Thrombotic Complications in Children with Cancer

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Summary: The last decade has seen advances in treatment of life-threatening disease in children – especially cancer where the overall cure rate is now in the region of 80%. Similar to adults, children with cancer are at a substantial risk of developing thromboembolism (TE). One of the costs of achieving this has been more children developing thrombotic disease, the majority of which are related to indwelling vascular catheters and as a result TE is being diagnosed with increasing frequency in these younger patients. In the Canadian Paediatric Thrombophilia Registry, 20% of the patients with TE had cancer. This figure is in contrast to only 2.3 cases of malignancy/1000 children and an estimated incidence of thrombosis of 0.7/100,000 in the general paediatric population. However, the true prevalence of TE in children with cancer is unknown as rates can vary from 1% to as high as 44% [5] and this reflects the heterogeneity of such studies in terms of; (i) type of cancer, (ii) was the TE, symptomatic or asymptomatic and (iii) were the studies prospective or retrospective. Happening alongside these advances have been an explosion in our knowledge of the understanding at the molecular level of blood coagulation in particular how the natural anticoagulant and fibrinolytic pathways work and how they differ in children and adults. Stemming from these discoveries new anticoagulant therapeutics have become available to the paediatrian and over the next decade their true place in the treatment of childhood thrombotic disease will be established.

Key word: thrombotic complication – children – cancer – thromboembolism

Trombotické komplikace u dětí s onkologickým onemocněním

Souhrn: V posledním desetiletí bylo dosaženo značných pokroků v léčbě život ohrožujících chorob dětských pacientů – zvláště onkologických, u nichž se celková úspěšnost léčby pohybuje okolo 80 %. Podobně jako u dospělých existuje i u dětských pacientů trpících onkologickým onemocněním zvýšené riziko tromboembolizmu (TE). Cenou za úspěchy v léčbě je častější výskyt trombotických onemocnění, přičemž příčinou jsou většinou dlouhodobě zavedené cévní katétry. Následně je u těchto mladých pacientů častěji diagnostikována TE. 20% pacientů vedených v Kanadském registru trombofilie u dětí (Canadian Paediatric Thrombophilia Registry) trpí zároveň onkologickým onemocněním. Toto číslo je v rozporu s pouze 2,3 případů zhoubných nádorů/1 000 dětí a odhadovanou incidencí trombózy 0,7/100 000 v obecné pediatrické populaci. Skutečná prevalence TE u dětí s onkologickým onemocněním není známa, neboť udávané podíly se pohybují mezi 1 a 44% [5], což odráží heterogenitu studií s ohledem na: (i) typ rakoviny, (ii) zda šlo o symptomatický nebo asymptomatický TE a (iii) zda šlo o prospektivní nebo retrospektivní studii. Souběžně s pokroky v léčbě došlo k explozi našich znalostí týkajících se pochopení krevní koagulace na molekulární úrovni, obzvlášť fungování přirozených antikoagulačních a fibrinolytických pochodů a rozdílů v nich mezi dětmi a dospělými. Na základě těchto objevů byly vyvinuty nové antikoagulační preparáty, které jsou nyní pediatrům k dispozici a které v průběhu nadcházející dekády získají pevné místo v léčbě dětských trombotických chorob.

