Augmented Genetic Risk of Thrombophilia in Pediatric Acute Lymphoblastic Leukemia: Case report and Review of Literature

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Abstract

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Venous thromboembolism (VTE) is relatively common in children with acute ALL that usually appears after the diagnosis or during therapy secondary to many associated risk factors. Here in we report for the first time a child who developed cerebral venous sinus thrombosis (CVST) prior to the diagnosis of ALL.

Introduction

Acute lymphoblastic leukemia (ALL) is considered the most common type of cancer in pediatrics that represents about one-fourth of all form of cancers in 0-14 age group¹.

Central nervous system (CNS) affection in ALL can occur due to CNS infiltration, CNS radiation and intrathecal or systemic chemotherapy. The risk of Cerebral Sino-venous Thrombosis (CSVST) in ALL is rare and represents about 0.5- 1% of all stroke cases².

A substantial proportion of venous thromboembolism (VTE) in ALL is due to CVST with a reported mortality between 0% and 28%³. The risk of thrombosis in ALL patients is variable depending on several factors. Systemic Chemotherapy especially L-asparaginase with or without steroids carries the highest risk. The presence of thrombophilic genetic mutations and central lines are frequently associated with increased risk of thrombosis⁴.

Here in we report for the first time a child who developed CVST prior to the diagnosis of ALL and review of literature.

Case Report

A previously healthy 3-years-old female patient presented to the emergency department with fever, diarrhea, abdominal pain, and severe dehydration necessitating hospital admission.

The patient was critically ill necessitating pediatric intensive care unit admission. On admission, the child was feverish (temperature was 39.5°C), tachypneic with rapid shallow breathing (respiratory rate was 40 breaths/minute) and hypotensive (blood pressure was 60/40 mmHg). There was evidence of severe dehydration with dry tongue, sunken eyes, poor skin turgor and oliguria (urine output <1ml/kg/h). The patient was pale with purpuric eruption all over the body. There were no organomegaly or lymphadenopathy.

Her initial laboratory investigations revealed pancytopenia with absolute neutropenia (WBCs: 500/ mm³, absolute neutrophil count: 200/mm³, HB: 6.4gm/dl, Platelets: 2000/cmm³), renal impairment with electrolyte imbalance (BUN: 104mg/dl, Creatinine: 2.5mg/dl, K: 6.5 mmol/L, ph: 7.21, Na: 128 mmol/L, Ca: 5.3mg/dl), hyperuricemia (Uric acid: 37 mg/dl), coagulopathy with disseminated

intravascular coagulation (PT: 16.3 sec, PTT: 40.1 sec, D. dimer: 17ng/ml) and high inflammatory markers (CRP: 287 mg/l). Her blood culture was positive for gram negative bacilli [Escherichia coli](#).

Pelvi-abdominal ultrasound was normal apart from medullary nephrocalcinosis.

Bone marrow aspirate was done due to the severe pancytopenia with absolute neutropenia. It revealed hypocellular marrow and was negative for any abnormal cells.

Supportive therapy was initiated in the form of intravenous fluid therapy, blood component transfusion, correction of electrolyte disturbance and antibiotic therapy. She was provisionally diagnosed as Acute Infectious gastroenteritis complicated by severe dehydration, acute renal failure and DIC.

Two weeks later, the patient showed gradual improvement in her general condition as well as her laboratory data and she was discharged home with follow up.

Unfortunately, three weeks later, she developed unexplained irritability and hallucinations with failure to recognize her parents. She had normal hydration status, stable vital signs, normal hematological, coagulation and electrolyte profile. Brain imaging studies in the form of MRI, MRA and MRV revealed thrombosed left sigmoid and transverse sinus (figure1). Low molecular weight heparin was initiated in a dose of 1 iu/kg every 12 hours.

Thrombophilia gene mutations were tested and revealed that the patient had positive factor XIII V34L and MTHFR A1298C mutations in homozygous state and positive factor V Leiden at heterozygous state. The patient improved and discharged on LMW heparin on therapeutic dose for follow up.

After two weeks, the patient was readmitted for the third time with fever (temperature was 39.5°C), pallor and abdominal enlargement. CBC showed leukocytosis (total leukocytic count 68.000 /mcL), anemia (hemoglobin level 8.4 g /dl) and thrombocytopenia (platelet count 20.000 /mcL). Peripheral smear revealed % blast cells. Abdominal ultrasonography revealed hepatosplenomegaly.

