Cerebral sinus thrombosis in a young adult with activated protein C resistance and homocysteinaemia

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INTRODUCTION

Thrombosis is a well-recognized association of activated protein C resistance and homocysteinaemia. This article reports a patient with a family history of thrombosis presenting with cerebral sinus thrombosis. This was found to be the result of a coincident occurrence of two thrombophilic diseases: activated protein C resistance and homocysteinaemia. The importance of fully investigating young patients with unexplained thrombosis and testing for homocysteinaemia are emphasized.

DISCUSSION

This case highlights one serious consequence of an increased tendency to spontaneous thrombosis. This patient had two predisposing conditions for thrombosis: activated protein C resistance and homocysteinaemia. Both can be familial and may have been responsible for his brother's and/or mother's past illnesses.

Activated protein C resistance is usually caused by mutation in the gene coding for coagulation factor V resulting in an enhanced and uncontrolled activation of the latter factor by thrombin (Bertina et al, 1994). This so-called factor V Leiden mutation seems to be the commonest cause of familial thrombophilia (Mateo et al, 1997).

Homocysteinaemia on the other hand has been recognized as an important risk factor not only for thrombosis but also for ischaemic heart disease and stroke (Wald et al, 2002). Both nutritional and genetic factors may lead to increased homocysteine level (Kang, 1995). The former is primarily associated with deficient intake of the B vitamins

CASE REPORT

A man of 28 years of age with no past history of note was admitted with a history of progressive severe diffuse headache, nausea, vomiting, blurring of vision and diplopia of 3 weeks' duration. He denied any fever or recent head trauma and had no preceding ear, nose or throat symptoms. He occasionally experienced oral ulcers, usually when he missed his routine daily brushing of his teeth. He denied having any genital ulcers. He never smoked and did not drink alcohol. He had a brother who died at a young age from possible thrombosis. His mother developed leg deep venous thrombosis after her first child was born. His father was diabetic. He worked as an interpreter. On examination, he looked ill and was slightly drowsy. He was afebrile, in sinus rhythm and normotensive. The major findings were confined to the nervous system. He had bilateral sixth nerve palsy and bilateral papilloedema, more pronounced on the right side. There were no other neurological signs. Ear, nose and throat examinations were normal.

Magnetic resonance imaging of the brain showed a right sigmoid and superior sagittal sinus thrombosis with no cerebral infarction (*Figures 1, 2* and *3*). Full blood count, erythrocyte sedimentation rate, liver, renal and thyroid function and glucose levels were all normal. His vitamin B_{12} level was 694 pg/ml (normal 180–710 pg/ml). Autoantibodies including antinuclear antibodies, double-stranded DNA and antineutrophil cytoplasmic antibodies were negative. Cryoglobulins, anticardiolipin antibody, haemoglobin electrophoresis, immunoglobulin levels, antithrombin III, protein C and protein S were all normal or negative. Homocysteine level was markedly raised (confirmed on repetition) at 48.5 μmol/litre (normal <10.3 μmol/litre). Activated protein C ratio was low (less than 2) suggesting resistance. Genotypic confirmation for factor V Leiden mutation was not possible.

He was fully anticoagulated with intravenous heparin and later warfarin was started. The international normalized ratio was kept between two and three. Dexamethasone at a dose of 4 mg intravenously 6-hourly was added initially and slowly tapered over a 3-week period. He gradually improved with complete resolution of his headaches, ocular palsies and papilloedema.

Figure 1. T2-weighted axial image showing a hyper-intense lesion (acute thrombosis) in the posterior aspect of the superior sagittal sinus.

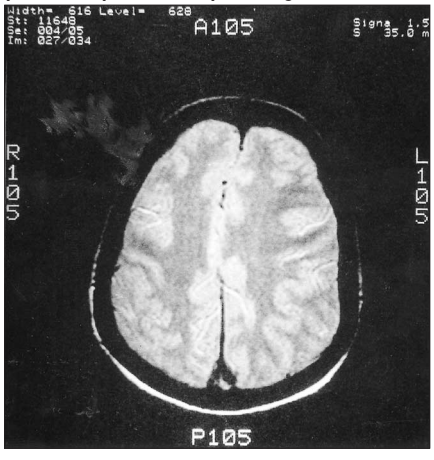
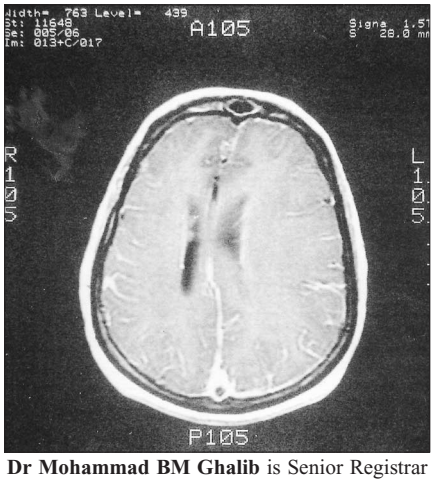


Figure 2. Enhanced T1-weighted axial image showing a filling defect at the confluence of the sinuses with associated midline shift.



