

Clinical features and outcome of acquired haemophilia A

Interim analysis of the Düsseldorf Study* §

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Keywords

Acquired haemophilia A, autoantibodies, morbidity, mortality, underlying disorder

Summary

We have performed a monocenter study on 29 consecutive patients with acquired haemophilia A who were referred for diagnosis and treatment to the Düsseldorf Haemophilia Comprehensive Care Center between March 2001 and February 2010. **Patients, methods:** 18 men (age: 44–86 years) and 11 women (age: 20–83 years). For laboratory evaluation, a standardized staged protocol of aPTT, FVIII:C activity and concentration, mixing studies with patient and normal plasma, and quantification of inhibitor titers (Bethesda assay) was used. Diagnostic work-up included elaborate examinations for any underlying disease. **Results:** In 18 (62%) of the 29 patients with acquired haemophilia A, an underlying disorder was identified, including 9 patients with respiratory diseases (31%), 7 patients with autoimmune disorders (24%), one with malignancy, and one with postpartum state, while in 11 patients (38%) acquired haemophilia A remained idiopathic. Haemotherapy of bleeding, suppression or elimination of the inhibitor, and induction of immunotolerance to endogenous FVIII:C were performed according to a treatment algorithm. Predefined clinical endpoints were control of bleeding, eradication of the inhibitor, complete or partial remission (CR, PR), relapse, or early death (≤ 30 days). Of the 29 patients in total, 22 individuals achieved CR (76%), three had PR,

one relapsed, and three died within 30 days (one of acute myocardial infarction while on antihaemorrhagic treatment, one of sepsis while on immunosuppression due to active acquired haemophilia A, one of lung bleeding in association with pre-existing pulmonary sarcoidosis). **Conclusion:** This monocenter study demonstrates that control of life-threatening bleeding, eradication of the inhibitor, and induction of tolerance to endogenous FVIII have significantly improved the clinical outcome of acquired haemophilia A. Our data also suggest a shift in underlying disorders associated with acquired haemophilia A, whereby, in comparison to published studies, a relative increase in the proportion of patients with respiratory diseases is present.

Schlüsselwörter

Erworbene Hemmkörperhämophilie A, Autoantikörper, Morbidität, Mortalität, Grunderkrankung

Zusammenfassung

In einer Monocenter-Studie haben wir bei 29 konsekutiven Patienten mit erworbener Hemmkörperhämophilie A, die unserem Hämophilie-Behandlungszentrum zwischen März 2001 und Februar 2010 zur Diagnostik und Therapie zugewiesen wurden, eine Zwischenauswertung vorgenommen. **Patienten, Methoden:** 18 Männer (Alter: 44–86 Jahre), 11 Frauen (Alter: 20–83 Jahre). Die Laboratoriumsanalytik erfolgte nach standardisierter Stufendiagnostik unter Einschluss von aPTT, Bestimmung der

