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ORIGINAL RESEARCH REPORT

Acquired factor X deficiency in light-chain (AL) amyloidosis is rare and associated with advanced disease

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Abstract
Introduction: Systemic light chain (AL) amyloidosis can lead to an acquired coagulopathy secondary to acquired factor X (aFX) deficiency. However, it is not very clear who develops aFX deficiency in AL amyloidosis.
Methods: We therefore undertook this single centre, retrospective study to better characterize AL amyloidosis-associated aFX deficiency.
Results: Out of 121 AL patients who had FX testing at the time of their first evaluation at our institution, including 17 patients on warfarin at the time of testing, 10 out of 104 patients (9.6%) with systemic AL amyloidosis were found to have FX levels below 50%. Acquired FX deficiency was associated with advanced stage of AL amyloidosis and elevated cardiac biomarkers. Lower FX activity, advanced stage, and cardiac involvement by disease were associated with higher hazard of death on univariate analysis. On multivariate analysis, stage of AL amyloidosis was the only significant predictor of survival. Median survival time of patients with FX deficiency was 9.3 months compared to 118.4 months in those without.

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Conclusions: We conclude that while aFX deficiency is rare in systemic AL amyloidosis, it is a marker of advanced disease.

Introduction

Systemic light-chain (AL) amyloidosis is a plasma cell dyscrasias characterized by formation of aberrant monoclonal immunoglobulin light chains which aggregate and deposit as amyloid fibrils [1]. Deposition of these fibrils in various organ systems results in damage, dysfunction, and the subsequent clinical manifestations seen in this condition. One such manifestation is acquired factor X (aFX) deficiency, which is an uncommon but well-studied consequence of systemic AL amyloidosis. It has been long speculated that the adsorption of FX by amyloid fibrils in circulation leads to FX deficiency [2]. More recently, pentraxin-2 has been identified as an essential partner for FX to prevent internalization into macrophages, and both FX and pentraxin-2 may be targeted to amyloid plaques [3]. Because aFX deficiency does not occur in every patient with AL amyloidosis, it has been postulated that a higher load of amyloid fibrils in the circulating blood may contribute to its development [2]. This theory is supported by studies describing a correction of aFX deficiency in AL amyloidosis patients following splenectomy [4,5], treatment with chemotherapy [6], and autologous hematopoietic cell transplantation [7]. However, there are limited studies in the literature directly investigating the relationship between FX activity and burden of disease in systemic AL amyloidosis patients. In this report, we describe the prevalence of aFX deficiency in relation with disease stage, organ involvement, and early mortality in AL amyloidosis patients.

Patients and methods

This study was approved by the Institutional Review Board at the Medical College of Wisconsin (Milwaukee, WI, USA). We conducted a retrospective chart review of all patients with systemic AL amyloidosis that were evaluated at our institution from January 1, 2007 to December 21, 2016. We identified 121 patients who had the FX level drawn at their first evaluation at our center. Patients who were on warfarin at the time of FX testing ($n = 17$) were excluded from further analysis leaving a sample size of 104 patients. We also recorded standard blood and urine test results drawn at the time of FX level, bone marrow biopsy results when available, organ involvement by AL amyloidosis, type and date of bleeding and clotting events that occurred within 12 months following FX measurement, comorbidities, and last follow-up or death. Patients were staged using the 2012 Mayo Clinic revised staging system which required N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), and free light chains. Patients who did not have NT-proBNP or cTnT at diagnosis could not be staged and were categorized as ''missing" stage.

Patients were divided into two groups based on FX activity: <50% and ≥50%. We labeled FX activity of <50% as aFX deficiency based on literature review [6,7]. Baseline characteristics were compared between the two groups using the Fisher's exact test for categorical variables and Wilcoxon rank-sum tests for continuous variables. Kaplan—Meier methods were used to plot survival for all patients and by aFX group. The log-rank test was used to compare survival distributions between aFX groups. Univariate and multivariable Cox proportional hazards regression were used to model time from FX measurement to death or last follow-up. In the multivariable analysis, FX (continuous), age, stage, cardiac involvement, and number of noncardiac organs involved were included as significant variables from the univariate analysis. Multivariate analysis with aFX as a binary predictor (<50% vs. ≥50%) was not performed due to the small number of patients in the <50% group and the resulting quasi-complete separation for many outcomes.

Results

Of 104 patients, 10 had FX activity <50% and only two had FX activity <10% (Table 1). The median FX activity level of the aFX group was 40.5% (range: 6—47%). While we excluded patients on warfarin from analysis owing to drug-induced FX depletion, we allowed other anticoagulants with limited or no influence on FX activity measurement [8,9]. The median age was 63.4 years and 54% of patients were male. Compared with patients with normal FX activity, patients with aFX deficiency were more likely to have higher stage ($p = .05$). FX-deficient patients were also more likely to have higher NT-proBNP (median 8732.5 vs. 1497.0, $p = .002$) and cTnT (median 0.1 vs. <0.011, $p = .03$). There was no statistically significant difference between the groups in the number of organs involved or the presence of cardiac involvement; however, 100% of aFX group had cardiac involvement compared with 70% in the other group ($p = .06$).