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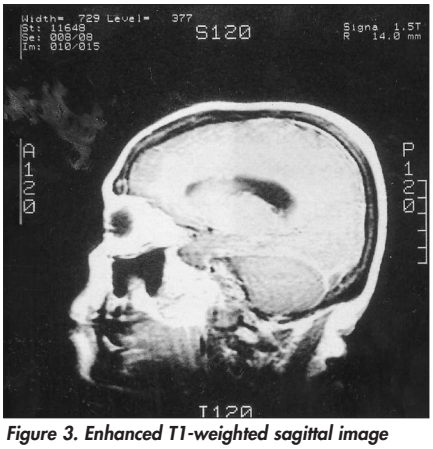

Figure 3. Enhanced T1-weighted sagittal image showing a filling defect at the confluence of the sinuses.

folate, pyridoxine and B_{12}. Homocysteine is thought to increase thrombotic tendency by various mechanisms including endothelial cell injury, reduced nitric oxide production and increased platelet aggregation (Stamler et al, 1993; Thambyrajah and Townend, 2000). The risk of thrombosis is increased appreciably when an individual has both hyperhomocysteinaemia and factor V Leiden mutation (Ridker et al, 1997). In the latter study, the relative risk for idiopathic venous thromboembolic disease compared to patients with neither abnormality was 3.4 with hyperhomocysteinaemia, 2.3 with the factor V Leiden mutation, and 21.6 when both disorders were present (Ridker et al, 1997).

This patient was advised to continue on warfarin indefinitely and to have supplemental vitamin B_{12}, folic acid and pyridoxine. Family screening was recommended. HM

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Ridker PM, Hennekens CH, Selhub J et al (1997) Interrelation of hyperhomocysteinemia, factor V Leiden, and risk of future thromboembolism. *Circulation* **95:** 1777–82

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In the Public's View...

Plastic fantastic

Medicine makes good telly. Whether factual, sensational or scurrilous, the channels are hungry for medical programmes and audiences love them. Last year went out with Channel 5's *Hear the Silence*, technically a docu-drama which, depending on your point of view, was either factual or scurrilous but either way a sensational representation of what has become known as the MMR 'debate'. There is no debate; MMR is as safe as a vaccine can be expected to be, but the media's way of 'balance' – large scientific studies against one or two families' experiences – makes it look like a debate.

I found *Hear the Silence* and the studio discussion that followed it profoundly depressing. Take a look at the BMJ e-letters that it provoked, but take care that the first one you read is Thomas Valentine's (http://bmj.com/cgi/eletters/327/7428/1411#44658). In it, he encapsulates all that is wrong with unregulated responses to published work: opinion as fact, distortion and selection, downright rudeness, and obdurate refusal to see anyone else's point of view. Meanwhile, more and more children are unprotected against a disease that maims and kills.

Firmly in the scurrilous category is Phil Hammond's latest comedy offering, *Doctors and Nurses* (BBC1). One of the leads is Adrian Edmondson, who played the punk medical student in *The Young Ones* and is now qualified, presumably. The *BMJ* gave *Doctors and Nurses* a three-star preview but I failed to find a good review in the general press. Most reviewers complained the situations were hackneyed and the characters were stereotypes. That does not seem to have been a disadvantage for lots of other sitcoms, but won't tempt me to watch it.

The Guardian (SocietyGuardian, 14 Jan 2004, p2) previewed a forthcoming Channel 4 series, *No Angels*, that concentrates just on nurses. Factual it isn't. Sex and drinking feature highly and one of the story lines includes trying to warm up an elderly patient's dead body so the doctors won't realize that she has been dead for some time. I'm not tempted to watch that either.

I did take a look at the opening episode of *Nip/Tuck* (SkyOne), about a pair of plastic surgeons in partnership in Miami. Dr Smarmy takes money from anyone, but Dr Tortured has a conscience. I'm not sure I'll stay the course to find out how they develop. A child molester, who has paid many dollars for a face change (shown in graphic detail), is shot and killed by his brother (don't ask) during liposuction. The suction tubing detaches and sprays sucked out fat all over the operating theatre, after which the anaesthetist storms out in a huff.

It being Miami and, thus, close to the Everglades, the body is disposed of by leaving it on the bank of a creek covered in hams to tempt the alligators. Dr Smarmy has noisy sex with starlets. Later, a mobster injects him with his own botox. Dr Tortured has sad sex with his wife, played by Joely Richardson. She seems on course to have an affair, and maybe a boob job, with Dr Smarmy.

It wouldn't happen in *Holby City*. HM

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