FACTOR V LEIDEN MUTATION IN PATIENTS WITH POLYARTHRALGIA – CASE REPORTS AND REVIEW OF LITERATURE

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Abstract. *Patients with rheumatological diseases might be at increased risk of venous thromboembolism (VTE) because of inflammation, autoimmune disturbances, prolonged immobilization, and corticosteroid (CS) use. Therefore, more efforts are needed to identify additional prothrombotic factors and provide preventive strategies. Herein, we presented two cases of young men with polyarthralgia who have undergone unprovoked VTE. The first patient underwent VTE after several intra-articular CS applications, while the other had no concomitant risk factors. The hereditary thrombophilia testing revealed a heterozygous Factor V Leiden (FVL) state in the first patient and homozygous FVL carrier status in the second patient. Both cases suggest a possible benefit of thrombophilia testing in men under the age of 50 years with polyarthralgia, unprovoked VTE, and impending CS therapy. Estimating the complex thrombotic risk in rheumatological patients before CS use is crucial for preventing thromboses.*

Key words: *arthralgia, factor V Leiden, corticosteroid treatment, thrombosis*

Introduction

Patients with rheumatological diseases might be at increased risk of venous thromboembolism (VTE), because of chronic inflammation, decreased physical activity, and concomitant autoimmune disturbances [1]. However, other concomitant hereditary or acquired factors might also contribute to the increased thrombotic risk, e.g., factor V Leiden (FVL) variant (F5 c.1691G>A), the prothrombin gene variant F2 c.20210G>A, protein C deficiency, protein S deficiency, antithrombin deficiency, paroxysmal nocturnal hemoglobinuria, and neoplasms. [2]. For instance, factor V Leiden variant could increase the prevalence of VTE 3.5-fold in heterozygous patients with systemic lupus erythematosus compared to the lupus patients with the wild-type factor V genotype [3].

FVL is a genetic variation associated with the inherited resistance to activated protein C and impaired inactivation of factor Va, leading to an increased presence of thrombin and a tendency to hypercoagulability [4]. However, FVL is only one of many risk factors, thus, most carriers of the factor V variant would never develop thrombosis [5]. Currently, thrombophilia investigation is not recommended in the typical population of patients with VTE because of the absent clinical benefits and specific preventive strategies [6]. The common risk of VTE depends on multiple factors, including but not limited to age, obesity, immobilization, surgery, cancer, and use of thrombogenic drugs, while the prescription of anticoagulant therapy does not depend on specific genetic background [5]. However, the role of the inherited prothrombotic genetic variants is still unclarified in patients with rheumatologic diseases, who are at increased risk of VTE and frequently on corticosteroid treatment.

Herein, we present two cases of young men with polyarthralgia who have undergone unprovoked VTE. Both patients are FVL carriers. The cases suggest a potential benefit of thrombophilia testing in men under 50 years with rheumatological symptoms, unprovoked VTE and impending CS therapy.

Case reports

Case 1

A 39-year-old man complained of generalized joint pains and muscle weakness after the cessation of chronic alcohol intake. During the long-lasting alcohol abuse, the patient had been diagnosed with chronic hepatitis and alcohol-related seizures. However, he had not complained of joint pains despite his job associated with intensive physical exertion. After quitting the ethanol exposure, the patient's hepatic markers normalized, and no seizures were observed; however, polyarthralgia emerged. Because of the diffuse joint pains, short-term therapy with vitamin B complex and non-steroid anti-inflammatory drugs (NSAIDs) was prescribed by the local neurologist without any improvement. Additionally, due to the pronounced shoulder pain, five intraarticular applications of depo-corticosteroid (CS) were provided. Afterward, the patient developed femoropopliteal venous thrombosis, and anticoagulant treatment was started.

