SUPERIOR SAGITTAL SINUS THROMBOSIS COMPLICATING MAINTENANCE TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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□ A girl with acute lymphoblastic leukemia in remission had two seizures during the maintenance phase of her treatment. Magnetic resonance imaging with angiography identified a superior sagittal sinus thrombosis as the likely explanation for her symptoms. Possible causes are considered, and previous reports of the neurotoxicity of agents used in the treatment of leukemia are reviewed.

Keywords acute lymphoblastic leukemia, chemotherapy, magnetic resonance imaging, sagittal sinus thrombosis

While survival figures for childhood malignancies improve, complications of treatment are playing an increasing role in morbidity. Nonmetastatic cerebrovascular events, including sagittal sinus thrombosis, have been reported in patients with systemic malignancy [1, 2], and some of these are attributed to chemotherapy. Previous reports of sagittal sinus thrombosis in children treated for acute lymphoblastic leukemia (ALL) have occurred during induction, and most have been associated with L-asparaginase [3, 4]. We describe the case of a girl who developed seizures, secondary to superior sagittal sinus thrombosis, during maintenance therapy for ALL.

CASE REPORT

Common ALL without central nervous system (CNS) involvement was diagnosed in our patient at the age of 12 years. She was entered into

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Pediatric Hematology and Oncology, 13:287–291, 1996 Copyright © 1996 Taylor & Francis 0888-0018/96 \$12.00 + .00 287



Received 3 July 1995; accepted 8 September 1995.

the UKALL X1 trial and received standard induction therapy, two intensive blocks of therapy at weeks 5 and 20, and three courses of high dose intravenous methotrexate at weeks 9, 11, and 13. In addition to vincristine, prednisolone, and intrathecal methotrexate given during induction and both intensifications, she received L-asparaginase as part of induction and daunorubicin, etoposide, cytarabine, and thioguanine during intensification. Apart from febrile neutropenic episodes, during remission induction and following both intensification blocks, these phases of treatment passed without complication.

Four weeks after completing her second intensification block and 10 days after receiving intrathecal methotrexate, intravenous vincristine, and oral prednisolone, she complained of multiple brief headaches, nausea, and vomiting. Three days later, she developed a severe right-sided headache and numbness of her left hand, and had a partial seizure, commencing with left sided facial weakness, with secondary generalization. A second seizure, which occurred 3 days later, had similar features but, in addition, was associated with ataxia of the patient's left arm during the prodrome. After the seizures, the patient remained generally weak for 2 days and had blurred optic disc margins but no other focal signs. Investigation revealed normal blood indices, routine chemistry and coagulation studies, including antithrombin III and proteins C and S, and resistance to activated protein C was later excluded. A cranial computed tomography (CT) scan, with contrast, showed no significant abnormalities. Lumbar puncture revealed an opening cerebrospinal fluid (CSF) pressure of greater than 40 cm H_2O and a normal cytospin. The patient then underwent magnetic resonance imaging (MRI) and MR angiography, which showed a superior sagittal sinus thrombosis anteriorly (Figure 1) and a small area of ischemic infarction in the right parietal lobe, adjacent to the interhemispheric fissure.

Because of the patient's clinical recovery, no antithrombotic treatment was initiated. She restarted maintenance therapy, without intrathecal methotrexate, and had no further seizures or neurological symptoms, although her CSF pressure remained elevated throughout the course of her treatment. At the end of this period, the patient's bone marrow remained in remission and her optic discs appeared normal. A repeat MRI with angiography showed complete resolution of the previous abnormalities.

DISCUSSION

Cerebrovascular accidents and, in particular, venous thromboses, are uncommon events in childhood. Recognized causes include dehydration,



Figure 1. Magnetic resonance angiogram showing absence of flow in the superior sagittal sinus anterior to the bregma.

coagulation disorders, sickle cell disease, metabolic disorders, and abnormalities of the vascular endothelium. In children with cancer, thrombotic events may also be due to disseminated intravascular coagulation, bacterial or fungal sepsis, metastatic tumor, or chemotherapy [5].

Encephalopathy due to cerebral venous thrombosis during induction treatment for ALL is well documented and has been attributed to the administration of L-asparaginase [3, 4]. It appears to exert its procoagulant effects through depletion of plasma proteins involved in coagulation and fibrinolysis, although abnormalities of the von Willibrand factor have also been implicated [4]. Neurotoxicity is frequently encountered as a complication of treatment with vincristine, with peripheral neuropathy being the most common manifestation [3]. A series of four cases of seizures in children has been described, occurring 5 days following administration of vincristine in each case and in the presence of normal serum-



sodium [6]. Computed tomography scans, when performed, were normal, and all continued on vincristine without recurrence of seizures. Intravenous and intrathecal methotrexate have been associated with CNS complications, including progressive leukoencephalopathy and seizures, although the latter have only been reported in conjunction with cranial radiotherapy [3]. Methotrexate has been noted to exert cumulative toxicity with delayed clinical effects, but the syndrome described is characterized by fever, headache, dizziness, and vomiting, and therefore is quite unlike our case [7]. A series of four children who developed superior sagittal sinus thrombosis, diagnosed by CT and digital angiography, while receiving treatment for lymphoma, has been reported in the French literature [8]. Their presentations were similar to our case, and all recovered with time, although only one had a complete radiological resolution. Unlike our case, all of these occurred early in the course of treatment. All had received intrathecal methotrexate, but only two had received L-asparaginase. Of the other two, one had a platelet count of 10 $\times 10^{9}$ /L, in keeping with the chemotherapy and of uncertain significance in the development of the thrombosis, and in the fourth case, with Burkitt's lymphoma, no explanation could be found.

We have described a child receiving maintenance chemotherapy in whom a cerebral venous thrombosis developed at a time when there was no evidence of leukemia, sepsis, or a coagulopathy. Our case does not fit any of the recognized patterns of sagittal sinus thrombosis nor of neurotoxicity associated with L-asparaginase, vincristine, or methotrexate, and the authors are not aware of any previous reports of neurotoxicity following treatment with mercaptopurine. Our findings confirm that MRI is superior to CT scan for identifying the changes associated with sagittal sinus thrombosis and may be combined with noninvasive angiography. This is supported by the work of Medlock and coworkers [9], and raises the question of how many similar cases may have been missed prior to the availability of MR facilities. It is possible that our case brings to light a mechanism that may account for some of the unexplained seizures, such as those attributed to vincristine [6], or one by which methotrexate exerts some of its neurotoxic effects, in addition to those already described.

Treatment of sagittal sinus thrombosis in children is controversial. Strategies have included prophylaxis with fresh-frozen plasma and antithrombin III, treatment with anticoagulants or thrombolysis, and measures to control symptoms of raised intracranial pressure, using steroids, mannitol, and acetozolamide [4, 9]. Spontaneous recovery without treatment has been recorded in several cases [8, 9] including our own, al-

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though we noted unexplained persistent raised intracranial pressure, despite resolution of clinical signs and radiological changes.

In summary, we have found that the risk of cerebral venous thrombosis may persist beyond the induction phase of treatment for leukemia. Magnetic resonance imaging with angiography is important for the identification of these cases, but further observations are needed to establish the cause of these events so that steps may be taken toward prevention.

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