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RESEARCH LETTER

Systematic search for the *UBA1* mutation in men after a first episode of venous thromboembolism: A monocentric study

In December 2020, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome combining systemic autoinflammatory disease and hematological disorders was first described.[1] This syndrome is caused by somatic mutations of the ubiquitin like modifier activating enzyme 1 (*UBA1*) gene located on the X chromosome, which encodes the enzyme E1, important in the process of ubiquitylation. The reported mutations are mainly located in exon 3 and in the splice region, and are all detected by Sanger sequencing. VEXAS syndrome is mostly described in men and appears progressively after 50 years with systemic inflammatory disease with episodes of fever, but also pulmonary, skin, vascular, cartilage, and joint involvement.[1] Furthermore, patients with VEXAS suffer from hematologic disorders, including macrocytic anemia, thrombocytopenia, and progressive bone marrow failure, which can evolve to hematologic malignancy.[2] Additionally, approximately 40% of VEXAS patients experienced at least one thrombotic event, affecting predominantly the veins (36.4%) rather than the arteries (1.6%).[1,3] Among the venous thromboembolic events (VTE), deep vein thromboses (DVT) were more frequent than pulmonary embolisms (PE). Pathophysiology of VTE during VEXAS is still unknown, but it is suggested that thrombosis is due to chronic inflammation and cytokine release from abnormal crosstalk among innate immune cells, platelets, and endothelium resulting in coagulation activation and endothelial dysfunction.[3] Prevalence of VEXAS syndrome within VTE cohorts has not yet been reported.

The aim of our study was to determine the frequency of *UBA1* mutations in a cohort of men older than 50 years with a first episode of VTE.

Between January 2003 and January 2009, the FARIVE multicenter case–control study included consecutive unselected subjects treated as inpatients or outpatients for a first episode of proximal DVT and/or PE, as previously described.[4] The Paris Broussais-HEGP ethics committee approved the study 2002-034A1, and the patients gave their informed consent before enrollment. Patients were excluded if they were younger than 18 years, had a previous VTE, had a diagnosis of active cancer or a history of malignancy <5 years previously, or had a short life expectancy owing to other causes. Acquired risk factors for VTE were defined as pregnancy, post partum, use of oral contraceptives or estrogen replacement therapy, trauma or surgery within 3 months, prolonged immobilization, or travel lasting over 5 h.[5,6] Patients were categorized as having a provoked VTE event if they had at least one of these acquired risk factors. All other patients were categorized as having an unprovoked VTE event. All patients underwent a biological collection including a genomic DNA extraction from leukocyte pellet. In the present study, exon 3 of *UBA1*, as in previous studies[1,7,8] was sequenced in all men older than 50 years old included in the Georges Pompidou European Hospital Centre, Paris, France. Continuous data are expressed as median and interquartile range (IQR; 25th–75th percentiles). Categorical data are expressed in numbers (*n*) and percentages.

The demographic, clinical, and biological characteristics of the 97 patients analyzed in the present study are reported in Table 1. Briefly, patients were 65.0 years old (IQR 56.0–74.0), with body mass index of 25.5 (24.2–27.3) kg/m^2, and 37 (38.2%) patients had hypertension. Interestingly, 49 (50.5%) patients had unprovoked VTE. Thrombophilia assessment was available for 56 of 97 (57.7%) patients and no cases of severe thrombophilia were diagnosed among tested patients. No *UBA1* mutations were detected among the 97 patients.

VEXAS syndrome is associated with a high incidence of VTE (36.4%).[1,3] But, our study does not foster seeking *UBA1* exon 3 mutations in all men over 50 years with a first VTE event, without taking into account other clinical symptoms related to VEXAS. Of note, VEXAS syndrome was also described in women with chromosome X monosomy.[7,9,10] Moreover, the underlying mechanisms involved in the VEXAS syndrome–associated VTE is currently unknown and will require more investigations in the future.

