RESEARCH LETTER

Diagnosis and treatment of acquired hemophilia: a single-center experience

Bożena Sokołowska[1], Justyna Kozińska[1], Magdalena Kozioł[1], Ewa Wąsik-Szczepanek[1], Dariusz Szczepanek[2], Marek Hus[1]

1 Department of Haematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland
2 Department of Neurosurgery and Pediatric Neurosurgery, Medical University of Lublin, Lublin, Poland

Introduction Acquired hemophilia (AH) is a sudden severe blood diathesis, caused by autoantibodies that inhibit coagulation factor VIII (FVIII).[1] The disease is estimated to develop in 0.2 to 1 patient per 1 million inhabitants.[2] The disorder is idiopathic in 50% of cases, while the other cases are associated with autoimmune conditions, lymphoproliferation, cancer, pregnancy, or postpartum period.[3] The diagnosis of AH is often delayed; therefore, mortality rates in these patients are high and reach 22%.[1] The delayed diagnosis is related to some specific characteristics of AH. Firstly, both men and women may be affected by the disease. However, the knowledge of hemophilia among physicians is mostly based on the classic form of the disease, which commonly affects male patients. Therefore, in the case of diagnosis in women, few specialists take AH into consideration. Secondly, diathesis develops suddenly in patients with AH without a history of hemorrhage.

The aim of this study was to present the diagnostic procedure and different treatment options of AH based on a 13-year experience of the Department of Haematooncology, Medical University of Lublin, Lublin, Poland.

Patients and methods We retrospectively analyzed patients with AH treated at our department from 2002 to 2015. During this period, a total of 9 patients with AH were treated: 4 men and 5 women (mean age 53 years; range, 29–74 years). All patients provided their informed consent to participate in the study. Laboratory tests were performed to measure activated partial thromboplastin time (APTT), FVIII activity, and FVIII inhibitor activity (using the Bethesda method)[1]. To confirm the presence of the inhibitor, the mixing studies (based on APTT evaluation) were performed. The baseline characteristics of the patients and laboratory test results are presented in Supplementary material, *Table S1*.

Results The most common manifestations of the disease included extensive subcutaneous hemorrhages (6 patients) and intramuscular hematomas (3 patients). FVIII inhibitor was detected in all patients, and the mixing studies showed no APTT correction. Eight patients received hemostatic treatment (patient 2 did not receive the therapy because of mild bleeding).

The treatment strategy was based on the availability of blood products for patients with AH: 3 patients were treated with recombinant active factor VII (rFVIIa), 1 female patient with activated prothrombin complex concentrate (aPCC) as a monotherapy and one was treated first with rFVIIa and then with aPCC.[4] In the other patients, desmopressin (a synthetic vasopressin analogue), FVIII, and fresh frozen plasma (FFP) were used. Patient 3 received FVIII concentrate despite the fact that the inhibitor level was 16 BU/ml and she should have received bypassing agents[5]; however, they were not easily available at the time. Four patients (1, 5, 6, and 7) received blood transfusion. All patients received immunosuppressive therapy, including a glucocorticoid, intravenous immunoglobulin, cyclophosphamide, or azathioprine. After the administration of FVIII concentrate, the level of the inhibitor increased in patient 3 (to 31 BU/ml at day 2 of treatment). Immunotherapy was intensified and the patient received high-dose dexamethasone, immunoglobulin, and cyclophosphamide.[6]

In most patients (n = 5), immunosuppressive therapy was well tolerated. Side effects occurred in 4 patients. Inhibitor eradication was achieved in all patients over a period from 3 weeks to 9 months. Complete remission, defined as FVIII activity exceeding 50% and inhibitor eradication, was achieved in all patients and lasted until the end of follow-up. In patient 9, complete remission was achieved after 8 months and lasted 3 months until the inhibitor was again revealed

Correspondence to:
Bożena Sokołowska, MD, PhD, Klinika Hematoonkologii i Transplantacji Szpiku, Uniwersytet Medyczny w Lublinie, ul. Staszica 11, 20-081 Lublin, Poland,
phone: + 48 81 534 54 96,
email: besokolowska@o2.pl
Received: August 2, 2017.
Revision accepted: October 10, 2017.
Published online: November 6, 2017.
Conflict of interests: All authors have received travel grants and/or honoraria for lectures from Novo Nordisk and/or Baxter.
Pol Arch Intern Med. 2017; 127 (11): 796-799
doi:10.20452/pamw.4139

in laboratory tests (5.4 BU/ml) and FVIII activity dropped to 11.9% without any clinical symptoms. Immunotherapy was slightly intensified and remission was achieved again after 6 months. Remission was monitored by the assessment of APTT and FVIII activity every 1 to 3 months during the first year and then once or twice a year (sometimes only APTT was evaluated). Only patients 4, 5, and 9 are still followed in the outpatient clinic. Patient 3 moved to another city. Other patients were lost to follow-up. The details on hemostatic and immunosuppressive treatment are presented in TABLE 1.

