British Journal of Medicine & Medical Research
4(3): 873-882, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Clinico-Demographic Analysis and Outcome of Childhood Thrombosis in a Pediatric Hematology-Oncology Unit: A single Center Experience

Galila M. Mokhtar[1], Randa M. Matter[1], Iman A. Ragab[1*] and Nanies M. Salah-Eldeen[1]

[1]Ain Shams University, Pediatrics Department, Hematology-Oncology Unit - Cairo, Egypt.

Authors' contributions

Author GMM designed the study, author RMM managed the analysis of the study, revised the manuscript, author IAR wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Author NMSE collected the data and performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

Received 24th March 2013
Accepted 30th August 2013
Published 23rd October 2013

ABSTRACT

Aim of the study: Thrombosis is rare in childhood with limited studies. Our retrospective study was designed to evaluate children with documented thrombotic events registered in our pediatric hematology -oncology unit over the last 3 years as regards clinical features, etiology, management and outcomes.
Methods: Among 963 newly registered, 30 patients (16 females and 14 males, median age 4.5 years) with clinical and radiological evidence of thrombosis were identified. Data collection included clinical presentation, identifiable risk factors, thrombophilia screening, radiologic investigations, treatment and outcome.
Results: Age at first thrombotic event was higher for patients with secondary than primary etiology (p=0.018). In 66.7% of patients, there was at least one identified risk for thrombosis, and cancer chemotherapy was the most frequent etiology. Inherited thrombophilia were proven in 13.3%. Secondary thrombophilia presented mostly with neurological symptoms (70%) while inherited thrombophilias with purpura fulminans (80%) (p=0.001). The recurrence was higher with primary (30%) compared to secondary

**Corresponding author: Email: hragab68@hotmail.com;*

thrombophilias (10%). Patients' outcome included neurologic deficit (26.7%), recurrence (16.7%), amputation (6.7%) and death (16.7%).
Conclusion: Thrombosis secondary to an acquired risk factor occurred at older age, commonly presented by central thrombosis with no significant difference between primary and secondary thrombosis in the residual effects. Further studies are warranted to determine proper duration of anticoagulant therapy to prevent recurrence.

Keywords: Childhood; clinicodemographic; thrombosis; outcome; Egypt.

1. INTRODUCTION

Venous thrombosis is an infrequent cause of hospitalization in children; it increased from 5.3/10,000 hospital admissions in a previous Canadian registry to a recent recorded incidence of 21.9 per 10,000 admissions (0.22%), due to improvements in diagnosis[1,2].

The etiology of pediatric venous thromboembolism (VTE) is often multifactorial, related to risk factors comprising one or more components of Virchow's triad [3].Underlying conditions were present in the majority of children and congenital thrombophilia was reported in 43 % of children presenting with symptomatic VTE [1,4]. Acute complications of childhood thrombosis consist of antithrombotic therapy–associated bleeding, thrombus progression, limb/organ infarction, pulmonary embolism, and death. Chronic sequelae include persistent thrombosis following an appropriate course of anticoagulant therapy, recurrent VTE, and the development of post thrombotic syndrome (PTS); overall mortality reached 20% in a study [5,6]. The development of registries increased awareness of thrombosis in children. This paper aimsto study the characteristics of patients developing childhood thrombosis at our center, their clinical outcome, prevalence of inherited thrombophilic condition and provided treatment.

2. METHODOLOGY

A retrospective study was conducted in the Pediatric Hospital's Haematology-Oncology Clinic at Ain Shams University surveying patients up to 16 years of age with objectively documented thrombotic events diagnosed in the period from January 2008 to December 2010.

Patients were divided into two groups: group 1 included patients with primary thrombotic events with no pre-existing known co-morbidity or apparent risk factor; group 2 included patients with at least one identified acquired risk factor for thrombosis; these included pre-existing hematological disorder as sickle cell anemia or thalassemia, pre-identified cancer disorder with or without chemotherapy or other risk factors as sepsis, immune disorders or catheter insertion. Patients with thrombosis secondary to non-hematologic and oncologic causes such as congenital cyanotic heart diseases and nephrotic syndrome were excluded. Clinical data also included age at thrombotic event, gender, detailed history for childhood cancer, chemotherapy protocol, pharmacological agents used including steroids and l-asparaginase and drug usage.

