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Fibrinogen Łódź a new cause of dysfibrinogenemia

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A 51-year-old woman was referred for thrombophilia testing due to recurrent thromboembolism. She had three episodes of embolism at the age < 50: to the right brachial artery, to the left external iliac artery and common femoral artery with thromboembolectomy and to the right popliteal artery. She was treated with acenocumarol (target international normalized ratio (INR) 2-3). Due to nontherapeutic INR values, in 2017 she was switched to rivaroxaban 20 mg and aspirin 75 mg per day. The patient had a single short episode of paroxysmal atrial fibrillation however without any abnormalities in repeated electrocardiogram, 24-hour Holter recordings and transthoracic echocardiography. She had four miscarriages and one successful pregnancy. Her son had myocardial infarction at the age of 23 years. At the first clinic visit in August 2018 she was in good medical condition. After switching to enoxaparin, thrombophilia screening was performed and yielded negative results. However, a low fibrinogen concentration by von Clauss assay (1.17 g/L; normal range: 2.1-4.0 g/L) combined with prolonged thrombin time of 22.7 seconds (normal range: 10.3-16.6 seconds) and normal fibrinogen antigen level determined nephelometrically (2.5 g/L; reference range 1.8-3.5 g/L) were found. Thrombotic-related dysfibrinogenemia (3B) according to the new classification by Cassini [1] was diagnosed in January 2019. To confirm it, whole exome sequencing (WES) analysis 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. The presence of variants in the fibrinogen genes was confirmed by Sanger sequencing.

Computer tomography angiography (January 2019) showed large thrombi in several arteries including the ascending aorta despite the use of rivaroxaban and aspirin (Figure 1A-D). The patient was referred to vascular and cardiac surgeons for consultations. In March 2019 while
on rivaroxaban 20 mg per day and aspirin, ischemic stroke with left sided paresis and aphasia occurred due to the right internal carotid artery occlusion. The patient was switched on apixaban (5 mg twice a day) in combination with low-dose aspirin.

The WES analysis identified a novel heterozygous missense mutation in $FGG$ exon 8: c.998 A>G; p.His333Arg (p.His307Arg without the signal peptide) which we named “Fibrinogen Łódź”. This mutation, predicted to be deleterious by SIFT and probably damaging by Polyphen2, affects the same amino acid as "Fibrinogen Mannheim II" [2]

Fibrinogen Łódź is unique due to numerous severe arterial thrombotic manifestations below 50 years of age without any venous thrombosis or bleeding and apparent resistance to rivaroxaban. Such clinical phenotype in patients with dysfibrinogenemia is quite uncommon, although 25% of cases of dysfibrinogenemia are associated with mainly venous thrombosis, for example Fibrinogen Dusart [3]. This case suggests that dysfibrinogenemia should be taken under consideration in subjects with arterial thromboembolism at young age. Establishing a proper diagnosis of dysfibrinogenemia allows the initiation of anticoagulant therapy and genetic counselling in asymptomatic family members like in other thrombophilia’s [4,5].

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References


Figure 1. Computed tomography angiography in a dysfibrinogenemic woman with massive thrombosis in the aorta and its branches. Mural and free-floating thrombus in the ascending aorta (arrow) (A). Thrombi in the left common carotid artery (arrow 1) and aortic arch (arrow 2) (B). Thrombi in the left common carotid artery (arrow 1), aortic arch (arrow 2), aortic arch and descending aorta (arrow 3) and descending aorta (arrow 4-5) (C). Thrombi in the ascending (arrow 1) and descending (arrow 2) aorta (D).