Subsequently, he was referred to a rheumatologist for further evaluation. The patient had normal levels of C-reactive protein - 2.9 mg/l /< 5.0/), uric acid, and creatine phosphokinase, normal X-rays of shoulders but clinical and ultrasound data for bilateral mm. supraspinatus tendinopathy. No other objective signs of rheumatological or neurological abnormalities were found. Physical therapy, NSAIDs, and resting lead to an improvement of the shoulder pain over time. Because of the developed thrombosis at a young age, investigations for genetic and acquired thrombophilia were recommended. The patient was negative for rheumatoid factor, anti-cardiolipin and anti-nuclear antibodies, but heterozygous factor V Leiden carrier status was established by thrombophilia genetic testing. The patient was referred to an angiologist and hematologist for further treatment.

Case 2

A 44-year-old man was referred to a rheumatologist for polyarthralgia last year. The patient was a hard-working physical worker and complained of pain and stiffness in the knees, ankles, hips, spine, and small joints of the hands. He did not suffer from any concomitant diseases, but seven months ago, he had developed a thrombosis of the right arm. At the time of admission, he did not have additional systemic symptoms, and his laboratory parameters, including C-reactive protein (0.2 mg/l /< 5.0/), full blood count, erythrocyte sedimentation rate, uric acid, creatine phosphokinase, and rheumatoid factor were all normal. X-rays and ultrasound examinations of all joints were normal. The diagnosis of polyarthralgia related to heavy physical work was suspected. Lifestyle changes, resting, analgesics, and short-term application of NSAIDs were recommended. Because of the unprovoked venous thrombosis of the arm, investigations for congenital or immune-mediated thrombophilia were ordered. The results showed that the patient was a homozygous factor V Leiden carrier, while immunological (rheumatoid factor, anti-cardiolipin and anti-nuclear antibodies) and other genetic (factor II G20210A, MTHFR C677T, PAI I 4G/5G) markers were normal. The patient was referred to an angiologist and hematologist for follow-up and treatment. Avoidance of corticosteroid therapy was also recommended, if possible.

Discussion

The presented cases of polyarthralgia demonstrate a common and relatively simple clinical problem associated with multiple joint pains related to continuous physical activity overload. The diagnosis of arthralgia requires the exclusion of inflammation, autoimmune disorder, traumatic injury, and infections, and the therapeutic opportunities include lifestyle changes, analgesics or non-steroidal anti-inflammatory drugs, physical therapy, etc. [7, 8].

Interestingly, the polyarthralgia in our first case developed in the context of alcohol withdrawal, while during his long-lasting alcohol abuse, no complaints were registered despite the presence of shoulder tendinopathy. Recent studies have emphasized the significant associations between chronic pain and alcohol use/abuse disorders [9-12]. Excessive alcohol abuse might provoke chronic pain because it is associated with an increased prevalence of traumatic injuries, worse pain-related outcomes after the injuries, development of vitamin B deficiency, and alcohol-related neuropathy (reviewed in 9). On the other hand, alcohol is a well-known pain inhibitor, and the oral administration of ethyl alcohol has the same analgesic effects as low-dose subcutaneous morphine [13]. A meta-analysis including more than 400 healthy participants shows that alcohol intake could induce a slight increase in pain threshold and a pronounced decrease in pain intensity perception [10]. Moreover, the exacerbation of chronic pain has been described as an essential risk factor for relapse in abstinent heavy drinkers [14]. Experimental studies explain the ethanol analgesic effects mainly with the activation of GABA and opioid systems and suppression of excitatory glutamate signaling [9, 11]. The same neuromediators, along with some hypothalamic stress-modulating systems including corticotropin-releasing factor and vasopressin, could contribute to the development of alcohol-related hyperalgesia and allodynia [9, 11, 12,1 5]. Thus, joint pain complaints should be interpreted cautiously in patients recovering from alcohol or other substance abuse. Moreover, psychological help should be offered instead of aggressive pharmacologic pain treatment.

The other considerable co-morbidity in both cases was the presence of unprovoked thrombotic events in young men without significant risk factors.