Presenting symptoms were also analyzed and included skin and/or limb gangrene, neurological disorders (paresis, convulsions or disturbed level of consciousness) and any abnormalities in general or systemic examination. Laboratory tests were recorded with initial

blood picture at onset of thrombosis, initial and follow up coagulation profile, basic thrombophilia screening which included activity of protein C, protein S, Antithrombin III, mutation analysis for factor V Leiden, prothrombin 20210 and methylene tetra-hydrofolate reductase. Levels of anticoagulant proteins were compared to age matched reference [7]. All thrombotic events were confirmed by an objective radiological evidence. In patients with central thrombosis, computed tomography (CT) Scan was done initially to all patients ,if negative and/or equivocal CT brain results , or at the advice of the treating neurologist, magnetic resonance imaging (MRI)/MR arteriography (A)/MR venography (V); doppler study was done for extremity thrombosis.

Details of initial management with different anticoagulation regimens (heparin, oral anticoagulation and/or thrombolytic therapy) included doses, duration of therapy and choice of laboratory test used to monitor therapy; maintenance type, duration and laboratory monitoring and complications of treatment including inadequacy of treatment (reflected by recurrence of thrombosis despite anticoagulation) and bleeding (if severe enough to require blood transfusion or treatment stoppage). Outcome of thrombotic events included residual effect (neurocognitive impairment, weakness and convulsions), recurrence or post-phlebitic syndrome.

Patients were further sub classified according to the site of thrombosis into central thrombosis involving the central nervous system (CNS) and peripheral thrombosis, which included any thrombosis outside the CNS (e.g. limb deep venous thrombosis, superficial skin in the form of purpurafulminans and/or central venous line). They were also divided in arterial or venous thrombosis.

Regarding statistical analysis, continuous variables are presented as mean ± standard deviation (SD), whereas discrete variables are described using absolute and relative frequencies. Means were compared by t-test or Mann–Whitney test in cases of small samples of two groups or non-parametric data. Proportions were compared by Chi square or Fisher's exact test. A p-value of $<0.05$was considered significant. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software version 17, 2008.

3. RESULTS

Among a total number of 816 newly diagnosed patients with hematologic disorders and 147 newly diagnosed patients with childhood malignancy in the pediatric hematology-oncology clinic, 30 patients with documented thrombosis (10 patients in group1 and 20 patients in group2) were registered during the study period. There were 14 males and 16 females, aged from 1 month to 16 years, with a median age of 4.5years at the first thrombotic event. Central nervous system thrombosis was present in 16 patients (53.3%), while peripheral in 14 patients (46.7%). The mean initial prothrombin time (PT) and activated partial thromboplastin (PTT) were 26±12 seconds (secs) and 38±14secs respectively, with a control range of 11-15 secsfor PT and 28-40 secs for PTT.

Screening for inherited thrombophilias was performed in 14 patients (46.6 %) (10 patients from group1 and 4 cancer patients from group 2). It included testing for protein C/S deficiency and antithrombin III (ATIII) deficiency done initially and after 3 months of thrombotic event, factor V Leiden mutation and prothrombin 20210 mutationanalysis. Antithrombin III deficiency was diagnosed in one patient (3.33%) at the age of 2 months

(0.39 U/ml, reference for age 0.73-121 U/ml); she presented with purpurafulminans and accidentally discovered CNS thrombosis by imaging. During her treatment, she received fresh frozen plasma, low molecular weight heparin (LMWH) and oral anticoagulation; she had several recurrences of her skin gangrene. Decreased level of both protein C (0.12 U/ml) at one month (age reference 0.21-0.65 U/ml) and protein S (0.1 U/ml; age reference 0.33-0.93 U/ml) was found in one (3.33%) patient; both deficiencies were confirmed after 3 months. She presented with purpurafulminans with 1 month of age and after replacement with FFP, she received lifelong oral anticoagulation. Protein S deficiency was found in 2 patients (6.67%), both presenting deep venous thrombosis, at the age of 2.5 years (0.3 U/ml) and 6years (0.43Uml) respectively (age reference 0.6-1.24 U/ml); both of them did not have thrombotic recurrences and were treated with LMWH and oral anticoagulation. Factor V Leiden mutation was found in 2 patients (6.67%). One patient proved positive for mutant prothrombin 20210 gene. (Table 1.)

