Original Article

Awareness and Perspectives of Non-Haematologist in the Management of Acquired Haemophilia in Arab Gulf Countries

Ahmed F Mady, Basim Huwait, Muhammad Asim Rana, Omar E. Ramadan, Abulrahman Al-Harthy, Waleed T Alatribi, Mohamed A Alodat, Hossam A Saad and Abdulkareem Almomen

Objective: To assess the awareness around AH among healthcare professionals in the Gulf region to whom patients with this serious disorder are likely to initially present and possibly receive initial life saving treatment measures.

Methods: A survey was carried out in May 2013 among non-hematologist health care professionals in 10 Arabian Gulf tertiary medical care centres to assess the degree of awareness regarding AH diagnosis and management and to identify the difficulties they face during initial management of such cases.

Results: The total number of responders to our survey was 1104, 953 of them were physicians, 57 laboratory staff physicians, and 94 pharmacists. Out of all physicians who responded, 42% were not aware of AH, 45% would not consider mixing test for isolated prolonged aPTT and 47% of them would start bypassing agents in bleeding AH, but only 26% would use inhibitor eradication immediately upon confirmation. Almost half of the clinicians showed the hematologist's response in more than 24 hrs. The majority of clinicians, lab and pharmacists agreed that the lack of awareness about AH, and its complications, is the most important obstacle to achieving optimal management. Despite the shortage of hematologists in the Arab Gulf countries, 46 of them did not believe in empowering other health care professionals to start bypassing agents and inhibitor eradications in such fatal disorders although they agreed with the need of increasing the awareness among non hematologist health care workers

Conclusions: There is a general lack of awareness of Acquired Hemophilia in all non-hematology specialized Healthcare providers in the Gulf region. Specific areas for improved awareness were identified for different specialties. Some health care system areas for improvement could be identified as well. There is still an unmet need to assess the current management practices of the condition in the region to be able to formulate recommendations to optimize practices based on local experience and available resources.

Keywords: acquired haemophilia, aPTT, recombinant factor VII, Mixing Studies, coagulopathy.

Introduction

Acquired hemophilia (AH) is a rare but potentially life-threatening hemorrhagic disorder, requiring intensive care management.[1] The disorder is caused by the development of inhibitory autoantibodies against the coagulation factor VIII (FVIII).[2] The clinical presentation may vary from mild to life-threatening bleeds.[3] The majority of patients present with hemorrhage in the skin, muscles, or soft tissues and mucous membranes. Hemarthrosis, which is typical of congenital hemophilia, is rarely seen.[4] Prolonged postpartum bleeding and excessive bleeding following trauma or surgery are other serious manifestations.[5]

The diagnosis of AH is often difficult because the patients do not have a personal or family history of bleeding episodes.[5] Usually these patients are seen by several specialists, and are subjected to various investigations, including potentially serious interventions, before the correct diagnosis is made.[4] Though there are approved clinical and laboratory findings that should raise suspicions for a diagnosis of AH,[1] definite diagnosis of AH in a patient with no previous personal or family history of bleeding is based on a single prolongation of the activated partial thromboplastin time (APTT) which is not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study) along with decreased FVIII levels, to provide evidence of FVIII inhibition quantified by the Bethesda assay.[4]

Thus, it is clear that the diagnosis and management of AH is complex. Moreover, it is difficult to draw any firm conclusions about the epidemiology, clinical aspects, and therapy of this disease from the

Because most of the reports are anecdotal and include only a few cases.

The incidence of AH has been estimated to be 0.2-1.48 million per year,[2] but this figure may be an underestimate given the difficulty in making a diagnosis. Moreover, many of the low titer inhibitors may be unrecognized unless patients undergo surgery or trauma. The peak age of disease manifestation is 60-80 years,[4] with another peak for the higher preponderance in women between 20-30 years of age because of its association with pregnancy.[5] Various autoimmune disorders, malignancies, pregnancy, drugs hypersensitivity and infections are the most commonly associated co-morbidities.[2]

Patients with AH have a high mortality rate of 922%, with most of the deaths occurring within the first few weeks after presentation.[4] These deaths have been frequently attributed to delays in diagnosis and appropriate treatment.[1] The treatment of AH is a sequential process aimed at controlling both active and recurrent bleeding.[1] The clinical phenotype does not correlate with FVIII level or inhibitor titer, and patients remain at risk of spontaneous, life-threatening bleeding until the inhibitor has been eradicated.[6]

