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REVIEW ARTICLE

CONGENITAL FIBRINOGEN DEFICIENCY IN HAEMOPHILLIA: A REVIEW

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Abstract

Afibrinogenemia is a rare blood clotting disorder with an estimated prevalence of 1: 1,000,000. It is an autosomal recessive disease caused by mutations in one of the three genes encoding the three polypeptide chains of fibrinogen located on the long arm of chromosome 4. Spontaneous bleeding, bleeding after minor trauma, and excessive bleeding during interventional procedures are the main symptoms. Replacement therapy is the mainstay of management of bleeding episodes in these patients, with plasma-derived fibrinogen concentrate being the drug of choice. Cryoprecipitate and fresh frozen plasma are alternative treatments that should only be used when fibrinogen concentrate is not available. Secondary preventive treatment can be considered after life-threatening bleeding, but primary preventive treatment is currently not recommended. We also discuss alternative treatment options and management of surgery, pregnancy, and thrombosis in these patients. New tests to identify at-risk patients and the development of safer replacement therapies will improve the treatment of afibrinogenemia in the future.

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Introduction:-

Afibrinogenaemia is an extraordinary bleeding ailment with an envisioned occurrence of 1: 1,000,000 (Acharya, et al., 2004) and it's far an autosomal recessive ailment and maximum sufferers are normally descendent of consanguineous marriages (Acharya, et al., 2004, Mannucci et al., 2004, and Lak et al., 1999). Afibrinogenaemia outcomes from mutations in any of the three

genes (FGA, FGB and FGG) that encode the three polypeptide chains of fibrinogen (Aα, Bβ and γ) and are positioned in a 50 kb vicinity on 4q31.three and those mutations have an effect on the synthesis, assembly, intracellular processing, balance or secretion of fibrinogen. (Asselta et al., 2006). Fibrinogen performs an vital position in clot formation thru its conversion to fibrin via way of means of the motion of thrombin and it's also vital in number one hemostasis because it contributes to platelet aggregation via way of means of binding to glycoprotein IIb/IIIa at the activated platelet surface (Acharya and Dimichele in 2008 and Castaman., 2008). The prognosis of afibrinogenaemia is primarily based totally at the presence of extended prothrombin, thrombin, reptilase and activated partial thromboplastin time, undetectable useful fibrinogen and lack or hint quantities of immunoreactive fibrinogen (Acharya and Dimichele in 2008).

Fibrinogen deficiency can be inherited (congenital) or acquired. Congenital fibrinogen deficiency (CFD) is a rare inherited bleeding disorder characterized by low fibrinogen levels, lack of circulating fibrinogen, or abnormal fibrinogen function. CFD may be associated with fibrinogen dysfunction and defects in synthesis and stability (Obeagu, 2022).

Rabe and Salomon first commented on afibrinogenemia in 1920. A 9-year-old boy was an unusual case of recurrent bleeding episodes due to gastrointestinal hemorrhage shortly after his birthday (Peyvandi et al., 2012). Afibrinogenemia is a congenital bleeding disorder of fibrinogen that, along with other fibrinogen deficiencies, affects the amount of fibrinogen in human blood and is considered a rare disease (Moerloose et al., 2013, De Moerloose et al., 2016, and Snahnicanova et al. ., 2016), ranging from asymptomatic to life-threatening and dangerous bleeding or thromboembolic episodes (Ozdemir 2015 and Simurda et al., 2020) .

Disorders affecting fibrinogen are hereditary or acquired. Congenital fibrinogen disorders are a heterogeneous group of rare inherited blood coagulation disorders (Simurda et al., 2020), which can be divided into type I and type II disorders. Type I diseases (affibrinogenemia and hypofibrinogenemia) affect the amount of fibrinogen in human blood (fibrinogen levels decreased to <1.8 g/l). On the other hand, type II diseases (dysfibrinogenemia and hypodysfibrinogenemia) mainly affect the quality of fibrinogen in human blood. (Simurda et al., 2020, and Moerloose et al., 2013) The Orphanet classification of rare hematologic disorders and the Orphanet classification of rare genetic disorders are afibrinogenemia (ORPHA98880) and congenital hypofibrinogenemia (ORPHA101041). (Tziomalos et al., 2009 and Vakalopoulou et al., 2006).