Klíčová slova: trombotické komplikace – děti – rakovina – tromboembolizmus

Historical Perspective

The rapid transformation of fluid blood to a gel like substance (clot) has been recognised since antiquity. Around 2650 B.C. in China, Huang Ti wrote "when it coagulates within the pulse the blood ceases to circulate beneficially; when the blood coagulates within the feet it causes pains and chills" [1]. At the beginning of the 18th century (1731) Petit appreciated that blood clotting was a means to stem blood loss from wounds and indeed John Hunter some 80 years later ruled, "where there is full power of life, the vessels are capable of keeping the blood in the fluid state" [1]. By 1852 Rokitanksy differentiated one type of venous thrombosis that arises as a consequence of primary inflammatory or chemical changes in the blood. This idea was later developed and stated in a more specific fashion by Virchow (1856) in his classic triad describing the causes of thrombosis; "abnormalities of the blood vessels, alternations in the constituents of the blood and aberrations of blood flow" [1]. Although the association between cancer and thrombosis is attributed to Armand Trousseau in 1865, is it was likely that Bouollaud was the first to describe this association when he described 3 patients with deep vein thrombosis and cancer. That being so, it is still worth remembering the insightful quotation of Armand Trousseau from a lecture he delivered at the Hotel-Dieu, Paris in 1865:

"Gentlemen: Those following my clinical work have surely noticed that there is a frequency of special diseases which attract attention due to the numerous circumstances in which they are observed. ***I want to talk about plegmasia alba dolens.*** *You will remember that we have studied together the white painful oedema not only in women with recent parturition* ***but more often in patients of either sex affected by pulmonary phthisis or internal cancerous tumours****. This is a rare example of generalised*

intravenous coagulation in the four limbs. What are the conditions where blood acquired this tendency of spontaneous coagulation? You know, gentlemen, in cachetic states in general, ***tuberculosis and cancer cachexia*** *in particular,* ***the blood is modified****…"*

In 1874 Osler helped describe platelet aggregation and six years later Hayem sited the importance of platelet plugs in preventing blood loss after tissue injury [1]. Howell and Holt's landmark paper in 1918 described the isolation of the first physiological anticoagulant molecule, antithrombin [1]. They suggested that antithrombin and heparin are normal constituents of blood and together act as a safeguard against inappropriate intravascular clotting. By 1938 Silberberg stated that the endothelial layer of blood vessels was probably acting as a negative regulator of procoagulation [1]. It was not until 1965 that the first hereditary basis of thrombosis ("thrombophilia") was established by Egberg reporting antithrombin III deficiency as an autosomal disorder associated with recurrent familial venous thrombo-embolic phenomenon [1].

So, in the second millennium we now know that normal blood coagulation or haemostasis is a complex sequence of inter-related events (that differ in children and adults) by which the body prevents blood loss from the vascular tree. This is achieved by a multi-pathway interactive system with multiple negative and positive feedback loops, which ultimately ensure that blood is at all times fluid within the vasculature, but it also needs to be transformed into a clot when there is a breach in the integrity of the vascular tree. The protein and cellular components have also shown to be intimately involved in the inflammatory response, vasculogenesis, metastasis, cellular proliferation and tissue repair.

Haemostatic differences between children and adults

Plasma levels of many of the haemostatic coagulation factors are lower in newborns than in older children and adults. At the end of gestation, a healthy normal newborn should have approximately half the adult values of the vitamin-K dependant coagulant factors (factors II, VII, IX and X) and contact factors (factors XII, and XI, prekalikreinin and high molecular weight kininogen) [2]. In pre-term infants these levels are even lower. The natural anticoagulants, antithrombin and protein S are also approximately 50% at term with a similar relationship to gestational age. The plasma levels of the procoagulant co-factors, factor V and factor VIII and fibrinogen are the same in term infants as is in adults [2]. Like the coagulation system the fibrinolytic system is also physiologically immature in the neonate. Overall the fetus and neonate are less efficient in generating thrombin and as a result thrombotic disease in early childhood is rare and when seen is either secondary to an acquired prothrombotic state or indeed an inherited gene defects predisposing to clot formation.

Thromboembolism

The last couple of decades have seen advances in treatment of life-threatening disease in children. One of the costs of achieving this has been more children developing thrombotic disease, the majority of which are related to indwelling vascular catheters and as a result thromboembolism (TE) is being diagnosed with increasing frequency in these younger patients [3]. The peak incidence for TE is undoubtedly the neo-natal period where the use of indwelling catheters in the tertiary care paediatric setting is almost the norm [3].