Correction of FVIII can be achieved by plasma-derived, recombinant FVIII concentrate or deamino-delta-D-argenine vasopressin (DDAVP), in patients with persistently low inhibitor titers (<5 BU/mL) or presenting with minor bleeds.[5] In patients with high titer (>10 BU/mL) or presenting with life-threatening bleeding, bypassing therapy using recombinant Activated Factor seven (rFVIIa-NovoSeven) or Factor Eight Inhibitor By passing Agent (FEIBA) is effectively applied.[7] For the purpose of inhibitor eradication, modalities like plasmapheresis, immune-suppressive medications (e.g. rituximab and corticosteroid) or immunoadsorption are now commonly used.[3] The optimal therapy is controversial and available data are derived from observational and retrospective studies, including a limited number of patients with different primary clinical conditions.[7] To avoid AH's high morbidity and mortality, diagnosis is a prerequisite to initiate definitive therapy. The diagnosis however is delayed because of its rarity and general lack of awareness about the disease.[8] Optimal management of AH can be ensured by the combined participation of non-hematologist physicians, pharmacists and laboratory staff with hematologists.

Methods

This was carried out in two phases. In first phase, a cross-sectional survey was carried out in May 2013 among non-hematologist health care professionals including clinicians, clinical pharmacists and laboratory staff in 10 Arabian Gulf tertiary medical care centres to assess the degree of awareness regarding AH diagnosis and management, and to address the difficulties they could face during the management of such cases. The survey was sent out by email to an assigned person in each department who distributed and collected the survey forms. Also, the survey was distributed directly to the target population during awareness sessions of AH performed in different Arabian Gulf countries. During those meetings, we had the chance to get the opinion of hematologists about improving awareness among non-hematologists and avoiding complications of such a rare and lethal disease. Data collection was closed in April 2015. In December 2013, the second phase of our work commenced. We established a network of health care workers among all Gulf countries to promote our mission. This network had been named Acquired Hemophilia Network (AHN). Board members were designated representatives from 6 Gulf countries and included hematologists, pathologists and other healthcare specialists involved in the treatment and management of patients with AH. A case report form (CRF) was prepared and posted on the AHN website to collect and document cases of AH in Gulf countries.

The questionnaire was developed in three forms: for clinicians, pharmacists and lab physicians. Each form consisted of three sections. The first and third sections were the same for the three groups of respondents, but the second section was group specific. Section one measured the interest of physicians, lab staff and pharmacists regarding AH and their appreciation of the importance and severity of AH. Section three highlighted the most important obstacles in achieving optimal diagnosis and treatment of AH from the participants' perspective. The second section was

specifically tailored for each group. For clinicians, it measured their clinical experience regarding management of such cases, and measured the response of hematologist and checked the availability of resources. For lab staff, it was designed to assess the level of collaboration between lab staff and treating physicians, and throw light on the availability of necessary resources. For pharmacists, it assessed their awareness about the management of AH, and

Results

Out of 1104 respondents to this survey, 953 (86%) were physicians, 57 (5%) were laboratory staff physicians, while 94 (9%) were pharmacists. The respondents represented 6 Arabian Gulf Countries: Saudi Arabia 803 (73%), United Arab of Emirates 76 (7%), Kuwait 66 (6%), Qatar 73 (7%), Bahrain 37 (3%) and 49 (4%) from Oman. All responders are working in Central Hospitals with the median bed capacity of 350 beds (200-1200 beds). General characteristics of responders are present in **table-1.**

Table-1: General characteristic of the responders (n = 1104).

Subspecialty of responded physicians	%(n)
Intensivist	21.4 (203)
Medical	14.9 (128)
Oby/gyn	13.4 (128)
General surgeon	12.1 (115)
Not Mentioned	10.7 (102)
Orthopaedics	4.6 (44)
Emergency Dep.,	3.2 (30)
Neuro Surgeon	3.2 (31)
Nephro	2.6 (25)
Anaesthesia	2.3 (22)
Urologist	2.1 (20)
Titles of responders	
Consultants	8.3 (79)
Registrar	23.3 (221)
Residents	16.1 (153)
Intern	6.3 (61)
NA	46.5 (442)
Clinical Pharmacist	33 (31)
Pharmacist	67(63)
Lab Physicians	100 (57)