Acquired fibrinogen deficiency includes decreased fibrinogen production or increased fibrinolysis. This can occur due to a variety of disorders such as disseminated intravascular coagulation surgery, trauma, and placental abruption (Besser et al., 2016).
According to the Factor XIII and Fibrinogen Subcommittee of the ISTH Scientific Standards Committee, congenital quantitative fibrinogen deficiency requires an accurate diagnosis and

classification of patients according to clinical phenotype, not just fibrinogen levels (Simurda et al., 2020, and Casini et al., 2018).

Afibrinogenaemia / hypofibrinogenaemia

Afibrinogenaemic / hypofibrinogenaemic cases determine the worldwide prevalence for these disorders is based on the large amount of genetic data deposited in publicly available databases from approximately 140,000 individuals showed that the worldwide prevalence for recessively inherited fibrinogen disorders could be 10-fold higher than that so-far and it was confirmed that prevalence rates change considerably among populations, going from 1 in 1 million individuals in East Asia, to 24.5 in 1 million people in Europe and that heterozygous individuals could be present in the general population at a frequency of approximately 1 in 100 (Paraboschi et al., 2017).

The largest study based on NGS screening of affected patients appeared in 2019 concerning fibrinogen disorders where a total of 17 Spanish patients suffering from hypofibrinogenaemia or dysfibrinogenaemia) were screened by using a next generation sequencing (NGS) approach based on sequencing the complete FGA, FGB and FGG genes (i.e., also including introns). All patients were associated with one/two mutations, thus underlying the overall good performance of the adopted strategy (Moret et al., 2019).

However, it should be noted that some encouraging examples related to congenital fibrinogen disorders come from the literature where dysfibrinogenaemias are often related to pathogenic variants affecting residues p.Gly17, p.Pro18, p.Arg19, and p.Val20 in the amino-terminal region of the fibrinogen Aα-chain. However, while mutations at residues p.Gly17, p.Pro18, and p.Val20 are exclusively linked to bleeding tendency, the clinical phenotype of patients with mutations at amino acid p.Arg19 can vary from bleeding to thrombotic tendency (Bor et al., 2021).

A final concern is the treatment of recessive coagulopathy, which relies on two fundamental steps:

genetic counseling in consanguineous marriages and at-risk families with members with severe disorders prenatal diagnosis in pediatrics, but these approaches are not trivial. practical implementation (Mannucci et al., 2004).

Pregnant women with a family history, especially those with a consanguineous relationship, should be properly counseled about the risk of having a child with this disorder. If the mutation is known, prenatal analysis could be planned for conditions such as afibrinogenemia, where bleeding after loss of the umbilical stump is common and potentially fatal. I have. bleeding symptoms. However, the problem of prenatal diagnosis of rare bleeding disorders, especially given that most of them are performed with invasive procedures (such as chorionic villus rectification) that can have dramatic consequences for the fetus, It is still being debated (Tabibian et al., 2018).1 g/L is recommended for women with fibrinogen activity (Mumford et al., 2014; Casini et al., 2020).

A Palestinian family with her two affected daughters reported by Neerman-Arbez et al. Tabibian et al., 2018).

Fibrinogen replacement therapy, particularly the most commonly administered concentrated hemocompletan P/riatap, may be used as treatment for spontaneous bleeding events, as prophylaxis before surgery, or for uninduced bleeding in individuals with congenital and acquired fibrinogen deficiency. (Simurda et al., 2020; Levy and Goodnuff, 2015). To assess the extent of the CFD literature on
fibrinogen molecules and available therapies, and the advantages and disadvantages of plasma-derived human fibrinogen concentrate (HFC) as a bleeding disorder, a rare bleeding disorder with a prevalence of approximately 8% prevalence is estimated at 1 million to 1 million (Tziomalos et al., 2009; Tiscia and Margaglione, 2018; Peyvandi, 2013).

CONCLUSION

Congenital afibrinogenemia and hypofibrinogenemia are rare bleeding disorders. Despite recent advances, many questions remain, particularly regarding the correct way to achieve more effective treatment and the establishment of optimal schedules for prophylactic treatment of affected patients.

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