Cancer

Similar to adults, children with cancer are at a substantial risk of developing TE. In the Canadian Paediatric Thrombophilia Registry, 20% of the patients with TE had cancer [4]. This figure is in contrast to only 2.3 cases of malignancy/1000 children and an estimated incidence of thrombosis of 0.7/100,000 in the general paediatric population. However, the true prevalence of TE in children with cancer is unknown as rates can vary from 1% to as high as 44% [5] and this reflects the heterogeneity of such studies in terms of; (i) type of cancer, (ii) was the TE, symptomatic or asymptomatic and (iii) were the studies prospective or retrospective.

Leukaemia

Leukaemia is the most common form of childhood cancer representing approximately 30% of all cancers in children [6]. Acute lymphoblastic leukaemia (ALL) is the dominant type, accounting for approximately 80–85% of childhood leukaemia with acute myeloblastic leukaemia (AML) representing approximately 15–20% and chronic myelomonocytic leukaemia (JMML) 2–3% [6]. To date, acute lymphoblastic leukaemia is the one paediatric cancer where there is some reliable information in terms of epidemiology, pathophysiology, and management of TE.

Acute lymphoblastic leukaemia

In a randomised control trial, Mitchell et al reported a prevalence of 5% symptomatic TE and a 31.7% asymptomatic TE [7]. The risk factors for TE identified in this cohort of patients were; (i) age, (ii) asparaginase, (iii) the type of corticosteroid, (iv) the type of protocol used and (v) the presence of an indwelling catheter.

Age

Parallel to the development of the haemostatic system in children, development of TE is most commonly observed in the neonatal and pubertal age groups and one would expect this to be exaggerated in the paediatric oncology population. Supporting this view is the recently published study in children with ALL where hey found there to be an age-related disturbances in coagulation and fibrinolysis parame-

ters during the induction phase of the antileukemic treatment [8]. Sixty-four children were classified by age into three groups (1–5, 6–10, 11–16 years). There were analysed during induction treatment, including four weeks of dexamethasone, followed by two weeks tapering of dexamethasone during which 6,000 IU/m^2 native L-Asparaginase (total 4 doses) was administered intravenously twice weekly. Children were deemed to be in a hypercoagulable state after four weeks of dexamethasone due to upregulation of coagulation parameters. Upregulation was highest in the two youngest age groups. During L-Asparaginase treatment the 11- to 16-year-olds showed lower values in procoagulant and, even more, in anticoagulant factor levels compared to the younger children. Activation markers of thrombin generation and fibrinolysis did not change over time during the study period. Decreased synthesis of α-2-antiplasmin and plasminogen during L-Asparaginase treatment resulted in less potential of clot lysis by plasmin in children older than 11 years of age. They concluded, "a more severe decline of anticoagulant and fibrinolytic parameters in children between 11 and 16 years of age underline that these children are at higher risk of thrombosis during ALL induction treatment".

L-Asparaginase

Acquired deficiencies of antithrombin (AT) have been associated with a large number of diseases, which in turn have an increased rate of venous and arterial thrombosis. In paediatric oncology, acquired AT deficiency is classically seen children following the administration of L-asparaginase (a potent protein synthesis inhibitor) and in those with nephrotic syndrome secondary to Wilms tumour [9]. It should also be remembered that plasma turnover of AT is increased by approximately one quarter during heparin therapy and reverses on removal of the drug i.e. there is a rebound state. Antithrombin concentrates are available and should be considered when there is a significant deficiency as its administration ensures smooth anticoagulation with heparin therapy.

Type of Protocol

Not only does dose density and intensity of chemotherapeutic agents differ between the different international children's cancer group consortia protocols but also within successive protocols from the same study group. For example two German studies showed that, despite studies done at similar times and on similar ethnic populations, there is a 10-fold difference on the incidence of TE associated with different chemotherapeutic protocols [10,11].

