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Afibrinogenemia caused by a novel homozygous missense mutation, *FGB* p.Cys241Tyr, in a male patient with recurrent intracranial bleeding: case report and review of literature

Short title: Afibrinogenemia and intracranial bleeding

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Abstract:

Introduction: Congenital afibrinogenemia is a severe bleeding disorder, sometimes manifesting as thrombosis and/or pregnancy complications. Intracranial haemorrhage (ICH) constitutes the major cause of death in this disease.

Methods: We present the case of a male patient with congenital afibrinogenemia, who presented with recurrent intracranial hemorrhages, despite prophylactic fibrinogen substitution. We also review the literature for the risk of intracranial hemorrhages in afibrinogenemia.
Result: Molecular analysis revealed a novel homozygous missense mutation in *FGB* exon 5, p.Cys241Tyr, that was named "Fibrinogen Krakow V".
Discussion and conclusion: Intracranial hemorrhage is a severe manifestation of afibrinogenemia, also in children. The clinical presentation of afibrinogenemia is variable. Fibrinogen substitution carries a risk of thrombotic complications.

Keywords: afibrinogenemia, intracranial bleed, bleeding disorders, fibrinogen

Introduction

Afibrinogenemia is an autosomal recessive bleeding disorder with a prevalence of about 1: 1 000 000, characterized by complete absence of fibrinogen[1]. It is usually caused by null mutations of the *FGA* gene: large deletions, frameshift and splice-site mutations. The most common mutation causing afibrinogenemia in Europe is a donor splice mutation in intron 4, c.510+1G>T [1,2,3].

Over 80% of afibrinogenemia cases manifest in the early neonatal period with umbilical cord bleeding [3]. Menorrhagia, gastrointestinal and skin bleeds are frequent, whereas joint and muscle bleeds are uncommon. Women with afibrinogenemia are at risk of miscarriage, postpartum haemorrhage and placental abruption [1,4,5]. Spontaneous splenic rupture was noted in afibrinogenemia, unlike other inherited bleeding disorders [6]. Afibrinogenemia may rarely manifest as venous or arterial thrombosis, either spontaneous or following fibrinogen substitution, particularly after surgery [5]. Some patients manifest both bleeding symptoms and thrombosis, whereas only a few remain asymptomatic [4,5].

Plasma-derived fibrinogen concentrate or (if unavailable) cryoprecipitate is used for prophylaxis and treatment of bleeds. The therapeutic fibrinogen plasma activity of 0,5-2 g/L should be achieved, depending on clinical setting. Trough fibrinogen activity of at least 0.5 g/L is recommended during prophylaxis; dosing schedule should be individually adjusted, however [1,5]. Thromboprophylaxis is strongly recommended after all surgeries at high thrombosis risk, but individual history and risk factors should be taken into consideration [1,5].

Recently, a new classification of congenital fibrinogen disorders has been published, based on the clinical phenotype and fibrinogen levels. It divides afibrinogenemia into type 1A (asymptomatic and bleeding patients) and type 1B disease (all patients with thromboembolic events, regardless their bleeding phenotype) [4].

Intracranial haemorrhage (ICH) constitutes the major cause of death in afibrinogenemia. It can be prevented by regular prophylaxis that is usually implemented and held lifelong after the first life-threatening bleed.

Case report

We present a case of a 46-year-old patient with congenital afibrinogenemia, diagnosed in the neonatal period following an excessive umbilical cord bleeding. Fibrinogen activity was found undetectable at that time and other coagulation factors deficiencies were excluded. Blood tests performed in 2019 confirmed severe fibrinogen deficiency, with undetectable functional fibrinogen activity (von Clauss method) and nephelometric fibrinogen level below the detection limit (0.1 g/L). Thrombin time, activated partial thromboplastin time and prothrombin time were undetectable. Afibrinogenemia (1A) according to the new classification by Casini et al. [4] was diagnosed.

The patient suffered lifelong from extensive bruising, gum bleeds, subcutaneous hematomas, posttraumatic muscle and wound bleeds. In childhood a tooth extraction hemorrhage and hematemesis during infections were noted. He was treated with multiple blood, plasma and cryoprecipitate transfusions. At the age of 18 he suffered from splenic rupture following minor trauma and underwent splenectomy with blood and fresh frozen plasma transfusions. At the age of 30 a posttraumatic peritoneal bleeding occurred with the subsequent peritonitis and the patient required surgery.

