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L-ASPARAGINASE INDUCED CENTRAL VENOUS THROMBOSIS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background

To report a case of central venous thrombosis following treatment of acute lymphoblastic leukemia with L-asparaginase. A 13-year-old master presented with an acute lymphoblastic leukemia associated with three episodes of focal onset convulsions with secondary generalization, headache and altered sensorium. He was initially treated with 5000 u/m^2 of L-asparaginase followed by 10,000 u/m^2 every third day for 4 weeks. After a week's course of L-Asparaginase, the patient experienced central venous thrombosis. MRI showed thrombosis of the sagittal, transverse and straight sinuses on the right side with partial recanalisation, suggesting a drug induced neurotoxic reaction. According to the Naranjo probability scale, the central venous thrombosis was probably caused by L-Asparaginase. L-Asparaginase-induced central venous thrombosis is rarely reported shortly after beginning L-asparaginase therapy in patients with acute lymphoblastic leukemia. However, bleeding or thrombosis occurring as a direct result of changes in coagulation factors has not been frequently reported. The purpose is to evaluate the current knowledge of central venous thrombosis in association with ALL in children. Health care professionals should be aware of this potential adverse reaction and monitor the patients regularly during L-asparaginase therapy.

Key Words: *L-asparaginase, Central Venous Thrombosis, Acute Lymphoblastic Leukemia.*

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is more frequent in children than in adults; indeed, two thirds of all cases occur at pediatric age[1]. The risk of thrombosis is increased in ALL patients, and its occurrence may complicate the treatment course with a negative prognostic impact[2]. L-asparaginase hydrolyses L-asparagine which is a non essential aminoacid. L-asparaginase is used particularly in acute lymphoblastic leukemia (ALL) and in other hematological malignancies such as acute myeloblastic leukemia (AML) and lymphoma [3,4]. Therapy has been associated with various forms of toxicity, including hypersensitivity, coagulation abnormalities and others[5,6]. L-asparaginase shows this effect by decreasing the synthesis of coagulation proteins [7,8]. In literature, thrombosis is emphasized more than hemorrhagic complications due to L-asparaginase. This report describes a case who developed central venous thrombosis confirmed by Magnetic Resonance Imaging (MRI) during L-asparaginase therapy.

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CASE REPORT

A 13-year-old boy was presented to Kovai Medical Center and Hospital, India in January 2005, with complaints of three episodes of focal onset convulsions with secondary generalization. History revealed head turning to left follow by generalized tonic-clonic convulsions. Hemoglobin was 10.6 g/dl, leukocytes 1700 cells/cumm, and the platelet count 1, 07,700 cells/cumm. The differential count revealed 16% lymphocytes, 81% neutrophils, and 3% monocytes. The patient's bone marrow aspiration showed 90% blasts (L1 type according to French-American-British (FAB) classification) with Periodic acid Schiff reaction (PAS), sudan Black and myeloperoxidase stains negative. The patient was on prednisolone, vincristine, daunorubicin, l-asparaginase, methotrexate and cytosine. Computed Tomography (computerized type of x-ray that gives very detailed images of internal organs such as the brain) scan of the brain was normal but during the next 48 hours, he developed weakness of the left upper limb. The prothrombin time was 29 seconds, the partial thromboplastin time 48 seconds fibrinogen, protein C, protein S, antithrombin III levels were normal. Serum

ammonia was 443 µg /dl (normal value 25-94 µg/dl). L-asparaginase toxicity was suspected. Throat swab and urine cultures were negative. As cerebral venous sinus thrombosis was suspected a MRI and Magnetic Resonance Venography (MRV) of the brain were done, which revealed thrombosis of the sagittal, transverse and straight sinuses on the right side with partial recanalisation. Low dose subcutaneous heparin 2500 I.U 8th hourly was started and continued for 10 days. The patient regained normal power in the left upper limb and did not have any further convulsions. Acetyl salicylic acid 150 mg/day orally was given for 7 to 10 days and the patient was discharged.

Anterioposterior (AP) view of MRV showing absence of filling of sagittal sinus and right transverse and sigmoid sinuses is shown in picture 1. Lateral view of MRV showing venous filling defects as noted above are shown in picture 2.

DISCUSSION

L-asparaginase enzyme has a molecular weight of 133.000 daltons and hydrolyses L- asparagine. L-asparagine is synthesised by transamination of L-aspartic acid. In tumor cells, lacking of L-asparagine synthase, the L-asparagine can be obtained from the circulating pool of amino acids. As the L-asparaginase will decrease the amount of extracellular L-asparagine, tumor cells use this amino acid which is necessary for protein synthesis. But in normal cells, this synthesis may be re-done because of enzyme existence.

Cerebrovascular symptoms dependent on L-asparaginase appear in two forms; either increased or normal coagulation factors-especially fibrinogen-and thrombotic cases developing by decreased Antithrombin III (AT Ill) and Plasminogen or decreased fibrinogen level and hemorrhagic cases developing by normal AT III and plasminogen concentration[9,10].

AI-Mondhiry reported that, in two of the four patients whom vincristine and prednisone treatment applied, fibrinogen level decreased but Prothrombin time (PT), Partial thromboplastin time (PTT) and Thrombin time (TT) remain in normal limits [11]. Ramsay et al used vincristine, prednisone, and L- asparaginase in 26 ALL cases. In these cases, after cessation of L-asparaginase coagulation tests were turned to normal limits. Consequently those coagulation abnormality were found to be due to L-asparaginase[12].

In the study of Miniero et al., when the patients are treated by prednisone, vincristine and L-asparaginase, compared with patients treated by only L-asparaginase more common coagulopathy was observed [13]. In the previously treated ALL cases, some hemorrhagic and thrombotic complications due to L-asparaginase have been reported [14,15,16,17].

