Cerebral Vein Thrombosis due to Hereditary Antithrombin III Deficiency

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ABSTRACT: Cerebral vein thrombosis, also called superior sagittal sinus thrombosis, is a well recognized clinical and radiologic entity associated with a variety of medical disorders. We report a patient with fatal cerebral vein thrombosis following myelography, in whom the cause was familial antithrombin III (AT3) deficiency. Unsuspected AT3 deficiency should be considered in cases of unexplained cerebral venous thromboses.

RÉSUMÉ: Thrombose veineuse cérébrale due a une déficience héréditaire en antithrombine III. La thrombose veineuse cérébrale, également appelée thrombose du sinus sagittal supérieur, est une entité associée à des affections médicales variées et bien reconnue au point de vue clinique et radiologique. Nous rapportons le cas d'un patient qui a présenté, suite à une myélographie, une thrombose veineuse cérébrale causée par un déficit familial en antithrombine III (AT3). Un déficit insoupçonné en AT3 devrait être envisagé dans les cas de thrombose cérébrale veineuse inexpliquée.

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Cerebral vein thrombosis consists of thrombosis of the superior sagittal sinus, other cortical veins, and sometimes deep cerebral veins. The use of the previous term "superior sagittal sinus thrombosis" is to be discouraged, because the involved veins usually extend beyond the superior sagittal sinus. Neurologic symptoms and signs usually include those of raised intracranial pressure, seizures, and focal neurological deficits. Cerebral vein thrombosis was initially described in association with skull trauma and pyogenic infections of the scalp, sinuses and meninges, but since then an extensive list of other causes or associated medical disorders has accumulated (see Table 1).[1-5] A variety of coagulation abnormalities occur in some of these disorders. However we are aware of only one case report linking antithrombin III (AT3) deficiency with cerebral vein thrombosis. Ambruso et al. described a 15-year-old boy with prior history of a calf deep venous thrombosis which was initially treated with heparin, then warfarin.[6] Three months after warfarin was discontinued the patient developed cerebral sinus thrombosis and testing revealed AT3 deficiency. AT3 is a heparin cofactor that blocks the coagulation cascade by inhibiting activated coagulation factors (Figure 1). AT3 deficiency can be familial or acquired and these patients are at risk for thrombotic events.[7]

Case Report

A 24-year-old man was admitted to hospital because of seizures and headache. He had previously been well except for chronic low back pain for which he had been electively admitted to another hospital for investigation three days earlier. A myelogram had been performed (Isovue non-ionic contrast medium, Squibb, Princeton, NJ) and was normal. The following day he complained of headache, neck pain, photophobia, nausea and vomiting. The headache worsened and he then had a right arm focal motor seizure. This recurred five times over the next 24 hours. He was treated with intravenous phenytoin and transferred to our hospital.

Past medical history was negative for seizures or other medical or surgical illness. His father had developed a spontaneous deep venous thrombosis at age 47 and was on long-term warfarin therapy.

On admission the patient's temperature was normal and there was no neck stiffness. He was alert and oriented, but had a moderate expressive dysphasia. A right central facial paresis was present along with a moderate right hemiparesis. There was a right-sided impairment of all sensations. Cerebellar testing was normal.

Initial investigations showed a white cell count of 13.5 (neutrophils 11.5); hemoglobin, platelets, prothrombin time and partial thromboplastin time, glucose, electrolytes including calcium and magnesium, chest radiographs and ECG were all normal. A plain brain CT scan revealed a left parietal hematoma with a mild midline shift.

On the second hospital day, the dysphasia and right hemiparesis worsened. A bilateral carotid angiogram showed a right midline shift and non-opacification of the superior and inferior sagittal sinuses indicating sagittal sinus thrombosis. A pressure monitor was inserted and revealed an increased intracranial pressure (ICP) of 40 mmHg and this was treated with intravenous mannitol and dexamethasone.

On the third hospital day the patient became somnolent and agitated. ICP rose as high as 90 mmHg. He was intubated, hyperventilated and given intravenous furosemide, but the ICP was difficult to control despite these measures. Blood samples were sent for protein C and S (these levels were normal) and AT3 (the level of which was low at 0.52 units/ml [normal range 0.75 - 1.25 units/ml]; this result was not available until after the patient's death). A CT scan revealed increasing swelling of the left hemisphere; the hematoma was unchanged.

