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Commentary

Stressful experiences and venous thromboembolism

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Despite stress being an accepted cause of arterial thrombotic events (ATE) [1,2], for which underlying pathophysiological processes have also been identified, it has not yet been widely recognised as a risk factor for venous thrombosis [3]. Stress is a comprehensive concept and can take many forms, from physical trauma to severe or repetitive emotional stress. It is important to be mindful of this as doctors, and also to ask out the emotional stressors in the case of acute VTE.

The search for causal factors remains a holy grail in patients with unexplained venous thromboembolism (VTE), or in those with only mild or transient risk factors, like oral contraceptives (OC) in relatively young women [4,5]. One reason for searching for such factors is to *explain* why the thromboembolism occurred in the first place. Understanding the etiology helps to accept the next steps in management.

Another advantage of identifying the causes of VTE is that it allows a better assessment of the risk of recurrent VTE, after a period of anticoagulant treatment has been completed. VTE recurrence depends on the nature of the underlying risk factors (mild, moderate, strong) and whether these risk factors are transient or not [6]. An example of a mild transient risk factor is exposure to an estrogen containing oral contraceptive (OC). In an otherwise healthy woman, discontinuing OC will reduce the risk of VTE to the point that anticoagulation can be stopped after initial treatment for VTE for 3–6 months [5], although in some guidelines this decision is also influenced by underlying thrombophilia [7]. The presence of additional risk factors like obesity, smoking and comorbidities, influences the decision to continue anticoagulants for a prolonged time.

Importantly, incident VTE may also be a *warning sign*, not only of an underlying disease, rarely even a malignancy in the younger female population, but also of a harmful environment. Such environmental factors include problems associated with lower socioeconomic status, such as poor living conditions, inappropriate eating and drinking habits, smoking and a range of psychological stressors associated with financial and social constraints [8].

In a recent case series and literature review, Gris and colleagues raise awareness of intimate partner abuse in relation to incident VTE. Based on the description of 19 women of childbearing age, the authors show a possible association between domestic violence and thrombosis [9]. In the current issue of the European Journal of Internal Medicine the same authors present a multicenter, international matched case-control study addressing the question whether intimate partner violence is indeed associated with an increased risk of VTE [10]. The answer is yes. Using a standardized and validated questionnaire (Women Abuse Screening Tool, or WAST), the authors analyze evidence of violence in the patient's relationship over the past 12 months. 997 case-control pairs were included, with cases being women referred for thrombophilia screening after completion of 6–12 months of anticoagulation following VTE diagnosis. Controls were drawn from a cohort of non-thrombotic women under regular gynecological surveillance. Cases and controls were also selected on the basis of combined OC use. Risk factor analysis was comprehensive and included clinical factors such as body mass index (BMI), thrombophilia testing and selected laboratory biomarkers such as d-dimer and factor VIII. Analysis of the WAST score showed an adjusted odds ratio (aOR) of 3.720 (95 %CI 2.438–5.677) for VTE with a WAST score >5 in the multivariate analysis. This effect was similar in strength to the persistent presence of antiphospholipid antibodies or factor V Leiden carriership. When the effects of the different elements of WAST were separated, both psychological and physical elements, including sexual violence, were positive risk factors for VTE. While acknowledging the many known weaknesses inherent in the design of a case-control study, these data are alarming.

Physical trauma is a known risk factor for VTE, and in general the severity of trauma is positively associated with risk. Inflammatory responses to any tissue trauma activate coagulation and thrombosis may be a consequence (as in surgery). Psychological trauma is recognized as a thrombotic risk factor, particularly so for arterial vascular disease including atherosclerosis and myocardial infarction; the causal effect on VTE is less well recognized.

In 1952, "nervous stress" was proposed as a risk factor for VTE by Stoker, who observed a young woman who died of a pulmonary embolism shortly after experiencing severe emotional stress ("… sometimes

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a clot is found suddenly during emotional stress") [11]. Later, larger and much better studies showed that exposure to trauma and post-traumatic stress were indeed associated with an increased risk of VTE (almost 2-fold overall in 49,296 women followed up over 22 years; risk increased with the number of symptoms) [12]. A Swedish study in 6958 men showed that compared with men with no apparent stress at baseline, persistent stress was associated with a hazard ratio of 1.80 (95 % CI 1.21–2.67) for incident pulmonary embolism; this risk was slightly lower but still significant after multivariable adjustment [13]. The present data from Gris et al., extend this literature base, and suggest that the combination of physical and mental stress, but also mental stress alone, may provoke VTE.

Many possible mechanisms have been proposed to link stress to thrombosis risk, recognizing acute and chronic stressors [3,8]. Acute stress is associated with thrombo-inflammatory responses as part of an adaptive response involving activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Several studies have demonstrated evidence of increased thrombopoiesis, platelet activation, activated coagulation and fibrinolysis during acute stress [reviewed in 3,8]. While many of these acute responses have a physiological role under "fear-fight-flight" conditions, exposure to chronic stressors is less likely to have protective effects. Indeed, prolonged exposure to problems associated with low socioeconomic status, air pollution or noise, and high work demands, may all contribute to endothelial dysfunction, and have a thromboinflammatory effect on the vasculature. This includes an increased risk of VTE. Whether the risk is similar for venous thrombosis and pulmonary embolism, remains to be demonstrated.

What are the implications of these findings for society? Firstly, the data from the case-control study require further research into the extent of the impact of domestic violence, also including men and older people of both sexes. Secondly, the data should already alert caregivers to include elements related to WAST factors in the history taking. More importantly, patients need to be informed that stressors, including domestic violence, can increase the risk of VTE, so that they can raise the issue when they see a doctor, social worker or other trusted person.

The most important message for us, internists, is to keep our eyes and ears open when managing a patient with VTE and not to limit the assessment to the affected limb (or lung).

Declaration of competing interest

No relevant to report.

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