Bone marrow examination was repeated which revealed hypercellular BM heavily infiltrated with 96% blast cells. Immunophenotyping was done with +ve CD10, CD20 and CD79a.

The diagnosis of Common ALL was established. We started ALL Protocol adopted from St. Jude total XV protocol. She received induction therapy followed by consolidation. Follow up MRV was done during induction phase which showed complete recanalization of the thrombosed left transverse sinus with no new thrombi.

The patient finished here chemotherapy protocol during which she did not develop any thrombotic events. She is currently in complete remission.

Discussion

Most thrombotic events in ALL occur initially during induction phase of treatment due to intense treatment especially during the use of asparaginase in combination with corticosteroids⁵.

Surprisingly, our patients had thrombotic event in the form of left sigmoid and transverse sinus thrombosis before the diagnosis of ALL as evidenced by normal BM at 1st admission. Of interest, De Stefano et al, reported that increased thromboembolic events can take place even prior to the diagnosis of acute leukemia, similar to the situation seen in solid tumors, indicating that a prothrombotic state is present even at the earliest phase of leukemia ⁶. In our patient, it might be an aplastic phase of leukemia was there at 1st admission that is why the BM didn't show blast cells.

During infection, inflammatory cells, and mediators, can induce the expression of tissue factor on monocytes and endothelial cell surfaces which is a major activator of coagulation, this can lead to widespread intravascular fibrin deposition⁷.

Also, enhanced fibrin formation is caused by tissue factor-mediated thrombin generation. In addition to depression of inhibitory mechanisms, such as the protein C and S system and impairment of endogenous thrombolysis secondary to high circulating levels of Plasminogen activator inhibitor 1.

Taken together, a state of imbalance between procoagulant and anticoagulant occur during infection that might overwhelm the balance of hemostasis and result in microthrombi⁸.

Our patient developed thromboembolic manifestations in absence of infectious causes.

In view of this thrombotic event the child developed, thrombophilia gene mutations were done, and the child was positive for MTHFR A1298C at homozygous state and factor V Leiden mutation at heterozygous state.

To date, several studies have attempted to correlate the association of genetic variants of inherited thrombophilia and the risk of childhood ALL but has yielded discordant reports.

Kałużna et al,⁹ studied the relation between inheritance of MTHFR C677T and A1298C polymorphisms, and risk of ALL development in a population under 18 years of age of Caucasian ancestry. They reported that The MTHFR 677T allele alone or in combination with the MTHFR 1298C allele significantly increases the risk of development of ALL (two-folds compared to control).

Also, Roy Moulik et al,¹⁰ examined this association in north Indian children with ALL and they found that Polymorphisms in the MTHFR gene possibly modulate risk of ALL in north Indian adults but not in children.

Tripathi et al,⁴ reported a case of 14-year-old boy with ALL who had MTHFR mutation presented with recurrent venous thrombosis in the absence of asparaginase therapy.

However, some studies reported no influence of presence of genetic mutation for hereditary thrombophilia and risk of ALL development. Atashrazm et al¹¹, reported in their studies in pediatric ALL patients that the MTHFR C677T and A1298C gene variants lack a major influence on the susceptibility for pediatric ALL. Also, Sazawal et al¹² reported no statistically significant difference was evident between MTHFR C677T and A1298C Polymorphism and susceptibility to ALL in children.

Moreover, Bahari et al,¹³ documented that MTHFR rs1801131 (A1298C) heterozygous genotype decreased the risk of ALL in comparison with AA homozygous genotype (OR=0.43, 95%CI=0.21-0.90, p=0.037).

We represent a child with acute lymphoblastic leukemia who presented initially with CSVT that can be due to a prothrombotic phase of acute leukemia in addition to the presence of underlying genetic base of inherited thrombophilia as an incriminated factor.

The question to be answered is can we rely on whether hereditary thrombophilia is a genetic risk factor for acute leukemia in our case, or it is just a concomitant association. There is still a need for further studies on different ethnicities about the biological role of these genetic variants in ALL patients and their parents to determine their influence on the patho-mechanisms of ALL development.

Declarations

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Figures

Figure 1

Magnetic resonance venography (MRV) showing reduced flow to left transverse sinus

Supplementary Files

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