From the fourth to eighth hospital days his neurologic status was difficult to monitor because of paralysis with vecuronium; however the pupils remained reactive and doll's eye responses were present. Serial

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Table 1: Cerebral Vein Thrombosis: Causes and Associated Disorders

Cardiovascular
Congestive heart failure
Dehydration
Connective tissue/inflammatory disorders
Behçet's disease[b]
Polyarteritis nodosa
Sarcoidosis
Systemic lupus erythmatosus[b]
Wegener's granulomatosis
Drugs
Oral contraceptives[a]
L-asparginase[a]
Head and neck pathology
Infections (mastoiditis, meningitis, otitis media, scalp, sinusitis)
Skull tumors (primary and metastatic)
Hematologic
Antithrombin III (AT3) deficiency
Protein S deficiency
Afibrinogenemia
Cryofibrinogenemia
Disseminated intravascular coagulation[a]
Hemolytic anemia
Monoclonal gammopathy
Myelogeneous leukemia[a]
Paroxysmal nocturnal hemoglobinuria
Polycythemia rubra vera
Sickle cell trait
Thrombocytopenia
Obstetric
Pregnancy
Puerperium
Other
Budd-Chiari syndrome
Diabetes mellitus
Intravenous central catheter placement
Trichinosis

[a] Demonstrated association with AT3 deficiency
[b] Possible association with AT3 deficiency

EEGs revealed gradual deterioration with severe generalized slowing. The ICP remained markedly elevated despite the above treatments and acute renal failure developed. On the ninth hospital day brainstem reflexes were absent. The following day the EEG was isoelectric, the patient was declared brain dead and life support was terminated.

Subsequent hematological investigations on other family members showed that the patient's brother and nephew also have AT3 deficiency (Figure 2).

Pathology

Autopsy showed anemic kidneys without evidence of renal vein thrombosis, total atelectasis of the left lung and hyperinflation of the right lung. Examination of the brain showed thrombosis of the sagittal, straight, and right transverse sinuses and cortical veins on the left convexity. There was bilateral uncal herniation with deformation of the midbrain, in which there was a midline hemorrhage. On section, large roughly symmetrical hemorrhages were found involving cortex and white matter in the superior portions of frontal, parietal and occipital lobes. The spinal cord along with its vessels appeared normal.

Microscopically, partially organized thrombus filled the superior sagittal and straight sinuses. Unorganized antemortem thrombus was seen in many subarachnoid veins as far caudally as the cerebellum. The cerebral cortex, except for the temporal lobes and other basal areas, showed perivascular hemorrhages which were either almost confluent or sparse and associated with the pallor of early infarction. Hemorrhages in the white matter tended to be larger and more confluent. The cerebellar cortex, pituitary, and spinal cord were microscopically normal.

Discussion

This patient was a previously healthy young man with asymptomatic familial AT3 deficiency until he developed fatal cerebral vein thrombosis and hemorrhagic venous infarcts following a routine myelogram. Patients with inherited AT3 deficiency are known to be at risk of venous thrombosis at times of surgery, but to our knowledge this has not been reported as a complication of myelography. There are two possible links between this procedure and the development of cerebral vein thrombosis: the contrast may have acted as an irritant in the cerebrospinal fluid and in combination with the AT3 deficiency precipitated cortical venous and sagittal sinus thrombosis; and/or the myelogram may have caused nausea and vomiting which led to dehydration precipitating cerebral venous thrombosis. Insufficient clinical information prior to transfer to our hospital makes the distinction difficult in this case, although the one day delay in onset of headache and vomiting after myelography, and the subsequent very rapid development of focal neurologic signs, argue against a simple low pressure headache syndrome with secondary dehydration.

AT3 is a plasma glycoprotein that functions as an endogenous circulating anticoagulant. It inhibits all coagulation proteinases (thrombin and factors IXa, Xa, XIa, and XIIa), but its principal sites of action appear to be at the level of thrombin and factor Xa (Figure 1). The AT3 molecule inhibits the target proteinase by binding to it and creating a complex that is rapidly cleared from the circulation.

AT3 deficiency is either hereditary or acquired. The hereditary deficiencies (often autosomal dominant), are divided into type 1 (normal molecules synthesized at a reduced rate), type 2 (abnormal molecules with normal plasma level) and type 3 (decreased amount of abnormal molecules).

The prevalence of hereditary deficiency in the general population has been estimated to be between 1:2000 and 1:5000.[8,9] But in patients being investigated for venous thromboembolism the prevalence is 1.8 - 3%.[10-12] Thrombotic and thromboembolic events may occur anywhere in the body in these patients, and the prevalence of thromboses in these individuals is as high as 26%.[13] About half of these events are spontaneous; the remainder are related to precipitants such as trauma, major surgery, infections, pregnancy, the postpartum period[14] and the use of oral contraceptives.

