CEREBRAL SINUS VENOUS THROMBOSIS DUE TO ASPARAGINASE THERAPY

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BACKGROUND:
Cerebral Sinovenous Thrombosis (CSVT) is a serious complication of L-asparaginase chemotherapy for leukemia in children. Clinical features of headache, altered consciousness, focal neurological deficit, and seizures developing during or immediately after treatment with L-asparaginase should alert the treating physician to the possibility of CSVT. Immediate imaging of the brain should be done using CT and MRI and the veins should be visualized noninvasively by CT and MR venography.

OBJECTIVE:
We stress the importance of early diagnosis of CSVT using CT and MRI in children with leukemia being treated with L-asparaginase.

CASE REPORT:
We report three cases of infant lymphoblastic acute leukemia complicated by cerebral sinus venous thrombosis due to Asparaginase therapy.

Case 1: A 10 years old girl who developed a tonic-clonic convulsion with revulsion of eyeball within a few days after the first administration of L-asparaginase. Magnetic resonance of the brain showed thrombophlebitis of the superior sagittal sinus. Treatment was started, after stopping the asparaginase therapy, with anticoagulation due to thrombophlebitis in the superior sagittal sinus. The patient recovered fully 1 month later.

Case 2: A 10-year-old boy with newly diagnosed ALL, presented with seizures developing during or immediately after administration of L-asparaginase. Magnetic resonance of the brain showed thrombophlebitis of the superior sagittal sinus. Treatment was started, after stopping the asparaginase therapy, with anticoagulation due to thrombophlebitis in the superior sagittal sinus. The patient recovered fully 1 month later.

Case 3: A 8-year-old boy who presented frontal headache 1 day after administration of L-asparaginase. Magnetic resonance of the brain showed thrombophlebitis of the lateral sinus has extended right internal jugular vein. The patient recovered fully 1 month later.

DISCUSSION:
Cerebral events in leukemia may be due to ischemia, hemorrhage, infection, or spread of the primary disease to brain. Venous thrombosis may cause as many as 30% of the acute central nervous system events in acute leukemias. L-asparaginase is an enzyme derived from Escherichia Coli that is used in the treatment of acute lymphoblastic leukemia. In ALL, induction therapy with L-asparaginase sometimes causes venous thrombosis. L-Asparaginase hydrolyzes asparagine to aspartic acid, depleting asparagine and inhibiting protein synthesis. This inhibition is thought to be the basis of its antineoplastic effect, but it also leads to the depletion of other plasma proteins involved in coagulation and fibrinolysis. The clinical manifestations of CSVT are variable and include headache, vomiting, altered mental status, focal deficits, and seizures. The underlying pathology responsible for these symptoms is the spectrum of unilateral and bilateral venous infarcts and hemorrhages. The evaluation of patient with suspected CSVT has been made considerably easier by the modern neuroimaging techniques of CT and MRI. Thrombosed sinus may appear hypointense on noncontrast CT. Contrast-enhanced CT reveals enhancement around the thrombosed sinus in the form of the empty delta sign. Parenchymal infarcts in the distribution of the thrombosed draining vein/sinus, with or without hemorrhage, are additional findings on CT. MRI is more sensitive for detection of early infarction. The diagnosis is established by demonstrating lack of flow in the dural sinuses and cerebral veins, with or without typical imaging of brain infarcts. Parenchymal MR and MRV are important in the demonstration of both the infarct and the thrombus with in the sinuses. On MRI, the thrombus is readily recognizable in the subacute phase, when it is of high signal intensity on T1-weightedimages; MRV is then often not required. In the acute phase, the thrombus shows isointense signal intensity on T1-weighted and low signal on T2-weighted imaging. This can be mistaken for flowing blood but MRV will demonstrate an absence of flow in the thrombosed sinus. Treatment of CSVT resulting from L-asparaginase-induced antithrombin deficiency includes general supportive measures, anticonvulsants for seizures, and anticoagulation. L-asparaginase may be stopped for some time.

CONCLUSION:
Diagnosis of CSVT in leukemic patients being treated with L-asparaginase requires a high index of clinical suspicion in the presence of seizures, a focal neurological deficit, and features of raised intracranial tension. Early diagnosis demands a low threshold for imaging, and MRI should be preferred over CT. Identification of relevant findings such as venous infarcts, the empty delta sign, and absent flow in the dural sinuses on CT and MR venography enables proper diagnosis and management.