Cerebral Infarction in Childhood Acute Lymphoblastic Leukaemia Treated with Low Dose *E. coli* Asparaginase

LM Pesquera-Lepatan, GCF Chan, C Lam, MHK Ho, TL Lee, AKS Chiang, SY Ha, YL Lau

**Abstract**

The occurrence of thrombosis complicating L-asparaginase therapy in childhood acute lymphoblastic leukaemia has been supported by both laboratory and clinical evidences, but the exact pathogenic mechanism and predisposing factors remain elusive. Two children with acute lymphoblastic leukaemia (ALL) treated with chemotherapy developed cerebral infarction during the third week of induction therapy which consists of relatively low dose *E. coli* asparaginase (6,000 iu/m²/dose three times weekly). Altered hemostatic profile was observed in both patients during the attack but they were likely to be induced by the asparaginase treatment as shown by the return of normal profile in the post-chemotherapy period for the survived patient. There were inconsistent observations on the role of pre-existing prothrombotic conditions in previous studies and our findings further suggest that the cause is likely to be multifactorial. More investigations are needed to clarify if co-existing prothrombotic defects, either inherited or acquired, play a significant role in the causation of thrombosis in local childhood ALL patients receiving asparaginase therapy.

**Key words**

Childhood acute lymphoblastic leukaemia; Cerebral thrombosis; L-asparaginase

**Introduction**

Alterations in haemostasis have been well documented in patients with acute lymphoblastic leukaemia (ALL), but the role of other predisposing factors such as co-existing congenital thrombophilic condition remain elusive. We report two cases of cerebral thrombosis in children with ALL managed in our unit using the Hong Kong Children Cancer Study Group (HKCCSG-93) protocols which was modified from the UKALL-XI and UKALL-R1 regimens. The thrombosis in these two cases has been attributed as sporadic complication of L-asparaginase treatment.

These thrombotic events are typically seen during the period of induction therapy consisting of L-asparaginase, which is an essential drug in the treatment of childhood ALL. Both laboratory and clinical evidences supported the occurrence of thrombosis as a complication of L-asparaginase therapy, but the role of other predisposing factors such as co-existing congenital thrombophilic condition remain elusive. We report two cases of cerebral thrombosis in children with ALL managed in our unit using the Hong Kong Children Cancer Study Group (HKCCSG-93) protocols which was modified from the UKALL-XI and UKALL-R1 regimens. The thrombosis in these two cases has been attributed as sporadic complication of L-asparaginase treatment.

**Case 1**

An 8-year-old Chinese girl with standard risk B-lineage ALL (low initial white count of 2.8 x 10⁹/L; CD 10(+), cytoplasmic mu chain negative; hyperdiploidy by cytogenetics study) developed cerebral infarct during the third week of induction therapy using the HKCCSG chemotherapy regimen A protocol. The induction therapy...
Cerebral Infarction in Childhood ALL

Case 2

A 7-year-old Chinese girl with ALL was initially diagnosed and treated in Mainland China. She received intensive chemotherapy without L-asparaginase and a complete remission (CR) was attained. Following an event-free survival of 31 months, she was referred to Queen Mary Hospital for a suspected relapse. On admission, her leukocyte count was 15.7 x 10^9/L with 88% circulating blasts, haemoglobin of 7.8 g/dl and a platelet count of 30 x 10^9/L. Bone marrow aspiration showed plenty of blast cells and cerebrospinal fluid cytology had a cell count of 194/uL with 88% blasts. She was then diagnosed to have systemic and central nervous system leukaemic relapse. Immunophenotype was consistent with common ALL. Cytogenetics and FISH analysis supplemented by DNA ploidy determination revealed a near-haploidy associated with hyperdiploidy. Her cytogenetic abnormality has been reported previously. She was started on ALL-Relapse (UKALL-R1) chemotherapy protocol consisting of vincristine, epirubicin and L-asparaginase with triple intrathecal chemotherapy. On day 18 of induction treatment, she developed generalised tonic-clonic convulsions. There was no fever. Her leukocytes count was

Table 1  Clinical and laboratory findings at diagnosis of cerebral infarction

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal/Control values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of onset</td>
<td>17</td>
<td>18</td>
<td>-----</td>
</tr>
<tr>
<td>WBC x 10^9/L</td>
<td>1.58^a</td>
<td>0.43^a</td>
<td>3.0-18.0</td>
</tr>
<tr>
<td>Haemoglobin (gm/dl)</td>
<td>12.2^a</td>
<td>9.6^a</td>
<td>9.5-16.5</td>
</tr>
<tr>
<td>Platelets x 10^9/L</td>
<td>49^a</td>
<td>30^a</td>
<td>150-400</td>
</tr>
<tr>
<td>Prothrombin Time (sec)</td>
<td>11.8</td>
<td>13.6</td>
<td>9.5-12.5</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>46.9</td>
<td>47.5</td>
<td>22-34</td>
</tr>
<tr>
<td>APTT inhibitor screen</td>
<td>Negative</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>Thrombin time (sec)</td>
<td>16</td>
<td>13.8</td>
<td>11-15</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1</td>
<td>2.23</td>
<td>1.46-3.38</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>8-32</td>
<td>2.0-8.0</td>
<td>&lt; 0.5 mg/L</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>118%^b</td>
<td>33</td>
<td>80-120</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>79%^b</td>
<td>34^a</td>
<td>70-140</td>
</tr>
<tr>
<td>Total protein S</td>
<td>78%^b</td>
<td>78^a</td>
<td>57-112</td>
</tr>
<tr>
<td>Free protein S (%)</td>
<td>32%^b</td>
<td>18^b</td>
<td>19-36</td>
</tr>
</tbody>
</table>

