The Clotting Times

ECAT FOUNDATION

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Issue 7

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Editorial

In issue 6 we introduced the new logo of the ECAT foundation. In line with this new logo the layout of the Clotting Times has been partially adjusted. The content of every rubric is still easy recognizable with its own colour.

The "focus article" in this issue describes the possibilities for further standardization of FVIII inhibitor testing. The next rubric is "ECAT information" with information about the ECAT programme in 2014. This summer boxes were packed and the ECAT Foundation moved to another location. It was a hectic time but now we have settled in and would like to tell you how happy we are with our beautiful new location. Finally we hope you agree with us that it is easier to find the Corporate Corner on the new website. It gives you easy access to information of a company you are searching for.

We would like to draw your attention especially to the ECAT pre-congress symposium at the ISLH congress in The Hague in May 2014.

In the "Case report" an acquired Factor X deficiency is described. It illustrates the bleeding tendency in and a therapeutic approach to a patient with non-amyloid-related acquired isolated Factor X deficiency after respiratory illness.

The editorial board and advisory committee wish you a healthy 2014. Enjoy reading.

Yours sincerely, Petra ter Hark

Content

News

New address and contact details

On August 1st, 2013 the ECAT Foundation moved to new facilities.

Please be aware of the new address and contact details.

Postal address:
ECAT Foundation
P.O. Box 107
2250 AC Voorschoten
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Visiting address:
Dobbeweg 1
2254 AG Voorschoten
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After January 1st, 2014 neither the old telephone numbers nor the postal address will be active any more.

Save the dates

In 2014 there are a number of important ECAT activities.

14 May:
Special ECAT symposium on "Quality Assurance of the Diagnostic Process"
Venue: Worldforum, The Hague, The Netherlands
(for details see page 5 of this issue).

13-14 November:
ECAT Symposium, Leiden, The Netherlands

Follow ECAT on Twitter

The ECAT will start to use social media to communicate with our participants. Short messages regarding the EQA programme, e.g. the availability of electronic reports, will also be announced via Twitter. Please start to follow ECAT on Twitter: **@ecatfoundation**

Focus Article:

Factor VIII inhibitor testing - a way to comparable results

B. Verbruggen PhD and P. Meijer PhD

ECAT Foundation, Leiden, the Netherlands

Introduction

In 2005 the ECAT started external quality control surveys for the factor VIII-inhibitor assay. From the beginning a high between-laboratory variability of the results (>30-40%) in inhibitor positive samples was observed. Unfortunately, this variability did not improve over the years (figure 1). Remarkably, the Nijmegen assay performed only slightly better than the original Bethesda assay in spite of the higher degree of standardization of the former assay.

Figure 1. Coefficient of Variation of ECAT Surveys since 2005 of Inhibitor Positive Samples

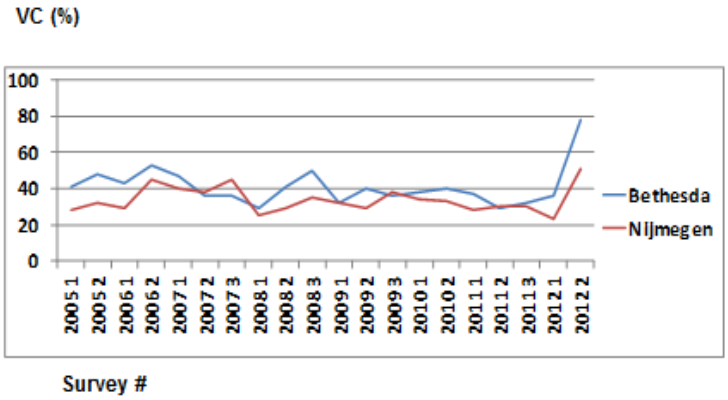


Table 1. False positive results in inhibitor negative samples of ECAT surveys

Survey	False positive results (%)
2005	6
2006-2	7
2006-4	17
2008-4	5
2009-4	32
2011-4	11

Moreover, the percentage of falsely positive results in factor VIII inhibitor negative samples was rather variable (5-32%) but also remained quite high during the years (Table 1).

The lack of improvement in the inter-laboratory results of the factor VIII inhibitor surveys was already reported in 2009 by Piet Meijer [1]. These results prompted us to start a quality improvement cycle.

Methods

General

The aim of the quality improvement cycle was to investigate components that contribute to the high inter-laboratory variability of the results of the factor VIII inhibitor assays and to come up with suggestions to reduce the variability of the assay.

