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**Case Report**

# Homozygous methylenetetrahydrofolate reductase -a1298c mutation in a case of precursor B acute lymphoblastic leukemia

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## ABSTRACT

Thrombotic events are well recognized during treatment for acute lymphoblastic leukaemia. We report a case of recurrent thrombosis off asparaginase wherein thrombophilia evaluation yielded specific etiology. A 14 year old boy with precursor B cell acute lymphoblastic leukemia (ALL) (high risk) presented with generalized tonic clonic seizures on day +22 of induction. Asparaginase associated thrombotic event was suspected. MRI brain with MRV done showed right frontal lobe infarct and superior sagittal sinus thrombosis with reduced blood flow in left transverse sinus. He was managed conservatively. However, after the first dose of systemic methotrexate therapy he presented with right sided hemiparesis. In view of his recurrent episode thrombosis in the absence of asparaginase, thrombophilia workup was done which showed homozygousity for methylenetetrahydrofolate reductase (MTHFR)-a1298c mutation. MTHFR mutation is a rare cause of thrombophilia which was found in a case of precursor B cell ALL as a cause of recurrent venous thrombosis precipitated by methotrexate therapy.

**Keywords:** ALL, MTHFR mutation, Recurrent thrombosis, Thrombophillia

## INTRODUCTION

Thrombotic events are well recognized during treatment for acute lymphoblastic leukaemia. The risk of thrombosis in children with acute lymphoblastic leukaemia (ALL) reportedly ranges between 1% and 37%.[1] Evaluation for thrombophilia is usually not recommended in view of known risks with certain specific drugs. We report a case of recurrent thrombosis off asparaginase wherein thrombophilia evaluation yielded specific etiology.

## CASE REPORT

A 14 year old boy with precursor B cell ALL (high risk) positive for CD34, CD20, CD10, CD19 and HLA-DR. His CSF cytospin was acellular for malignant cells. He was started on steroid pre-phase on 03.03.15. He showed good response to pre-phase. He was planned to give 4 drugs induction as per COG high risk protocol followed by BFM consolidation. On day +22 of induction chemotherapy, he presented with generalized tonic clonic seizures without any focal neurological deficit. Asparaginase associated thrombotic event was suspected. MRI brain with MRV had done showed right frontal lobe infarct and superior sagittal sinus thrombosis with reduced blood flow in left transverse sinus. Enoxaparin was commenced. There was no central line in situ.

Follow-up MRI after 6 weeks showed near total resolution with complete clinical recovery. Enoxaparin had to be discontinued at this point because of thrombocytopenia post cyclophosphamide. The plan was to re-initiate enoxaparin during reinduction. However, after the first dose of systemic methotrexate (5 gm/sqm) therapy he presented with complaints of weakness of right side of body, sudden in onset, progressive in nature, associated with mild pain in right upper and lower limbs,

with difficulty to move right half of body and hemiparesis. He was restarted on inj enoxaparin and supportive care. MRI brain with contrast and MRV showed left cortical venous thrombosis.