Hemorrhagic complications due to L-asparaginase are seen rarely and important for morbidity, once in 2 or 3 days the coagulation parameters (PT,PTT, Fibrinogen, Plasminogen,and AT III levels) must be measured and when necessary, fresh frozen plasma, AT III and thrombolytic therapy must be given. However, bleeding or thrombosis occurring as a direct result of changes in coagulation factors has not been frequently reported [18].

Table No 1: Treatment Schedule for Induction Therapy

Variables	*Mg/m2*	*Day*
vincristin	1.5	8,15,22,29
prednisolone	60	1-28
daunorubicin	30	8,15,22,29
L-asparaginase	10,000	19,22,25,28,31,34,37,40
methotrexate	BY AGE	1

Figure no.1: AP view of MR Venogram showing absence of filling of Sagittal sinus and right transverse and sigmoid sinuses.

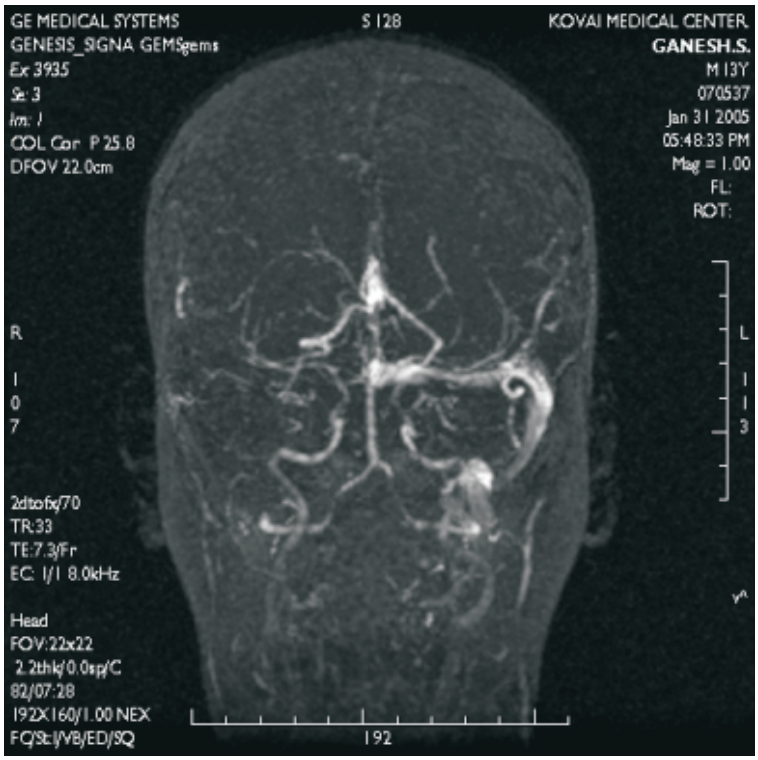
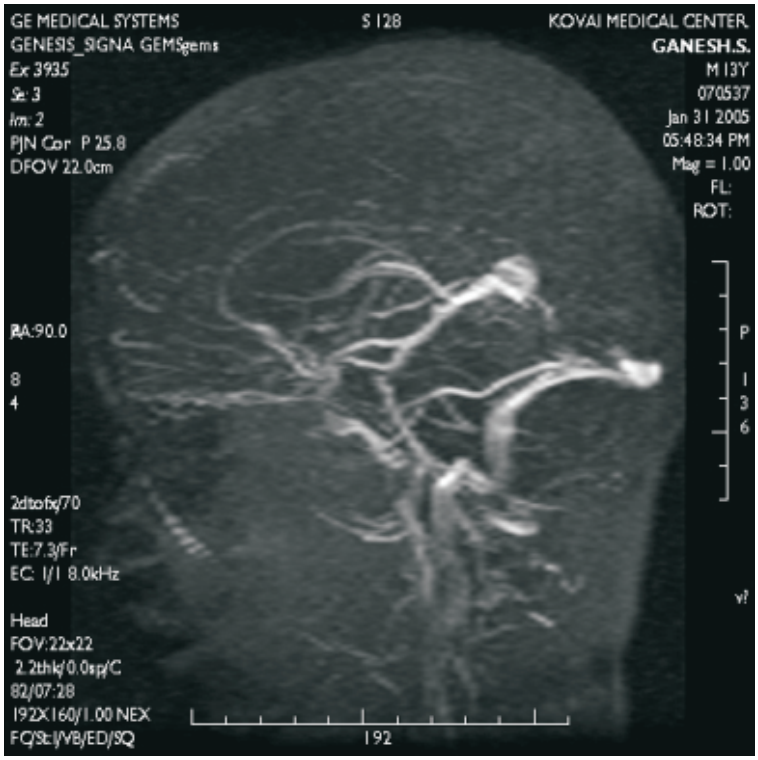


Figure no.2: Lateral view of MR venogram showing venous filling defects as noted above.



CONCLUSION

Treatment related to thrombotic complications during the induction therapy and recent evidence indicates that concomitant administration of L-asparaginase is likely to be associated with higher incidence of central venous thrombosis, especially in children with atleast one prothrombotic risk factor. This result in prolongation of the prothrombin time (PT), activated partial thromboplastin time (aPTT) and hypofibrinogenimia. These coagulation abnormalities resolve within 1-2 weeks after cessation of the drug.

At present, there is no general agreement on the need to monitor the coagulation/fibrinolytic systems in patients treated with L-asparaginase. There are also no guidelines on ways to avoid either the haemorrhagic or the thrombotic complications. It is suggested to replace the coagulation factors with fresh frozen plasma and at the same time, give AT III and heparin; but the consensus is to treat expectantly.

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