A five-step cycle was defined. The cycle included (1) a decentralized zero-measurement, (2) a centralized zero measurement, (3) a centralized measurement with standardized methods, (4) a decentralized result measurement and (5) a decentralized measurement with standardized methods.

In each stage of the cycle, an identical set of 7 samples was used. The characteristics of the samples are described in table 2.

Table 2. Identity of the samples used

Sample	Inhibitor activity (BU/mL)	Characteristics of inhibitors
1	1.6	Monoclonal Ab against C2-domain
2	0.8	Monoclonal Ab against A1-domain
3	1.4	Moderate titre patient sample
4	0.7	Low titre sample (1:1 dilution of sample 3)
5	1.9	Moderate titre patient sample
6	15.4	High titre polyclonal inhibitor
7	-	Negative control

Detailed description of different stages

Stage 1: decentralized zero-measurement

A survey among 51 laboratories that participated on a regular basis in the factor VIII-inhibitor program of the ECAT (2009). After evaluation of the results, 15 out of 51 participants were invited for a 3-days workshop in November 2009. The laboratories were selected on basis of a wide variation of methods, techniques and assay results.

Stage 2: centralized zero-measurement

During the first session of the workshop, the participants performed the FVIII inhibitor assay on the identical samples, using their own reagents and methods.

Stage 3: centralized measurement with standardized methods

During the final session of the workshop, the participants performed the FVIII inhibitor assay on the same samples, using uniform reagents (including buffered pool plasma, factor VIII deficient reference plasma and APTT reagent) and a standard procedure (including uniform plasma dilution rates).

Stage 4: decentralized result

In 2010, shortly after the workshop, an external survey was organized among the workshop participants in order to test the direct effect of the workshop on the inter-laboratory variation. Participants were asked to use their current in-house method.

Stage 5: decentralized measurement with standardized methods

All 51 laboratories, that also participated in the survey in 2009, were asked to participate in a final survey in 2012 thereby using a standard assay protocol including buffered normal pool plasma, FVIII deficient plasma as reference sample and a standardized sample dilution rate (see protocol final survey). 22/51 laboratories agreed and participated.

Results

The means and coefficients of variation (CV) of the results of the assays of inhibitor positive samples at the various stages of the study are shown in table 3.

Stage 1, 2 and 3.

The high inter-laboratory variation of the assay, found in the regular surveys, was confirmed in the initial survey of the current project (zero measurement) and the first session of the workshop. The CVs decreased dramatically in the final session of the workshop when all participants used universal reagent and a standardized protocol. The full results of the workshop have been described in a publication in JTH in 2011 [2].

Protocol Final Survey (stage 5)

1. ***Normal Pool Plasma in incubation mixture***
   - FVIII activity between 95% and 105%
   - Calibrated against international standard
   - Buffered at pH 7.4
2. ***Reference Sample***
   - Factor VIII deficient plasma, preferably containing normal amounts of von Willebrand factor.
3. ***Inhibitor sample***
   - Measure undiluted when titre ≤ 2 BU/ml
   - When inhibitor activity > 2BU/ml, use the lowest possible dilution
   - Dilute with FVIII deficient plasma

Stage 4.

The results of the post-workshop survey in 2010 among workshop participants showed a high variation of results indicating that the outcome of the workshop had not lead to improvement of the inter-laboratory variation. Most probably, the participating laboratories did not (yet) implement the recommendations of the workshop.

Table 3. Inhibitor activity in BU/ml and between brackets the inter-laboratory Coefficient of Variation.

	Pre-Workshop Survey (2009)		Workshop (2009)	results	Post-workshop survey (2010)	Standardized final survey 2012
Sample no. and nominal inhibitor activity	51 Laboratories	15 laboratories selected for the workshop	First Session	Last Session	13 Laboratories	22/51 Laboratories
1 1.6 BU/ml	2.7 (43%)	2.7 (43%)	3.0 (39%)	1.9 (8 %)	2.9 (41%)	2.7 (31%)
2 0.8 BU/ml	0.8 (49%)	1.0 (31%)	1.3 (69%)	0.9 (5%)	1.1 (88%)	0.7 (17%)
3 1.4 BU/ml	1.0 (41%)	1.2 (39%)	1.2 (30%)	1.2 (6%)	1.1 (31%)	1.0 (23%)
4 0.7 BU/ml	0.4 (70%)	0.6 (69%)	0.61 (45%)	0.50 (13%)	0.6 (61%)	0.5 (30%)
5 1.9 BU/ml	1.7 (36%)	1.7 (37%)	2.3 (41%)	2.2 (12%)	1.9 (31%)	1.8 (22%)
6 15.4 BU/ml	11.0 (36%)	11.5 (44%)	14.9 (41%)	14.6 (6%)	12.0 (36%)	12.4 (27%)
Mean CV	*45%*	*44%*	*44%*	*8%*	*48%*	*25%*

