Case Report

Deep venous thromboembolism after a trauma in a football player double heterozygous for factor V Leiden and prothrombin G20210A mutation: The role of genetic testing in sport

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ABSTRACT

Traumatic vascular injuries to the lower limb are frequent in athletes, particularly in sports characterized by high-speed collisions. However, the diagnosis is not always straightforward, for the lack of clearly visible abnormalities without provocative testing or appropriate imaging. The failure of an early diagnosis can lead to devastating consequences. In these subjects, it may be useful to investigate the personal susceptibility to thrombotic events such as the presence of a hereditary hypercoagulable state. We experienced a case of a soccer player with progressive swelling and severe pain of the calf after a trauma during a football match 3 days previously, who came to our hospital for suspected deep vein thrombosis, confirmed by echo-Doppler ultrasound. A thrombophilia screening detected a double heterozygosity for factor V Leiden and prothrombin G20210A mutation in the presence of a strong family history for thromboembolism. Immediate treatment with elastic stocking compression and enoxaparin was started. The patient was discharged on warfarin therapy maintained for six months, with the warning to avoid trauma activities during anticoagulation. Thrombotic genetic testing in athletes who experience episodes of deep vein thrombosis might offer important opportunities for patient management, such as prolonged anticoagulant therapy or avoidance of risk factors such as trauma-related sports.

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Introduction

Venous thromboembolism is a typical multifactorial disease, in which genetic testing for inherited causes of thrombophilia, when clinically indicated, is an important component of patient care [1]. In 2003, the US Food and Drug Administration approved the first DNA-based laboratory tests specifically for factor V Leiden and prothrombin G20210A mutation, the most common causes of inherited thrombophilia.

Deep vein thrombosis (DVT) of the limb after a strenuous exercise or trauma is a rare but well-recognized condition. Athletes, also during non-competitive sports, are susceptible to a variety of vascular injuries because of exposure to high-speed collisions [2]. However, extremity pain in these subjects seldom results in a diagnosis of venous or arterial abnormalities, although an early recognition and aggressive treatment of these disorders has been recommended to avoid the long-term limb-threatening implications [3]. In these subjects, the identification of the personal susceptibility to thrombotic complications and, in particular, the screening of factor V and prothrombin mutations that are strong hereditary risk factors for venous thromboembolism, may be clinically useful [4].

We describe a case of a trauma-associated DVT in an amateur football player double heterozygous for factor V Leiden and G20210A prothrombin mutations, who presented with a strong family history of venous thromboembolism.

Case report

We report the case of a 63-year-old man referred to our cardiovascular ultrasound laboratory for progressive swelling of the left calf after a blunt trauma during a football match 3 days before. He denied experiencing any sensation of acute pain and was able to continue the game with only minor discomfort. On day 1 post-trauma, the patient suffered severe pain in his left leg and underwent physical therapy with massage of the leg. Because of lack of relief of symptoms and progressive swelling of the limb he came to our hospital with suspected DVT.
At the examination, the affected leg appeared swollen, hot and painful, and also showed positivity to Homans maneuver (pain in the calf during passive dorsiflexion of the foot), the sign of Neuholz (decrease of calf tossing with the patient’s leg relaxed and flexed on thigh) and the sign of Bauer (pain provoked by palpation of the heel, foot, and calf). A lower extremity echo-Doppler ultrasound confirmed the suspected diagnosis showing dilatation and occlusion of the medial branches of the posterior tibial vein that was not compressible, with no flow inside and thrombotic material (Fig. 1A).

The D-dimer result was suggestive for a suspected thrombosis (1540 ng/ml; normal value < 400 ng/ml). Immediate treatment with elastic stocking compression and enoxaparin (0.1 UI/kg) was started and after a few days the warfarin therapy was initiated.

The patient was an old football player and denied any thrombotic risk factors. He had undergone meniscectomy with only one-day heparin therapy after surgery, without any clinical consequences, a few years previously.

Interestingly, his family history was strongly positive for thromboembolic events, since his father suddenly died at the age of 52 years during sleep after a probable thromboembolic event a few days after upper limb trauma treated with immobilization and limb compressive bandage without any prophylaxis.

In our patient, a thrombophilia screening detected a double heterozygous genotype for factor V Leiden (FVL) and prothrombin G20210A (PT G20210A) mutation. MTHFR C677T variant was absent. Other laboratory tests (protein C, protein S, antithrombin III) were within the normal range. The level of factor II was 134.2% (normal values 79–131%). As expected, he was resistant to activated C protein (1.77; normal values 2.61–3.32). No lupus anti-coagulants were found (Table 1).

The patient was discharged on warfarin therapy (with target international normalized ratio between 2 and 3) and was maintained for six months, with the warning to follow-up with his physician for regular monitoring, and to avoid traumatic activities during anticoagulation. Moreover, he was educated about his hereditary hypercoagulable state, and in particular his high risk of DVT recurrence, with the advice to perform the genetic test to his first-degree relatives. The results of the family genetic screening are shown in Fig. 2. All mutated subjects are asymptomatic.

At the follow up, we found in our patient progressive evolution of thrombus with partial recanalization of the vessel (Fig. 1B and C) and finally with retraction of the thrombus and complete recanalization of the vessel (Fig. 1D).

**Discussion**

This study demonstrated the importance of considering hereditary prothrombotic risk factors in an otherwise healthy subject with a strong family history of thrombosis who suffered DVT after sport-related extremity trauma.