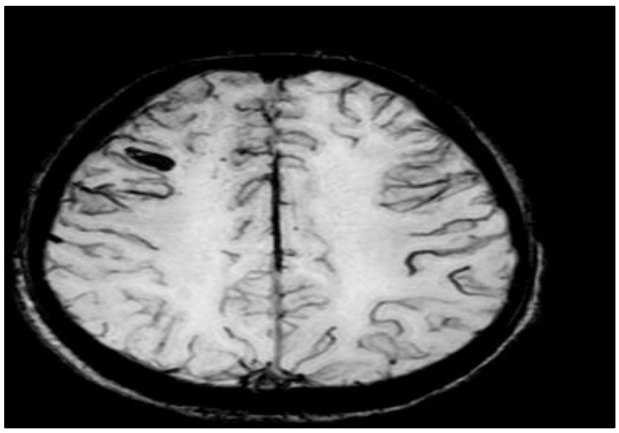

**Figure 1: Right frontal lobe infarct in MRI.**

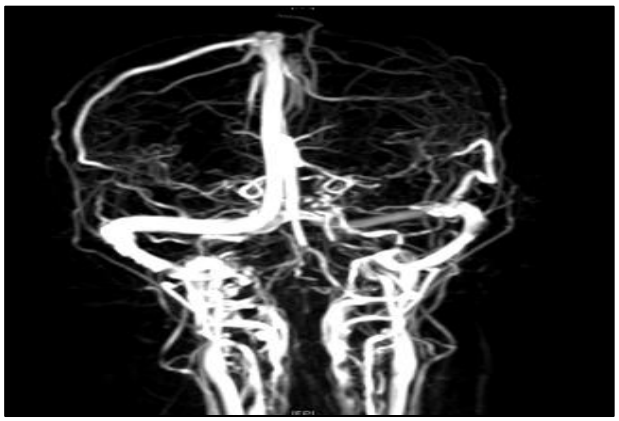

**Figure 2: MRV of reduced blood flow to transverse sinus.**

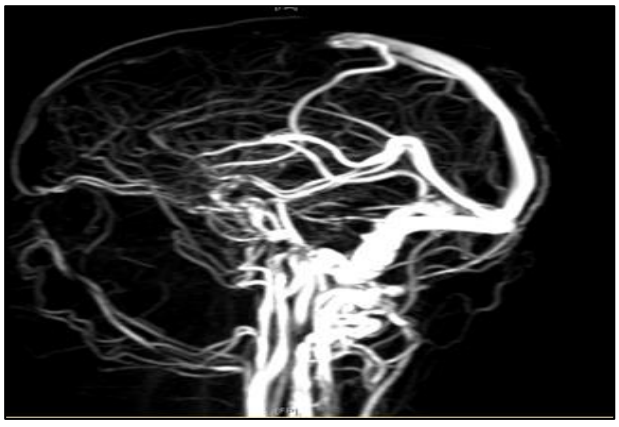

**Figure 3: MRV - blockage of flow of superior sagittal sinus.**

In view of his recurrent episode thrombosis in the absence of asparaginase, thrombophilia workup was done which showed homocysteine level - 7.4 (normal), protein C and S level and factor VIII level - normal. However he was found positive homozygousity for MTHFR-a1298c mutation. He was continued on further chemotherapy including methotrexate and L-asparaginase on folate supplementation along with enoxaparin.

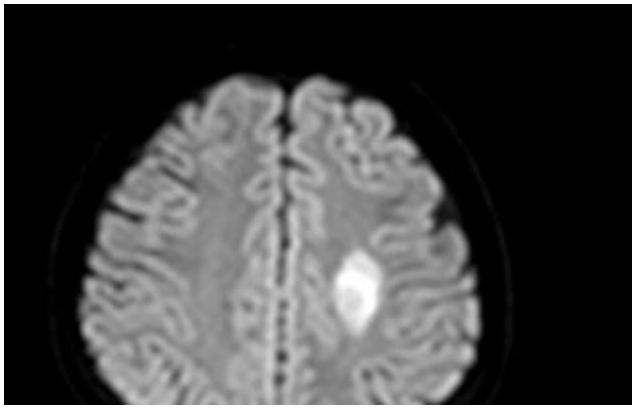

**Figure 4: MRI of new infarct in left side of cortex.**

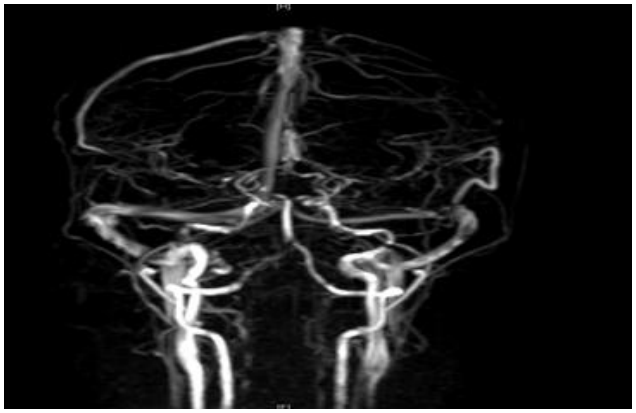

**Figure 5: MRV of cortical venous thrombosis.**

## DISCUSSION

The risk of thrombosis in ALL patients varies depending on several factors. Most of the events occurred during the induction phase of therapy. Lower doses of asparaginase (ASP) for long periods were associated with the highest incidence of thrombosis, as were anthracyclines and prednisone (instead of dexamethasone).[1] The presence of central lines and of thrombophilic genetic abnormalities also appeared to be frequently associated with thrombosis.

In this case report, patient with high risk ALL was having first thrombotic event thought to be due to L-Asparaginase and no further thrombotic workup was done. In view of recurrent new event, the detailed workup detected MTHFR mutation as a cause of these events. Vascular insults reported in children with ALL are discussed mainly in association with acquired quantitative deficiencies of protein C, protein S, or antithrombin associated with enhanced thrombin

generation.[2,3] In our case, patient was not having any central line.

## CONCLUSION

MTHFR mutation is a rare cause of thrombophilia which was found in a case of precursor B cell ALL as a cause of recurrent venous thrombosis precipitated by Methotrexate therapy.

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