Table 1. Classification of thrombosis according to etiology

		N(30)	%
Inherited thrombophilia	Factor V Leiden	2	6.67%
	Mutant prothrombin 20210	1	3.33%
	Protein C/S deficiency	3	10%
	Unidentified*	4	13.33 %
Oncology- related	AML	1	3.33%
	T cell ALL	2	6.67%
	pre B ALL	7	23.3%
	Catheter –related thrombosis	1	3.33%
Hematology- related	β-thalassemia major	1	3.33%
	sickle cell anemia	3	10.0%
	Hemolytic anemia	2	6.7%
	Catheter –related thrombosis	1	3.33%
Others	Sepsis/ DIC	2	6.7%

** Patients were investigated for inherited thrombophilias, yet results were negative, in absence of any identified acquired risk factor.*

Type of radiological imaging was chosen according to the presenting symptom. All patients with neurological symptoms (18 patients) underwent initial brain CT scanning. Ten patients showed evidence of thrombosis in their initial scan, while 8 had normal findings; 4 of these confirmed the initial diagnosis byMRI. Patients (8 patients) with normal initial CT brain underwent MRI/MRA/MRV that proved central nervous system thrombosis.

Duplex study was performed in 50% of patients with peripheral limb and/or skin thrombosis. Comparing secondary with primary thrombosis, patients with identified acquired risk factors for thrombosis showed significantly older age at first thrombotic event (median 6 years) compared to patients with no identified underlying risk (median 0.7 year) (P=0.018).

The study showed significantly higher incidence of CNS thrombosis in patients with secondary thrombosis (70%) in comparison to those with primary thrombosis (30%); the latter presented most commonly by limb gangrene and/or purpura fulminans. There was no significant difference in treatment regimens or outcome between patients with primary

thrombosis versus those with acquired risk factors . Cancer related thrombosis was present in 11 patients (36.7%) and with underlying hematologic disease in 7(23.3%). Four patients from the secondary thrombosis group were tested for Protein C, Protein S, AT III activities and FVL mutation and all had normal levels for their age and wild type FVL except for one patient who had PS deficiency. two patients only (6.67%) had CVL related thrombosis; one of them had histiocytosis and the other autoimmune hemolytic anemiaIn the 10 patients (33.3%) with no identifiable acquired risk for thrombosis, 40 % proved negative for baseline inherited thrombophilia screening.

Comparing arterial and venous thrombosis, primary thrombosis in our patients was predominantly arterial (70%) while secondary thrombosis presented mainly by venous thrombosis (73.3%) ($p=0.043$). CNS sino-venous thrombosis was more common than arterial stroke, 11 (61.1%) and 7 (38.9%) respectively; while in peripheral thrombosis, 7(46.7%) were venous ($P=0.046$).

Central thrombosis presented at a median age of 7 years, while non-central thrombosis occurred at a median age of 1.3 years ($p<0.05$). Patients with primary thrombosis had mostly non-central thrombosis (57.1%), whereas most patients with identified risk factors were had stroke (87.5%) $P=0.002$.

Regarding individual lines of therapies, LMWH was used in 22 (73.3%) patients, oral anticoagulation in 19 (63.33%), thrombolytic agent in 2 (6.7%), exchange transfusion in 2(6.7%) and fresh frozen plasma in 4(13.3%). Regimens used were as follow, sixteen (53.3%)patients were treated with LMWH and maintained on oral anticoagulation for variable period from 6 months to lifelong according to the underlying etiology. Two (6.67%) patients received FFP, LMWH, then thrombolytic and life-long oral anticoagulation; FFP and LMWH was used in one patient (3.33%), LMWH in 3 patients (10%) and oral warfarin in one patient (3.33%) for 6 months Exchange transfusion was performed in two (6.67%)of 3 the patients with sickle cell disease. Five patients received hydration and supportive care without anticoagulation (Table 2). Both primary and secondary groups differed in the duration of anticoagulation, 5 patients with primary thrombosis (50%) were prescribed a lifelong anticoagulation regimen, while duration of anticoagulation in secondary thrombosis ranged from 3-6 months. Recurrent thrombosis occurred in two patients (10%) from the secondary group and three patients (30%) from the primary group, all three had identified inherited thrombophilia (PC/PS/AT III deficiency).

Regarding the different outcomes of thrombosis, neurological deficit was the most common sequelae in 8 (26.7%) patients in the form of residual paresis, impaired intellectual function or seizures; five (16.7%) patients suffered recurrent thrombosis and amputation was done in 2 patients (6.7%); five patients died (16.7%) patients as a result of massive cerebral thrombosis (Table 3).

Table 2. Different Treatment Regimens of the studied patients

Treatment Regimen	Diagnosis	N(%)
LMWH, Oral^ Warfarin	Cancer related	6 (20)
	Hematology	4 (13.3)
	Primary	6 (20)
FFP, Thrombolytic therapy, LMWH, Oral Warfarin^	Primary (PC and AT III deficiency)	2 (6.67)
FFP,LMWH	PF secondary to sepsis	1 (3.33)
LMWH	Cancer related	3 (10)
Oral Warfarin	Cancer related	1 (3.33)
Exchange Transfusion	Sickle cell Anemia	2 (6.67)

LMWH low molecular weight heparin, FFP fesh frozen plasma, PC protein C, AT antithrombin III, PF purpura fulminans, ^ LMWH was started with oral warfarin till the target International normalization ratio (2-3) was reached then LMWH was stopped.

