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LETTER TO THE EDITOR

WILEY Haemophilia

Diagnostic delay in acquired haemophilia: Analysis of causes and consequences in a 20-year Spanish cohort

Dear Sir,

Acquired haemophilia represents a rare autoimmune disease in which, through the production of autoantibodies against factor VIII (FVIII), a severe haemorrhagic diathesis is initiated. Prompt recognition is critical, since early therapy directed towards achieving hemostasis and inhibitor eradication can be life-saving. Some of the studies on acquired haemophilia[1-3] did not address diagnostic delay issues, and the only data in this regard were published in the European Registry of Acquired Haemophilia (EACH2), the largest registry of patients ever reported.[4] Authors found that most of the patients achieved a diagnosis in the first week after bleeding onset, with a median of 3 days (interquartile range [IQR]: 0-12 days) and that diagnostic delay had a significant impact on the interval between onset of bleeding and the start of haemostatic therapy. However, authors did not find influence on severity of bleeding, doses or duration of haemostatic therapy, time to bleeding resolved or overall survival. Less well recognized are the causes of diagnostic delay, that as far as we know, no study has addressed. To review all these aspects, we performed a retrospective study of our historical cohort of patients with acquired haemophilia.

Between 1997 and 2017, 28 patients were diagnosed, treated and/or supervised in our reference centre. Four of the 28 patients were not referred to our hospital and were treated together in their district hospitals or centres of origin. Our population (Table 1) included predominantly males (69%), with mean (±standard deviation, SD) age of 69±16 years, high morbidity index (mean Charlson score 5) and with idiopathic forms of acquired haemophilia (43%) or associated with autoimmune entity (39.2%). We included two patients with gestational acquired haemophilia. Patients received different immunosuppressive regimens along those years and from 2001 mainly induction with cyclosporine or tacrolimus and methylprednisolone intravenous pulses.[5] After a mean follow-up period of 46 months, the rate of complete (FVIII > 50% and negative inhibitor without immunosuppressant) or partial (FVIII > 50% and negative inhibitor under immunosuppressant treatment) remission has been reached in almost 90% of cases, with overall mortality of 46.4% (13/28 patients, all cases in remission at death). We had 3 cases in which death could be attributed directly to acquired haemophilia (2 cases of fatal bleeding and one opportunistic infection under immunosuppression), while the rest of cases accounted for senility or chronic disease.

All the patients debuted with haemorrhagic symptoms. Median time to achieve a definitive diagnostic of acquired haemophilia from first bleeding was 19 days (IQR 2-180 days). Clinical causes of delay were analysed (Table 1). A commonly issue acting as cause for diagnostic delay in our patients was the use of anticoagulant/antiaggregant treatment (17/28 patients, 60.7%), a fact to which easily attribute the cause of the initial haemorrhage. One patient was under dabigatran anticoagulant treatment due to an atrial fibrillation 6 months before developing acquired haemophilia.

Pseudothrombosis is the clinical situation in which in distal extremity, usually in calf, swelling, pain and oedema develop with no external sign of haemorrhage thus resembling peripheral venous thrombosis but caused by deep muscle haemorrhage. Echographic findings secondary to deep muscular haemorrhage may be nonspecific or difficult to differentiate from venous stasis oedema, visualization of the venous system may be difficult, there may even be venous compression that mimics thrombosis, and so it will sometimes be difficult to rule out venous thrombosis, and in case of doubt, the clinical decision may be to start anticoagulation. In our cohort, we found 8 of 28 patients (26.8%) with clinical onset in form of pseudothrombosis. Echography was performed in 6 patients (arm in one case, distal legs in the rest) diagnosing deep muscle haematomas in 3 of them, thrombophlebitis in one patient and possible deep vein thrombosis in 2 cases. Those last 3 patients received anticoagulant low molecular weight heparin between 24 and 48 hours but subsequent repeated ultrasound studies in our reference hospital ruled out the presence of deep venous thrombosis, considering initial out hospital ultrasounds as false positives. All three anticoagulated patients developed a severe haemorrhagic diathesis, complicated in one case with compartmental syndrome that required surgery. Finally, comment that in 2 other patients with calf pseudothrombosis echography was not considered necessary because of a clinical bleeding setting with clear cutaneous and subcutaneous haemorrhages.

