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Thrombosis in pediatric patients with leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common type of cancer diagnosed in children. It is reportedly the most common malignancy associated with thromboembolism in the pediatric age group. Over the last 2 decades, venous thromboembolism (VTE) has been increasingly diagnosed among pediatric ALL patients with an estimated incidence ranging from about 5% (for symptomatic cases) to about 30–70% (following sequential imaging studies in asymptomatic children). The etiology is multifactorial and may stem from alterations of the hemostatic system following various chemotherapy protocols (including use of L-Asparaginase), the presence of central venous lines (CVL), as well as comorbidities, e.g. inherited thrombophilia risk factors. Most symptomatic thrombotic events occur in the upper venous system or in the central nervous system (CNS). Prospective studies on the establishment of guidelines for treatment or prevention are lacking. The following review will address the epidemiology, etiology and risk factors for thrombosis, describe the currently available evidence, and address issues associated with diagnosis and treatment.

1. Introduction

Venous thromboembolism (VTE) is a rare disease in children that is being increasingly diagnosed, usually as a secondary complication [1]. The risk factors include perinatal diseases, medical interventions (e.g., central lines), sepsis, drugs and malignancies [2–6]. Cancer is found in 20% of pediatric patients with VTE [7]. Interestingly, hematological malignancies have a higher incidence of VTE compared to solid tumors [8,9]. Since the most common malignancy in children is acute lymphoblastic leukemia, it has an important role and considerable impact on the pathogenesis and occurrence of VTE in children [10]. The reported incidence of symptomatic VTE in children with ALL ranges between 3% and 14%, however this may range up to 73% in reports of all cases, including asymptomatic ones. Variations in the reported incidence can be explained by differences in diagnostic methods, study design, presence of comorbid risk factors and the use of a variety of chemotherapy protocols [7, 10]. Prospective studies find more cases than retrospective studies: for example, reports on the incidence of DVT in children treated according to the Berlin-Frankfurt-Munster (BFM) protocol reported an incidence of 1.7% in a retrospective study of 1100 children [11], while a prospective study showed an incidence of 14.3% [12]. As expected, studies that used radiographic tests to screen for asymptomatic VTE reported a higher prevalence compared to studies on symptomatic VTE. The number of reported cases has been constantly growing, a feature that can potentially be attributed to more aggressive chemotherapy or better detection techniques. This review provides an overview of the risk factors, clinical presentation and treatment of children with ALL that is further complicated with thrombosis.

2. Risk factors

2.1. Hemostatic changes in leukemia – pre-therapy

Changes in hemostasis can be detected in children with leukemia prior to therapy. Mitchell et al. [13] detected significant elevations in coagulation factors VIII, IX, von Willebrand, alpha 2-mactoglubilin and protein. In contrast, other hemostatic pro-coagulant proteins, such as prekallikrein and XIIIA and XIIIS, or natural coagulation inhibitors, such as protein C, were significantly reduced. The net effect of these alterations may promote hypercoagulability, while reduced clot firmness and increased fibrinolysis may preserve the delicate hemostatic balance prior to the initiation of chemotherapy protocols.

2.2. Treatment-related hemostatic changes - chemotherapy

Treatment for ALL has improved during the last decades, leading to cure in over 80% of affected children. These high rates are attributable to the aggressive chemotherapy protocols that are currently

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implemented [14]. However, chemotherapy bears significant morbidity and mortality. It affects the hemostatic system through the direct effect of the chemotherapeutic agents on hemostatic proteins, causing endothelial damage, or through complications, such as infections secondary to immunosuppression [15]. Chemotherapeutic agents have been shown to directly activate platelets and monocyte–macrophage tissue factor (TF) [16,17]. In addition, cellular apoptosis resulting from chemotherapy leads to increased expression and activation of TF [18]. Asparaginase (ASP) and steroids are backbones of chemotherapy protocols for ALL. They induce an acquired prothrombotic state by affecting different hemostatic pathways [19]. Most cases of VTE are diagnosed during the induction of chemotherapy, with about 10% of them being diagnosed at the consolidation or the intensification phase.

ASP has been reported to cause a decrease of natural anticoagulants, such as anti-thrombin, protein C and protein S following which there is an increase in thrombin generation and a prothrombotic state [20,12]. The risk of thrombosis does not seem to be significantly affected by the type of ASP being utilized [21], however, different commercial preparations exhibit various half-lifes of ASP enzymes and may result in prolonged periods of hemostatic impairment [7]. Steroids heighten the risk of thrombosis by increasing the production of the pro-coagulant factors FXII, FXI, FIX, FX, FVIII, FVII, FV, and FII as well as inhibitors of proteolysis, such as PAI-I and anti-plasmin. Steroids also cause a decrease of fibrinolytic proteins, tPA and plasminogen, leading to a shift towards thrombosis [20]. Ulrike et al. [22] demonstrated that dexamethasone may have some protective role in induction therapy compared to prednisone, illustrating how changes in protocols pose different risks of thrombosis.