FVIII:C-Aktivität und -Konzentration, Plasma-tauschversuchen mit Patienten- und Normalplasma sowie quantitativer Bestimmung der Inhibitortiter (Bethesda-Assay). Die Diagnostik umfasste zugleich gezielte Untersuchungen zum Nachweis einer Grunderkrankung. **Ergebnisse:** Bei 18 (62%) der Patienten mit erworbener Hemmkörperhämophilie A wurde eine Grunderkrankung identifiziert: 9 Patienten mit Atemwegserkrankungen (31%), 7 mit Autoimmunerkrankungen (24%), ein Patient mit Malignom, eine Patientin erkrankte in der Postpartalphase. Hingegen lag bei 11 Patienten (38%) eine idiopathische erworbene Hemmkörperhämophilie A vor. Die Hämotherapie aktiver Blutungen, Suppression bzw. Elimination des Inhibitors und Induktion der Immuntoleranz folgten nach einem festgelegten Behandlungsalgorithmus. Prädefinierte klinische Endpunkte waren: Beherrschung der Blutung, Eradikation des Inhibitors, komplette oder partielle Remission (CR, PR), Rezidiv bzw. Frühmortalität. Von den insgesamt 29 Patienten erreichten 22 Individuen eine CR (76%), drei eine PR, ein Patient erlitt ein Rezidiv, und drei Patienten starben innerhalb der ersten 30 Tage (ein Patient am akuten Myokardinfarkt unter antihämorrhagischer Therapie, ein Patient an einer Sepsis unter Immunsuppression, ein Patient an einer Lungenblutung bei pulmonaler Sarkoidose). **Schlussfolgerung:** Diese Studie zeigt, dass sich die Behandlungsergebnisse bei erworbener Hemmkörperhämophilie A durch Beherrschung lebensbedrohlicher Blutungen, Eradikation des Inhibitors und Toleranzinduktion gegenüber endogenem FVIII signifikant verbessert haben. Im Vergleich zu publizierten Daten weist unsere Zwischenanalyse darauf hin, dass bei erworbener Hemmkörperhämophilie ein Wandel in der Häufigkeit assoziierter Grunderkrankungen eingetreten sein dürfte und nunmehr eine relative Zunahme an Atemwegserkrankungen zu beobachten ist.

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Klinische Erscheinungsbilder und Ergebnisse bei erworbener Hemmkörperhämophilie A: Zwischenauswertung der Düsseldorfer Studie* §
Hämostaseologie 2010; 30: 156–161

* Dedicated to Prof. Peter Hanfland, Bonn, on the occasion of his 70th birthday.

§ This study is part of the MD thesis of Roya Gheisari.

Acquired haemophilia A is a rare but significant haemostatic disorder caused by autoantibody inhibitors against factor VIII coagulant protein (FVIII:C). The incidence of acquired haemophilia A has been estimated at about 1 to 4 cases per million per year (4, 5, 7). No such data are available of acquired haemophilia B but its annual incidence is even less frequent. Acquired haemophilia A affects patients with (7)

- pre-existing autoimmune disorders (such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, myasthenia gravis, multiple sclerosis, hyperthyroidism, Goodpasture syndrome, and others),
- underlying haematologic malignancies or solid cancers,
- concomitant viral infections,
- dermatologic disorders,
- patients on certain drugs, and also
- previously healthy subjects.

Interestingly, in the past, only a few patients were reported in whom an association of acquired haemophilia A with respiratory disorders such as chronic obstructive pulmonary disease was observed (9, 20). In approximately 50 to 60% of cases, autoantibodies against FVIII:C are detected in patients with serious or life-threatening haemorrhages who are lacking any relevant concomitant disease (5, 9, 14).

The incidence of acquired haemophilia A increases with age, and it is likely that this haemostatic disorder is underdiagnosed in the elderly (22). The age distribution of autoantibodies against FVIII:C is typically biphasic with (5, 7)

- a small peak in women between 20 to 40 years of age, due to inhibitors associated with pregnancy or the postpartum state,
- a major peak in patients aged 65 to 85 years.

In any case, acquired haemophilia A is associated with increased morbidity and mortality. In the past, fatal bleeding was high, ranging from 22% (9) to 31% (15) in several series related to age, persistence of inhibitor levels, and resistance to treatment (4, 5, 9, 15). The mortality rate has decreased in recent years and is currently at 9% (5).

We now report on the 10-year experience of our monocenter study conducted

on 29 patients with regard to the overall outcome and their clinical features. In comparison to other reports (9, 12, 14), an interim analysis of our patients suggests a shift in underlying disorders associated with acquired haemophilia A. Thus, we observed an increase in the proportion of patients with respiratory disorders, specifically in chronic obstructive pulmonary disease (COPD).

Patients, methods

Patients

The study was conducted on 29 consecutive patients with acquired haemophilia A who were referred for diagnosis and treatment of the Düsseldorf Haemophilia Comprehensive Care Center (HCCC) between March 2001 and February 2010. The cohort of patients included 18 men (age range: 44–86 years) and 11 women (age range: 20–83 years). In only two of the 29 patients (7%), the diagnosis of acquired haemophilia was made prior to admission to the Düsseldorf HCCC.