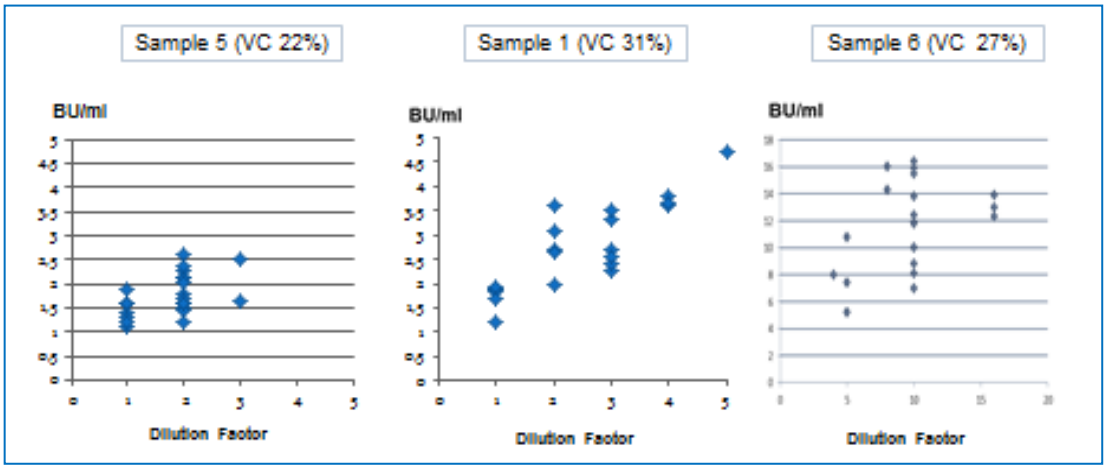
Table 4. Overview of exclusion of results

Sample	No. of included responders	No. of excluded responders	Reason for exclusion
1	19	3	Sample diluted with buffer (2) or with heat-inactivated plasma (1)
2	22	0	-
3	20	0	No results from 2 participants
4	21	1	Outlier (> 3 sd different from mean)
5	19	3	Sample diluted with buffer (2) or with heat-inactivated plasma (1)
6	17	5	Measured undiluted (1), diluted with buffer (2) or with heat-inactivated plasma (2)
7	22	0	-

Stage 5.

All laboratories that participated in stage 1 of this project were invited to participate in the final survey. Twenty-two out of 51 laboratories signed up. The participants were requested to use reagents and procedures that were standardized according to the recommendations of the workshop, including plasma dilution procedures (see protocol final survey).

Figure 2. Effect of dilution ratio on inhibitor titre



A number of results were excluded because of non-compliance with the requirements of standardization, one result was excluded because of being outside mean result ± 3sd, (see table 4). The CV's in the standardized final survey ranged from 17% to 31%, which was subsequently lower than the CV's in the previous decentralized surveys (see table 3).

Samples 2, 3 and 4 were tested undiluted by all laboratories. The CV's were 17%, 23% and 30% respectively. The highest CV was found in the sample with the lowest inhibitor activity (sample 4, 0.5 BU/ml).

Samples 1, 5 and 6 were tested undiluted or diluted at different ratios. A graphical representation of the correlation between dilution ratio and measured inhibitor activity of these samples is shown in figure 2. There appears to be a minor (sample 5 and 6) to strong (sample 1) influence of the dilution rate on the inhibitor activity. Although the correction of this defectiveness was the basis for the development of the Nijmegen assay [3], this problem is still not fully solved. Lowering the VC of inter-laboratory survey results will need a solution for this phenomenon.

The inhibitor activity of the negative sample in the final survey was below the cut-off value in all participants but one.

No significant differences in inhibitor activity were found between the results of the final survey and the results of any of the other surveys.

