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Women with Low Rate Hemophilia a Carrier or Severe von Willebrand Disease: How Facing Up in Low-Income Countries?

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Abstract

Introduction: In resource-limited regions, comprehensive care for congenital bleeding disorders remains deficient due to constraints such as limited resources and inadequate healthcare infrastructure. As a result, a substantial number of affected individuals remain undiagnosed. **Aim:** This study underscores the pressing requirement for enhancing healthcare infrastructure, diagnostic capabilities, and healthcare professional training in these areas. The World Federation of Hemophilia has initiated humanitarian aid initiatives in economically disadvantaged nations to improve the care of patients with rare bleeding disorders. **Methods:** Collaborating with select French-speaking African countries, the African French Alliance for the Treatment of Hemophilia conducts missions involving specialized French teams partnering with local healthcare providers to identify patients and deliver optimized care, training, and essential diagnostic tools. **Results:** This study presents two cases from Guinea Conakry featuring patients grappling with substantial bleeding problems. Limited diagnostic capabilities posed challenges in distinguishing between hemophilia carriers with low factorVIII levels and severe von Willebrand disease. These cases underscore the necessity for accurate diagnosis and specialized testing accessibility, particularly for women with bleeding disorders. The study displays the feasibility of transporting plasma samples for von Willebrand factor testing in resource-constrained settings, assisting clinicians in therapeutic decision-making. Furthermore, a novel mutation in the von Willebrand factor gene was identified, warranting further investigation. **Conclusion:** While humanitarian aid programs make strides in enhancing care for congenital bleeding disorders in developing nations, considerable challenges persist. This study provides interim solutions for diagnosis and care in scenarios where local resources fall short, emphasizing the ongoing imperative to strengthen healthcare infrastructure and diagnostic accessibility.

Keywords: Low-Income Countries; Hemophilia A Carrier; Von Willebrand Disease; Women with Bleeding Disorders; Diagnostic Challenges; Therapeutic Decision-Making.

Introduction

In developing nations, less than 25 % of patients with congenital bleeding disorders have access to a specific care from diagnosis to treatment [1]. These challenges can be attributed to factors including financial constraints, government commitments, local beliefs, healthcare priorities, and inadequate healthcare infrastructure. As a result, expected number of patients with hemophilia all over the world has been estimated at up to 1 200 000 while less than 420,000 males have been diagnosed so far [2]. Although more than 80 % of patients are properly diagnosed for hemophilia in Europe, less than 8% are diagnosed in Africa, and likely fewer in Sub-Saharan countries compared to North Africa [3]. The estimated global number of hemophilia patients exceeds the number of diagnosed cases. This disparity is particularly pronounced in the case of von Willebrand disease (VWD). The prevalence of these disorders is higher in high-income regions like Europe and North America compared to low and middle-income countries, where diagnosis rates are much lower. A recent study from the World Federation of Hemophilia (WFH) registry has showed that the mean prevalence of all type of VWD in worldwide was about 25, 6 per millions people [4-5]. In high income countries as Europa or North America, the mean prevalence increase until 60, 3 per million whereas this prevalence drastically decrease to only 2,5 and 1,1 per million people in middle-low and low income countries respectively. Some cases were described in some countries as Cameroon, Zimbabwe or Nigerian with few data [6- 8]. The lack of comprehensive data on the prevalence and diagnosis of these disorders in many developing countries hinders our understanding of the extent of the problem and the design of effective interventions.

One major barrier to proper care is the lack of diagnostic hemostasis laboratories, leading to the absence of appropriate diagnostic tools. The biologic heterogeneity and variable presentation of these disorders, particularly von Willebrand disease, make accurate diagnosis difficult [9]. Even in high- income countries, diagnostic errors can occur due to the complexity of testing. Routine coagulation assays, like Factor VIII (FVIII) or Factor IX (FIX) activities for hemophilia, are challenging to perform in low-income country laboratories due to a lack of reagents, specialized equipment, and trained personnel [10]. The situation is even more complex for von Willebrand disease diagnosis, as the required tests are even less accessible in these areas.

Another issue is the diagnosis of women with a bleeding disorder in these developing countries. Several factors have a negative impact on the diagnosis of these women, such as certain mystical beliefs related to genetic diseases, their social status in some of these societies, or even the feeling of family shame. Very few data in the literature are available regarding the prevalence of women carriers of hemophilia or affected by bleeding disorders [11].

This emphasizes the urgent need for improved healthcare infrastructure, increased access to diagnostic facilities, and specialized training for healthcare professionals in developing countries.

AFATH organization and Guinea Conakry experiences

For several years now, the WFH has been offering a humanitarian aid program to countries with limited economic resources, aiming to enhance the care of their patients affected by rare bleeding disorders such as hemophilia or von Willebrand diseases [12]. This includes facilitating access to expensive treatments for some of these countries through donations, enabling the management of bleeding incidents, and enabling the establishment of prophylactic regimens for the most severe patients using coagulation factor concentrates and non-replacement therapies [13].