Despite prolonged aPTT, surgery had been performed in five patients resulting in major postoperative haemorrhagic complications. According to the Declaration of Helsinki, informed consent was obtained from all patients participating in this single-center study.

Laboratory methods

For evaluation of haemostasis, a standardized staged protocol of aPTT, FVIII:C activity and concentration, mixing studies with patient and normal plasma, and quantification of inhibitor titers (Bethesda assay) was applied, using established procedures. Samples of whole blood were collected in vacuum tubes containing 3.8% (w/v) sodium citrate in a ratio of 1:9 (v/v) anticoagulant to blood. APTT and FVIII:C were determined on a Behring Coagulation System (BCS) by established coagulometric methods using Pathromtin SL or FVIII-deficient plasma (Siemens Health Care Diagnostics, Marburg, Germany, formerly Dade Behring), as described previously (8).

The FVIII:C reference plasma (Siemens Health Care Diagnostics) was calibrated against the WHO standard (10). Residual FVIII:C activity was measured photometrically using a two-stage chromogenic assay (Siemens Health Care Diagnostics, Newark, DE, USA). FVIII:Ag was determined by ELISA (Affinity Biologicals, Ancaster, ON, Canada) accordingly to the manufacturer's instructions. Mixing studies with patient and normal plasma were performed by conventional coagulometric techniques (8). For quantification of autoantibodies against FVIII, the Nijmegen modification of the Bethesda assay was used (13, 24). Inhibitor titers were expressed in Bethesda units (BU).

To exclude any other disorder than acquired haemophilia A, the haemostasis profile also included testing for the activity of factors II, V, VII, X (Thromborel S assay, Siemens Health Care Diagnostics), IX, XI, XII, and XIII (Berichrom assay, Siemens Health Care Diagnostics), screening of lupus anticoagulant, using a lupus sensitive APTT (Pathromtin SL, Siemens Health Care Diagnostics), the DVV test and the DVV confirmation test (American Diagnostica, Pfungstadt, Germany). In addition, evaluation of the von Willebrand profile was performed, including determinations of the ristocetin cofactor activity (Siemens Health Care Diagnostics) and plasma concentration of VWF (Instrumentation Laboratory, Milan, Italy).

Diagnostic work-up

A standardized staged protocol of clinical examinations and imaging procedures for any underlying disorder associated with acquired haemophilia was used including a clinical pathology profiling, X-ray examination of the thorax, sonography of the abdomen, retroperitoneum and the thyroidea and, whenever indicated, computerized tomography of the thorax, abdomen, or pelvis.

Study protocol

For control of active bleeding, elimination or eradication of the inhibitor, and induc-

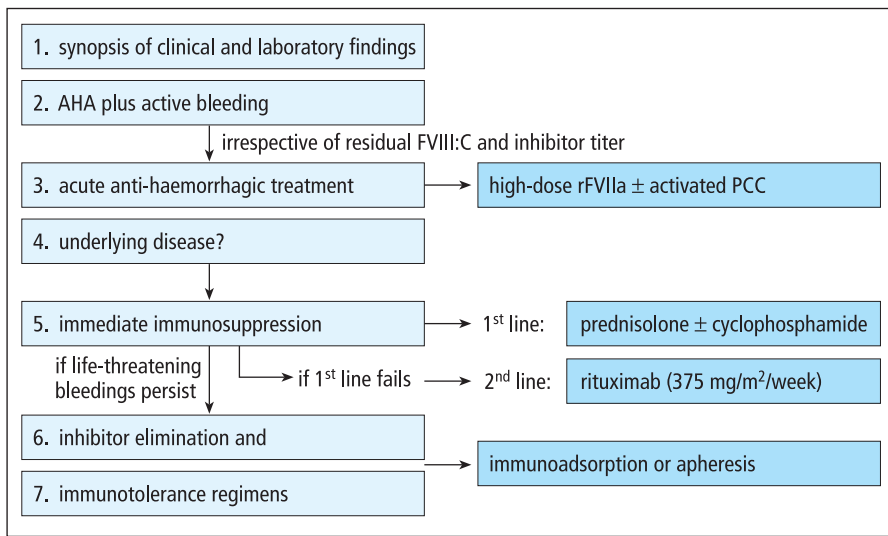


Fig. 1 Study protocol and treatment algorithm
 AHA: acquired haemophilia A; rFVIIa: recombinant activated factor VII (NovoSeven®);
 aPCC: activated prothrombin concentrates (FEIBA®)

