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Rosenthal's Disease (Hemophilia C or factor XI Deficiency) Revealed by Chronic Epistaxis: The First Observation in Sub-Saharan Africa.

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Abstract

Objective

Rosenthal's disease (RD) is a rare constitutional hemorrhagic disorder defined by factor XI deficiency. It is clinically characterized by the presence of minimal haemorrhage. We report the first observation of RD in Togo.

Observation

Mrs. G. A., 45 years old with no particular pathological antecedents, was referred for anemia in a context of chronic epistaxis. It was a spontaneous anterior exteriorization epistaxis often of great abundance, rocking and which evolved episodically. The patient received several transfusions for anemia. The ear-nose-throat examination was normal and a sinus CT scan found only an inflammatory process of the right maxillary sinus. The blood count showed microcytic severe anemia (2,2g/dl). Hemostasis tests showed a prolonged aPTT (57,9 seconds). Clinical examination documented an anemic syndrome with dry skin. Iron deficiency was found. The hemostasis balance confirmed aPTT elongation. Coagulation factors activity showed normal VIII and IX level, but moderate decrease of factor XI (32%). The family survey was not possible (orphan patient). It is recommended the setting under fresh frozen plasma (FFP) in case of a new episode. Follow-up is in progress.

Conclusion

In the event of any hemorrhagic syndrome, the isolated elongation of the aPTT must lead to a systematic analysis of intrinsic pathway factors

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Introduction

Rosenthal's disease (RD) or hemophilia C is a rare constitutional bleeding disorder that, unlike hemophilia A and B, is not related to sex. It is defined by a deficit in Rosenthal factor or factor XI [1]. This variety of hemophilia is clinically characterized by presence of minimal haemorrhage, often caused by trauma or surgery. Factor XI deficiency is exceptional, ubiquitous. Two "outbreaks" defined the molecular abnormalities and associated clinical signs: in Israel, in Ashkenazi population, and in northwestern Great Britain. Two major mutations definning types II and III induce a severe deficit in homozygotes (genotype II / II or III / III) or composite heterozygotes (genotype II / III) between 1 and 4%. Haemorrhagic syndrome then has unusual characters. Haemorrhages usually occur after trauma or in the postoperative period. Their importance depends on the genotype (greater in homozygote II / II), and the tissue involved (interventions on the ENT or urinary tract rich in fibrinolytic activity are particularly haemorrhagic [1]. However authors have reported spontaneous haemorrhages such as hemarthrosis [2] and hematemesis [3]. To our knowledge, in Togo as elsewhere in South Africa Saharan no case of factor XI deficiency has ever been reported. We report then the first case of factor XI deficiency revealed by chronic epistaxis complicated by iron deficiency anemia in a 45-year-old patient followed at Campus teaching hospital of Lomé (Togo).

Observation

Mrs GA 45 years old, of hemoglobin phenotype AA, sixth gesture and sixth parous (G6P6), with 6 deliveries by low void without notion of menorrhagia or post partum haemorrhage, born of a non-consanguineous marriage, orphan of father and mother, was referred from ear-nose-throat (ENT) service on 17th April 2019 for severe anemia (2.2g/dl) in a context of chronic epistaxis and disturbance of the hemostasis balance. The beginning was about 15 months earlier by the occurrence of a spontaneous anterior exteriorization, rocking epistaxis that evolved episodically (one episode every 15 days) on a chronic background. Each bleed was of great abundance, lasted between 10 and 12 hours and was often triggered by fits coughing. Accompanying signs were headache and facial swelling that regressed when bleeding stopped. Several consultations were made at a Regional Center Hospital. The patient had received several transfusions for decompensated anemia. The patient decided to consult in ENT at Campus Teaching Hospital of Lomé. The ENT examination was normal in particular there was no active bleeding, the nasal passages were free. A sinus CT had only found an inflammatory process of the right maxillary sinus. In biological assessment, hemogram found bicytopenia with microcytic (MCV:75,1fl) hypochromic (MCH:18.8pg) argegenative anemia (2,2g/dl) (Reticulocytes at 18000 / mm3) and thrombocytopenia (94000/mm^3), white blood cells were normal at 4300/mm^3, neutrophils normal at 3130 / mm^3 but lymphopenia at 910 / mm^3 were observed. The haemostasis report showed a normal Bleeding time (3mn 30) and Prothrombin index at 87,7% but an a prolonged actived partial thromboplastin time (aPTT) which is corrected by the contribution of normal control plasma.The patient was then referred to hematology. Clinical examination showed: Normal temperature at 37,2°C, weight = 63kg, height = 1.61m, TA = 11/7. The general condition was relatively good. The physical examination founded an anemic syndrome with exertional dyspnea, cutaneo mucous pallor, systolic murmur 3/6 at all foci associated with dry skin. There was no hepatomegaly or splenomegaly, peripheral ganglion areas were free. The study of iron metabolism found iron deficiency with a low serum iron at 2µmol / l (Standards 12 to 28), high transferrin, a low saturation coefficient and ferritinemia collapsed at 5,8µg/l. The search for another chronic bleed outside this chronic epistaxis (gynecological examination, digestive endoscopy, concept of hemorrhoids) was negative. The haemostasis assessment confirms aPTT elongation at 57.9 seconds (control 29 = seconds) which was corrected by the supply of normal control plasma. The assay of factors VIII and IX in Lomé shows normal level of VIII and IX at respectivily 140% and 84%. Fibrinogen was normal at 3.92 g / l. The remainder of the hemostasis assessment carried out at CERBA laboratory in France showed a normal level of factor, V (77%), VII (105%), X(97%), XIII(89%), there was no deficit either in alpha 2 antiplasmin (94%) or in plasminogen activator inhibitor. The only anomaly found was a moderate decrease of factor XI at 32%. The serologies of HIV, hepatitis B were negative, the radiography of the lungs was normal. On the immune

level, no speckled anti-nuclear antibodies, no soluble anti-nuclear antigens, absence of anti-cardioloipin IgG antibodies and rheumatoid factor were negative. A family survey could not be performed (patient orphan). Our most likely hypothesis is Rosenthal's disease causing chronic epistaxis complicated by iron deficiency anemia.