Conclusion

Further standardization of the FVIII inhibitor assay has proven to be possible by performing a cycle of activities that is described in this report. Results of the workshop has shown that optimal standardization of the inhibitor test may lead to low inter-individual variation, suggesting that the variation in individual liquid handling only has a limited contribution to the total assay variation. The dilution-rate dependency of inhibitor assay results needs to be further investigated.

It is striking that, despite a number of reports on further standardization of the assay, a number of laboratories do not implement these improvements at all or only to a limited extent [1]. The compliance for implementation of amendments needs to be a point of intention in the near future.

References

1. Meijer P, Verbruggen B. The between-laboratory variation of factor VIII inhibitor testing the experience of the external quality assessment program ofthe ECAT foundation. Semin Thromb Hemost. 2009; 35(8): 786-93.
2. Verbruggen B, Dardikh M, Polenewen R, van Duren C, Meijer P. The factor VIII inhibitor assays can be standardized: results of a workshop. JThromb haemost. 2011; 9(10):2003-8.
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ECAT programme 2014

In 2014 we will start with three new modules in the ECAT external quality assessment programme.

The first two modules are related to the measurement of **ADAMTS13**. The measurement of ADAMTS13 is important in the diagnosis of Thrombotic thrombocytopenic purpura (TTP). There will be a module introduced for activity and antigen testing as well as one for inhibitor testing. Both modules will include two samples and will run 4 times per year.

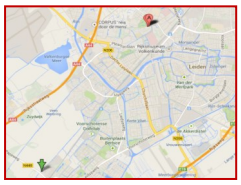
The 3rd module concerns the quantitative testing of Apixaban. Apixaban is one of the novel direct anti-Xa drugs and nowadays used for the treatment of artrial fibrillation and venous thromboembolism. After the successful introduction of external quality control for, for instance, rivaroxaban and argatroban a module for apixaban also has now been added to our programme. This module will run, like the other modules for the novel anticoagulation drugs, 2 times per year.

If you are interested in one of these modules and not yet registered please contact the ECAT office (info@ecat.nl).

New facilities

From 2004 onwards the ECAT was located in a small building named “Luistervink”, part of a larger property belonging to the Dutch research organisation TNO (location A on the map). Because the whole TNO property had been put up for sale the rental contract with the ECAT was not renewed anymore, so we had to search for new facilities. We found modern facilities in the small town of Voorschoten near the city of Leiden. Here we were able to rent sufficient offices and working space for our organisation on the first floor of the building. Since August 1st, 2013 we have been located at the Dobbeweg 1, 2254 AG Voorschoten, The Netherlands (location marked with the green arrow on the map).

Please be aware of the new contact details of the ECAT Foundation (see front page).



Special ECAT symposium on “Quality Assurance of the Diagnostic Process”

In conjunction with the ISLH congress 2014 the ECAT Foundation will organise a special symposium on **Wednesday 14 May 2014**. This symposium, entitled “Quality Assurance of the Diagnostic Process” will be hold in the Worldforum, The Hague, The Netherlands (the same venue as the ISLH congress).

In external quality assessment the major focus so far has mainly been on the analytical phase. However, the whole diagnostic process covers more than just laboratory testing. Also the pre- and post-analytical phases are important. And even more so, the interaction between the laboratory and the physician is an essential part in the diagnostic process. Therefore during this symposium we will discuss how the quality of the entire process can be assured. For this purpose we have drafted an interesting programme.

Programme

- The relevance of quality assurance of the entire diagnostic process, Sverre Sandberg, Norway
- How to manage the quality of the pre-analytical phase, Ana-Maria Simundic, Croatia
- Quality assurance of the post-analytical phase, Eva Ajzner, Hungary
- Quality assurance of the analytical phase in haemostasis, Piet Meijer, The Netherlands
- Quality assurance of the analytical phase in haematology, Sjef van de Leur, The Netherlands
- Quality assurance of the entire diagnostic process, the ECAT experience, Moniek de Maat, The Netherlands

For further details and registration see the website of the ISLH congress 2014 (http://www.islh.org/2014/).

Report complaints

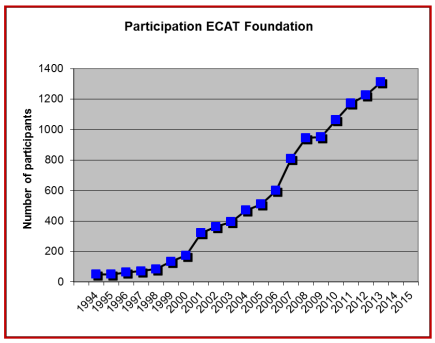
We would like to remind you that we changed our policy regarding survey report complaints in 2013. Any complaint regarding a survey report should be sent to the ECAT within 6 weeks after the issue date of the report. Complaints received after this period are no longer considered.