Presence of an indwelling catheter

Central venous catheter devices (CVCDs) have revolutionised the medical management of paediatric patients with a variety of different illnesses, not just cancer and these include neonates requiring indwelling vein or artery catheterisation to older children undergoing bone marrow transplantation and high dose chemotherapy, which is usually in the short term [3]. Unfortunately, thrombosis related to the placement of such catheters continues to be a therapeutically challenging complication in terms of diagnosis, prophylaxis against thrombosis and also treatment of established thrombosis within the catheter. Regarding suspected thrombosis within the catheter or within the vessel, venography continues to be the gold standard investigation and linograms should be discouraged from being performed as these will give a high false negative value. Once diagnosed the line should be treated with heparin to prevent subsequent venous embolic events, and the very troublesome post-phlebitic syndrome [3]. The vast majority TE events occurring in children occur in the upper limbs as most of catheter placement in young children occurs there. Once the catheter is in place prevention of clot formation can be achieved using regular flushes of either unfractionated heparin or low molecular weight heparin into the catheter device. Removal of the catheter may be required depending on the severity of symptoms and also what the future clinical needs for the child are. Once clot formation occurs the catheter may be salvaged using either/or antithrombotic or antifibrinolytic agents however, it should always be remembered that these therapeutics pose special risks in the paediatric age group compared to the adult age group, in relation to haemorrhage [3].

Other Cancers

Some childhood cancers have a modest increase in the risk of TE development – for example brain tumours would appear to carry very little risk (prevalence ranges 0.6%–3.2%) [12,13]. Others such as sarcomas confers as much a risk as ALL as demonstrated by Athale et al in a recent study showing a prevalence of TE of 14.3% [14].

Primary thromboprophylaxis

Ruud et al failed to show that prophylactic anticoagulation against CVAD-related thrombosis with warfarin could decrease its incidence, the study being terminated early [15]. The PARKAA trial studied use of AT concentrate in children with ALL treated with L-asparaginase, however there was only a trend towards reduced TE in the L-asparaginase cohort [16]. Low molecular weight heparin in small case series has been shown to statistically significantly reduce the incidence of thrombosis in children undergoing chemotherapy for ALL [17] and Ewing Sarcoma [18]. Once catheter occlusions occur these can be treated successfully with the instillation of intraluminal urokinase. It should also be remembered that whilst, although very uncommon, death from TE disease in children does occur. Therefore early detection of such thrombotic events

and adequate treatment are absolutely mandatory in this group of children.

Future directions

The pathogenesis of TE in children with cancer is complex and reflects the interaction of different mechanisms involving the activation of various haemostatic components, such as the pro-/anti-coagulation and fibrinolytic pathways, the endothelium, white cell and platelets as well as the tumour cell itself and the therapeutic modality used. It is only by a better understanding of these interactions that will help to identify better-targeted strategies to prevent TE in children with tumours. An excellent example of this is the current therapeutic approach to children with Kassabach-Merritt syndrome with consumptive coagulopathy secondary to Kaposiform Haemangioendothelioma where platelet transfusions are omitted and double-block anti-platelet agents are administered to prevent platelet degranulation with its associated release of pro-angiogeneic substances. In the meantime we also urgently need interventional randomised clinical trials with anticoagulants in children with cancer at risk of TE.

Conclusion

The last decade has seen advances in treatment of life threatening disease in children – especially cancer where the overall cure rate is in the region of 80%. One of the costs of achieving this has been more children developing thrombotic disease, the majority of which are related to indwelling vascular catheters. Happening alongside these advances have been an explosion in our knowledge of the understanding at the molecular level of blood coagulation in particular how the natural anticoagulant and fibrinolytic pathways work and how they differ in children and adults. Stemming from these discoveries new anticoagulant therapeutics have become available to the paediatrian and over the next decade their true place in the treatment of childhood thrombotic disease will be established.

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