CASE REPORT

Posterior knee pain: primary symptom of a small non-occlusive venous clot

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A healthy 9 year old girl presented with severe posterior knee pain and a small segmental non-occlusive popliteal venous thrombosis. The case is relevant for its unique presentation and symptoms. Lack of recanalisation persisted at one year follow up.

A n apparently healthy 9 year old girl was referred after two days with pain at the posterior of her right knee. This pain developed suddenly while the girl was walking. There was no history of trauma. Two weeks before admission, the child had been confined to bed because of an episode of acute respiratory tract infection. Thrombocytosis (700 000/mm³) and a high erythrocyte sedimentation rate (ESR, 60 mm/h) were detected. When admitted to our clinic, the child was incapable of walking or bearing weight on the limb. Her knee was completely flexed. Passive extension was impossible as it caused her extreme pain. Contraction of the biceps femoris was also present, especially when attempting limb extension. Even suggesting that she might attempt to extend the limb caused her extreme anxiety. Both of her knees had similar dimensions and there were no signs of arthritis. No clinical signs of bone, ligament, nerve, or vascular involvement were apparent. The only sign was severe pain in the popliteal fossa, without any sign of swelling or masses.

Administration of anti-inflammatory agents for several days gave no relief. Routine laboratory blood data were all normal, except that the ESR was still slightly increased (22 mm/h). Examinations by knee x ray, ultrasonography, and magnetic resonance imaging (MRI), all performed with the knee in a flexed position, showed no abnormalities. As the child could not extend her limb, it was impossible to explore her leg fully. We therefore performed a knee MRI and angio-MRI after extending the limb under general anaesthesia. When the muscles were relaxed by such sedation, the limb could be completely extended without any effort. MRI findings continued to be negative, showing normal knee anatomy. There were no joint effusions, nerve or bone involvement, tendinitis, bursitis, meniscal pathologies such as tears, nor any ganglions or lesions of the cruciate ligaments. Furthermore, there were no masses (for example, Baker’s cysts or soft tissue tumours) in the popliteal fossa, and no masses, such as a primary venous leiomyosarcoma, arising from the vessels.

A simple venous angio-MRI (lacking contrast medium) showed a partial occlusion of the popliteal vein (fig 1A,B). A complete study of the occlusion could have been performed by the intravenous administration of gadolinium, but this was impossible as we were unable to obtain venous access in the dorsal foot. To better clarify the clinical picture of the observed reduced blood flow, an ultrasonographic study of the vessels of the popliteal fossa was performed, according to standard techniques (grey scale evaluation of vein compressibility and colour Doppler evaluation of venous flow). This was performed immediately after the angio-MRI. The ultrasonographic study confirmed incomplete filling of the lumen of the popliteal vein due to a very small, non-occlusive clot with a maximum thickness of 7 mm (fig 1C), extending for about 10 mm along the major axis of the vessel lumen. Partial compression with the ultrasound transducer and the slightly decreased blood flow suggested a segmental and partially occluding thrombosis of the popliteal vein (fig 1D).

At this point, assessment of blood coagulation showed a slight increase of D-dimer (0.4 mg/l; normal value: <0.3 mg/l). Screening for risk factors associated with venous thromboembolism was performed. The child had decreased levels of free protein S antigen levels (24%; normal values 70–123%) and moderately increased levels of homocysteine (18 µmol/l; normal levels 5–15 µmol/l). She was homozygous for the C677T polymorphism in the MTHFR gene. All the other results (anti-thrombin, protein C, resistance to activated protein C, factors II, VIII, IX, and XI, fibrinogen, lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein antibodies) were within the normal range; factor V Leiden and prothrombin G20210A were absent. A family study showed that her father, an apparently healthy 34 year old man (whose mother had died of a cerebral vascular thrombosis when elderly), had slightly decreased free protein S levels (63%), severely increased levels of serum homocysteine (141 µmol/l), and was homozygous for the C677T polymorphism in the MTHFR gene. The mother, a 32 year old woman, had a clear free protein S deficiency (41%) and was heterozygous for the MTHFR C677T polymorphism. Accordingly, a diagnosis of inherited deficiency of protein S associated with mild hyperhomocysteinaemia could be established.