Other aspects of diagnostic delay were related with coagulation testing. In our cohort, 10 of 28 patients (35%) did not have a basic coagulation test performed when attending to medical centres in the first consultations for haemorrhage. In other cases, results of coagulation studies were simply not evaluated (10.7% of patients) or incorrectly interpreted as normal (25% of patients). Activated partial-phase cephalin or thromboplastin time (APTT) was not initially performed in some of our patients (4 of 28 patients, 14.3%) because it was not included in coagulation routine tests in certain laboratories of district hospitals or primary care centres. In our sanitary area, we have observed that most of district hospitals have the technical capacity to perform mixing tests and suspect inhibitor existence, but lack of technical equipment to confirm or quantify the inhibitor (Bethesda or Nijmegen method). In 17 of our 28 patients (60.7%), the complete study (mixing test and quantification of inhibitor) could be performed. Regarding the remaining 9 patients, in two

TABLE 1 Basic characteristics and causes of diagnostic delay in our cohort of patients with acquired haemophilia

N (n)	28
Sex (M/F)	19 (69%)/7 (33%)
Age (mean years, SD) at diagnosis	69 (16)
Period (years)	1997-2017
Follow-up (mean months, SD)	46 (55)
FVIII at diagnosis (mean %, SD)	1.7 (2.4)
FVIII inhibitor at diagnosis (mean BE, SD)	40 (62)
Associated disease (n, %)	
Idiopathic	12 (43)
Neoplasia	5 (17.8)
Autoimmune	11 (39.2)
Gestational	2 (7.1)
Hyperparathyroidism	1 (3.5)
Charlson (mean, SD)	5 (3)
Acquired haemophilia status (n, %)	
Partial remission	6 (21.4)
Complete remission	19 (67.9)
No remission	3 (10.7)
Death (n, %)	13 (46.4)
Centre of origin (n, %)	
District hospital	18 (64.2)
Private hospital	5 (17.8)
Socio-health centre	1 (3.5)
In-hospital	3 (10.7)
Outside country	1 (3.5)
Diagnostic delay (from first haemorrhagic episode) (median days, IQR)	19 (2-180)
Coagulation test (n, %)	
Not ordered at first haemorrhagic consultation	10 (35)
Result not evaluated	3 (10.7)
Wrongly interpreted as normal	7 (25)
Not including aPTT	4 (14.3)
Pseudothrombosis (n, %)	8 (28.6)
Use of anticoagulant treatment (n, %)	17 (60.7)
Impossibility of performing FVIII in centre of origin (n, %)	8 (28.6)
Impossibility of performing Inhibitor in centre of origin (n, %)	17 (60.7)

aPTT, activated partial thromboplastin time; BU, Bethesda units; IQR, interquartile range; SD, Standard deviation.

cases the mixing test was performed but Bethesda assay could not be completed while in the other 7 neither mixing test nor quantification of inhibitor could be carried out.

We analysed the consequences of diagnostic delay in our patients (Table 2). For study purposes, we divided patients into subgroups with delay under or over one month (11 and 17 patients, respectively). FVIII activity and inhibitor titre did not differ between groups. Regarding bleeding, patients with diagnostic delay under and over one month presented similar mean haemoglobin levels at diagnosis (6.8 ± 1.6 vs 7.3 ± 2.4 mg/dL, respectively, $P = .8$) and transfusions requirements throughout evolution (7.3 ± 6.5 vs 7.5 ± 6.8 blood concentrates, respectively, $P = .60$). We found differences in aspects referring to haemostatic therapy. The time to initiate haemostatic agents (bypassing or FVIII) was greater in the subgroup with more delay (55 ± 49 vs 10 ± 6 days, respectively, $P = .01$), but furthermore, delay was associated with the needs of those agents. Firstly, we found that the interval of days between first and last bleeding episode along disease (including relapses) was greater in patients when diagnostic delay exceeded one month respect to subgroup or early diagnosis (49 ± 52 vs 20 ± 20 days respectively, $P = .05$). The subgroup of patients with more than one month of diagnostic delay required significantly more days of haemostatic therapy along disease (23.8 ± 13 vs 7.6 ± 5.7, respectively, $P = .003$). Recombinant activated factor VII (rFVIIa-Novoseven^{R}) was

