Could factor V Leiden defect cause Addison’s disease?

Sir,

We describe a case of Addison’s disease caused by bilateral suprarenal haemorrhage in a patient heterozygous for factor V Leiden defect. This is the first reported case of isolated bilateral suprarenal haemorrhage in a patient with this disorder. Because of the unique blood supply of the suprarenal glands, we believe that suprarenal haemorrhage was secondary to venous infarction caused by venous thrombosis in suprarenal veins and venous plexus.

A 68-year-old man was admitted to hospital with a 3-week history of anorexia, lack of energy, dizziness and weight loss. There was a history of iléo-femoral deep-vein thrombosis in his left leg treated with anticoagulation 4 weeks previously. He was on warfarin and senna tablets.

On examination, he was hypotensive and tachycardic, and his left leg was swollen. The rest of the examination was unremarkable. Sodium was low (125 mmol/l), potassium was 6.6 mmol/l and glucose 5.6 mmol/l. ECG showed right bundle branch block, and chest X-ray showed clear lung fields. He was treated with low-molecular-weight heparin, rehydration with normal saline, fluid balance and insulin and dextrose to treat his hyperkalaemia. Further investigations showed a low random cortisol level at 117 nmol/l. Subsequently, a short synacthen test suggested primary adrenal failure: pre-synacthen cortisol was 107 nmol/l and post-synacthen was 117 nmol/l. Supra-renal autoantibodies were negative. Ultrasound scan of the lower limbs showed bilateral extensive deep-vein thrombosis. Abdominal computerized tomography showed bilateral suprarenal masses suggesting bilateral haemorrhage into suprarenal glands (Figure 1), extensive venous thrombosis affecting the distal splenic vein, inferior mesenteric veins, distal inferior vena cava below the level of renal veins and pelvic veins. Thrombophilia screen showed increased activated protein C resistance, and the heterozygous factor V Leiden defect was confirmed by genetic studies. Anti-cardiolipin antibodies were weakly positive, but this was thought not to be significant.

He was started on life-long hydrocortisone and fludrocortisone. He made a good recovery and was discharged from hospital. A repeat CT scan 2 years later showed that the changes in suprarenal glands has resolved.

Suprarenal glands are particularly vascular. They are supplied by the superior, middle and inferior supra renal arteries, which arise from the inferior phrenic arteries, abdominal aorta and renal arteries, respectively. Most of the branches of the suprarenal arteries ramify over the capsule before entering the gland and dividing to form a narrow sub-capsular plexus. This plexus supplies the zona glomerulosa and then passes through the zona fasciculata to form a deep plexus located in the zona reticularis. From this, small venules pass between the chromaffin cells of the medullar to the medullary veins, and then into thick-walled, relatively muscular suprarenal veins.

Because of this unique vascular plexuses and venous drainage of suprarenal glands, they are vulnerable to venous stasis and thrombosis. This may lead to ischaemic necrosis, with subsequent secondary haemorrhage into the gland. Clearly, anticoagulation may also contribute as an additional factor.

A case of bilateral renal vein thrombosis and suprarenal haemorrhage complicated by Addison’s disease requiring life-long replacement therapy has been described in a neonate with heterozygous Factor V Leiden defect. In a review of cases of suprarenal gland insufficiency secondary to suprarenal haemorrhage, 10 of the 12 patients who underwent anticoagulation received the heparin for deep-vein thrombosis and/or pulmonary embolism.

Figure 1. CT scan of abdomen showing bilateral suprarenal masses, suggesting bilateral haemorrhage into suprarenal glands. SRM, suprarenal mass.
This strongly suggests some thrombophilic tendency in these patients prior to anticoagulation. In seven other patients, there were other risk factors for venous stasis and thrombophilic conditions including pneumonia, post-operative immobility and hypotension.\(^3\)

In a personal study, Fox described 32 cases of supra-renal infarction due to thrombosis of the suprarenal blood supply. In these cases, he demonstrated suprarenal haemorrhage, necrosis and thrombi in cortical and sub-capsular sinuses extending into suprarenal veins.\(^4\) In the same study, the contention that suprarenal haemorrhage is secondary to thrombosis was also suggested by seven other cases in which there were venous thrombosis with haemorrhage and necrosis in one gland but venous thrombosis without haemorrhagic changes in the other gland.

We believe we have shown a case of bilateral suprarenal haemorrhage secondary to thrombosis in a patient who was later found to have heterozygous factor V Leiden defect. Anticoagulation may have contributed to bilateral suprarenal gland haemorrhage with subsequent permanent damage of both suprarenal glands resulting in acute Addisonian crisis.

Intuitively, one might believe that anticoagulant therapy would prevent venous thrombosis and reduce the likelihood of haemorrhage, but the temporal relationship between starting warfarin and adrenal failure would suggest that it precipitated the bleed. A speculative mechanism would be that small haemorrhages caused by venous thrombosis become substantive bleeds in the presence of anticoagulation.

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The plasma concentrations of phytanic and pipecolic acid should be in μmol/l rather than mmol/l.