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## **PEG Asparaginase Induced Superior Sagittal Sinus Thrombosis with Status Epilepticus Pediatric in Acute Lymphoblastic Leukemia (ALL): A Report of 2 Cases from India**

<sup>1</sup>SirishaRani Siddaiahgari, <sup>1</sup>Darshak Makadia and <sup>2</sup>Lokesh Lingappa

<sup>1</sup>Department of Pediatric Hematology and Oncology,

<sup>2</sup>Department of Neurology, Rainbow Childrens Hospital and Perinatal Centre, Hyderabad, India

*Corresponding Author: SirishaRani Siddaiahgari, Department of Pediatric Hematology and Oncology, Rainbow Childrens Hospital, Hyderabad, India*

### **ABSTRACT**

Among all pediatric malignancies, acute lymphoblastic leukemic children are more prone for venous thrombosis, with an estimated incidence of 1-36% which includes both symptomatic and asymptomatic cases detected on screening. The risk of thrombosis is secondary to increased thrombin generation at the time of diagnosis combined with decreased clearance of thrombin secondary to PEG asparaginase. This further gets aggravated by concomitant use of steroids in induction along with indwelling central venous catheters. Role of antithrombin concentrates and anticoagulants is still not in practice for primary prevention. For children who are at high risk of thrombosis, prophylactic fresh frozen plasma is recommended. Though central nervous system thrombosis, cerebral venous thrombosis is a known complication with L asparaginase, none has been reported secondary to PEG asparaginase from India. Here two cases of PEG asparaginase induced Superior Sagittal Sinus Thrombosis (SSST) have been reported presenting with status epilepticus in Acute Lymphoblastic Leukemia (ALL) children described for the first time from India. Case 1 presented soon after induction and case 2 in third week of induction. Case 1 had low protein S and antithrombin which got normalised 3 months post episode and case 2 had normal thrombophilia work up. Both continued on further chemotherapy smoothly with concomitant usage of low molecular weight heparin at therapeutic dosage for 3 months and at prophylactic dosage until reinduction completion.

**Key words:** Acute lymphoblastic leukemia, L-asparaginase, superior sagittal sinus thrombosis

### **INTRODUCTION**

Acute Lymphoblastic Leukemia (ALL) accounts for one fourth of childhood cancers. With risk-adapted intensive chemotherapy, the cure rate of pediatric ALL approaches nearly 80%. Thrombosis is a one of the frequently encountered complication of ALL. Reported incidences of thrombosis for children receiving chemotherapy for ALL range from 1.7-36.7% (Mitchell *et al.*, 2003; Sutor *et al.*, 1999; Wermes *et al.*, 1999; Mauz-Korholz *et al.*, 2000; Nowak-Gottl *et al.*, 2001, 2003). This wide variation in incidence is mainly because of the type of studies performed, a retrospective surveys report clinically symptomatic thrombosis in <5% of cases, whereas, prospective

studies with routine radiological screening report largely asymptomatic events in 11.5-36.7% of children with ALL. Although, less frequent than infection, bleeding and mucositis, thrombosis is equally important pediatric oncological emergency which needs early recognition to limit the neurodisability in children on ALL therapy. In case of solid tumours, non central venous catheter related thrombosis are unusual. In ALL most of the times thrombosis is related to chemotherapy and often affects the Central Nervous System (CNS). In a study by Gugliotta *et al.* (1990), effect of antithrombin III supplementation was looked at to prevent thrombosis during asparaginase therapy. Despite of maintaining AT-III higher than 70% the rate of decline of fibrinogen, factor IX, protein C and protein S were unaffected. Hence its use is undetermined. Prophylactic fresh frozen plasma and cryoprecipitate had been administered by Abbott *et al.* (2009). High risk of thrombotic tendency at diagnosis, concomitant central venous catheter, usage of medications like asparaginase and steroids in induction increase the thrombotic tendency.

Here, two cases of SSST secondary to chemotherapy while on induction and just post induction have been reported.

## **MATERIALS AND METHODS**

Prospective analysis of 2 children who developed complication of SSST was done.

## **RESULTS**

Case 1 is 2 year 4 months-old boy with standard risk Common Acute Lymphoblastic Leukemia-associated Antigen (CALLA) positive ALL by WBC count, CNS negative status and by genetics. He received induction as per UK ALL 2003 protocol, went into remission. Three days after starting consolidation, he developed fever followed by left focal seizures evolving into generalized tonic-clonic seizures and subsequently to status epilepticus. Left hemiparesis was noted. He neither had past history of epilepsy nor febrile convulsions. No family history of hypercoagulable status or seizures was observed.

Complete blood count showed WBC  $2,600 \text{ mm}^{-3}$  with 15% neutrophils, Hb- $10.3 \text{ g dL}^{-1}$  and platelet  $13,000 \text{ mm}^{-3}$ . Serum electrolytes, calcium and magnesium were normal. Coagulation profile and C-reactive protein were normal. Antibiotics and antiepileptics were started to give him. Brain Magnetic Resonance Imaging (MRI) showed thrombosis of superior sagittal sinus (Fig. 1). Thrombophilia screening revealed low protein S and antithrombin III. He was treated with Low Molecular Weight Heparin (LMWH) and antiepileptic drugs. Left hemi paresis improved within 5 days. Further anticoagulation medication with LMWH in the therapeutic dose ( $1 \text{ mg kg}^{-1}$  twice daily) was maintained for next 6 months, until his Protein S and antithrombin were normalized.