The most common and severe acquired AT3 deficiencies occur in consumption coagulopathies associated with disseminated intravascular coagulation, major surgery, pre-eclampsia, and various malignancies. Impaired synthesis of AT3 can occur in cirrhosis, severe thalassemia, and malnutrition. Loss of AT3 can be caused by protein-losing conditions such as the nephrotic syndrome and inflammatory bowel disease. Finally, drugs such as oral contraceptives and L-asparginase can also lead to an acquired deficiency.

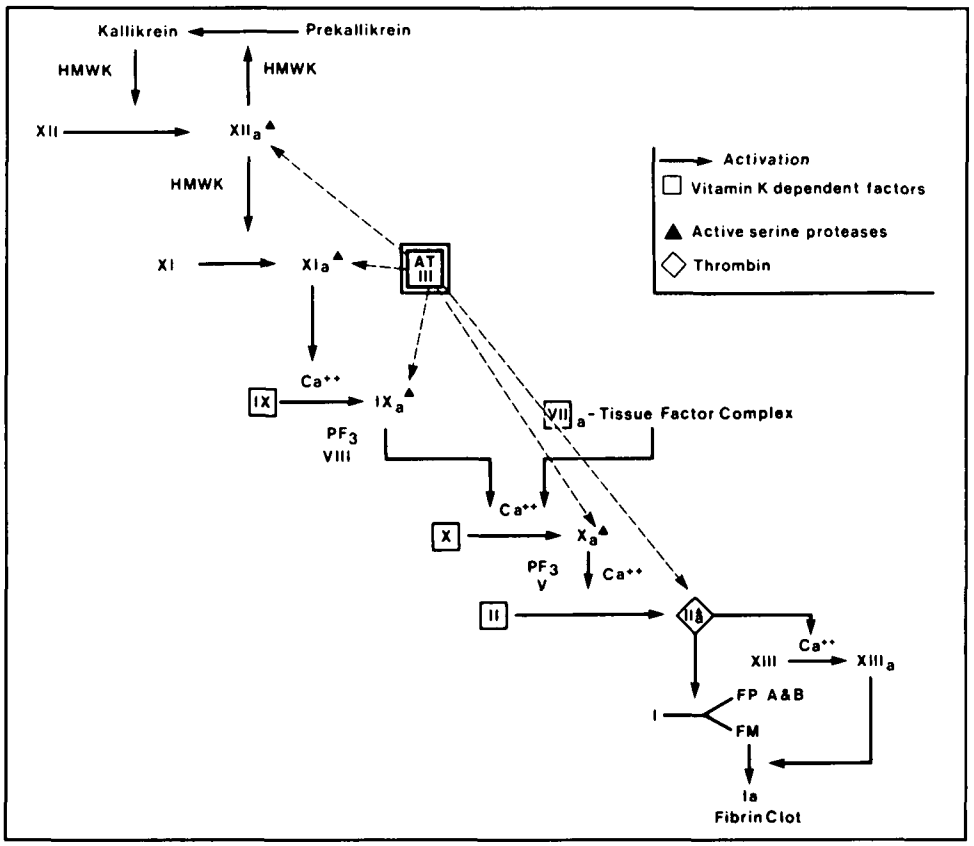

Figure 1 — Role of antithrombin III (AT III, AT3) in the coagulation cascade. AT III acts by forming complexes with the active serine protease forms of factors XII, XI, IX, X and II with the interaction with thrombin (factor IIa) and factor Xa being the most important. HMWK = high molecular weight kininogen; AT III = antithrombin III; PF_3 = platelet factor 3; FP A & B = fibrinopeptides A & B; FM = fibrin monomers. Reprinted with permission from Sirridge MS, Reaner S. Laboratory evaluation of hemostasis and thrombosis, 3rd ed. Philadelphia: Lea & Febiger 1983; 15.