However, accessing the WFH assistance program requires prior identification of the number of patients affected by rare bleeding disorders and in need of care, with a comprehensive and regularly updated registry. To address this, the African French Alliance for the Treatment of Hemophilia (AFATH) has formed partnerships between France and select French-speaking African countries, conducting routine humanitarian missions [14]. This involves the deployment of specialized French teams in these countries to manage these bleeding disorders, consisting of doctors, biologists, physiotherapists, nurses, and voluntary members of the French Hemophilia Association (AFH). Through close collaboration with local teams, these various missions ensure optimized care for patients, provide training, and offer necessary tools, including main coagulation tests.

Between February 2022 and April 2023, three 7-day missions were carried out in Guinea Conakry, facilitating the identification of nearly 60 individuals affected by rare bleeding disorders. Among them, over twenty have been able to initiate a regular prophylactic regimen on a weekly basis through the WFH donation program. One of the critical stages involved the implementation of biological hemostasis tests, supported by specific materials, reagents, and the training of Guinean laboratory staff. Although routine testing is now feasible, including prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen, as well as measuring FVIII and FIX activity, along with inhibitor detection, local exploration of primary hemostasis such as analysis of the von Willebrand factor remains unattainable. However, certain clinical scenarios necessitate making this distinction due to the profound impact on potentially life-critical therapeutic decisions. This notably pertains to the issue of women with a severe bleeding phenotype.

Women with bleeding disorders and low rate of FVIII activity: a real life dilemma.

To provide context, here are two cases of patients managed during the missions carried out in Guinea Conakry. Blood was drawn in Vacuette tubes (Greiner bio-one) containing 0.109 M sodium citrate (1 volume trisodium citrate to 9 volumes blood) and centrifuged (10 min at Cell2250 g) to obtain platelet- poor plasma used for initial haemostasis tests. The excess PPP was centrifuged twice and frozen immediately (-30°C). Cell pellets to collect the Buffy Coat for DNA extraction were kept at +4°C before air travel. All initial laboratory tests PT, APTT, Clauss fibrinogen assay, FVIII and FIX one stage assay were performed in Ignace Deen hospital (Conakry, Guinea) on a semi-automated coagulometer (START-4, Diagnostica Stago) with reagents kindly provided by Diagnostica Stago. Von Willebrand factor antigen and activity were run on ACLTOP (Werfen) in Necker Hospital (Paris, France) with VWF Ag (Siemens Healthineers) and von Willebrand Factor Ristocetin Cofactor Activity® (VWF:GPIbR,

Werfen)) respectively. After DNA extraction and library preparation with Twist chemistry, analysis of F8 and VWF genes were performed using Next Generation Sequencing on Novaseq 6000 sequencer (Illumina). The identification of intron 22 inversion in the F8 gene was performed using Inverse Shifting PCR [15].

Firstly, the case of a 2-year-old girl who has been experiencing frequent externalized bleeding episodes since birth. In her family history, there is a mention of a paternal aunt who passed away due to a significant hemorrhage. No known consanguinity between the parents. She has a 3-year-old sister with no particular health issues. The bleeding symptoms primarily appear to be superficial, with frequent instances of nosebleeds, gum bleeding, and skin bruises. As she started walking, she also developed a painful swelling around her right knee, which resolved spontaneously. Initial laboratory tests showed a PT expressed in percentage of 90%, a prolonged APTT of 43.8 seconds, with FVIII activity measured at 5 IU/dL and FIX at 50 IU/dL and normal fibrinogen concentration (3.4 g/L). The absence of an exploration of primary hemostasis hindered the objective differentiation between a carrier of hemophilia A with low levels and a severe von Willebrand disease.

The second case involves a 14-year-old young woman who has been experiencing severe bleeding symptoms since birth. There are no known family antecedents, and her older sister does not present any specific symptoms. Regarding bleeding, she reports spontaneous occurrences of nosebleeds, gum bleeding, and non-traumatic bruises several times a month. She also experiences almost continuous and heavy menstrual periods, accompanied by signs of iron deficiency. Additionally, she has been experiencing pain in her right knee for several months, causing functional impairment. Clinical examination reveals a slightly inflammatory swelling around the right quadriceps recessus. A simultaneous joint ultrasound assessment confirms the presence of a moderately joint effusion with moderate synovial hypertrophy and a positive Doppler signal. Initial laboratory tests revealed a PT of 85%, a prolonged APTT of 52 seconds, with FVIII activity measured at 2 UI/dL and normal FIX level (50 UI/dL) and fibrinogen concentration (2.4 g/L). At this stage, similar to the previous clinical case, there is no possibility of distinguishing between a carrier of hemophilia A with low levels and severe von Willebrand disease.