Although we introduced this policy in 2013, probably not everybody was aware of this change. Therefore we have tried to be accommodating. However, beginning in 2014 we will strictly follow this policy.

Increasing number of participants

Almost at the end of 2013 we can inform you that the number of participants again has been increased this year. At the end of 2012 we had 1225 laboratories participating in at least one of our modules. Currently there are 1312 laboratories. This means a growth of 7% in 2013.

Larger numbers in the different modules means a more reliable assessment of the assigned values and also better possibilities for reporting the results for different method groups.

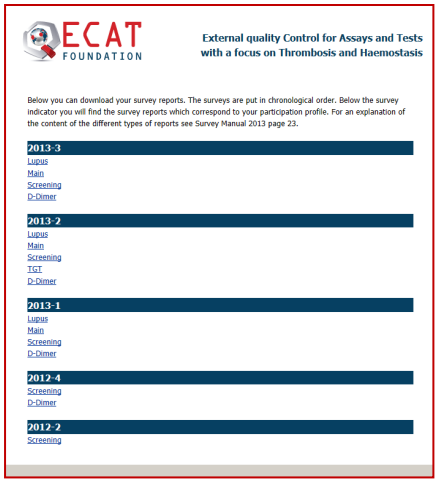


Electronic reports

In 2013 we are started providing the survey reports electronically. The survey reports can now be downloaded from the Participants Area at our website (select Login, enter your labcode and password, select Survey Reports and Download reports). Here you can download the survey reports. This option makes it also possible to store electronic copies of the survey reports on your own computer.

Electronic reports will be available for a period of **three years**. After three years the oldest survey will be replaced by the latest one.

In the coming month we will make the reports of 2011 and 2012 available to be downloaded. In **June 2014** we will start with the replacement of the survey reports older than 3 years.


ECAT FOUNDATION

External quality Control for Assays and Tests with a focus on Thrombosis and Haemostasis

Below you can download your survey reports. The surveys are put in chronological order. Below the survey indicator you will find the survey reports which correspond to your participation profile. For an explanation of the content of the different types of reports see Survey Manual 2013 page 23.

2013-3
Lupus
Main
Screening
D-Dimer

2013-2
Lupus
Main
Screening
TGT
D-Dimer

2013-1
Lupus
Main
Screening
D-Dimer

2012-4
Screening
D-Dimer

2012-2
Screening

The Corporate Corner, a portal to companies on the website of the ECAT Foundation

This year the new website of the ECAT Foundation was launched. On this website you can now find our Corporate Corner more easily. It is now an item in the main menu on the home page of the ECAT website. The Corporate Corner provides you with easy access to the websites of diagnostic companies in the field of thrombosis and haemostasis. There are two ways companies can participate in the Corporate Corner: the Advanced and the Basic version. The page of the Corporate Corner is divided in these two groups.

Companies who participate in the Advanced version have their own page with highlights on the ECAT website. Just click on the logo to discover this.

These companies also have in the item 'Assays'; per assay there is a direct link to the reagent-specific information on their own website and, if available, a direct link to the package insert. 'Assays' gives the laboratory professional an overview of which reagents are available for different haemostasis assays.

You can find the item 'Assays' in the protected part of the educational section 'ECAT Education' of the ECAT website, www.ecat.nl/ecat-education/education/assays .

Companies who participate in the basic version have their logo placed on the site with a direct link to their website. This is an easy way to search for information you need.

The following companies are available in the Corporate Corner:

Advanced: Affinity Biologicals, Hyphen Biomed, Immucor, Instrumentation Laboratory (IL), George King Bio- Medical, Inc., Precision Biologic, Technoclone
Basic: Chrono-Log, Kordia, Multiplate, Nordic Biomarker, R^2 Diagnostics, Roche, Clinical education, Siemens, Stago

Case Report:

Acquired factor X deficiency

L. Coucke, MPharm and K. Devreese, MD, PhD

Coagulation Laboratory, University Hospital Ghent, Ghent, Belgium

Case Report

A 52-year-old male visited the emergency department with fever, coughing and severe abdominal pain. Two weeks prior to admission amoxicillin, clarithromycin, and moxifloxacin were subsequently prescribed for a non-resolving pharyngitis. The patient had no relevant family or personal medical history. He was taking no medication other than acetaminophen. He smoked 10 cigarettes a day (15 pack-years). Over the days following to his admission he developed macroscopic haematuria and epistaxis. A CT of the thorax demonstrated a pneumonia in the right lobe. Laboratory data showed leukocytosis 13.8 $x10^9$/L (3.7 – 9.5 $x10^9$/L) with left shifted differentiation, a platelet count of 274 $x10^9$/L (150 – 450 $x10^9$/L), C-reactive protein of 7.3 mg/dL (0 – 0.7 mg/dL) and normal renal and liver function tests. Serum protein electrophoresis showed minimal deviation in the gamma-globulin fraction but the free light chain ratio was within normal limits.

First screening coagulation test results showed a prolonged activated partial thromboplastin time (aPTT) of 144.1 s (28.0 – 39.0 s) and a prolonged prothrombin time (PT) of 6% (70 – 116%) with an INR of 17.7. Thrombin time was 17.8 s (14.0 – 21.0 s). There was no evidence of disseminated intravascular coagulation. D-dimers were 0.3 mcg/mL (<0.5 mcg/mL) and the fibrinogen concentration was slightly elevated 594 mg/dL (180 – 401 mg/dL) reflecting the patient's inflammatory state. In the diagnostic work-up of combined aPTT and PT prolongation, we performed a mixing study of patient plasma (PP) and normal pooled plasma (NP) in a 1:1 proportion. The mixing studies showed a correction (aPTT correction of 81%, PT correction of 93%) of aPTT and PT values (Table I) after one and two hours of incubation at 37°C. To exclude vitamin K deficiency factor IX was determined and found to be within the normal range. Factors II, V and X levels were measured: Factor II and V levels were within the normal range, factor X was <1% (70 – 120%) (Table I). The Bethesda assay could not demonstrate the presence of an inhibitor. Lupus anticoagulant testing was negative.

The patient was initially treated with IV methylprednisolone 80 mg, fresh frozen plasma (FFP), platelet transfusion, vitamin K and tranexamic acid. The pneumonia was treated with meropenem and clarithromycin. There was an improvement of the patient's aPTT, PT and FX levels. He was discharged 9 days after admission with methylprednisolone in tapering dose, clarithromycin for 7 more days and pantoprazole. Twenty days after discharge a normal aPTT of 36.5 s, normal PT of 97% and normal FX level of 107% were measured (Figure 1).

Discussion

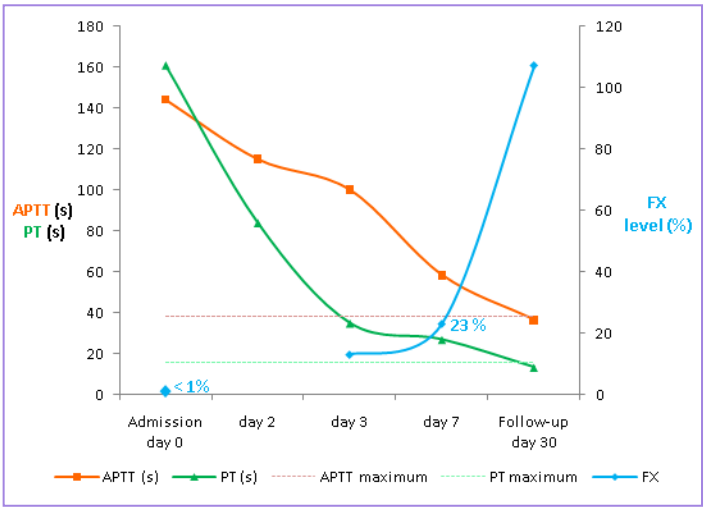
We report a patient presenting with macroscopic haematuria and epistaxis and laboratory tests (screening tests, factor assays and Bethesda assay) indicating an isolated factor X deficiency (FXD). Even though the FX level of the 52-year-old patient was undetectable at diagnosis (<1%), he had no previous clinical history of bleeding diathesis. He recovered within a few weeks under corticosteroid therapy with normalization of the coagulation parameters. This suggests an acquired and transient FXD. Both acquired isolated FXD as well as the congenital FXD are rare coagulation disorders. Homozygous FXD has an incidence of 1:1 000 000 [1], acquired FXD is