Only 30.9% of responding physicians, 8.7% of laboratory physicians and 25.6% of pharmacists were involved in management of AH cases. 42.5% (405) of responding physicians did not know that AH should be suspected in cases with unexplained isolated prolonged aPTT and about half of physicians 53.2% (507) would consider mixing test in such cases, however 51.3% (48) of laboratory staff physicians would suggest a mixing test for cases presented with unexplained isolated prolonged aPTT. However 62.7% (59) of reporting pharmacists know that bypassing agents are crucial in the management of bleeding in AH, about two third of them 67 % (63) are not aware of the ideal dosing of by-passing agents in AH. 43.2% (412) of the clinicians indicated that their hematologist response time was more than 24 hours while 30.3% (289) reported that haematologists responded within 24 hours **(Fig-1).**

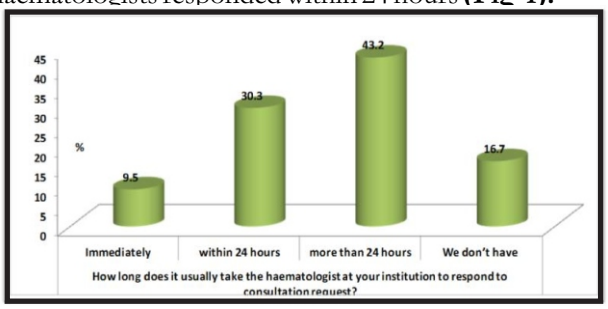

Fig-1: How long does it take the hematologist in your instituation to respond.

Upon confirmation of AH in severely bleeding patients, 42.6% of clinicians would start giving by-passing agents to stop the bleeding, while others will continue conventional resuscitation and wait for hematologists. Although the responding non-hematologist clinicians are not empowered in their centres to prescribe inhibitor eradications, 26.7% of them would consider corticosteroids as inhibitor eradications once confirmed for AH. The majority of physicians, laboratory staff and pharmacists (55.2%, 39.4%, 34.5%) are agreed that lack of awareness about the disorder and its complications is the main barrier in achieving the optimal management of AH

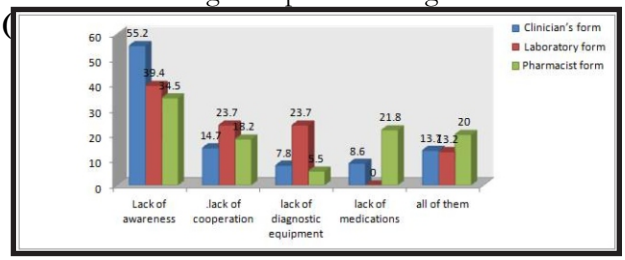

Fig-2: In your opinion what is the most important obstacle (s) in achieving optimal management of AH?

42 of responding hematologists (92%) believed that they have an important role in improving the

rare but fatal disorder. Despite lacking of hematologists in Arab Gulf Countries, only 27% of them allowed non-hematologists to start by-passing agents in severe bleeding of AH, but 92% of them refused to empower non-hematologists. (The questionnaire is available on request.)

Results

Out of 1104 respondents to this survey, 953 (86%) were physicians, 57 (5%) were laboratory staff physicians, while 94 (9%) were pharmacists. The respondents represented 6 Arabian Gulf Countries: Saudi Arabia 803 (73%), United Arab of Emirates 76 (7%), Kuwait 66 (6%), Qatar 73 (7%), Bahrain 37 (3%) and 49 (4%) from Oman. All responders are working in Central Hospitals with the median bed capacity of 350 beds (200-1200 beds). General characteristics of responders are present in **table-1.**

Only 30.9% of responding physicians, 8.7% of laboratory physicians and 25.6% of pharmacists were involved in management of AH cases. 42.5% (405) of responding physicians did not know that AH should be suspected in cases with unexplained isolated prolonged aPTT and about half of physicians 53.2% (507) would consider mixing test in such cases, however 51.3% (48) of laboratory staff physicians would suggest a mixing test for cases presented with unexplained isolated prolonged aPTT. However 62.7% (59) of reporting pharmacists know that bypassing agents are crucial in the management of bleeding in AH, about two third of them 67 % (63) are not aware of the ideal dosing of by-passing agents in AH. 43.2% (412) of the clinicians indicated that their hematologist response time was more than 24 hours while 30.3% (289) reported that haematologists responded within 24 hours **(Fig-1).**

Upon confirmation of AH in severely bleeding patients, 42.6% of clinicians would start giving by-passing agents to stop the bleeding, while others will continue conventional resuscitation and wait for hematologists. Although the responding non-hematologist clinicians are not empowered in their centres to prescribe inhibitor eradications, 26.7% of them would consider corticosteroids as inhibitor eradications once confirmed for AH. The majority of physicians, laboratory staff and pharmacists (55.2%, 39.4%, 34.5%) are agreed that lack of awareness about the disorder and its complications is the main barrier in achieving the optimal management of AH **(Fig-2)**

42 of responding hematologists (92%) believed that they have an important role in improving the awareness among non-hematologists about such a rare but fatal disorder. Despite lacking of hematologists in Arab Gulf Countries, only 27% of them allowed non-hematologists to start by-passing agents in severe bleeding of AH, but 92% of them refused to empower non-hematologists.

