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Hemostatic abnormalities in patients with Ehlers-Danlos Syndrome

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Background

The Ehlers-Danlos Syndrome (EDS) represents a heterogeneous group of disorders of the connective tissue affecting skin, bones, vessels and other organs and tissues (1). EDS is often associated with an increased risk of bleeding, but a comprehensive study of hemostasis in patients with EDS is lacking.

Aim:

- To evaluate the bleeding tendency in a cohort of patients with EDS in terms of bleeding severity score (BSS) using the ISTH Bleeding Assessment Tool (ISTH-BAT) (2).
- To correlate the results of coagulation tests with the bleeding tendency and calculate the bleeding risk

Patients and Method

- Patients, with EDS aged >18 years, seen at our EDS outpatient clinic between Sept 2014 and Sept 2016 were included in this case-control study.
- ISTH-BAT questionnaire was administered to each patient by a trained physician. Bleeding tendency was defined as BSS>4 for males or BSS>6 for females (3).
- Primary and secondary hemostasis tests were performed (whole blood count, PT and aPTT ratio, fibrinogen, von Willebrand factor antigen, ristocetin co-factor (RICOF), endogenous thrombin potential (ETP), platelet aggregation and platelet secretion (by lumi-aggregometry).
- EDS patients with bleeding tendency were compared to those without.
- The risk of bleeding in patients with abnormal *vs* those with normal BSS according to the presence of hemostatic abnormalities was calculated in terms of odds ratio (OR) and 95% confidence interval (CI).

Results

- In the 144 EDS patients (M/F:35/109) included in the study, BSS ranged from 0 to 16 and was abnormal in 60 patients (42%) (Table 1).
- PT and/or aPTT ratios were slightly prolonged in 10 patients (7%), because of mild deficiencies of coagulation factors. RICOF and ETP were normal in all patients. Among patients with abnormal BSS, 33 (55%) had a reduction of platelet aggregation and 28 (47%) had a secretion defect in response to ADP as aggregating agent.
- At least one platelet function abnormality was present in 54 patients (90%) with abnormal BSS and in 66 patients (79%) with normal BSS. Having at least one platelet function abnormality was associated with an approximately 3-fold increased risk (OR 2.84, 95%CI 0.99-8.10) and having >3 abnormalities with a 5-fold increased risk of bleeding (OR 5.15, 95%CI 1.37-19.38) (Table 2).
- No difference in the distribution of platelet function abnormalities in the various types of EDS was observed (Table 3).

Table 1. Baseline characteristics of the study population.

Variables	Total EDS patients n = 144	BSS normal n = 84	BSS abnormal n = 60
Male/Female	35/109	22/62	13/47
Age at diagnosis, years, median (IQR)	35 (23-44)	30 (21-42)	36.5 (30-45)
Age at blood sampling, years, median (IQR)	38 (27-47)	35 (23-45)	41 (34-48)
BMI, kg/m2, mean (SD)	22.8 (4.9)	22.4 (4.9)	23.3 (4.8)
BSS, median (IQR)	5 (3-8)	3 (2-5)	8 (7-11)
EDS type, n (%)			
Classical	83 (57.6)	50 (59.5)	33 (55)
Hypermobile	44 (30.6)	26 (31)	18 (30)
Vascular	7 (4.9)	2 (2.4)	5 (8.3)
Combined	9 (6.3)	6 (7.1)	3 (5)
Cyphoscoliotic	1 (0.7)	-	1 (1.7)

Table 2. Association between presence of platelet abnormalities and risk of bleeding diathesis

Platelet functions, n (%)	BSS normal n=84	BSS abnormal n=60	OR (95%CI)	Adj. OR (95%CI)
Patients with normal platelet functions	18 (21.4)	6 (10)	**Ref**	**Ref**
At least one platelet function abnormality	66 (78.6)	54 (90)	2.46 (0.91-6.62)	2.84 (0.99-8.10)
One platelet function abnormality	18 (21.4)	12 (20)	2.00 (0.60-6.50)	1.88 (0.53-6.65)
Two platelet functions abnormalities	18 (21.4)	13 (21.6)	2.17 (0.67-6.96)	2.62 (0.76-9.01)
Three platelet functions abnormalities	20 (23.8)	17(28.3)	2.55 (0.83-7.88)	2.84 (0.86-9.40)
More than three platelet functions abnormalities	10 (11.9)	12 (20)	3.60 (1.03-12.5)	5.15 (1.37-19.38)

BSS, bleeding severity score; OR, odds ratio; Ref, reference group; Adj, Adjusted for sex, age at blood sampling and body mass index.

Table 3. Prevalence of platelet function abnormalities according to EDS diagnosis

Platelet function test, n (%)	Ehlers-Danlos diagnosis			
	Classic N=83	Hypermobile N= 44	Vascular N= 7	Other N=9
Normal aggregation	34 (41.0)	23 (52.3)	1 (14.3)	3 (33.3)
Aggregation defect	49 (59.0)	21 (47.7)	6 (85.7)	6 (66.7)
Normal secretion	15 (18.1)	10 (22.7)	2 (28.6)	3 (33.3)
Secretion defect	68 (81.9)	34 (77.3)	5 (71.4)	6 (66.7)
Absence of combined defects	44 (53.0)	32 (72.7)	2 (28.6)	5 (55.6)
Combined defects	39 (47.0)	12 (27.3)	5 (71.4)	4 (44.4)
Normal platelet function	13 (15.7)	8 (18.2)	1 (14.3)	2 (22.2)
At least one platelet function defect	70 (84.3)	36 (81.8)	6 (85.7)	7 (77.8)

BSS, bleeding severity score; OR, odds ratio; Ref, reference group; Adj, Adjusted for sex, age at blood sampling and body mass index.

Conclusions

- Nearly 1/2 of the patients with EDS had abnormal BSS.
- In the majority of EDS patients with abnormal BSS, coagulation test were normal or not significantly altered, but platelet function were detected in 90% of cases.
- The risk of bleeding was proportionally correlated to an increase number of platelet function abnormalities.
- Our findings suggest that abnormalities in primary hemostasis underline the bleeding risk of patients with EDS.

References

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