Table 1. Results of mixing assays and factor dosage

	aPTT (s)	normal	PT (%/s)	normal
Patient plasma	144.1	28.9 - 38.1	6 / 161	70 - 116 % 12.2 – 15.8 (s)
Patient + normal plasma (1:1) 0h	63		43 / 21.4	
Patient + normal plasma (1:1) 1h	63		45 / 20.7	
Patient + normal plasma (1:1) 2h	71		37 / 23.7	
Conclusion mixing assay	% aPTT correction*: 81%		% PT correction*: 93%	
	Patient plasma		normal	
Factor II (%)	75%		70 – 120%	
Factor V (%)	86%		70 – 120%	
Factor X (%)	< 1%		70 – 120%	

* % Correction formula = $\frac{\text{patient plasma aPTT (or PT)} - \text{1:1 Mix aPTT (or PT)} \times 100}{\text{patient plasma aPTT (or PT)} - \text{normal pooled plasma aPTT (or PT)}}$ [7]

Figure 1. Evolution of coagulation tests during hospitalization and in a control sample 30 days after admission. Initially, there is a strong prolongation of both aPTT and PT. Soon after initiation of therapy the APTT and PT declined. The FX level was over 20% by day 7, corresponding to the FX level necessary for normal haemostasis. Thirty days after initial admission all results were within the normal range.



described in case reports [3]. FXD is associated with a variable bleeding tendency.

Acquired factor X deficiencies (FXD) are well known in the setting of vitamin K deficiency, vitamin K antagonist therapy, or liver disease. In those circumstances, other coagulation factor levels are simultaneously affected. In this case, a normal factor IX and factor V were measured. Isolated acquired FXD is extremely rare and should be considered especially in cases of monoclonal immunoglobulin deposition diseases due to direct factor X binding to amyloid fibrils [1]. FXD is associated in 8.7 % with AL amyloidosis and rarely seen in AA amyloidosis. Only a few case reports describe an association of acquired FXD with myeloma, acute leukemia, solid tumours and infection [2]. Since 1965, there have been as few as 34 cases reporting isolated acquired FXD in the absence of amyloidosis or plasma cell dyscrasia [3].

The patient's echocardiography, bone marrow examination and fat pad aspiration showed no amyloidosis. There was no evidence of other underlying malignancy. One third of the isolated acquired FXD cases reported occurred after a respiratory tract infection for instance with *M. pneumoniae*, which might also be an explanation for this case [3]. However, no causative organism could be found. Infection with *M. pneumoniae* was not confirmed by serology, which only indicated previous immunologic exposure. It is postulated that foreign epitope exposure might cause the formation of antibodies to coagulation factors. In this case, no neutralizing inhibitor was demonstrated but non-inhibitory antibodies have been described that accelerate the clearance of clotting factors such as FII [4, 5] and FX [6]. It is impossible to recognize a non-neutralizing inhibitor by means of a clotting test. Non-neutralizing inhibitors can be assayed by immunochemical techniques such as immunoelectrophoresis where antibody-bound FX will show retarded electrophoretic mobility [4].

This patient was admitted with macroscopic haematuria and epistaxis. In acquired FXD the bleeding tendency varies from absence or mild bleeding to life-threatening haemorrhage. Most frequently gastrointestinal bleeding, haematuria and ecchymoses occur but a minority of patients experience haemarthroses or musculoskeletal bleeds [3]. All reported patients with severe acquired FXD (factor X < 1%) showed overt bleeding.

In most patients, the syndrome is self-limiting with complete recovery after a period of one week to one month. No mortality has been described. In this patient, normal coagulation results were measured within one month after initial admission. This confirms the transient nature of the FXD with full recovery after supportive therapy (FFP, tranexamic acid), treatment of the infection and corticosteroid therapy to retard the clearance of possible FX-antibody complexes, without the necessity for plasmapheresis. Given the rarity of this disorder, there are no standardized treatment procedures. In most cases, FFP and vitamin K were given [3]. Any associated primary disorder should be treated if feasible.

This case illustrates bleeding tendency and a therapeutic approach in a patient with non-amyloid-related acquired isolated FXD after respiratory illness. Recovery of normal coagulation took less than one month.

(Based on the publication: Coucke L., Trenson S., Deeren D., Van haute I., Devreese K. Life-threatening bleeding tendency provoked by an acquired isolated factor X deficiency associated with respiratory infection. Annals of Hematology, published online 6 March 2013).

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