2.3. Potential interactions of comorbid thrombophilia

Inherited thrombophilic risk factors have been previously implicated in increasing the risk of VTE in both adults and children. They include factor V leiden (FVL), deficiencies of Protein C, Protein S and antithrombin, as well as increased FVIII, FIX and FXI [19,20,23–25]. Mutations of prothrombin gene G20210A and MTFR C677T are common, and they are considered as harboring a mild increase in the risk of VTE [19,20]. One multicenter prospective study that evaluated children with ALL who were treated with the BFM 90/95 protocol revealed that 20% of those who developed DVT had at least one inherited risk factor [23]. Those authors also found a significant positive correlation between DVT and the use of CVL in patients with thrombophilia. Combining these risk factors with chemotherapy together with the procoagulable state in ALL may increase the overall risk by ten-fold. A review of these data revealed that the major determinants for the risk of thrombosis were mainly associated with the chemotherapy protocols that were followed.

ASP therapy is likely to exacerbate the inherited deficiency of AT, PC and PS, even in heterozygous patients [26]. FV Leiden may exacerbate the effects of the suppression of PC and PS as a result of ASP therapy. Prothrombin mutation (PTM) exerts a mild risk and the presence of PTM may further increase it and predispose for VTE in ALL where there is increased generation of thrombin. Steroids increase prothrombin levels, therefore a PTM may render patients vulnerable to even higher levels, leading to increased risk of DVT [23]. MTHFR C677T homozygosity in the presence of folic acid deficiency may lead to increased risk of DVT due to endothelial activation attributed to increased homocysteine levels. Being as it is, part of most ALL chemotherapy protocols, methotrexate (MTX) therapy may cause intracellular depletion of folates which, in turn, causes inhibition of homocysteine methylation, leading to increased levels of homocysteine and promoting the risk of thrombosis.

3. Clinical presentation

3.1. Location of thrombosis

Thrombosis may be arterial or venous, although most thrombotic events are of a venous origin [7]. Caruso et al. [27] large meta-analysis found that the most common location for thrombosis was the CNS in 50% of cases, of which the majority were cerebral venous thrombosis. The second most common location was the upper limb associated with CVL that comprised 27.5% of cases. The rest of VTE episodes included pulmonary emboli (PE = 1%), the right atrium (1%) and superficial thrombosis (2.2%).

3.2. Central venous lines

The standard of care to maintain venous access and to safely administer chemotherapy is the insertion of central venous lines. This may be internal (subcutaneous port-a-cath) or external (Broviac/Hickman catheter). However, these central lines are associated with morbidity, such as infections and thrombosis. Most of the CVL associated VTE are asymptomatic clots [28] and they are located at the entry site into the vein, although they may evolve and lead to recurrent VTE, PE, post-thrombotic syndrome and death [29]. A meta-analysis of 11 studies found that peripherally inserted central catheters were associated with a 2.5-fold higher risk of DVT than centrally inserted venous catheters [30]. External CVL was reported to carry a higher risk of DVT than internal CVL [31].

3.3. Arterial thrombosis

Venous thrombosis is much more prevalent than arterial thrombosis among pediatric patients with ALL. A meta-analysis of thrombotic complications in childhood ALL did not report peripheral arterial thrombotic events, suggesting that the prothrombotic imbalance could predispose ALL patients mainly to venous thrombosis [27]. Acute ischemic stroke (AIS) in the context of childhood ALL has also been reported. In large retrospective study on ischemic stroke among 2318 children treated for ALL, 11 symptomatic ischemic strokes occurred in 11 patients (0.47%), and all the stokes were due to sinus vein thrombosis [32]. Parasole et al. studied neurological complications among children treated for ALL and reported that five of their 253 treated patients experienced a stroke during therapy. Three of the strokes were hemorrhagic and two were ischemic [33], and all occurred during ASP treatment. Pediatric cases of severe cerebral vasospasm leading to AIS in the context of intrathecal cytarabine administration in ALL patients have been reported, with the authors strongly suggesting a true association between them [34]. Finally, Moyamoya syndrome occurs in increased frequency in survivors of childhood ALL, a finding that may be attributed to treatment with cranial irradiation [35].

4. Treatment

Low molecular weight heparin (LMWH) is the most commonly used treatment for DVT in children. There are no evidence-based studies on VTE treatment in children with hematological malignancies, however, it is the preferred anticoagulant agent. Several treatment trials of cancer-associated VTE have been conducted in adults. The CLOT study [36] compared LMWH to warfarin and found that the incidence of recurrent DVT was lower in patients treated with LMWH. Other studies with similar results included ONCENOX [37] that found no difference, and LITE [38] and CATCH [39] that found decreased recurrence with LMWH, leading to LMWH being the preferred anticoagulant for active cancer in adults.

In 2012, the American College of Chest Physicians published the latest guidelines on thrombosis treatment in children [40] and recommended 3 months of anticoagulation for DVT associated with