Therapeutically, to treat iron deficiency anemia, we put the patient under ferrous fumarate at a dose of 200 mg per day per day for 30 days then we will continue with100 mg/day for 60 days. For its deficit, we recommended the setting under fresh frozen plasma for 15 to 20ml/kg at the beginning of every epistaxis episode. Follow-up is in progress.

Discussion

Factor XI deficiency was described in 1953 by Rosenthal and al [1]. It is also called hemophilia C or Rosenthal's disease. It is a rare genetic deficit with a prevalence of $1/10^6$, discovered especially in adulthood [2] as the case of our patient. It is found in principle among Jews ashkenases [4] but half of the cases identified were discovered outside this group [5]. It differs from hemophilia A and B in that it doesn't cause joint or muscle bleeds.

Deficiency in factor XI causes a variable haemorrhagic tendency, rarely spontaneous, is manifested especially after trauma or surgical intervention unlike our patient who had spontaneous haemorrhages but with a triggering factor. Bleeding occurs most often in organs where fibrinolytic activity is important: oral and nasal mucosa, urogenital tract [3]. It's often an epistaxis, frequent bruising, heavy or prolonged menstrual bleeding (menorrhagia), excessive bleeding during or after an injury, surgery or childbirth [6]. Our patient had only chronic epistaxis, and no menorrhagia or haemorrhage was reported during her six deliveries. Very recently F Kamoun in Tunisia [3] reported a case of factor XI deficiency revealed by hematemesis.

Haemorrhagic manifestations of RD are often moderate or minor, but sometimes can be severe, requiring blood transfusions. The epistaxis of our patient was complicated by severe anemia (2,2g/dl) for which she was transfused several times before being referred.

The discovery of the iron deficiency of our patient demonstrates the importance and duration of bleeding. These haemorrhagic manifestations are, however, independent of the plasma factor XI level [7]. A severe deficiency (less than 20%) may remain asymptomatic for a long time. There is little correlation between the level of FXI and the severity of hemorrhagic manifestations, and for the same patient bleeding in the same procedure is variable. Among patients with FXI deficiency, 30 to 40% with FXI between 20 and 60% may bleed postoperatively [8]. Our patient had a moderate deficit but had very significant hemorrhagic manifestations as evidenced by the duration of each episode, the usual anemic decompensation and iron deficiency linked to this chronic bleeding. We have not found in the literature decompensated anemia induced by chronic epistaxis during factor XI deficiency in sub-saharan Africa. Our patient is probably the first description. The hypothesis of platelet factor XI compensatory activity has been advanced by some authors, other authors explain this bioclinic discordance by the fact that the usual methods underestimate the procoagulant activity of factor XI, related to its effects on platelet function and fibrinolytic system [2].

Therapeutically, because of scarcity of factor XI deficiency, it is difficult to make recommendations. Some have been proposed, such as those of hemophilia centers in the United Kingdom [9]; few cases (and usually cases of severe deficits) or expert opinion, and in the absence of good quality clinical studies with a sufficient number of observations, these recommendations are low grade. The difficulty is to better assess the risk of bleeding according to the symptomatology and factor levels, and to assess the benefit - risk balance. The fear of haemorrhage during an invasive or obstetric procedure often leads to substituting principle these patients. Unfortunately, this safety attitude can be a source of complications. The substitution of clotting factors exposes to a thrombotic risk, especially in case of over-correction of the deficit; In addition, there are risks related to the administration of blood derivatives, including the theoretical risk of transmission of infectious agents, an important additional cost especially in underdeveloped countries such as Togo and also the possibility of developing an inhibitor. specific directed against the deficient factor. Thus, as in haemophilia A and B, Blanchard and al [10] had advocated purified factor XI concentrates. However, the authors [8] have advocated factor substitution

products. In fact, the contribution of the deficit factor can be made either by factor concentrates (of recombinant origin or plasma derivatives) or by fresh frozen plasma (FFP), or even in some countries by cryoprecipitates for deficits mainly fibrinogen. The use of FFP, in addition to its own risks, exposes the risk of vascular overload given the large volumes needed to correct the plasma levels of a deficit factor. We proposed FPP to our patient because it is the only therapeutic alternative given because of our technical platform. We will, however, conduct rigorous surveillance during potential administrations and maintain a continuous follow-up of our patient.

Conclusion

Rosenthal's disease or factor XI deficiency (hemophilia C), a rare constitutional haemorrhagic disorder, becomes a reality in Togo and in sub-saharan Africa. In the event of any hemorrhagic syndrome, the isolated elongation of aPTT, which is corrected by the supply of normal control plasma, will have to systematically measure all the factors of the intrinsic pathway. This deficit imposes adequate preventive measures in order to avoid the occurrence of serious haemorrhagic accidents.

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