tion of immunotolerance to endogenous FVIII, we used a treatment algorithm, as depicted in ►Figure 1. In patients with acute bleeding symptoms, antihemorrhagic therapy was initiated without any delay using FVIII bypassing agents (i.e., recombinant FVIIa, NovoSeven® and/or activated prothrombin complex concentrates (aPCC), FEIBA®). Immunosuppression (prednisolone alone or, sequentially, in combination with cyclophosphamide as first-line treatment; rituximab as second-line therapy if first-line immunosuppression failed) was started immediately following diagnosis. Details of the regimens will be reported elsewhere (19). Predefined clinical endpoints were control of bleeding, eradication of the inhibitor, complete or partial remission, relapse, or early death (≤ 30 days). In accord with others (5), complete remission required the following criteria:

- normalization of FVIII:C activity ($\geq 80\%$),
- no inhibitor detectable, and
- withdrawal of immunosuppressive therapy, or
- reduction to dosages of immunosuppressants administered prior to acquired haemophilia A.

For example, patients with a pre-existing autoimmune disorder required low-dose

steroids that had to be continued, even when they had remitted from their acquired haemophilia.

Partial remission, as used in this study, was defined by increase of FVIII:C activity ($>50\%$ but $<80\%$), decreased but still detectable inhibitor (irrespective of the exact titer), requirement of immunosuppression but no bleeding diathesis at all for more than 6 months. With regard to inhibitor titers, no cut-off value was set to define partial remission because antibody levels against FVIII are neither useful for decision making of treatment nor an indicator of outcome (5, 11). However, inhibitor levels over time may be a predictive indicator with regard to response to immunosuppressive therapy (11).

Results

Presenting characteristics

Upon admission, only two of the 29 patients presented with minimal bleeds despite isolated prolongation of aPTT and subsequent identification of strongly reduced FVIII:C activity ($<10\%$) with evidence of an inhibitor against FVIII:C. Of the other 27 patients, 15/29 (52%) had life-threatening bleedings with haemoglobin levels of less than 7.0 g/dl requiring trans-

fusions of packed RBC, while 12/29 (41%) presented with non-vital extended ecchymoses and/or haemorrhages into muscles or soft tissues. Seven patients had gastrointestinal or urogenital bleeds. A typical cutaneous bleeding pattern of patients with acquired haemophilia A is depicted in ►Figure 2.

Among the 15 individuals with life-threatening bleeding complications was one patient with an extended retroperitoneal haematoma. Two other patients had developed cervical collar-like haemorrhages due to multiple unsuccessful attempts of puncturing the vena jugularis to get access for a central venous line. This manoeuvre had been undertaken prior to the patients' transfer into our center. None of the patients presented with intracranial haemorrhage or developed this type of bleeding complication during the course. The distribution pattern and sites of bleeding in our patient population are shown in ►Figure 3.

Underlying diagnosis

In 18 of the 29 patients (62%), an underlying disorder associated with acquired haemophilia A was identified. Seven of them had a pre-existing autoimmune disease (including three subjects with rheumatoid arthritis, two with autoimmune thyroiditis, and each one with multiple sclerosis or sarcoidosis). Nine patients suffered from respiratory disease, 8 had COPD, one asthma bronchiale. In one patient, a malignant melanoma was diagnosed; another one had a postpartum state. In 11 of 29 patients (38%), no underlying disorder could be detected. Thus, idiopathic acquired haemophilia was suggested. ►Figure 4 summarizes the data of the Düsseldorf Study in comparison to those from Heidelberg which were also evaluated in a single-center study.