Because the clinical diagnosis remained inconclusive until the venous angio-MRI could be performed, antithrombotic treatment was started late (two weeks after the onset of pain). Administration of low molecular weight heparins was started at a dosage of 100 IU/kg subcutaneously twice a day for two weeks. After the first week, oral anticoagulant therapy with a daily dose (about 0.2 mg/kg) of warfarin was started, with the child’s INR target set at 2.5. Hyperhomocysteinaemia was corrected using daily dietary supplementation with folic acid (7 mg), vitamin B₁₂ (1.25 mg), and vitamin B₉ (250 µg). Her pain did not disappear until after one month of anticoagulant therapy, when the child began to extend her leg and to bear weight on the limb. At three months, a new venous angio-MRI and ultrasonography continued to show the non-occluding clot, although blood flow in the vein was slightly improved. At six months, the clot was still present, although substantially reduced with a maximum thickness of 3 mm (images not shown). At one year, the clot was still present, extending for about 5 mm along the major axis of the vessel’s lumen, and with a maximum thickness of 1 mm (fig 1E). Lifelong anticoagulant therapy therefore appeared to be indicated for this child, as she had two genetic risk factors for developing thrombosis and had lack of recanalisation of the vein (that is, persistent residual thrombosis); both circumstances are associated with a higher risk of recurrence.¹ ²
of patients with recurrence carried one or more risk factors. Protein S deficiency is associated with a higher risk. Moreover, the lack of vein recanalisation is associated with a 2.4-fold higher risk for developing recurrence. Partially occluding thromboses are rarely observed, as they are often silent. In our patient the clinical signs were spontaneous pain in the popliteal fossa and increased pain at attempted extension of the knee. There was no evidence of infection or ischaemia. The pain might have been a direct result of the distension of the vein, where localised swelling possibly impinged on a sensory nerve. Negative findings on the initial ultrasound examinations contributed to the difficulty in making the diagnosis. The non-occlusive nature of the clot permitted the presence of compressibility and free flow on colour Doppler examination of the popliteal vein, suggesting a normal appearance. Simple venous angio-MRI without contrast medium performed under anaesthesia was a useful technique to support the difficult task of diagnosis. Secondary prophylactic treatment is focused on preventing recurrence; mild hyperhomocysteinaemia is considered to represent an intermediate or low risk of developing thromboembolism, whereas protein S deficiency is associated with a higher risk.1 In children, recurrence after a first spontaneous venous thrombosis occurred in 21% of cases after a mean of 3.5 years; 95% of patients with recurrence carried one or more risk factors.1 Moreover, the lack of vein recanalisation is associated with a 2.4-fold higher risk for developing recurrence.2

The risk of major bleeding episodes in children taking oral anticoagulants was reported as high as 0.5% patient-years;

long term oral anticoagulant treatment was therefore warranted in our patient.

DISCUSSION

The report describes a child who presents with severe posterior knee pain in whom initial investigation for a venous thromboembolism (VTE) is normal. After two weeks more detailed investigation reveals a small non-occlusive venous clot. Investigation for inherited thrombophilia shows low free protein S and raised homocysteine levels, and incomplete recanalisation of the popliteal vein. On the strength of these findings, lifelong anticoagulation is recommended. It is not certain from the history and findings that the clot in the case presented arose truly spontaneously. Non-occlusive venous thromboembolism is often asymptomatic and in this case was only demonstrated two weeks after the onset of

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severe knee pain. The pain started two weeks after an illness associated with a raised platelet count and significantly raised ESR. It is possible therefore that despite the clinical findings, the pain was secondary to inflammation or a vasculitis and that the clot was a consequence of this.

Predisposition to thrombosis was tested in this child soon after an illness associated with a significant acute phase response as shown by the thrombocytosis and raised ESR and also in the acute post-thrombotic state. Free protein S can fall in these circumstances and may return to normal once the episode is over. Also, the normal range in children varies from that in adults and has been quoted for 6–10 year olds as 0.22–0.62 U/ml. Therefore, protein S deficiency has not been conclusively shown and should be retested in a quiescent phase, off oral anticoagulants, and shown to be low on more than one occasion with reference ranges appropriate for age. Secondly, the homocysteine level is only marginally raised; an increased risk of thrombosis of approximately 2.5-fold has been shown in those whose levels are >18.5 µmol/l, which is higher than that seen in this child. Also, it is not stated if this level is fasting, and whether the patient had her normal diet in the weeks preceding the test; furthermore, a single measurement, particularly at this marginal level, is not enough.

The observation of lack of recanalisation of the popliteal vein at one year is claimed as evidence for continued presence of clot and an increased risk factor for rethrombosis. After one year, the clot will have organised and been replaced by fibrotic tissue; the paper quoted as showing lack of recanalisation predisposing to rethrombosis concludes that using multivariate analysis, only the presence of prothrombotic defects increases the risk of recurrent VTE.

The risks of rethrombosis in this child need to be examined against the risk of life long anticoagulation. Although the risk of recurrence after discontinuation of oral anticoagulant therapy after a first VTE in unselected patients is around 15–20%, this is associated with an increased risk of haemorrhage. On standard anticoagulant therapy, major haemorrhage occurs at a rate of 1% per year of treatment, and one quarter of these bleeds are fatal. In general, patients who have had two or more apparently spontaneous VTEs require consideration for indefinite anticoagulant thromboprophylaxis. However, patients who have had VTEs in association with identifiable prothrombotic triggers which are no longer present, may well not require anticoagulation long term except in high risk circumstances. For the patient who has had a first VTE, the benefits of long term treatment (more than six months) have not yet been shown to outweigh the risks. The risk of recurrent events in subjects with combined thrombophilias is not known.

In conclusion therefore, it has not been shown conclusively that the VTE was a primary event; it could have been secondary to an inflammatory trigger. The combined thrombophilia has not been confirmed in the quiescent state and the lack of recanalisation of the vein is probably non-contributory to risk. Recurrent VTE is rarely life threatening, and life long anticoagulation in this child could conceivably last for 60 years with the attendant cumulative risk of serious haemorrhage. There also is no family history given of VTE despite the thrombophilic defects identified in this child’s parents. I would argue that after initial anticoagulation, the child’s parents should be counselled regarding the signs and symptoms of VTE and to seek medical attention early if they suspect a recurrence. Advice should also be given to mention the history of VTE to medical attendants in the future so that appropriate decisions about short term thromboprophylaxis at times of increased thrombotic risk can be made.

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