^a Done before the onset of cerebral thrombosis; ^b Done at quiescent phase without any medications
The deranged haemostatic pictures in patient 2 was likely due to acquired therapy-induced effect.
0.43 x 10^9/L with no circulating blasts, hemoglobin of 9.6 mg/dl and platelet count of 47 x 10^9/L. Brain CT with contrast showed extensive infarction of the left occipital and frontal lobes. Repeat cerebrospinal fluid examination did not show any blast cells or any evidence of CNS infection. Haemostatic work-up is summarised in Table 1. The low level of protein C and S after the occurrence of cerebral thrombosis was likely to be caused by the drug. Lupus anticoagulant and anticardiolipin antibodies were both negative. She lapsed into a coma and died of the sequelae of massive cerebral infarct despite of active resuscitation.

Discussion

Thrombosis is a known though uncommon complication of acute lymphoblastic leukaemia in children receiving asparaginase treatment. Current studies have been focused on the extensive analysis of coagulation in ALL patients receiving asparaginase,2,3,5,10,14 but no definite causal relationship has been established between the deranged haemostatic profile and the thrombotic events in the studied population, which has been reported as between 1.5% and 11%.4,5,7,8,10,14 From our local data, 3 out of the 145 (2%) children treated with HKPHOSG-93 protocol developed cerebral thrombosis. [Unpublished data, HKPHOSG-annual scientific workshop 2002 report]

Previous data of thrombotic events in ALL treated with asparaginase showed prolongation of prothrombin Time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) which indicates an altered haemostatic state; decreased levels of fibrinogen, plasminogen, α2-antiplasmin with enhanced thrombin generation and increased D-dimer level12,5,8,14-17 which indicate blood coagulation activation in these studied group of patients. However, data from different investigations2,5,8,15-17 including ours, could not unequivocally correlate the pre-existing altered haemostatic state to the occurrence of thrombotic event. The sporadic occurrence of thrombosis in ALL patients receiving asparaginase treatment suggests that the cause is likely to be multifactorial.

Some of the studied cases have decreased levels of naturally occurring inhibitors such as protein C, protein S and antithrombin III2,5,8,14,16 and the presence of gene polymorphism of Factor V, prothrombin and methylene tetrahydrofolate reductase (MTHFR) which are identified potential prothrombotic risk factors. Previous study using BFM protocol showed a 46.5% risk of thrombosis with at least one prothrombotic risk factor.14 Whether the said prothrombotic risk factors were inherited or acquired was not established in this data. In contrary, a study using German Cooperative Acute Lymphoblastic Leukaemia (COALL) protocol failed to demonstrate such association of prothrombotic risk factor and symptomatic thrombosis.10 Two of the three cases in this study has no haemostatic alterations immediately prior to thrombosis, a data that further obscure the pathogenic mechanism of thrombosis in childhood ALL treated with asparaginase.

A positive correlation between thrombosis in children with ALL receiving chemotherapy and a central line has been demonstrated.14 This is in contrast with our data. Both patients did not have the central line prior to the thrombotic event. Our two cases were given E. coli asparaginase (ELSPAR) manufactured by Merck & Co., USA at 6,000 iu/m^2/dose subcutaneously three times weekly. Previous investigation failed to demonstrate the proposed assumption of a positive correlation of thrombosis in ALL patients treated with different asparaginase preparation.3,8,15,16 Both patients developed the cerebral thrombosis during the third week of induction therapy receiving a total of 6 doses of L-asparaginase. This conforms with the established time of occurrence of greatest coagulation abnormality which is between day 8 to 23 of asparaginase therapy.7,18 As to the dose, data of Korte et al showed no relevant change of haemostatic profile on day to day investigation. Cumulative rather than a single dose effect on coagulation system has been observed.17

Previous investigations demonstrated evidence of hypercoagulable state even with low dose (6,000 iu/m^2, three times weekly) asparaginase,2,3,5,8 but there is no clear cut imbalance of procoagulant and anticoagulant factors in two out of twenty five patients who developed thrombosis. As to the prevention, recent study has shown that the use of antithrombin decreased the incidence of thrombosis from 37% to 28% at the expense of increasing the risk of minor bleeding.19 With the low incidence of such complication that we identified locally, such approach may not be beneficial to our patients’ cohort.

In conclusion, our data suggested that severe thrombotic complications although sporadic, can occur in local children with ALL even receiving low dose of asparaginase. Its occurrence is more likely to be multifactorial. Like in the previous studies, a concomitant effect of the other chemotherapeutic drug administered together with asparaginase cannot be completely excluded. Further prospective studies are recommended to establish the exact pathogenic mechanism of thrombosis. Whether the prothrombotic defects identified in some studies9,10 play an
important role in the causation of thrombosis in ALL patients receiving asparaginase therapy remains to be explored.

References