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IATROGENIC CEREBRAL VASCULAR THROMBOSIS IN A CHILD WITH ACUTE LEUKAEMIA

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ABSTRACT
A 4 yr old girl previously diagnosed to have acute lymphoblastic leukemia developed intractable headache and altered sensorium during her chemotherapy. She was undergoing re- induction phase consisting of prednisolone, vincristine, L asparaginase and daunorubicin. There was no papilledema or fundal haemorrhage. There were no focal neurological deficits. A contrast enhanced CT brain showed filling defect in the confluence of sinus suggestive of cerebral sinus venous thrombosis. MR imaging of brain along with venography confirmed the thrombosis. She was started on aggressive anticoagulation therapy with low molecular weight heparin. She responded and her sensorium improved with no neurological deficits. The rest of chemotherapy was conducted smoothly with the concomitant use of low molecular weight heparin.

KEYWORDS: Thrombosis, L-asparaginase, Anticoagulation, Leukaemia.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a well-known but relatively rare complication associated with acute lymphoblastic leukemia and can be fatal. Various factors are known to be contributory including the disease itself or its treatment. Early clinical diagnosis of CVT can be difficult due to its non-specific clinical presentation. Most of the cases are often diagnosed retrospectively after the development of complications. This case report highlights the importance of early clinical suspicion and use of MR imaging to diagnose CVT at an early stage to prevent progression of the thrombus and development of neurological sequelae.

CASE

A 4-year-old girl was diagnosed with ALL with the presentation of intermittent fever for 2 weeks. Her initial white blood cell count was $100x10^9$/L, and bone marrow examination revealed 90% lymphoblasts, which were positive for CD19 and CD79a. She was started on chemotherapy as per multicentric protocol (MCP 841) without delay. She completed the induction phase (I1, I2) smoothly and achieved remission. Re-induction phase of chemotherapy was started four months after diagnosis (prednisolone 40 mg/m2 daily; daunorubicin 30 mg/m2 on days 8; vincristine 1.4 mg/m2 on days 1 and 8; L-asparaginase 6,000 u/m2 every other day for 5 doses and intrathecal chemotherapy with methotrexate on days 1 and 8). On day 12 of re-induction phase, she developed intractable headache and drowsiness. There was no fever, vomiting, seizures or loose stools. Her birth, development and family history was normal.

On examination her weight was 15 kg (below 3rd centile), height was 104 cm (on 15th centile). Her blood pressure was 110/70 mmHg. There was no pallor, lymphadenopathy or skin bleeds. Fundus examination was normal. Neurological examination was normal with no focal deficits. Examination of other systems was unremarkable.

Baseline haematological investigations revealed haemoglobin of 10.2 g/dL, platelet count of 2.3 lakhs/mm3, and white blood cell $4.2x10^9$/L with absolute neutrophil count of $1.3x10^9$/L. There were no blasts in the peripheral smear. Serum biochemical investigations were normal. Coagulation profile done showed-prothrombin time 15.2 seconds (INR-1.05), activated partial thromboplastin time 30.2 seconds (control-32.3 sec, D-dimer 1.2 ug/mL, and fibrinogen 210 mg/dL. Contrast CT brain revealed ‘empty delta’ sign, a filling defect in the posterior part of left sagittal sinus and in left sigmoid sinus suggestive of venous sinus thrombosis (fig.1).

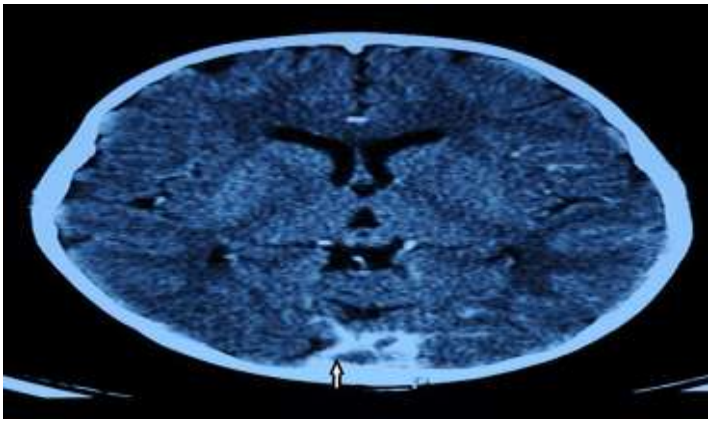

Fig.1 CT brain showing 'empty delta' sign (arrow)

Brain magnetic resonance venography (MRV) on the next day showed loss of flow related enhancement in the inferior sagittal sinus, straight sinus, torcula of Herophili, left sigmoid and transverse sinuses confirming dural sinus venous thrombosis (fig.2).