Overall outcome

Of the 29 patients in total, 22 individuals achieved complete remission (76%), three had a partial remission, one relapsed, and three died within 30 days. Among the cases

of death, one patient suffered from acute myocardial infarction while still on anti-haemorrhagic treatment, one patient died of acute sepsis and subsequent multiple organ failure while on immunosuppression, one patient with pre-existing pulmonary sarcoidosis died of lung bleeding in association with active acquired haemophilia A. Details of individual patients with respect to their specific treatment and outcome have been published (23) or will be reported elsewhere (19).

Discussion

The interim analysis of this monocenter study conducted on a limited number of patients stresses several features of acquired haemophilia A.

1. A major characteristic of this rare haemostatic disorder is given by the fact that its bleeding pattern differs significantly from that of congenital haemophilia. Thus, most patients with autoantibodies against FVIII have haemorrhages into skin, muscles and soft tissues, or mucous membranes (including epistaxis, gastrointestinal or urogenital bleeds), retroperitoneal hematomas, or intracranial haemorrhages. By contrast, haemarthroses, a classic feature of congenital FVIII deficiency, are uncommon in acquired haemophilia (2, 7, 9). Moreover, haemorrhages are much more severe in acquired than congenital haemophilia. Although this is a general clinical experience, the reason for the different bleeding phenotype with regard to localisation and severity is poorly understood. This is also in contrast to drug-induced haemorrhages, for example in patients using antithrombotic drugs (17, 18).
2. Acquired haemophilia A appears to be more difficult to diagnose in general clinical practice than otherwise suggested by well-trained haemostasis consultants. Thus, those patients are seen in an array of clinical settings that are not usually equipped to tackle them (16). Among the individuals recruited for this study, only in two of the 29 patients (7%), the diagnosis of acquired haemophilia A had been made prior to admission to the Düsseldorf HCCC. Moreover, despite pro-

longed aPTT, five patients had undergone surgery, and in two other patients hazardous invasive manoeuvres had been performed, resulting in major postoperative or postprocedural haemorrhagic complications, respectively. These obser-

vations suggest that acquired haemophilia is underdiagnosed and also underestimated with regard to its life-threatening complications.

3. Even in specialized centers, appropriate treatment of high-risk patients with



Fig. 2 Extended ecchymosis in a patient with acquired haemophilia A: Note the sharply demarcated haematomas typical of a plasmic haemostatic disorder

Fig. 3 Sites of bleeding in patients with acquired haemophilia A (Düsseldorf Study): To avoid multiple allocations, only the site of the predominant major bleed is indicated.

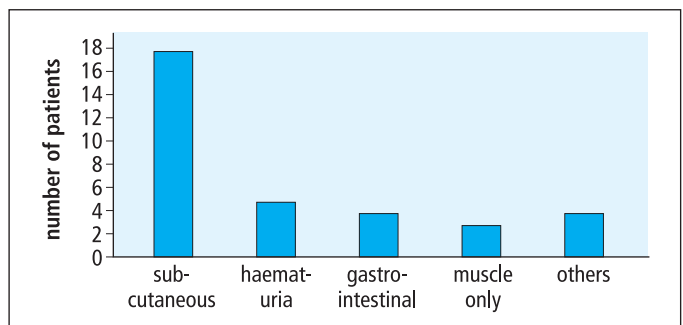
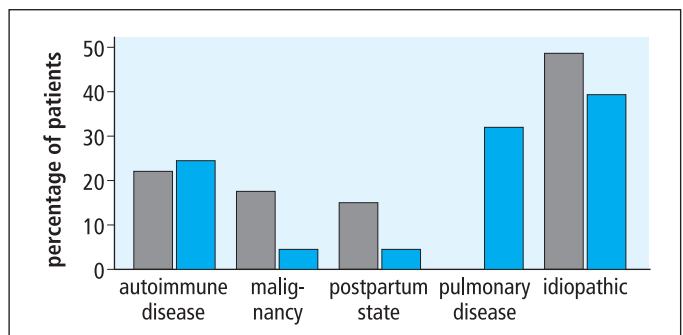