At the age of 38 the patient was diagnosed with chronic left-hemispheric subdural hematoma, preceded by a head trauma two months earlier. Neurosurgery was scheduled due to progression of bleeding. Cryoprecipitate infusions increased fibrinogen level over 2.0 g/L before surgery and maintained it over 1.0 g/L for seven days and over 0.5 g/L for the following 3 weeks. The post-operative period was uneventful.

At the age of 39 the patient required cryoprecipitate treatment due to a spontaneous intracerebral hematoma of the temporo-occipital region and shortly after that he was hospitalized again due to extensive intramuscular bleeding in the thigh (without apparent trauma). Since that time cryoprecipitate was administered prophylactically every 3 weeks,

with good outcome: no major bleeds occurred and minor bleeds were eliminated, which significantly improved the patient's quality of life.

Three months later tuberculosis was diagnosed and the patient was treated with isoniazid, rifampicin, ethambutol and pyrazinamide. Other co-morbidities in the patient included arterial hypertension and chronic hepatitis C, both diagnosed at the age of 38.

At the age of 40 low-dose home prophylaxis was initiated and 1 g of fibrinogen (14 mg/kg) was administered every 4 weeks. Within two years of follow-up three minor intramuscular bleeds occurred (two were spontaneous), shortly before the planned prophylactic dose. The patient doubled the next prophylactic dose to 2 g each time, without the need for any additional treatment. In 2015, during interferon treatment of chronic hepatitis C, gastrointestinal bleed was diagnosed 4 weeks after the last fibrinogen dose and he required 3 doses of 2 g of fibrinogen every 2 days without blood transfusions. The next 4 years were uneventful except for one episode of a minor head wound bleed, two muscle bleeds and one early knee joint bleed, all posttraumatic and resolving after doubling of a single prophylactic dose. Recently, a repeated intracranial bleed occurred that resolved untreated within one week. The patient reported no trauma, but noted significant blood pressure peaks before the bleeding episode. Prophylaxis was therefore intensified to 2 g (28 mg/kg) every 2 weeks and antihypertensive treatment was modified.

The patient presents now with discrete neurological deficits (difficulties with handwriting), not interfering with his daily activities. He never suffered from thrombosis.

The patient reported that marriages of second- or third-degree relatives happened in his family in the past. His family history did not reveal bleeding, thrombosis or miscarriages. His children, 8-year-old dizygotic twins, present with mild fibrinogen deficiency (both 1.1 g/L with Clauss method, 0,9 g/L and 1.1 g/L with nephelometry), without any bleeding symptoms until now. He has no siblings and his parents are unavailable for testing.

To confirm the diagnosis of afibrinogenemia, after obtaining written informed consent, the blood sample was taken for whole exome sequencing (WES). This was performed at the Health 2030 Genome Center Sequencing Platform in Geneva, using IDT Research Exome Reagents, multiplexing 12 samples during library preparation, with an estimated mean coverage of 70X. Variant calling was filtered for variants located in a gene panel of 27 genes of the coagulation and fibrinolytic pathways i.e. *FGA, FGB, FGG, F2, F5, F7, F8, F9, F10, F11, F12, F13A1, F13B, VWF, TF, PROC, PROS, SERPINC1, TAFI, PLG, PAI-1, T-PA, SERPINF2, LMAN1, MCFD2, PROCR* and *MTHFR*. The presence of variants in the fibrinogen genes was confirmed by Sanger sequencing. The WES analysis identified a novel homozygous missense

mutation in *FGB* exon 5: c.722 G>A; p.Cys241Tyr (p.Cys211Tyr without the signal peptide), which we named “Fibrinogen Krakow V”. This mutation, predicted to be deleterious by SIFT and probably damaging by Polyphen2, has not been previously reported in the literature. It affects a Cys residue involved in one of the beta-chain disulphide bridges close to the “coiled-coil” region ($Cys^{B\beta211}$-Cys^{240} numbering without the signal peptide), which are important for fibrinogen assembly.

Discussion

The current case presents a new GGB (?) mutation in a man with afibrinogenemia with several serious bleeding episodes including recurrent ICH and a history of muscle and joint bleeding.

