Cerebral sinovenous thrombosis during asparaginase treatment

Case 3

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Summary
A boy (age: 7 1/12 years) with acute lymphoblastic leukaemia developed thrombosis of the sinus sagitalis superior with secondary haemorrhagic infarction while on induction treatment with vincristine, prednisone, and asparaginase. Based on this report, the potential pathogenic mechanisms are discussed with respect to congenital prothrombotic defects as well as to the role of antileukaemic treatment. Current hypotheses on mechanisms for thromboembolism in children and proposed prophylactic strategies are briefly summarized.

A previously healthy boy (age: 7 1/12 years) presented with fatigue, anaemia, neutropenia, and 1.72 x 10⁹/1 blasts in the peripheral blood. The platelet count (165 x 10⁹/1) was in the low normal range. Diagnostic work-up revealed a pre-B acute lymphoblastic leukaemia (ALL) without extramedullary disease. Cytogenetic analysis showed a translocation t(12;21), and a TEL-AML1 fusion product could be demonstrated by fluorescence in situ hybridisation (FISH).

Treatment and follow-up

Induction chemotherapy with daily oral prednisone (40 mg/m²), weekly intravenous vincristine (1.5 mg/m²), and intramuscular Escherchia-coli-L-asparaginase (6000 IU/m²) on days 2, 5, 8, 12, 15, and 19 according to the Pediatric Oncology Group protocol 9605 was initiated. In addition, the patient received prophylactic intrathecal methotrexate on day 1. Polychemotherapy was administered via peripheral veins only. Since coagulopathy is strongly associated with the administration of L-asparaginase, serial coagulation studies were done as shown in Table 1.

On day 25 of induction treatment the patient suddenly lost consciousness while cardiopulmonary function was preserved. About five minutes later he was responsive again; however, he showed reduced alertness and was disoriented. Neurological examination revealed expressive aphasia, apraxia, and motoric hemiplegia of the left side with increased deep tendon reflexes of the left leg and arm. A spontaneous Babinski’s sign presented on the left. Fundoscopy showed neither papilloedema nor retinal haemorrhage. MRI examination disclosed thrombosis of the sinus sagitalis superior with secondary haemorrhagic infarction of a large part of the right cerebral hemisphere (Fig. 1).

Initially the boy was substituted with fresh frozen plasma and platelets because of thrombocytopenia and low fibrinogen (Tab. 1). In addition, a prophylactic anticonvulsive treatment was initiated. Thereafter, intravenous therapy with unfractionated heparin was started. After clinical stabilization, chemotherapy was resumed, and subcutaneous treatment with a low molecular weight heparin was applied for 3 months. At that time, MRI showed complete revascularisation of the sinus sagitalis superior while a parenchymal defect remained in the right cerebral hemisphere (Fig. 2).

An intensive rehabilitation program by physical and occupational therapists, logopedists and psychiatrists led to recovery of most neurological and cognitive sequelae. After a few weeks, the child was well enough to attend school. Actually, 28 months after the cerebral sinovenous thrombosis with haemorrhagic insult, a minimal left-sided hemisyndrome with minor gate disturbances, a homonymous visual field loss in the lower left quadrant, some minor cognitive and learning deficits remain.

There was no family history with thrombotic events, neither in first nor second degree relatives. A laboratory screening for inherited prothrombotic defects will be performed after the end of polychemotherapy for ALL to allow evaluation in steady-state condition.
Cerebral sinovenous thrombosis in children is a rare disorder. The Canadian Pediatric Ischemic Stroke Study Group reported an annual incidence of 0.67 cases per 100,000 children, and neonates were the most commonly affected age group (1). Seizures at presentation and the presence of hemorrhagic or non-hemorrhagic infarcts seemed to be predictors of poor neurological outcome (1). Besides numerous clinical conditions (e.g., trauma, surgery, cancer, infections, and disorders requiring indwelling catheters), thromboembolism in otherwise healthy individuals is furthered by inherited or acquired haemostasiologic variations.

Not only in adults, but also in children, it was recently shown, that deficiency or dysfunction of proteins involved in the haemostatic process are independent risk factors of venous thrombosis, e.g., deficiencies of protein C, protein S or antithrombin, the presence of factor V Leiden (G1691A) or the G20210A prothrombin gene mutation, as well as elevated lipoprotein(a) (1, 3, 5, 6). Whereas in adults these genetic risk factors have little importance as risk factors for arterial thrombosis, these variants may play a role as risk factors of stroke in childhood and young adults (6). One of the most common acquired prothrombotic disorder in children with sinovenous thrombosis is the presence of antiphospholipid antibodies (1, 8).

On the other hand thromboembolic events are well-known complications of ALL treatment, particularly asparaginase therapy, resulting in significant morbidity and occasional mortality. L-asparaginase is established as an important treatment component during remission induction or intensification therapy of children suffering from ALL.