Discussion

Acquired hemophilia (AH) is a rare immune-mediated disorder, characterized by the development of autoantibodies against coagulation FVIII.[9] Patients with autoantibodies to coagulation FVIII may present initially to physicians in different specialties, who may not have experience with this rare disorder.[3] As reported in our survey result, 42% of responding physicians were not even aware of AH. Collaborative team work is essential by clinicians, laboratory workers, and a hematologist center experienced in the management of AH, because of its high mortality rate and variable presentation.[10] Any acute or recent onset of bleeding symptoms (especially a soft tissue bleed or bleeding following an invasive procedure) in a patient with no previous history of bleeding, especially in elderly or post-partum patients should raise a suspicion of AH.[3] Immediate referral to a hemotologist experienced in the management of inhibitors is essential to ensure accurate diagnosis and appropriate treatment. If consultation with or transfer to a hemophilia center is not immediately possible then investigation and treatment should be initiated.[6] Prolonged activated partial thromboplastin time with normal prothrombin time is typical of AH, and the diagnosis should be considered even in the absence of bleeding.[6] A useful diagnostic algorithm including coagulation and mixing studies, a thrombin time assay to rule out a heparin effect, and a Bethesda assay for specific detection of FVIII antibody should be followed for the appropriate diagnosis.[6]

A prolonged aPTT may be attributable to coagulation factor deficiencies, lupus anticoagulant or heparin therapy. Mixing tests are performed to distinguish between factor deficiency and the presence of an inhibitory substance. In these studies patient plasma is mixed with pooled normal plasma in a ratio of 1:1. If the patient has an inhibitor to FVIII, the aPTT will remain prolonged.[11] In our survey, 45% of physicians didn't consider the mixing test for isolated prolonged aPTT. It shows a dire need to increase awareness among physicians about the diagnosis and treatment

laboratory staff had sufficient knowledge regarding the importance of the mixing test for patients with isolated prolonged aPTT. This result again emphasizes the importance of collaborative team work consisting of physicians, laboratory staff and hematologists. If mixing tests are compatible with an inhibitor, or the clinical picture is suggestive of AH, the sample should be urgently referred to a specialized hemostasis laboratory for further investigation by the Bethesda assay to measure the strength of the FVIII inhibitor.[12] The usefulness of Bethesda titers is established in making treatment decisions and evaluation of therapeutic success.[9] Whereas, our survey indicated that 94% of our laboratories didn't carry the facility to measure inhibitor titre.

Collins and Baudo have suggested **t**hat physicians managing a patient with suspected or confirmed acquired hemophilia, with or without bleeding, should consult a hemophilia center with expertise in managing inhibitors as soon as possible.[6] Because of the lack of sufficient resources, immediate referral is not possible in many cases. In our survey, half of the clinicians reported that approach to a hematologist required more than 24 hrs. The principles of treating AH are to control bleeding, avoid procedures that may induce bleeding, initiate immunosuppression to eradicate the inhibitor and treat any underlying disease.[13] First-line treatment of bleeding in AH is with a bypassing agent like recombinant factor VIIa (rFVIIa-Novo Seven) and the activated prothrombin complex concentrate (aPCC-FEIBA).[14]. Our survey showed that 42% physicians were in favor of starting bypass therapy immediately in case of bleeding. However, the treating physician should be experienced in the use of these products or should transfer the patient to a center where this facility is available.[6] The risk of fatal bleeding continues until the FVIII antibody has been eradicated, therefore immunosuppression should be started in all patients as soon as the diagnosis has been made.[13] The incidence of potentially fatal bleeding in AH patients is high, ranging between 22% to 31%.[15] Fatal bleeding can occur up to five months after the first presentation, if the auto antibodies are not eliminated, and morbidity related to bleeding remains high.[7] Our survey result showed that half of the responding physicians didn't consider bypassing agents as crucial in the management of bleeding in AH patients. Moreover, 2/3 of them were not even aware about the ideal dosing of bypassing agents in AH. Therefore, involvement of a hematologic specialist for immediate and follow-up care is highly recommended. Diagnostic and treatment guidelines of AH should be continually reevaluated based on clinical evidence of successful management and treatment.[9]