Literature review reveals consistently high rate of intracerebral bleeds in afibrinogenemia patients. ICH recurrence despite prophylactic treatment is unusual, however. As early as in 1971 the German authors reported a 13% incidence of central nervous bleeds in this disorder [7]. In a large Iranian cohort of 55 afibrinogenemic patients from 48 different families, published in 1999, ICH was diagnosed in 3 individuals (10%), in comparison to 3% reported in severe hemophilia A. Unfortunately no further data were provided, regarding the cause or outcome of these episodes [8]. A review of questionnaire data on 72 afibrinogenemia patients treated in 34 hemophilia treatment centers identified 3 cases of ICH (4%), two of which occurred despite prophylactic treatment [9]. Another review established the frequency of ICH in afibrinogenemia at 5% [10]. A report on 21 afibrinogenemia patients revealed that about 20% suffered from ICH [11].

Literature search identified further 11 case reports and case series, presenting this phenomenon. In 1999 a young female patient was described, who was diagnosed with a spontaneous left occipital lobe bleeding with progressive hemiparesis, undetected in two consecutive CT scans. Empirical cryoprecipitate treatment improved neurological symptoms, but was complicated by pulmonary embolism. ICH recurred despite cryoprecipitate prophylaxis, also without trauma, and its treatment was complicated by pulmonary embolism again. Since the patient was switched on purified fibrinogen concentrate substitution, no further major bleeds and no thromboembolic events were noted. Negative initial CT scans were explained by abnormal clot forming in the absence of fibrinogen [12].

Two males with spontaneous ICH were described in 2000. The first one was a neonate with an intraventricular haemorrhage and chronic subdural hematomas, treated with cryoprecipitate for three month, who developed a recurrent, spontaneous ISH 6 months after cessation of

prophylaxis. The second case was a 27-year-old patient, who developed a spontaneous ICH in the frontal and occipital region. Prophylaxis with fibrinogen concentrate prevented further bleeding during the next 10 months of observation [13].

Another case of spontaneous extradural and subdural hemorrhage in a 32-year-old woman was described in 2009. Surprisingly, postsurgical prophylaxis with fibrinogen concentrate was complicated with massive pulmonary embolism, despite fibrinogen levels in the range 0.5-1 g/L [14].

In 2010 an antenatally detected ICH was described leading to elective cesarean section in the 29th week of pregnancy. The newborn experienced a repeated atraumatic ICH at 6 months of age (soon after cessation of cryoprecipitate treatment) [15]. Another case of an early, spontaneous ICH in a full term neonate can be found in the literature [16]. Of note, the child had two relatives with afibrinogenemia (the father and the sister), who did not suffer any bleeds lifelong. In contrast, Palestinian siblings with afibrinogenemia suffered ICH at the age of 4-5 months after minor trauma [17].

Unusually quick resorption of intracranial bleeds in an afibrinogenemia patient, similarly to our case, was reported earlier in two patients [18,19]. Subtotal or total regression of the bleed was noted as soon as in 2-3 weeks, in contrast to the usual time of resorption of posttraumatic bleeds of 5-7 weeks. The same phenomenon was observed in our patient. It can possibly be explained by abnormal clot formation in the extravasated blood, particularly in the absence or with delayed fibrinogen substitution [18].

Further reports on ICH recurrence can also be found in the literature mainly in neonates or young children [20-22]. To sum up, we identified in the literature 5 cases of ICH recurrence in afibrinogenemia patients, one posttraumatic and 4 spontaneous. In all these patients but one a repeated, spontaneous ICH episode was diagnosed after cessation of prophylaxis [12]. We also found two cases of a first ICH episode that occurred in a patient despite appropriate prophylaxis [9].

Regarding therapy and its impact of the bleeding risk in afibrinogenemia, historically, fresh frozen plasma was used in patients with afibrinogenemia to increase fibrinogen levels. Currently, congenital fibrinogen deficiencies are treated with fibrinogen concentrate, both prophylactically and on demand. In the presented case cryoprecipitate was used for prophylaxis and treatment of bleeds until fibrinogen concentrate became available in Poland. Due to limited resources a low-dose prophylaxis with fibrinogen concentrate was initiated in the present case. Bleeding episodes and surgery were covered with therapeutic doses of fibrinogen concentrate (trough level > 1 g/L). This case highlights the need for access to

appropriate therapy in afibrinogenemia to minimize the morbidity and mortality associated with ICH.

Conclusion

We presented an unusual case of three consecutive intracranial bleeds in an afibrinogenemia patient, with the last episode occurring despite prophylactic fibrinogen substitution, that all resulted in minor neurological sequelae. Of note,neurological outcomes of ICH in afibrinogenemia may be better than in the general population when fibrinogen substitution is administered promptly. ICH is an indication for long-term secondary prophylaxis to decrease the risk of its recurrence.

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