Fig. 4 Type and frequency of underlying disorders associated with acquired haemophilia A (12): Düsseldorf Study (■; n = 29) in comparison to Heidelberg Study (■; n = 42)



autoantibodies to FVIII and severe haemorrhagic complications remains challenging. This is due to the fact that, in the majority of cases, elderly patients are affected who have a high rate of comorbidity (6). Thus, anti-haemorrhagic treatment, any kind of immunosuppression and various procedures of inhibitor elimination regimens (i.e., extracorporeal circulation either for immunoadsorption or plasmapheresis) will require careful risk-benefit weighting in the individual patient. To date, no guidelines exist. However, recently published international recommendations on “how to treat” patients with acquired haemophilia are helpful (7, 11).

In accord with these recommendations, we have designed a treatment algorithm shown in ►Figure 1. This approach is based on a concise and straightforward diagnostic work-up with synopsis of clinical and laboratory findings. A mandatory element of this concept is the immediate interdisciplinary examination with imaging procedures including X-ray, sonography, and whenever required, computerized tomography. This program is essential to

- identify or exclude any underlying disorder associated with acquired haemophilia,

- provide a rational basis for careful risk-benefit assessment,
- allow appropriate decision making with regard to the kind and intensity of immunosuppression, and, when life-threatening bleeding persists,
- escalate treatment by application of inhibitor elimination regimens such as immunoadsorption and/or plasmapheresis.

In this study, immunosuppressive therapy was immediately initiated throughout, whenever possible. Using prednisolone alone or, sequentially, in combination with cyclophosphamide (either regimens as first-line treatment) and retuximab (as second-line immunosuppression) (►Fig. 1), 25 of the 29 patients (86%) recovered from acquired haemophilia A, 22 patients achieved complete (76%), and three had partial remission (10%). However, 15 of the 29 patients (52%), namely those with life-threatening bleeds also required inhibitor elimination procedures by immunoadsorption (n = 11) and/or plasmapheresis (n = 6). Details will be discussed in another publication (19).

More recently, there has been an increasing tendency to administer retuximab primarily for eradication of FVIII inhibitors with durable responses (for review: 7, 11,

16). Several small series have provided promising results with complete remission rates of >80% in acquired haemophilia A, when this monoclonal antibody (against the pan B-cell antigen CD20) is used as first therapy (1, 21, 25), capable of inducing a rapid in vivo depletion of normal B lymphocytes (3). However, in these trials the follow-up was usually too small to draw definite conclusions. Currently, therapy with retuximab in association with other immunosuppressive agents as first-line treatment is discussed for patients with high-titer FVIII autoantibodies (7). In agreement with others (11, 16), we used retuximab in this single-center study only after complete failure of or inadequate response to the above immunosuppressive regimens. It should be stressed that retuximab, apart from its potential side effects, is not officially approved for this indication and therefore represents an off-label use in acquired haemophilia.

Another serious concern with respect to eradication of autoantibody inhibitors to FVIII is that immunosuppressive agents can cause severe side effects, particularly in elderly patients with significant comorbidity. Sepsis resulting from or in association with immunosuppression in high-risk patients has been the most commonly reported adverse event in acquired haemophilia (5, 22). In the UK multicenter