Hence physicians should make prompt diagnosis, consult experienced hematologist,immediately send lab samples, and bypassing agents to control bleeding should be used promptly majority of clinicians, laboratory personnel and pharmacists agreed that the lack of awareness about the disorder and its complications is the most important obstacle in achieving the optimal management of AH. Hematology colleagues should direct their efforts to raise awareness of this disorder among physicians and provide guidance on how to diagnose and treat AH. Also, 20% of our survey responders also emphasized that lack of awareness, ,lack of diagnostic facilities and therapeutic agents are hindering achieving optimal management. Therefore, non-hematologist colleagues should facilitate early diagnosis by ensuring availability of clotting factor measurement, quantification of the inhibitor titre and mixing tests. Samples should be rushed to a specialist lab, if the institute's lab is not equipped.. Another important point raised in our survey but still questionable is despite lack of hematologists in high centers in Arab Gulf countries, the majority of them didn't accept non-hematologist physicians to either go through bypassing agents to stop sever bleeding or to start inhibitor eradication once diagnosis confirmed..We suggest the establishment of centers of excellence with the expertise in management of AH We established a network of health care workers among all Gulf countries to continue our mission. This network has been named "Acquired Hemophilia Network (AHN)". Board members were designated representing 6 Gulf countries including hematologists, clinical-pathologists and other healthcare specialists involved in the diagnosis and management of patients with AH. A case report form (CRF) was prepared and posted on AHN website to collect and document the cases of AH. Previous studies have also suggested establishment of such centers. The intention behind these recommendations is to increase the awareness of this disorder among health care professionals to whom AH patients are likely to present, and to empower them to contribute actively in the management of such a fatal disease.

Hreatening hemorrhagic disorder, requiring intensive care management. There is a general lack of awareness about the condition in all non-hematology specialized healthcare providers in the Gulf region. Specific areas of need to improve awareness were identified for different specialties. Additionally some health care system areas could be identified for improvement. There is still an unmet need to assess the current management p ractices of the condition in the region to be able to formulate recommendations to optimize practices based on local experience and available resources.

Department of General Suergery
Gulab Devi Hospital , Lahore
www.esculapio.pk

References

1. Shander A, Walsh CE, Cromwell C. Acquired hemophilia: a rare but life-threatening potential cause of bleeding in the intensive care unit. Intensive care medicine.2011; 37(8):1240-9.
2. Rezaieyazdi Z, Sharifi-Doloui D, Hashemzadeh K, Shirdel A, Mansouritorghabeh H. Acquired haemophilia A in a woman with autoimmune hepatitis and systemic lupus erythematosus: review of literature. Blood coagulation & fibrinolysis.2012;22(8):738-41.
3. Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. haematologica. 2009;94(4):566-75.
4. Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: a concise review. American journal of hematology. 2005;80(1):55-63.
5. Zaher G, Adam S. Successful Long Term Eradication of Factor VIII Inhibitor in Patients with Acquired Haemophilia A in Saudi Arabia. Mediterranean journal of hematology and infectious diseases.2012; 4(1).
6. Collins P, Baudo F, Huth-KÃ¼hne A, Ingerslev Jr, Kessler CM, Castellano MEM, et al. Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. BMC research notes.2010; 3(1):161.
7. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood. 2007;109(5):1870-7.
8. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired Haemophilia: Review and Meta-Analysis Focused on Therapy and Prognostic Factors. British Journal of Haematology. 2003;121(1):21-35.
9. Sborov DW, Rodgers GM. Acquired hemophilia A: a current review of autoantibody disease. Clin Adv Hematol Oncol.2012; 10(1):19-27.
10. Ma AD, Carrizosa D. Acquired factor VIII inhibitors: pathophysiology and treatment. ASH Education Program Book.Hematology. 2006;2006(1):432-7.
11. Kasper CK. Laboratory tests for Factor-VIII inhibitors, their variation, significance and interpretation. Blood coagulation & fibrinolysis. 2004 ;2:7-10.
12. Giles AR, Verbruggen B, Rivard GE, Teitel J, Walker I. A detailed comparison of the performance of the standard versus the Nijmegen modification of the Bethesda assay in detecting factor VIII: C inhibitors in the haemophilia A population of Canada. Thrombosis and haemostasis. 1998;79(4):872-5.
13. Hay CRM, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. British journal of haematology. 2006;133(6):591-605.
14. Astermark J, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood. 2007;109(2):546-51.
15. Lottenberg R, Kentro TB, Kitchens CS. Acquired hemophilia: a natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. Archives of Internal