Case 2 was 3½ years girl presented with left focal seizures evolving into status epilepticus, 3 weeks into induction. She was found to have SSST in Magnet Resonance (MR) venogram and was started on Low Molecular Weight (LMW) heparin. She was initially treated with levetriacetam and then received lacosamide to control seizures. These antiepileptics were selected to treat seizures as they do not interfere with chemotherapy.

Her procoagulant work up was normal. There was no family history of seizures or hypercoagulable status. She received therapeutic doses of LMW heparin for 3 months followed by prophylactic dose during reinduction while giving PEG asparaginase. Her hemiparesis improved within a week.

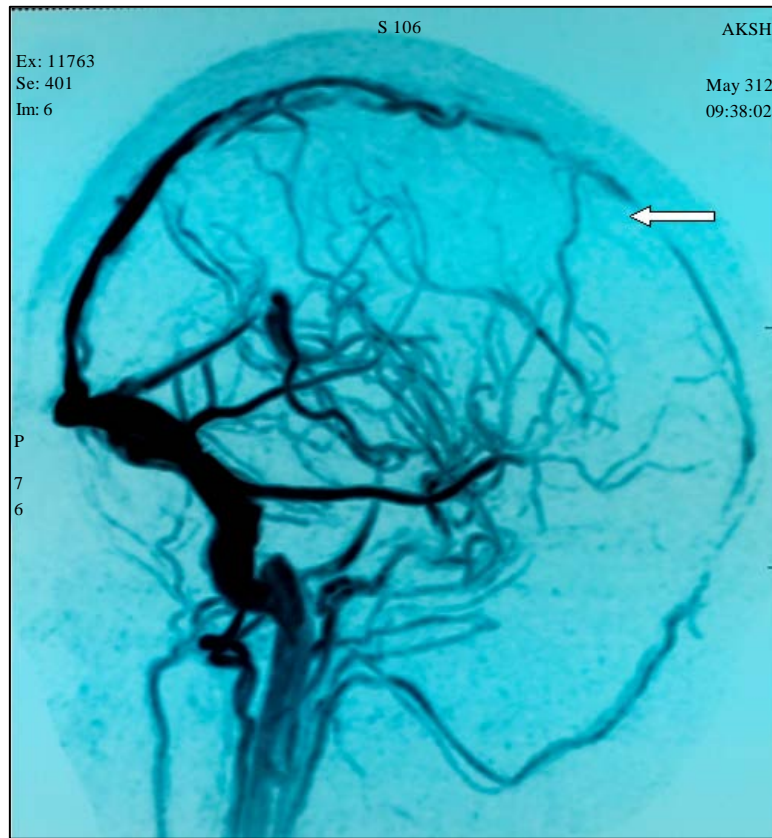


Fig. 1: Magnetic Resonance (MR) venogram demonstrates flow voids (white arrow) in anterior part of superior sagittal Sinus Suggestive of Sinovenos Thrombosis (SSST)

## DISCUSSION

The cure rate of around 80-85% in ALL is at the expense of some of the complications caused by chemotherapeutic agents. Incidence of thrombosis in children with haematological malignancies is about 12% (Tubergen and Bleyer, 2012). Central venous catheter, medications like L asparaginase and infections related to ALL treatment will add on to this.

Mechanisms for thromboembolic events in ALL children include the disease itself, exposure to L-asparaginase during induction with concomitant steroid usage and early insertion of central venous catheters (Payne and Vora, 2007). The L/Peg-Asparaginase is an important component, for effective treatment of ALL. The inhibition of protein synthesis caused by asparaginase is considered to be the basis of its antineoplastic effect which can cause depletion of other plasma proteins involved in coagulation and fibrinolysis. Feinberg and Swenson (1988) and Vicarioto *et al.* (1986) noticed significantly low fibrinogen and AT-III sequentially during remission induction in 20 ALL children. Impaired thrombin inhibition by anticoagulant deficiency has been proposed as the main pathogenesis of thrombosis (Mitchell *et al.*, 1995; Parsons *et al.*, 1997).

Case 1 had low protein S and AT-III level during episode due to Peg asparaginase. But normal thrombophilia screening after the episode excluded the possibility of inherited thrombophilia tendency.

Abbott *et al.* (2009) found a disproportionate number of Asian children with CNS thrombosis, although, statistically not significant, indicating possibly race related inherited polymorphisms.

Because the reported thrombosis incidence varies from 1-36%. Various efforts were tried to prevent the thrombosis. Cohen *et al.* (2010) reported neurologic complications associated with asparaginase-induced hypertriglyceridemia (TG) in two ALL children with extremely high TG levels suggested routine monitoring of TGs levels before and during asparaginase treatment. Prophylactic fresh frozen plasma and cryoprecipitate had been administered by Abbott *et al.* (2009).

The mainstay management for SSST is anticoagulation and supportive care.

Payne and Vora (2007) recommended the anticoagulation with LMWH over warfarin for SSST in the setting of ALL. Twice daily therapeutic dose (maintaining anti-Xa level at 0.5e1.0 IU mL<sup>-1</sup>) for 3 months and once a day for prophylactic usage.

## CONCLUSION

In conclusion, thromboembolic complications are not uncommon during the treatment of ALL, especially post asparaginase therapy with concomitant administration of steroids. Anticoagulation therapy with LMWH is effective for SSST with its advantages. Prophylactic usage of LMWH in ALL patients, who had ever developed SSST during re exposure to L asparaginase and steroid should be adopted to minimize the recurrence of SSST which was implemented in the study cases.

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