disorder	study, number of patients (%)				
	Düsseldorf Study* n = 29	Heidelberg Study* Huth-Kühne [12] n = 42	UK Study [§] Collins et al. [5] n = 150 [#]	Kessler & Ludlam [§] [14] n = 65	Green & Lechner [§] [9] n = 178 ^{##}
none	11 (37.9)	20 (47.6)	95 (63.3)	34 (52.3)	82 (46.1)
autoimmune disease	7 (24.1)	9 (21.4)	25 (16.7)	11 (17.0)	32 (18.0)
rheumatoid arthritis	3 (10.3)	not available	9 (6.0)	not available	14 (7.9)
systemic lupus erythematosus	none	not available	3 (2.0)	not available	10 (5.6)
others	4 (13.8)	not available	16 (10.7)	not available	8 (4.5)
malignancy	1 (3.5)	7 (16.7)	22 (14.7)	9 (13.9)	12 (6.7)
dermatologic disorders	none	none	5 (3.3)	1 (2.0)	8 (4.5)
respiratory disease	9 (31.0)	none	none	1 (2.0)	7 (3.9)
asthma	1 (3.5)				5 (2.8)
COPD	8 (27.6)				
pregnancy-related or post-partum	1 (3.5)	6 (14.3)	3 (2.0)	7 (10.8)	13 (7.3)

COPD: chronic obstructive pulmonary disease; *monocenter study, [§]multicenter study
The underlying disease was recorded in [#]150 of 172 or ^{##}178 of 215 patients, respectively.

Tab. 1
Underlying disorders in patients with acquired haemophilia A

study, sepsis contributed to the death of 12 of the 167 patients (7%) who were retrospectively analyzed for inhibitor eradication and survival following immunosuppression. In our monocenter trial, one early death was due to septicaemia. Another patient died of acute myocardial infarction while still on haemotherapy with rFVIIa. Thus, it cannot be ruled out that prothrombotic effects of antihaemorrhagic treatment contributed to this fatal outcome.

Conclusion

As a result of the elaborate diagnostic work-up that was performed throughout this monocenter study, we were able to identify an underlying disorder associated with acquired haemophilia A in 18 of the 29 patients (62%) (► Fig. 4). This proportion is higher than that of older and recent single- and multicenter studies, ranging between 37 and 54% (► Tab. 1). Thus, we conclude that comprehensive clinical, laboratory and imaging examinations being evaluated interdisciplinarily are essential for complete diagnosis in patients with acquired haemophilia.

With respect to underlying disorders, another distinct feature of this study is the high proportion (31%) of patients with respiratory disease (► Fig. 4; ► Tab. 1). In the past, only a few studies reported on patients with autoantibody inhibitors to FVIII and concomitant pulmonary disease (9, 20). For example, Shaffer et al. identified two subjects with COPD in a small series of 9 patients (20). In the multicentric survey on nonhaemophilic patients with inhibitors to FVIII by Green and Lechner including 215 patients, only 7 of 178 patients had respiratory disorders (3.9%), among them 5 individuals with asthma (9). By contrast, the recent UK multicenter study did not identify any patient with respiratory disorders among 150 of 174 patients whose underlying diagnosis was recorded (5). Likewise, in the Heidelberg single-center study by Huth-Kühne, none of the patients suffered from pulmonary disease (12). In comparison to these data, the proportion of patients with COPD found in our study is unusually high. By contrast, the rate of patients with autoimmune disorders (24% in

this study) is similar to that reported by others (► Tab. 1).

Although these “clusters” of autoimmune and respiratory diseases may be due to patient selection or could be biased by small numbers, the high proportion of patients with respiratory disease can be indicative of a shift in underlying disorders associated with acquired haemophilia. This observation deserves special attention and requires confirmation in larger studies.

Acknowledgements

This work was supported in part by grants from the Deutsche Forschungsgemeinschaft (Scha 358/3–1 and Sonderforschungsbereich 612, Project B2). Additional support was provided by the Biological Medical Research Center, Heinrich Heine University, Düsseldorf, Germany. The assistance of our haemophilia nurses (E. Metzen, U. Hoffmann, Britta Protz, and M. Völkl), our lab technicians (Ms. Morgenrot and Ms. Bluma), and our former team members (Priv.-Doz. Dr. A. Gerhardt, Prof. M. Stockschröder, Priv.-Doz. Dr. C. Sucker, and Priv.-Doz. Dr. R. B. Zotz) is also gratefully acknowledged.

Conflict of interests

The authors state that they have no conflict of interests.

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