LESSON OF THE MONTH

Congenital protein C deficiency and superior sagittal sinus thrombosis causing isolated intracranial hypertension

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Abstract

The first case of a superior sagittal sinus thrombosis causing isolated intracranial hypertension as a result of congenital protein C deficiency is reported. Such a possibility must not be overlooked. Anticoagulation is recommended as a treatment for cerebral venous thrombosis. In the case of congenital protein C deficiency, vitamin K antagonists must be started cautiously due to the risk of skin necrosis.

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Protein C is an important inhibitor of plasma coagulation and its deficiency may lead to thromboembolic events,¹ the most common of which occur in the venous vasculature. We report what is, to our knowledge, the first case of superior sagittal sinus thrombosis causing isolated intracranial hypertension as a result of congenital protein C deficiency.

Case report.

A 60 year old housemaid, with no previous history of thrombosis, was bitten by a dog in

December 1989. She was treated with oral doxycycline (200 mg) and ampicillin (1500 mg) daily. The bite healed without fever and no adenopathy. On day 5, the patient developed frontotemporal bilateral headache with nocturnal recrudescence, nausea, and drowsiness, and antibiotics were stopped. The symptoms worsened and were completed, two weeks later, by blurred vision and diplopia. When first examined in the department, the patient was awake and alert. She was found to have bilateral abducens palsy and papilloedema. There was no fever and no ear, nose and throat infection. Enhanced cerebral CT scan showed a discrete delta sign, small ventricles, and no mass effect. A right carotid angiography disclosed a thrombosis of the caudal part of the superior sagittal sinus (figure). The following blood tests were normal: erythrocyte sedimentation rate, white blood cell count, red blood cell count, electrolytes, glucose, creatinine, protein electrophoresis, complement, and antinuclear antibodies. Serological reactions were negative for *Treponema pallidum*, HIV 1 and 2, *Borrelia burgdorferi*, *Coxiella burnetii*, Epstein-Barr virus, Cytomegalovirus, *Herpes zoster* virus, and *Toxoplasma gondii*. Coagulation studies showed normal values

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Figure (A) Right carotid angiography showing thrombosis of the caudal part of the superior sagittal sinus (SSS). (B) Right carotid angiography performed two months later, showing recanalisation of SSS.

Plasma protein C activity and antigen concentration during consecutive examinations of the patient

	Protein C activity (%) [*]	Protein C antigen (%) [*]
22 December 1989	45	ND
8 January 1990	56	51
7 February 1990	45	ND
1 March 1990	52	ND

^{*}Normal (range) value = 100% (65%–135%). ND = Not done.

for partial thromboplastin time, prothrombin time, and the assessment of factors, I, II, V, VII, VIII, IX, X, XI, and XII. Antithrombin III and plasminogen assessed by a chromogenic technique (Coatest Antithrombin and Plasminogen, Diagnostica Stago, France) and free protein S assessed by an enzyme linked immunosorbent assay (ELISA) technique (Asserachrom Protein S, Diagnostica Stago, France) were also normal. By contrast, the assessment of protein C activity, measured by a chromogenic assay (Stachrom Protein C, Diagnostica Stago, France) showed a reduced value (table). No anti-cardiolipin antibodies² or lupus anticoagulant (by dilute tissue thromboplastin inhibition test) were detected.

The patient was immediately started on treatment with intravenous heparin (15 000 IU) and furosemide (60 mg) daily. Lumbar puncture was performed at day 15 after admission. Cerebrospinal fluid (CSF) opening pressure was 170 mm H₂O and the total protein content was 0.43 g/l with 5 white blood cells (91% lymphocytes) and <10 red blood cells per mm³. Glucose content and IgG index for CSF were normal. Oligoclonal banding was absent. The CSF was sterile. During the week after admission, outcome was favourable with the cessation of headache and visual disturbances. The papilloedema resolved in one month. Protein C activity and protein C antigen measurements showed persistent abnormalities (table). Two months later, the patient was symptom free and the cerebral angiogram showed an almost complete recanalisation of the superior sagittal sinus in its caudal part (figure). Heparin was discontinued and warfarin treatment was started. One year later, the patient is still symptom free under this treatment.

Discussion

Our patient presented a thrombosis of the superior sagittal sinus with isolated intracranial hypertension. The clinical picture mimicked the classical condition of pseudotumour cerebri according to established criteria.³ Protein C deficiency seemed to be the sole risk factor for thrombosis.