Discussion A sudden occurrence of hemorrhagic diathesis in a man or woman without previous tendency to bleeding should raise the suspicion of AH, especially if laboratory tests show an isolated prolonged APTT. In many cases of AH, APTT is significantly prolonged (2- or 3-fold), but caution is needed because sometimes APTT may be only slightly prolonged (by 12–17 seconds, as in patient 6).[4] Every prolongation of APTT should be diagnosed.[7] Such results have to be interpreted carefully, and these patients should not be administered FFP to "correct the APTT value" and undergo an invasive procedure. Such practice may lead to fatal hemorrhage.[4]

According to the Polish[1] and international recommendations,[8] as well as on the basis of a case report by Hellmann et al,[9] the first-line therapy for any active bleeding should involve rFVIIa or aPCC. In our analysis, 5 patients were treated according to this algorithm. In other patients, desmopressin, FVIII, and FFP were used. These different treatment strategies resulted from the fact that bypassing agents were difficult to obtain in Poland before 2010. Since 2012, AH has been managed according to the National Program for Treatment of Hemophilia and Related Bleeding Disorders financed by the Ministry of Health. The program was first introduced in 2005, but it did not clearly define the procedures for reimbursement of bypassing agents in AH treatment; therefore, the bypassing agents were not always available. Since 2010, the treatment of these patients with bypassing agents has been applied; thus, patient 5 was administered aPCC. The treatment strategy in patients 1 to 4 was different because they had been diagnosed before 2010.

FFP is no longer used in the treatment of AH due to its poor effectiveness. Patient 1 was given FFP because there were no other therapies available.[10] Patient 4 received desmopressin to control bleeding. This drug is used for minor bleeding episodes in patients with low inhibitor titers (<2 BU/ml).[11] In 2008, in our department, we could treat patients with AH only with FFP or desmopressin. The main reasons for not using desmopressin was its unpredictable efficacy, tachyphylaxis, and numerous side effects, especially in elderly patients. Fortunately, our patient was a young female soon after childbirth and without any severe concomitant disorders; therefore, she was administered the treatment and did not develop any side effects.

The treatment of bleeding is one of the two main goals in the management of AH. The other goal is inhibitor eradication, which is achieved through immunosuppressive treatment. The most effective first-line treatment is the combination of prednisone with cyclophosphamide,[8] which was administered in most patients in this analysis.

The outcome of the AH treatment depends both on antihemorrhagic treatment strategy and inhibitor eradication. Patient 1 was treated only with FFP to control bleeding. After the administration of prednisone and cyclophosphamide with the aim to eradicate the inhibitor, he finally achieved remission. To eradicate the inhibitor, patient 4 was given only prednisone because she was a postpartum woman. Cyclophosphamide is contraindicated in female patients or it should be used with caution due to the risk of infertility.[8] After FVIII administration, patient 3 had an increased level of the inhibitor so the patient was additionally treated with intravenous immunoglobulin. The usefulness of intravenous immunoglobulin in the eradication of FVIII inhibitor was investigated before. Only 10% of the inhibitors were completely suppressed and only in patients with low inhibitor titers (<5 BU/ml).[8] According to Polish and international recommendations intravenous immunoglobulin should not be used as monotherapy in patients with AH.[1,8]

According to a report by Tiede et al,[12] predictors of a positive response in AH include a low inhibitor level (<20 BU/ml), increased FVIII activity (≥1 IU/dl), and a short period between the appearance of the inhibitor and the beginning of the therapy. In 3 of our patients (3, 4, and 6), the level of FVIII inhibitor was low and the activity of FVIII was higher than 1 IU/dl. Presumably, due to such results, all the 3 patients achieved remission despite a slightly longer period (4, 2, and 2 weeks, respectively) between the occurrence of the symptoms and the beginning of the therapy. In other patients, the best predictor of a positive response was the possibility of proper treatment administration immediately after the diagnosis.

Conclusions Appropriate treatment introduced immediately after the diagnosis of AH can cause remission of the disease and save patients' lives. According to the presented results, the use of bypassing agents (rFVIIa or aPCC) seems to be the best treatment option.

Supplementary material Supplementary material is available with the article at www.pamw.pl.

REFERENCES

1 Windyga J, Chojnowski K, Klukowska A, et al. on behalf of the Working Group on Haemostasis of the Polish Society of Haematology and Transfusion Medicine. [Polish recommendations on the management of acquired haemophilia A]. Med Prakt. 2011; 10: 42-51. Polish.

