | Liver transplantation | Successful transplantation |
| Garcia-Monco 1996 [34] | 28 | Female | - | Medullary infarction due to vertebral artery dissection | Fibrinogen replacement, UFH, warfarin | Improvement (1 year) |
| Girard 2005 [35] | 41 | Female | - | Ischemic necrosis of toes | Plasma exchange and fibrinogen replacement every 6 weeks | Improvement (13 months) |
| Goudier 2007 [36] | 20 | Female | - | Ischemic necrosis of toes | Surgical amputation, reduction of monthly fibrinogen replacement | Recurrence |
| Grandone 2012 [37] | 36 | Male | Homozygous mutation in *FGB* gene | Ischemic stroke<br>Thrombosis right radial artery | Fibrinogen replacement (target trough levels >1.5 g/L) | - |
| Haberer 2008 [38] | 30 | Female | - | Postoperative deep vein thrombosis | Compression stocking | Stable complaints (9 days) |
| Hanano 1992 [39] | 37 | Female | - | Ischemic necrosis of toes | - | - |
| Jimenez Caballero 2006 [40] | 46 | Female | - | Pulmonary embolism | - | - |
| Karim 2011[16] | Newborn | Female | - | Sinus cerebral thrombosis<br>Internal jugular vein thrombosis | Fibrinogen replacement 3 times a week, LMWH | Recanalization (4 months) |
| Katsinelos [41] | 22 | Female | - | Intestinal ischemia | - | - |
| Kinebuchi 2002 [17] | 30 | Male | - | Leg ulcer due to suspected recurrent DVT | Fresh frozen plasma | Wound healing (2 months), reoccurrence after discharge |
| Kumar 2008 [42] | 27 | Male | - | Myocardial infarction | Aspirin, clopidogrel | Improvement (two days) |
| Lak 1999 [5] | 14 | Female | - | Gangrene foot due to thrombotic popliteal occlusion | Amputation | - |
| | 5 | Male | - | Sinus vein thrombosis | - | - |
| Laufs 2004 [18] | 32 | Female | - | Spinal cord infarction due to vertebral artery occlusion | Fibrinogen replacement (target trough levels >0.8 g/L) | Improvement, recanalization of vertebral artery |
| Lebreton 2015 [43] | 32 | Female | Homozygous mutation in *FGA* gene<br>Heterozygous factor V Leiden mutation | Pulmonary embolism<br>Deep vein thrombosis | Fibrinogen replacement every second day, intermediate-dose LMWH | - |
| MaKinnon 1971[44] | 36 | Female | - | Gangrene foot<br>Aortal thrombus | Initially fibrinogen replacement | Improvement of gangrene, died 18 month later |
| Matsumoto 2008 | 35 | Female | - | Catheter-related thrombosis | Fibrinogen replacement (initially every second day), | Improvement (6 months) |

| | | | | | | |
|---|---|---|---|---|---|---|
| [19] | | | | Pulmonary embolism | UFH, warfarin | |
| Molho-Sabatier 1991 [45] | 33 | Female | - | Ischemic necrosis of toes due to iliac artery thrombosis | - | - |
| Moscardo 2014 [46] | 32 | Female | - | Ischemic necrosis of toes and fingers | Aspirin, LMWH | Mild improvement (observation period not stated) |
| Oruc 2006 [47] | 16 | Female | - | Budd-Chiari syndrome | No treatment | Death |
| Ozdemir 2015 [64] | 23 | Female | - | Ischemic necrosis of toes and upper extremity venous thrombosis | LMWH, aspirin, nifedipine, fibrinogen replacement | - |
| Pati 2009 [48] | 32 | Female | - | Pulmonary embolism<br>Thrombosed vena cava inferior | No treatment | - |
| Roque 2004 [49] | - | Female | - | Placental infarctions<br>Renal vein thrombosis | Cryoprecipitate, LMWH | Recanalization (27 days) |
| Rupec 1996 [50] | - | - | - | Ischemic necrosis of toes | - | - |
| Sakai 2011 [51] | 34 | Female | - | Spinal cord infarction due to vertebral artery occlusion | - | - |
| Santoro 2015 [52] | 36 | Male | Compound heterozygous mutation in *FGA* gene | Lower limb arterial thrombosis | LMWH, fibrinogen replacement, iloprost | Progressing arterial thrombosis, amputation |
| Sartori 2012 [20] | 48 | Female | - | Aortic thrombosis<br>Ischemic necrosis of toes | Fibrinogen replacement (target trough levels >0.8 g/L), prophylactic dose LMWH, Aspirin | Improvement, recanalization of aortic thrombus (6 month) |
| Schuepbach 2004 [53] | 44 | Male | Homocygous mutation in *FGA* gene | Lower limb arterial thrombosis | Angioplasty, prophylactic dose LMWH/UFH/lepirudin, fibrinogen replacement (target through levels > 0.5 g/L) | Recurrent events |
| Simsek 2008 [54] | 20 | Male | Homozygous mutation in *FGA* gene | Deep vein thrombosis<br>Ischemic digital necrosis<br>Pulmonary embolism<br>Thrombus subclavian artery<br>Ischemic stroke | Prophylactic LMWH, intercurrent iloprost and fresh frozen plasma, intercurrent Aspirin | Recurrent events |
| Takasugi 2005 [55] | 19 | Male | - | Mesenteric vein thrombosis | Small intestine resection | - |
| Taslimi 2011 [21] | 27 | Female | - | Mesenteric and portal vein thrombosis | UFH, fibrinogen replacement (target trough levels 0.5 to 1 g/L), small intestine resection | Death 2 days postoperatively |
| Teresa 2015 [22] | 48 | Female | - | Ischemic necrosis of toes<br>Thrombus of abdominal aorta | Fibrinogen replacement (initially target trough levels >0.8 g/L, later on >0.4 g/L), prophylactic dose LMWH/fondaparinux, Aspirin | Full recovery of necrosis, resolution of aortal thrombus (two years) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Vu 2003 [65] | 0.5 | Male | Compound heterozygous mutation in *FGB* gene | Upper extremity venous thrombosis | Fibrinogen replacement | No recurrent event (four years) |

† no further information provided; * at first TE symptoms

## Extra table

| | |
|---|---|
| **What is known about this topic?** | • Thromboembolism has been reported in patients with congenital afibrinogenemia (CA).<br>• It is not known whether patients with CA are at increased risk for thromboembolism *in general*.<br>• Management of thromboembolic events is difficult and treatment recommendations for CA patients suffering from thromboembolic events are lacking. |
| **What does this paper add?** | • Patients with CA are at high risk for arterial and venous thromboembolic events.<br>• Frequent, low-dose Fbg replacement appears to be a safe and effective treatment option. |

## Figure legends

**Figure 1:** Atypical thrombotic lesions along the descending aorta of patient A2 before (A) and nine months after (B) orthotopic liver transplantation with major reduction in thrombus volume and only minor remnants (see white arrow).

**Figure 2:** Clinical course in a patient with congenital afibrinogenemia (A3)

**Figure 3:** Contrast enhanced CT angiography of partially floating thrombus of left subclavian artery before (A) and five months after (B) intensified prophylactic treatment with fibrinogen concentrate (patient A3). Thickness of thrombus decreased markedly and floating component resolved.

**Figure 4:** Changes of (A) thrombin-antithrombin complex levels (18 observations) and (B) D-dimers (8 observations) after administration of fibrinogen concentrate in three patients with congenital afibrinogenemia