Even if thrombophilia testing is not recommended in patients older than 50 years with a first episode of unprovoked VTE,[11,12] thrombophilia testing was performed in more than half of the study population according to the study protocol. As the inclusion period

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TABLE 1 Demographic, clinical, and biological characteristics of patients at inclusion

	N = 97
Age (years)	65 (56–74)
Weight (kg)	79 (72–88)
BMI (kg/m^2)	25.5 (24.2–27.3)
Smoking – *n* (%)	18 (18.7)
Hypertension – *n* (%)	37 (38.2)
Diabetes mellitus – *n* (%)	11 (11.3)
Dyslipidemia – *n* (%)	36 (37.1)
History of malignancy – *n* (%)	3 (3.1)
Type of VTE event – *n* (%)	
DVT	25 (25.8)
PE	50 (51.5)
PE + DVT	22 (22.7)
Acquired risk factor for VTE *n* (%)	
None	49 (50.5)
Bedrest	6 (6.2)
Acute medical illness[a]	7 (7.2)
Traumatic injury[a]	8 (8.2)
Surgery[a]	18 (18.6)
Flight travel[a]	22 (22.7)
Other[a]	3 (9.3)
Cancer[a]	1 (1.0)
Plaster cast[a]	1 (1.0)
Biological exam	
Leukocytes, G/L	8.05 (6.2–10.6)
Hemoglobin, g/L	136.5 (130.0–144.4)
Platelets, G/L	236.0 (209.3–271.5)
Fibrinogen, g/L	4.3 (3.5–5.6)
Factor VIII, %	168.0 (154.0–205.5)
Blood type – *n* (%)	
A	39/70 (55.7)
B	7/70 (1.0)
AB	3/70 (4.3)
O	21/70 (3.0)
Factor V Leiden mutation	
None	50/56 (89.3)
Heterozygous	6/56 (10.7)
Homozygous	0/56 (0.0)
Factor II G20210A mutation	
None	55/56 (98.2)
Heterozygous	1/56 (1.8)
Homozygous	0/56 (0.0)
Antithrombin (heparin cofactor activity), %	95 (84–103)
Protein C (anticoagulant activity), %	91 (78.3–113.8)
Protein S activity, %	95 (74.5–110)
Free protein S antigen, %	68 (46–93)
Antiphospholipid antibodies positivity	4/39 (10.3)
UBA1 exon 3 mutation	0 (0.0)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Patients may have more than one risk factor for VTE.

spanned from 2003 to 2009, VEXAS syndrome's clinical and biological characteristics were not recorded. Therefore, we cannot draw definitive conclusion on the absence of benefit to look for VEXAS syndrome after a first VTE episode in men over 50 years old, but we can conclude that systematic screening of *UBA1* exon 3 mutations shall not be recommended.

Further large-scale studies should investigate the frequency of *UBA1* mutations in patients with a first episode or recurrent VTE and symptoms related to VEXAS-like inflammation or macrocytosis or cytopenia.

In conclusion, there is currently no scientific argument supporting systematic screening for *UBA1* exon 3 mutations in men older than 50 years with a first unprovoked VTE. However, VEXAS syndrome should still be considered in the case of unprovoked VTE in men; in the presence of clinical features like systemic inflammation involving the skin, lungs, blood vessels, and cartilage; and hematologic disorder, including macrocytic anemia or thrombocytopenia.

AUTHOR CONTRIBUTIONS

MT, ED, AS, and OK perform the experiments. LK, MT, CB, ED, LD, AS, OK, and NG analyzed the data. LD, OS, BP, EM, DMS, JE, and TM were involved in the clinical management and the inclusion of the patients. LK, MT, AS, OK, and NG wrote the manuscript. All authors reviewed the manuscript.

KEYWORDS

hematologic malignancy, thrombophilia, thrombosis, venous thromboembolism, VEXAS syndrome

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CONFLICTS OF INTEREST

All authors have nothing to disclose with the present study.

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INFORMED CONSENT

This investigation was conducted according to the guidelines of the competent ethical board (Paris Broussais-HEGP ethics committee) upon its approval (protocol numbe 2002-034A1). Specific patient informed consent for the study was waived according to the French Guidelines on research involving human research. Patients were excluded in case of refusal of the research consent.

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