Thus, a femoropopliteal venous thrombosis was found in the first patient after repeated applications of intraarticular depot-CS. Systemic CS use has been associated with a double to triple risk of venous thromboembolism in the common population [16, 17]. Conversely, the intra-articular CS application is related to fewer side effects because of the decreased systemic absorption [18]. However, multiple intra-articular injections might induce systemic absorption sufficient to suppress the hypothalamic-pituitary-adrenal axis in most patients [19]. Therefore, side effects resembling exogenous Cushing syndrome might be observed after intra-articular CS applications [19, 20]. For instance, after intra-articular CS administration, pulmonary embolism has been observed in an HIV-infected patient [21]. Thus, the local CS treatment of rheumatic complaints should be consistent with the risk-benefit ratio of the patients, similar to systemic therapy.

Nevertheless, it is unclear if the local CS use had contributed to the thrombosis of the first patient. Therefore, additional risk factors were also explored. Similarly, the second patient had suffered unprovoked thrombosis; thus, thrombophilia tests were ordered. The results excluded autoimmune-related disturbances, but factor V Leiden carrier status was found in both patients - mild heterozygous variant in the first and severe homozygous variant in the second patient. Investigations for thrombophilia are contradictory because testing in some patients might be associated with more risks than benefits [22]. For instance, non-indicated testing might be associated with increased costs, false positive results, misinterpretation of clinical significance, and patient emotional damage [22, 23]. Therefore, testing should not be performed routinely but only when results could help to improve clinical management considering the patient's preferences [22, 24]. However, in selected individuals suffering from venous thromboembolism (VTE), thrombophilia testing might help to estimate the risk of relapses, duration of thrombotic prophylaxis, and the potential influence of other prothrombotic factors, thus contributing to the personalized medical approach [25]. Currently, thrombophilia investgation has been recommended for patients with unprovoked deep venous thrombosis (DVT) under 50 years, which justifies the examination in our patients [25, 26]. The established factor V Leiden variant could contribute to the thrombotic incidents because the same polymorphism has been related to a sevenfold increased risk of venous thrombosis in heterozygous and an 80-fold increased risk in homozygous carriers [27]. Moreover, the prevalence of factor V Leiden is more than 20% in patients with thromboembolism but only 5.5-7.1% in the common population on the Balkans [28, 29].

Identifying inherited factors related to hypercoagulability is especially important in patients suffering from rheumatic diseases because of frequent immobilization, systemic inflammation, and increased systemic and intra-articular CS use in their treatment plan [30]. While CS use might benefit some acquired autoimmune thrombophilic conditions, e.g., refractory or catastrophic antiphospholipid syndrome, because of the potent immunosuppression [31, 32], it might be an additional risk factor in case of inherited hypercoagulation states. Oral CS use has been associated with a significantly increased risk of venous thromboembolism in the first week after exposure, though it is not clear if the effect is related to the underlying inflammatory disease or CS per se [33]. However, the endogenous Cushing syndrome has been associated with an 18-fold increased risk of unprovoked VTE because of the direct effect of increased cortisol levels on clotting factor production, a fact overlooked by most current DVT guidelines [34, 35]. Thus, it is essential to recognize the thrombogenic nature of CS in patients suffering from rheumatologic disorders [35, 36], and to evaluate the additional risk factors that could increase the thrombotic risk. Unfortunately, studies investigating the role of inherited thrombophilias in VTE development in rheumatologic patients on corticosteroid treatment are still lacking. Nevertheless, the evaluation of the global thrombotic risk in rheumatological patients before CS application is crucial in order to avoid complications [25, 30].

In conclusion, we presented two cases of young men suffering from unprovoked thrombosis and polyarthralgia related to excessive physical exertion. The testing for inherited thrombophilia revealed a Factor V Leiden carrier status in both patients. Estimating the complex thrombotic risk in rheumatological patients before CS use is essential for the primary and secondary prevention of thromboses.

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