Protein C is a vitamin K dependent protein synthesised in the liver and activated by thrombin and thrombomodulin.¹ In collaboration with protein S, another vitamin K dependent factor, protein C inactivates cofactors Va and VIIIa, which exert a procoagulant effect through activated factor X and throm-

bin, respectively. Protein C deficiency has been described in association with thromboembolic events in the venous vasculature, notably, limb thrombophlebitis, recurrent superficial thrombophlebitis that is considered as particularly suggestive of the condition, pulmonary embolism, and other deep venous thromboses.^{1,4} It is found in 4% to 8% of venous thrombosis cases occurring before the age of 40.^{4,5} More recently, it has been noticed in non-haemorrhagic arterial stroke.⁶ Two types of protein C deficiency have been described: type I, with a reduction of both antigen concentration and activity of protein C, and type II, with reduction of activity but normal antigen level. Acquired causes of protein C deficiency are liver cirrhosis, leukaemia, disseminated intravascular coagulation, and treatments with antineoplastic drugs or vitamin K antagonists.¹ Protein C deficiency may also be congenital with a mode of inheritance thought to be autosomal dominant. The heterozygous state is usually asymptomatic and its estimated prevalence is 1 in 200 to 300 according to a prospective study from 5422 normal adults.⁷ Additional thromboembolic factors might be necessary for thrombotic manifestations to appear.^{7,8}

In our case, protein C deficiency is presumably congenital as acquired causes could be excluded and assessments of the protein concentration and activity were consistently found below the lower limit of the normal range during the follow up (table). A type I deficiency can be postulated, according to the aforementioned criteria, but familial history of thrombosis was limited to an episode of postpartum limb thrombophlebitis in the patient's mother. Our patient was single and had no children. Only one of her two sisters was available for examination. Assessments of her protein C concentration and activity were normal.

To date, only six cases of cerebral venous thrombosis with protein C deficiency have been reported.^{9–12} Wintzen *et al*¹¹ reported a well documented case with a thrombosis of the anterior part of the superior sagittal sinus which gave rise to headache, seizures, and frontal haemorrhagic infarct. Roos *et al*¹² recently presented a similar case but the presentation was not strictly isolated intracranial hypertension and it was found during the postpartum period. To our knowledge, our case is the first to be reported with a typical isolated intracranial hypertension presentation revealing a protein C deficiency. No alternative aetiological explanation has been found for the angiographically demonstrated superior sagittal sinus thrombosis. Our patient had received doxycycline for the first time in her life, however, at the onset of her disease. Thirteen cases of association between isolated intracranial hypertension and tetracyclines have been reported previously in adults.^{13–19} Among the seven that were studied angiographically, none showed a cerebral venous thrombosis. Furthermore, tetracyclines are not known to interfere with coagulation. We might speculate that the therapy

with doxycycline favoured the isolated intracranial hypertension clinical presentation for the cerebral venous thrombosis in our patient, but the classic association between antibiotic intake and isolated intracranial hypertension has recently been challenged.²⁰

In conclusion, this case report confirms that protein C deficiency may lead to cerebral venous thrombosis and shows for the first time that the clinical expression may be of the isolated intracranial hypertension type. Furthermore, it gives another example of the importance of (a) a systematic morphological examination of the cerebral venous sinuses by angiography²¹ or MRI in the aetiological expertise of isolated intracranial hypertension; and (b) a complete coagulation screening in cases of cerebral venous thrombosis, even when routine coagulation tests are normal. This strategy may be of the utmost practical relevance. In cases of thrombosis attributed to congenital protein C deficiency, anticoagulants are indicated but cautious starting is required as skin necrosis may develop.¹ Protein C half life is shorter than that of other vitamin K dependent coagulation factors and its plasma concentration decreases more rapidly in response to vitamin K antagonists with thrombosis as a result. Loading doses of vitamin K antagonists must be avoided in such patients and concurrent heparin administration must be maintained as long as the vitamin K antagonist has not reached its full effectiveness as determined by the appropriate coagulation tests. Lastly, lifelong treatment with vitamin K antagonists may be advocated in patients with thrombotic events and congenital protein C deficiency as well as in their asymptomatic heterozygotic relatives.²²

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