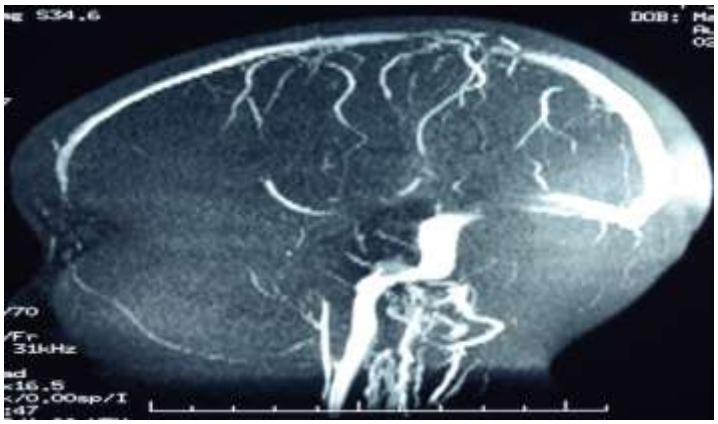

Fig.2 Brain MRV showing loss of flow related enhancement in the torcula of Herophili, left sigmoid and transverse sinuses

Workup for prothrombotic conditions including factor V Leiden, protein c and s deficiency, homocysteine levels, antithrombin III deficiency and prothrombin gene 20210 mutation was negative (during follow up after stopping anticoagulant therapy).

She was treated with LMWH (low-molecular weight heparin- enoxaparin sodium) 1 mg/kg/dose twice daily. Other supportive measures included mannitol and prophylactic anticonvulsant therapy. She responded to the above measures and sensorium improved over next 48 hours. LMWH in the therapeutic dose was continued for next 3 months. During follow up she was asymptomatic with normal development and no neurological deficits. The rest of chemotherapy was conducted smoothly with the concomitant use of low molecular weight heparin in the prophylactic dose (1 mg/kg/dose once daily). Repeat brain imaging was not done due to financial constraints.

DISCUSSION

Thrombo-embolic events are one of the less frequent but well recognized complications in a child with ALL. The risk of thrombosis in children with acute leukemia varies from 1% to 37%.[1] Early diagnosis is warranted to decrease morbidity and mortality. Although mortality is rare, children with cerebral VTE may endure long-term neurological morbidity.

Leukaemia itself may contribute by activating blood coagulation via procoagulant substances or by the impairment of anticoagulant pathways. Other factors including sepsis, leukocytosis, thrombocytopenia, chemotherapeutic agents and use of central venous catheters also contribute for the same. Concurrent presence of preexisting thrombophilia also increases the risk.[2] Thrombotic events occur more commonly during the induction phase reflecting intensive chemotherapy with active disease.[2, 3]

Chemotherapeutic agents like glucocorticoids and L-asparaginase (ASP) are well known to predispose the child to cerebrovascular events. ASP induces the hydrolysis of L-asparagine to L-aspartic acid and ammonia. Thus human lymphoblasts are destroyed as they are deprived of asparagine. It also inhibits synthesis of plasma proteins involved in both coagulation and fibrinolysis.[3, 4] Studies have proven decreased anti-

thrombin levels as the primary etiology of thrombotic events in patients treated with ASP.[5] Steroids induce an increase in coagulation factors, particularly factor VIII and Von Willebrand factor, and a decrease in fibrinolytic factors. Thus concurrent steroid use augments the procoagulant action of ASP. Prednisolone is known to be associated with higher VTE risk than dexamethasone.[6]

Central nervous system is the most common location of thrombosis in children treated with ASP.[7] A decreased level of consciousness, headache and seizures are the well-recognized clinical features of cerebral sinus venous thrombosis (CSVT). Other features include focal neurological deficits, irritability, visual disturbances and hypertension. However the clinical manifestations of CSVT are non-specific and may be subtle.[8]

Neuroimaging is the essential modality to confirm the diagnosis in children with suspected CSVT. The thrombosed sinuses appear hyperdense on CT and a contrast enhancement may demonstrate the 'empty delta' sign, a filling defect in the posterior part of sagittal sinus.[9] MRI reveals thrombosed sinuses hyper-intense instead of showing the normal void caused by blood flow.[8, 9] MR venography (MRV) is the imaging of choice for diagnosing CSVT. It demonstrates lack of flow in the cerebral venous sinuses.[10]

Treatment of cerebral venous thrombosis includes anticoagulation along with supportive measures. LMWH is safe and effective in prevention of thromboembolism in children with ALL during L‐asparaginase therapy.[11, 12] Grace et al. studied the management and outcome of asparaginase‐related venous thromboembolic events in both paediatric and adult patients with ALL. This study confirms that, after VTE, asparaginase can be restarted safely with closely monitored anticoagulation. Though recurrence of thrombotic event following re-administration of ASP is common in adults, it is rare in children. Anti-Xa levels should be monitored regularly in all age groups during anticoagulation while on asparaginase.[12]

CONCLUSION

L- Asparaginase, the key component of remission induction chemotherapy along with prednisolone increases the risk of thrombosis. This case report highlights the importance of early clinical suspicion and use of MR imaging to diagnose CVT at an early stage to prevent progression of the thrombus and development of neurological sequelae. Authors conclude that asparaginase should be temporarily withheld from that particular phase but can be given in subsequent courses safely under prophylactic anticoagulant measures.

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