TABLE 2 Impact of diagnostic delay in our cohort of patients with acquired haemophilia

	Diagnostic delay from 1st bleeding		
Variables	<1 mo	>1 mo	*P*
Patients (n, %)	17 (60.8)	11 (39.2)	
FVIII (activity %)	1.9 (2.9)	1.5 (1.2)	NS
Inhibitor title (BU)	46 (66)	36 (61)	NS
Hb (g/dL)	6.8 (1.6)	7.3 (2.4)	NS
Major bleeding (n,%)[a]	15 (88)	9 (81)	NS
Blood concentrates (n)	7.3 (6.5)	7.5 (6.8)	NS
Days to start haemostatic treatment	10 (6)	55 (49)	.01
Days to resolve bleedings[b]	20 (20)	49 (52)	.05
Days of haemostatic treatment	7.6 (5.7)	23.8 (13)	.003
Total dosage of Novoseven^{R} (mg)	62 (53)	190 (166)	.02
Total dosage of FEIBA^{R} (UI)	38000 (2800)	60000 (73539)	NS
Total dosage of FVIIIr (UI)	29000 (26000)	31000 (16750)	NS
Remission (n, %)[c]	15 (88)	10 (90.9)	NS
Recurrence (n, %)	3 (17.6)	3 (27.3)	NS

Quantitative variables are expressed as means (standard deviation).
[a]Major bleeding: Haemoglobin level below 8 g dL OR a drop by more than 2 g dL, OR life or limb threatening, central nervous system, deep muscle or retroperitoneal bleeding.
[b]Interval of days between first and last bleeding episode along disease (including relapses).
[c]Partial (FVIII > 50% and inhibitor negative under immunosuppressive treatment) or complete (FVIII > 50% and inhibitor negative without immunosuppressant).

the most frequently used haemostatic in our cohort, and the only that presented differences in the total dosage between groups of diagnostic delay (190 ± 166 vs 62 ± 53 mg, respectively, $P = .02$). When we delve into other consequences of diagnostic delay, we found no differences between subgroups under or over one month respect to remission (15 patients, 88% vs 10 patients, 90.9%, respectively, $P = .24$) or recurrences (3 patients, 17.6% vs 3 patients, 27.3%, $P = .84$). Finally, we found no association of diagnostic delay with survival (Kaplan test, $P = .85$).

A recent article on congenital haemophilia reviewed preanalytical issues causing misdiagnosis.[6] Blood collection and processing and interactions with anticoagulants accounted for frequent reasons. However, clinical requests and laboratory test choices depending on medical suspicion are considered relevant to avoid diagnostic errors. Our study has identified for the first time the specific causes of diagnostic delay in acquired haemophilia and has evaluated its frequency of presentation. Once our results have been evaluated, we consider that, apart from specific technical issues that limit the performance of complex coagulation tests in certain local laboratories, it is the lack of diagnostic suspicion of that disease that accounts for the greatest proportion causing diagnostic delay, since the clinician will neither order correct clotting tests nor provide all the information to the laboratory to adequately expand or interpret the coagulative studies. In that line, we have described here the first case in literature of acquired haemophilia while on dabigatran treatment, and, with the background of scarce published cases of acquired haemophilia under direct oral anticoagulants (DOAC),[7,8] we foresee similar situations of difficult differential diagnosis in the near future. Finally, and unlike results from EACH2 registry,[4] we found that delayed initiation of haemostatic treatment in the acute haemorrhagic phase of acquired haemophilia is associated with longer haemorrhagic time periods and greater haemostatic requirements along disease. These findings constitute the first report in acquired haemophilia of a major complication as consequence of diagnostic delay. In any case, the fact that we did not find influence of the diagnostic delay on survival seems more probably related to the small number of patients included and the bias of non-including never-diagnosed cases or those not referred to our centre.

We believe that the identification of those diagnostic delay issues could be a first step to design strategies for future improvement in the diagnosis of this serious and rare haemorrhagic entity in our and other health areas worldwide.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

JPG designed the research, collected data, analysed data and wrote the manuscript. NFD collected data. RP designed the research and collected data. VC contributed essential hemostasis reagents. CA designed the research and collected data.

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