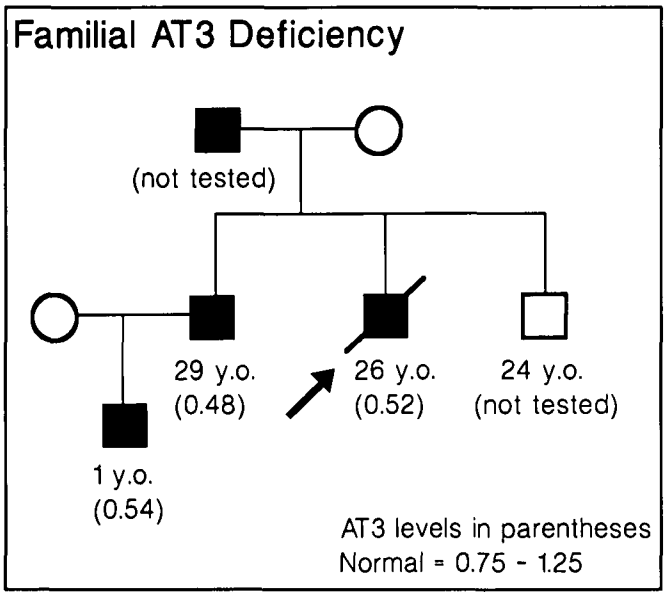

Figure 2 — Family pedigree and AT3 levels.

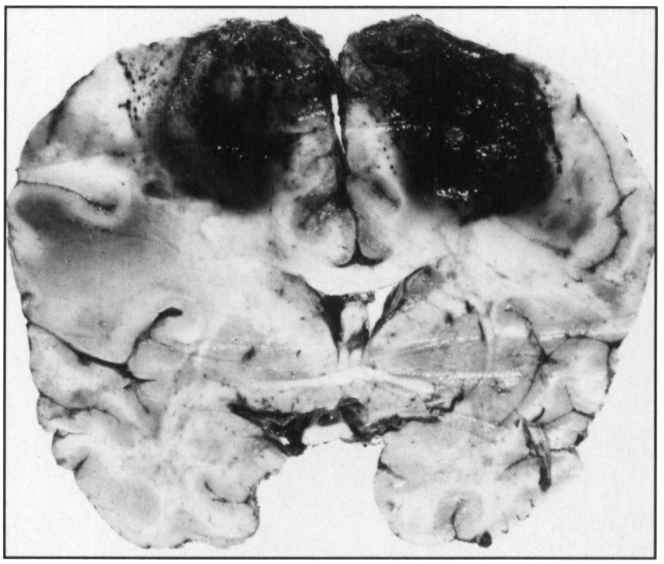

Figure 3 — Gross brain pathology. Coronal section of cerebral hemispheres at the anterior commissure reveals nearly symmetrical parasagittal hemorrhages involving the cortex and white matter of the frontal lobes.

In light of the fact that cerebral venous thrombosis can occur in otherwise healthy young individuals or as the result of diverse medical disorders, or merely in association with pregnancy, perhaps a common thread is either hereditary or acquired AT3 deficiency. Cerebral venous thrombosis as a complication of AT3 deficiency has been previously reported, mainly in the pediatric population.[6,15] In two reported cases in adults, the thromboses occurred in both cerebral and systemic venous territories;[14,16] isolated cerebral venous thrombosis in an adult, particularly in a post-myelogram setting, has not been described to our knowledge as a complication of AT3 deficiency. Unfortunately AT3 assays are not performed in routine hematological laboratories, so presently physicians treating such patients must act on clinical suspicion of this coagulopathy while awaiting laboratory confirmation.

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The treatment of cerebral venous thrombosis when AT3 deficiency is not the cause, has been controversial, apart from standard methods for reducing raised intracranial pressure. The use of anticoagulants or fibrinolytic agents is particularly debatable in patients such as ours with an associated intraparenchymal hemorrhage.[2,4,17-21] However, a recent small controlled study of the use of heparin in patients with cerebral venous thrombosis has shown significantly better outcomes in the treated patients.[18] In addition, a retrospective analysis by the same authors indicated that the presence of intracranial hemorrhage is not a contraindication to heparin treatment. When acquired or hereditary AT3 deficiency is either strongly suspected or confirmed by blood tests, a more rational therapeutic approach may be possible. Firstly, patients with known AT3 deficiency may benefit from prophylactic anticoagulation at the time when the risk factors for thromboembolism mentioned above are present. Otherwise, if a thromboembolic event occurs, the patient may be treated with heparin, with or without AT3 (either in purified form or as part of fresh frozen plasma), and subsequently placed on chronic oral anticoagulation. In our patient a coagulopathy was suspected because of his father's deep vein thromboses and long-term anticoagulant treatment but the diagnosis of AT3 deficiency was not made until after death. In retrospect this family history should have made the likelihood of hereditary AT3 deficiency highly probable. It would have been appropriate to treat this patient with heparin and AT3 supplementation to prevent the extension of cerebral vein thromboses. Such treatment might have aggravated the intraparenchymal hemorrhages or caused others, but extrapolating from Einhäupl's experience with heparin we believe this would have been a relatively low risk.[18]

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