L-asparagine, a non-essential amino acid on which many cells depend for normal metabolic processes, is used up by the drug. Cells with normal function compensate this asparagine deficiency by its biosynthesis from aspartic acid and glutamine via the enzyme asparagine synthetase. In contrast, most malignant lymphoid cells depend on intracellular pools of L-asparagine for protein biosynthesis and cell function, due to low levels of the synthetic asparagine synthetase (2).

Because of its interference with protein biosynthesis, asparaginase leads to acquired deficiencies of most coagulation proteins. Lack of fibrinogen and the coagulation factors II, IX, and X is well established. However, not only clotting factors but also inhibitors of the coagulation system, such as antithrombin, protein C, and protein S are decreased (4). In the present case, a significant drop of fibrino-
gen and the coagulation factors V, VII, and X was observed (Tab. 1). Prolonged thrombin time and reptilase time were probably not only due to low fibrinogen levels, but are suggestive of fibrinogen degradation products not determined in this case. Despite a reduction of both pro- and anticoagulant activity, the haemostatic balance appears to be shifted towards the hypercoagulable state.

Not only asparaginase but also other drugs used for the treatment of ALL (e.g. prednisone) significantly influence coagulation proteins. With the exception of fibrinogen concentration, which decreases, prednisone increases plasma concentrations of most coagulation proteins. Therefore, when the two drugs asparaginase and prednisone are administered simultaneously, the glucocorticosteroids may compensate – in part – for the effect of asparaginase (4).

In our case, despite 96% leukaemic blasts in the bone marrow, the platelet concentration was always >120 × 10⁹/l, at diagnosis as well as during induction therapy (Tab. 1). This phenomenon could have been a further contributing component for the patients hypercoagulable state. Only after the thrombosis, on day 25 of induction therapy, platelet concentration dropped to 35 × 10⁹/l, most probably due to increased consumption during the process of extensive sinovenous thrombosis.

In many centers caring for children with malignancies, central venous catheters are used routinely to facilitate the administration of chemotherapy, blood products, antibiotics, and parenteral nutrition. These devices simplify treatment delivery, but they are not without risks. The most common and potentially severe acute sequelae are infection and thrombosis (7, 9). Since the patient presented here received all treatment by peripheral veins, this prothrombotic risk factor can be excluded.

In their excellent review (4), Maureen Andrew and her group propose at least two potential mechanisms responsible for thromboembolic events in children with ALL:

- The first one is an increased endogenous generation of thrombin concurrent with an antithrombin deficiency induced by the application of asparaginase. This phenomenon is further intensified by the prednisone-induced change of multiple haemostatic and fibrinolytic factors.
- The second mechanism is based on the observation that some children with ALL have increased plasma concentrations of high molecular weight multimers of von Willebrand factor that potentiate platelet adhesion and aggregation.

Furthermore, it has been shown recently, that children with congenital prothrombotic risk factors suffering from ALL have a significantly higher risk for thrombosis as compared with ALL patients without inherited variations (7). Twenty-seven out of 58 children with a congenital prothrombotic defect suffered venous thromboembolism within 250 days after onset of leukaemia. This is highly significant different from children without a prothrombotic defect: only 5 out of 231 suffered venous thromboembolism (7).

As children with ALL seem to be at high risk to develop thromboembolic events, especially during induction therapy with asparaginase and prednisone, it is worth to consider prophylactic anticoagulation strategies. Unfortunately, in this group of children prophylactic therapy with coumarins is problematic because of several reasons: The coumarin effects are influenced by the health status and by the concurrent use of other drugs. In addition, thrombocytopenia and altered vitamin K dependent coagulation proteins could increase the risk of bleeding. Further, since these children need frequent lumbar punctures for the administration of intrathecal chemotherapy, oral anticoagulant therapy would need to be reversed for these procedures. Administration of intravenous heparin is impractical since during the whole risk period for thromboembolism hospitalization and close monitoring of the thrombin time or aPTT for several weeks would be required.

The only anticoagulant drug that could be used in this situation is a low molecular weight heparin, given subcutaneously. But also this approach is not ideal due to repeated injections and risk of infection in these immunocompromised children. Furthermore, the anticoagulant activity of heparin and low molecular weight heparin is mediated through antithrombin and in the presence of an acquired antithrombin deficiency would likely be reduced (4).

The only way to evaluate advantages and disadvantages of generally used antico-
agulant therapy for prophylaxis in children suffering from ALL, are prospective randomized studies, comparing the incidence of thromboembolic and bleeding events between homogeneous groups of patients, either treated or not with an anticoagulant. Another strategy would be a prospective screening of all children with ALL for hereditary and acquired prothrombotic risk factors, allowing to apply prophylactic therapy only in patients at high risk (7).

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References

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