Neither group had a significantly higher probability of experiencing a bleeding or thrombotic event. In the 10 patients with aFX deficiency, no bleeding events occurred in the first 12 months after FX level was measured. There was no difference in the number of comorbidities associated with thrombosis (hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, and history of tobacco use) between the two populations.

The median follow-up of survivors (73 evaluable out of 104 patients) was 21.5 months (range: 0—139.5 months). On Kaplan—Meier analysis, the median survival of patients with aFX deficiency was 9.3 months compared with 118.4 months in those without the deficiency (log-rank test; $p = .008$; Fig. 1). On univariate analysis (Table 2), lower FX level was associated with a higher hazard of death ($p = .001$). A stage III/IV compared with stage I/II was also

Table 1 Clinical characteristics and laboratory values of patients according to factor X level.

	All (n = 104)	FX < 50% (n = 10)	FX ≥ 50% (n = 94)	p
Age at factor X measurement (y)	63.4 (30.7—87.6)	66.1 (52.7—78.7)	62.4 (30.7—87.6)	.4
Sex	54 (52)	6 (60)	48 (51)	.7
Male				
Factor X activity	74 (6—150)	40.5 (6—47)	80 (50—150)	
AL subtype, lambda	73 (71)	6 (60)	67 (72)	.5
dFLC, mg/L	182.5 (51.1—59,983.1)	377.1 (52.2, 8119.2)	180.1 (51.1—59,983.1)	.1
NT-pro BNP, n = 80	1731.5 (32—50,835)	8732.5 (2,641—18,333)	1,497 (32—50,835)	.002
cTnT, n = 93	<0.011 (<0.011—1.1)	0.1 (<0.011—0.3)	<0.011 (<0.011—1.1)	.03
AL stage (2012)				.05
Stage I/II	41 (39)	1 (10)	40 (43)	
Stage III/IV	37 (36)	7 (70)	30 (33)	
Missing	26 (25)	2 (20)	22 (24)	
Alkaline phosphatase	87.5 (33—600)	145 (45—485)	86.5 (33—600)	.3
Albumin	3.4 (1.2—4.8)	3 (1.9—4.6)	3.4 (1.2—4.8)	.5
Creatinine	1.1 (0.4—9.8)	1.3 (0.8—4.2)	1.1 (0.4—9.8)	.2
Bone marrow plasma cells, n = 87	8 (0—70)	11 (1—29)	7.5 (0—70)	.5
Cardiac involvement	76 (73)	10 (100)	66 (70)	.06
Noncardiac organs involved				.7
0				
1	16 (15)	3 (30)	13 (14)	
2+	44 (42)	1 (10)	43 (46)	
	44 (42)	6 (60)	38 (40)	
Anticoagulant[a]				.7
None	96 (92)	8 (80)	88 (94)	
Heparins	4 (4)	0	4 (4)	
Apixaban	1 (1)	1(10)	0	
Rivaroxaban	3 (3)	1(10)	2 (2)	

Note. Continuous variables are presented as median (min—max) and categorical variables as frequencies (%). The n is listed if there are any missing entries. AL = light chain; cTNT = cardiac troponin T; dFLC = difference between involved and uninvolved free light chains; FX = factor X; NT-proBNP = N terminal of pro-brain natriuretic peptide; y = year.

[a] Other than warfarin.

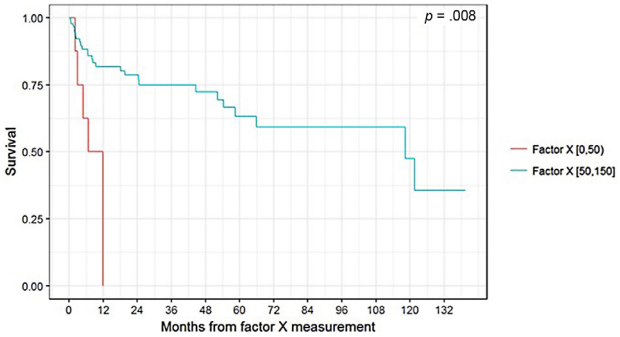

Fig. 1 Kaplan—Meier survival analysis.

associated with a higher hazard of death (p < .001), as was the presence of cardiac involvement (p = .02). On multivariable analysis, only stage was significantly associated with mortality (p = .03).