TABLE 1 Hemostatic and immunosuppressive therapy of patients with acquired hemophilia

Patient No.	Date of diagnosis	Hemostatic therapy	Treatment duration	Total dose	Blood transfusion	Immunosuppressive therapy	Adverse events	Date and time until inhibitor eradication	Date and time until remission	Date of the last visit / Time of observation / Duration of remission
1	September 27, 2002	FFP	12 days	24 units	5 units	Prednisone; cyclophosphamide	None	October 14, 2002 (3 weeks)	October 14, 2002 (3 weeks)	October 16, 2002 / 3 weeks / 3 days
2	March 25, 2005	None	0	0	–	Prednisone	None	June 9, 2005 (2.5 months)	June 9, 2005 (2.5 months)	July 25, 2014 / 9 years 4 months / 9 years 1.5 months
3	October 1, 2007	FFP FVIII concentrate (50 U/kg)	1 day 7 days	3 units 48 500 units	–	Prednisone Cyclophosphamide Dexamethasone Immunoglobulin	Steroid-induced diabetes	October 24, 2007 (3 weeks)	November 20, 2007 (7 weeks)	February 14, 2014 / 6 years 4 months / 6 years 2 months
4	October 6, 2008	Desmopressin	5 days	97.5μg	–	Prednisone Methylprednisolone Dexamethasone	Hyperglycemia Hypertension	October 23, 2008 (18 days)	November 6, 2008 (32 days)	April 1, 2016 / 7 years 6 months / 7 years 5 months
5	April 2, 2010	aPCC	16 days	105 000 units	4 units	Prednisone Cyclophosphamide Azathioprine	None	May 11, 2010 (7 weeks)	May 11, 2010 (7 weeks)	September 15, 2017 / 7years 5 months / 7 years 3 months
6	March 30, 2012	FFP rFVIIa aPCC	2 weeks 5 weeks 5 days	14 units 1442 mg 36 000 units	28 units	Prednisone Methylprednisolone Cyclophosphamide	None	May 7, 2012 (6 weeks)	May 7, 2012 (6 weeks)	November 15, 2012 / 7.5 months / 6 months
7	October 15, 2013	rFVIIa	3 weeks	454 mg	–	Prednisone Cyclophosphamide	Fungal pneumonia Thrombocytopenia	November 12, 2013 (4 weeks)	November 18, 2013 (5 weeks)	November 22, 2013 / 5 weeks / 4 days
8	April 8, 2014	rFVIIa	3 weeks	227 mg	–	Prednisone Cyclophosphamide	None	May 19, 2014 (5.5 weeks)	May 19, 2014 (5.5 weeks)	August 13, 2014 / 4 months / 3 months
9	January 7, 2015	rFVIIa	20 days	550 mg	2 units	Prednisone Cyclophosphamide Azathioprine	Steroid-induced diabetes	July 15, 2015 (6 months) April 14, 2016 (4 months)	September 15, 2015 (8 months) June 17, 2016 (6 months)	September 12, 2017 / 1 year 8 months / 2 years 3 months

Abbreviations: aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; rFVIIa, activated recombinant factor VII; FVIII, factor VIII

2 Collins PW. Therapeutic challenges in acquired factor VIII deficiency. Hematology Am Soc Hematol Educ Program. 2012; 2012: 369-374.

3 Baudo F, Collins P, Huth-Kuhne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophila (EACH2) Registry. Blood. 2012; 120: 39-46.

4 Górka-Kosicka M, Paluszkiewicz P, Krasowska D, et al. [Uncontrolled postoperative bleeding in woman with pemphigus and undiagnosed acquired haemophilia A]. Hematologia. 2013; 4: 71-75. Polish.

5 Zdziarska J, Musiał J. Acquired hemophilia A: an underdiagnosed, severe bleeding disorder. Pol Arch Med Wewn. 2014; 124: 200-206.

6 Sokołowska B, Walter-Croneck A, Gromek T, Dmoszyńska A. [Acquired hemophilia and life-threatening bleeding - difficult problem that affects not only males but also females]. Acta Haematol Pol. 2011; 42: 583-591. Polish.

7 Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. Semin Thromb Hemost. 2014; 40: 803-811.

8 Huth-Kűhne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009; 94: 566-575.

9 Hellmann RA, Hać S, Kostro J, et al. Severe complication of acquired hemophilia: active bleeding into gallbladder resulting in cholecystitis requiring surgery. Pol Arch Med Wewn. 2015; 125: 299-300.

10 Sokołowska B, Tomczak W, Gromek T, Legieć W. [Massive bleeding episodes in patients with acquired hemophilia – case report]. Pol Arch Med Wewn. 2006; 115: 351-355. Polish.

11 Kruse-Jares R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol. 2017; 92: 695-705.

12 Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from GTH-AH 01 /2010 study. Blood. 2015; 125: 1091-1097.