After the confirmation of these results during successive missions, unfortunately, no specific management could be established for these two patients due to the absence of a formal diagnosis. After obtaining informed and signed consent from their parents, two additional samples were taken from these patients. PPP and cells pellets were transported in a refrigerated box to France. Residual PPP from 10 consenting patients diagnosed with Haemophilia A were transported in the same conditions as a control. PPP was tested as soon as possible at Necker Hospital Hemostasis Laboratory in Paris for measuring von Willebrand factor antigen and activity, while cell pellets were sent to the laboratory of the university hospital center in Lille, the national coordinating center for von Willebrand disease in France, for genetic analysis of the F8 and VWF genes. Von Willebrand factor levels from controls were in the normal expected values, i.e. 114 ±45 UI/dL and 100.3 ±40 for antigen and ristocetin cofactor activity respectively, with activity/antigen ratio of 0.89±0.13.

For the 2-year-old girl, the results confirmed severe von Willebrand disease with an antigen level measured at 16 UI/dL, ristocetin cofactor activity below 10 UI/dL (lower limit of quantification for the method), and the detection in a homozygous state of the missense variation c.1108T>C , p.(Cys370Arg) in exon 9 of the VWF gene (D1 domain of the propeptide). This von Willebrand factor variant had never been described in international databases for von Willebrand disease but was considered as probably pathogenic and explaining measured von Willebrand factor levels. As for the 14-year-old young

Woman, ristocetin cofactor activity and von Willebrand factor antigen levels were found to be above 100 IU/dL. No mutations in the VWF gene were found, but a distal inversion of intron 22 of the F8 gene in heterozygous state was identified confirming the diagnosis of severe hemophilia a carrier with low levels of FVIII due to probably extreme lyonization.

These results enabled the adjustment of treatment requests to the WFH and facilitated discussions about initiating prophylaxis using FVIII concentrates for the young woman with a severe bleeding phenotype

Discussion

These two concrete clinical cases effectively illustrate the

complexity of managing congenital bleeding disorders in developing countries, particularly in women. However, humanitarian aid programs should be emphasized, and certain unconventional measures can even be implemented to sustain support for these particularly disadvantaged populations. We have demonstrated that it is possible to transport plasma samples in unfrozen conditions, (by plane and car) and obtain an informative measurement of von Willebrand factor, whether it is the antigen or ristocetin cofactor activity. Of course, this should not be considered as a rule and should in no way replace the standards and measures that have been in place for many years to ensure the quality of von Willebrand factor assay results [16]. However, in certain situations where von Willebrand factor measurement is not feasible locally, this can provide valuable assistance to clinicians in determining appropriate treatments, especially when immediate therapeutic decisions may be critical to a patient's prognosis. This should not, of course, delay the possibility of establishing biological laboratories in these developing countries, including appropriate equipment, local team training, and the ability to perform all of these tests on-site. To further substantiate this approach, we implemented it during our last mission with three individuals, two girls and a boy from the same family, all presenting with a hemorrhagic syndrome of hematological origin. The 8-year-old boy exhibited superficial and deep bleedings, with multiple hemarthroses of the right ankle documented by the presence of synovitis on ultrasound. His on-site FVIII activity test showed a level of 3.1 IU/dL, leading to a diagnosis of moderate hemophilia with a severe clinical phenotype. One of his sisters, aged 11, displayed similar symptoms with a FVIII activity found at 4 IU/dL, with an initial diagnosis of being a low-level carrier of Hemophilia A. Meanwhile, the other sister, aged 22, showed no symptoms of deep bleeding but had heavy menstrual periods and a FVIII activity of 31 IU/dL. Conducting the von Willebrand factor assay at Necker Hospital allowed for a corrected diagnosis with both antigen and ristocetin activity below 6 IU/dL and 10 IU/dL respectively (lower limits of quantification for the methods) for the boy and the 11-year-old girl, confirming severe von Willebrand disease. The 22-year-old woman had an antigen and ristocetin activity of 41 and 32 IU/dL respectively, confirming the diagnosis of moderate von Willebrand disease. The treatment request was therefore adjusted, and a prophylaxis with Willebrand factor concentrates was put in place."

Another important aspect of this experience is the identification of a new variant in VWF gene within the propeptide domain of von Willebrand factor. Currently, it is impossible to perform additional tests to identify the type of von Willebrand disease and the functional impact of this mutation. A more in-depth family investigation is also underway, involving new blood samples to screen for heterozygous individuals or those with a moderate bleeding phenotype.

Conclusion

Several humanitarian aid programs are currently being deployed worldwide, providing care for patients with congenital bleeding disorders in developing countries. However, in the field, many challenges persist, which healthcare professionals must individually address. This feedback provides the opportunity to offer a temporary solution, enabling diagnostic elements and care in complex situations where local resources are unable to meet the demand.

Authorship

MD, DL, and LF contributed to the conception of the work.

MD, AS, ID, EH, NAG, TS, MM, NG, DL, and LF contributed to the acquisition of data; AS, ID, EJ, SS, CZ, JG, and DL contributed to the analysis of data for the work.

MM, AS, ID, EJ, SS, CZ, JG, DL, and LF contributed to the interpretation of data for the work. All authors contributed to drafting the work and to the final approval of the version.

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