Discussion

In this single-center study of AL amyloidosis and aFX deficiency, we make the following observations: (a) aFX deficiency defined as FX activity < 50% was uncommon at 9.6%, with FX < 10% being even rarer (only 2 patients out of 104); (b) aFX deficiency correlated with advanced stage; (c) no bleeding events were seen in the first 12 months of follow-up after FX activity in this small population; and (d) while aFX deficiency was associated with worse survival, this was likely due to its association with advanced stage of AL amyloidosis.

Our finding of a 9.6% prevalence of aFX deficiency is consistent with other studies showing a frequency of 7.5% in a series of 358 patients[7] and 8.7% in another series of 368 patients.[6] Another study by Mumford et al.[10] with a series of 154 patients showed a prevalence of 14%; however, it is unclear if FX deficiency was defined as FX activity <50% as it was in the aforementioned studies.

Comparison between the group with normal FX activity and the group with aFX deficiency showed that FX deficiency was significantly associated with elevated levels of cardiac biomarkers. Both NT-proBNP [11] and cTnT [12] are sensitive and specific markers of cardiac involvement in AL amyloidosis. Indeed, 100% of patients with aFX deficiency in our study had cardiac involvement, although on univariate analysis, the difference between cardiac involvement in the

Table 2 Univariate and Multivariate Analysis of Survival.

	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Low FX activity	1.02 (1.01–1.04)	.001	1.01 (0.99–1.03)	.2
Age (y)	1.01 (0.98–1.04)	.6	1.00 (0.97–1.04)	.8
Stage				
– Stage III/IV versus Stage I/II	5.41 (2.15–13.58)	<.001	3.57 (1.32–9.69)	.01
– Missing versus Stage I/II	2.77 (0.96–7.99)	.06	2.55 (0.86–7.53)	.09
Cardiac involvement, yes vs. no	3.65 (1.28–10.41)	.02	1.73 (0.53–5.62)	.4
Number of noncardiac organs involved				
–1 vs. 0	0.64 (0.23–1.76)	.4	0.86 (0.30–2.44)	.8
–2+ vs. 0	1.56 (0.61–3.96)	.4	1.58 (0.60–4.12)	.4

Note. Values are shown as hazard ratios and 95% confidence interval of death. CI = confidence interval; FX = factor X; HR = hazard ratio; y = year.

group with FX deficiency was not statistically significant compared with cardiac involvement in the group without FX deficiency, possibly due to the small sample size. FX deficiency also was significantly associated with stages III and IV of disease compared with normal FX activity. Staging is based upon NT-proBNP, cTnT, and the difference between serum free light chain types [13].

There was no statistically significant difference between FX deficiency and normal FX activity in predicting bleeding or clotting events. Some previous studies found that AL amyloidosis patients with FX deficiency had higher rates of bleeding events [6,7] and more severe bleeding [10] than patients with normal FX activity. Other studies found that FX levels were not predictive for the risk of bleeding [14]. The occurrence of thrombosis in AL amyloidosis has been associated with low serum albumin [15] and renal involvement with nephrotic syndrome [16]. There have been no studies examining a relationship between FX activity and risk of thrombotic events in AL amyloidosis patients. In our study, we found neither any bleeding nor thrombotic events over a 12-month period in our patient population with both low and normal FX activity, although we are restricted by small numbers.

On univariate analysis, a lower FX activity level was associated with an increased hazard of mortality; on multivariable analysis when adjusted for stage and cardiac involvement, it was not significant. The poor prognosis associated with high stage in aFX deficiency is supported by the lower survival times in these patients seen on Kaplan–Meier analysis. Although aFX deficiency was not an independent predictor of survival, the association between FX level, cardiac involvement, and stage suggest that FX could be used as a marker of advanced disease in AL amyloidosis.

Our study is limited by its single-center nature and small sample size. Further, we do not have FX activity at diagnosis, as some of these patients had been diagnosed elsewhere and referred to our center after starting treatment. We also do not have detailed history of prior bleeding and/or clotting and thus may be underestimating these events. Our data may have been further strengthened with follow-up FX levels, but only one patient had follow-up testing after therapy and had improved FX activity from 38% to 56%. Despite these limitations, we are able to make some novel observations in this relatively uncommon manifestation in a rare disease.

In conclusion, we show that aFX deficiency in AL amyloidosis is uncommon and is associated with advanced stage of disease and with cardiac biomarkers. Although patients with FX activity <50% have higher hazard of mortality, this is driven by stage rather than by bleeding events from low FX. We conclude that FX may be a biomarker of advanced disease and suggest a larger cohort study to confirm our findings.

Conflicts of interest

The authors declare no competing financial interests.

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Authors' contributions

G.P. and A.D. designed the research, collected and analyzed the data, and wrote the manuscript; A.S. and L.R. performed the statistical analysis; P.H., L.B.K., S.C., and B.D. assisted in data collection and manuscript preparation; all authors approved the final draft of the manuscript.

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