Traumatic vascular injuries to the lower limb are frequent in athletes, particularly in sports characterized by high-speed collisions such as soccer [2,3]. DVT in such circumstances may not be a rare occurrence as a direct consequence of sport-induced trauma [3]. However, very few cases of lower extremity DVT involving

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Table 1

<table>
<thead>
<tr>
<th>Coagulation profile</th>
<th>Results</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated protein C resistance</td>
<td>1.77</td>
<td>2.61–3.32</td>
</tr>
<tr>
<td>Protein C activity (%)</td>
<td>116.3</td>
<td>70–140</td>
</tr>
<tr>
<td>Protein S activity (%)</td>
<td>124.81</td>
<td>64.4–128.8</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>84</td>
<td>80–120</td>
</tr>
<tr>
<td>Prothrombin factor II (%)</td>
<td>134.2</td>
<td>79–131</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>0.98</td>
<td>0.8–1.20</td>
</tr>
<tr>
<td>Activated partial</td>
<td>1.01</td>
<td>0.8–1.3</td>
</tr>
<tr>
<td>thromboplastin time (ratio)</td>
<td>234</td>
<td>170–410</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>1540</td>
<td>&lt;400</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>10</td>
<td>0–15</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

| Thrombophilia genetic variants             |         |                 |
| Factor V Leiden                            | Arg/Gln heterozygous |
| Prothrombin G20210A                        | G/A heterozygous    |
| MTHFR C677T                                 | C/C wild-type      |
direct sport-associated trauma are reported in the medical literature [5–9]. From these, there is one case report that specifically related DVT development to soccer-related trauma [5], and a case of a 42 year-old male semi-professional soccer player who sustained a right lower extremity popliteal contusion during a soccer game resulting in a traumatic DVT [6]. Moreover, lower extremity DVT was described in a soccer player with coagulation deficiencies [9]. The diagnosis of lower limb vascular injuries in healthy athletes is, in fact, not always straightforward, because classic symptoms, such as leg pain or swelling, are often not distinguishing and vascular injuries are unrecognized probably due to the lack of clearly visible abnormalities without provocative testing or appropriate imaging [3,10]. The failure of an early diagnosis, and then of appropriate anticoagulation therapy, can lead to devastating consequences for athletes [3].

In these subjects, it may be useful to investigate the personal susceptibility to thrombotic events such as the presence of a hereditary hypercoagulable state [4]. At the moment, controversy exists regarding the extent of prothrombotic genetic testing in a young, otherwise healthy athlete diagnosed with a DVT in whom no additional risk factors for thromboembolism are present [3,11].

In our patient, the presence of a trauma-associated DVT and of a strong family history of thromboembolism directed us to perform genetic testing of prothrombotic mutations, identifying a condition of high thrombotic risk such as the presence of a double heterozygosity for FVL and PT G20210A.

In general, it is considered that the carrier state for more than one inherited genetic defect enforces gene penetration and event manifestation and increases the risk of disease through stratification of multiple gene effects. FVL mutation has been found to interact with PT G20210A variant contributing to increasing the risk of the incidence of thromboembolic events and recurrent events.

Heterozygous carriers of FVL and the PT G20210A gene mutation have, respectively, a 5- and 3-fold higher risk for first venous thrombosis compared to the general population [12,13]. Noteworthy, the presence of double heterozygosity for FVL and PT G20210A, a rare event with an incidence of \(\sim 0.1\%\), is associated with an 18- to 20-fold higher risk of DVT compared with non-carriers [14]. Moreover, patients with prothrombotic mutations, especially double heterozygosity, are at increased risk of recurrent DVT compared with patients with DVT without these mutations [15–17].

However, uncertainty remains about the contribution of these genetic factors for the individualized risk assessment to thrombotic events as the interaction of complex combinations of variants of different genes with environmental factors may be relatively unpredictable at an individual level. Understanding the interaction and confounding effect of different factors is a target for research to maximize treatment benefits and minimize disease and treatment-associated risks.

In particular, the optimal duration of oral anticoagulant therapy after a first episode of DVT is still controversial. When anticoagulant treatment is stopped after an appropriate duration (at least 3 months), the incidence of recurrent DVT varies according to the individual risk factors associated with the initial event. Genetic testing of prothrombotic variants might be used to identify individuals in a “low-risk” cohort (e.g. a traumatic provoked first event) who might have an atypically high risk of recurrence and therefore might benefit from continued anticoagulation.

In fact, according to the American College of Chest Physicians Consensus on Antithrombotic Therapy, homozygous for FVL or PT mutation, or double heterozygous are candidates for extended long-term anticoagulation [18].

In our case, the detection of a strong prothrombotic state may be of crucial importance in an otherwise “low-risk” 63-year-old male, with post-traumatic DVT and without history of previous thrombotic events, in which the duration of anticoagulant therapy would remain controversial.

Conclusions

This case report supports the need for further studies in order to investigate the role of prothrombotic mutations in trauma-related thrombosis. Furthermore, our findings indicate the importance of considering testing for inherited thrombotic mutations in athletes who experienced episodes of DVT in order to improve treatment and to decrease the risk of recurrence, especially in the presence of a strong family history for thrombosis and in the absence of other known risk factors.

Conflict of interest

The authors declare no conflict of interest.

References


Fig. 2. Pedigree of the family: individuals are identified by generation and pedigree number. The proband is indicated by arrow and the grey dot indicates the presence of a mutated genotype. The subjects with a thrombotic episode are represented by filled symbol. The question mark indicates the individuals not genetically tested.