Table 3. Comparison between primary and secondary thrombosis (Fisher exact test)

		Primary		Secondary		P
		N	%	N	%	
Presentation	CNS symptoms	2	20.0%	14	70.0%	.001
	Gangrene	8	80.0%	1	5.0%	
	Peripheral DVT	0	.0%	5	25.0%	
Site	Central	2	20.0%	14	70.0%	.019
	Non central	8	80.0%	6	30.0%	
Individualized treatment	LMWH	6	60%	16	80%	.063
	Oral anticoagulants	6	60%	13	65%	
	Thrombolytics	2	20%	0	0%	
	Exchange transfusion	0	.0%	2	10%	
	Fresh frozen plasma	3	30%	1*	5%	
Residual effect	None	3	30%	7	36.8%	.139
	Neurological deficit	2	20%	6	31.6%	
	Recurrence	3	30%	2	10%	
	Death	0	.0%	5	26.3%	
	Amputation	2	20%	0	.0%	

**one patient with thrombosis secondary to fulminant sepsis received FFP.*

4. DISCUSSION

We had two third of the patients presenting with thrombosis associated with a precipitating factor. In a Canadian registry, they stated that the majority of children with VTEs had associated etiological conditions as well and inherited thrombophilia was proved in a minority of patients; however, in their study the presence of a central venous line (CVL) was the cause of VTE in more than 90% of neonates and in approximately 60% of older children (1). In our study group, two patients only (6.67%) had CVL related thrombosis. Another study found that inherited prothrombotic disorders did not contribute significantly to the pathogenesis of VTEs in neonates and children with an overall frequency of 13%of deficiency of inherited prothrombotic coagulation proteins [8]. In the current paper, 36.7% of the thrombosis associated with secondary causes were related to cancer; most of the patients had acute lymphoblastic leukemia during induction phase; this was probably related

to the combined use of steroids with L-Asparaginase. A previous report emphasized that chemotherapy regimens along with the inherited prothrombotic state were important in the pathogenesis of venous thrombo-embolism in cancer patients [9]. Thus, in settings where limited health resources is a reality, whether routine testing for inherited thrombophilia in children with cancer is cost effective or not should be studied.

Comparing secondary with primary thrombosis, patients with identified acquired risk factors showed significantly older age at first thrombotic event compared to patients with no identified underlying risk.Inherited thrombophilias were associated with early onset of spontaneous TE (including arterial stroke) in a previous report [10].However, Van Ommen et al have found that congenital prothrombotic disorders are more often in older children (21%) than in neonates (6%) and 98% of their patients had at least 1 risk factor[11]. The variability in age between studies could be attributed to the difference in the frequency of CVL, which is more commonly used in the neonatal period; nevertheless, others found no association between age at onset of VTE and presence of thrombophilia [11]. The present study showed no significant difference in gender between primary and secondary thrombosis. A Canadian Registry reported similar results (1). However, a population-based Californian study found that boys had a higher incidence of childhood (non neonatal) stroke than girls for both ischemic and hemorrhagic stroke [12]. Furthermore, studies of childhood arterial ischemic stroke and central sino-venous thrombosis from Europe, Israel, Argentina, and Turkey also showed a male predominance[13].

CNS sinovenous thrombosis was more common than arterial stroke in our patients; these results are in contrast to De Veber et al who had 75% of their pediatric strokes being arterial [14]. We found that central thrombosis presented at an older age than non-central thrombosis. Patients with primary thrombosis presented mostly by non-central thrombosis, whereas most patients with identified risk factors for thrombosis present by stroke. In contrast to this finding, Libourel et al found that a majority of cerebral VT and deep venous thrombosis (DVT) /pulmonary embolism patients show a single or multiple thrombophilic defects and no differences were observed in thrombotic risk profile between groups of comparable ages [15]; nevertheless, the International Society of Thrombosis and Hemostasis reported that homozygous protein C, protein S, antithrombinare usually present in newborns with severe clinical manifestations, such as purpurafulminans and severe large vessel thrombosis [16].

There is a paucity of evidence-based medicine for the management of patients with thrombophilia and VTE; in our cohort, a combination of LMWH and oral anticoagulant were given in 56% of primary and 58% of secondary thrombosis. Previous studies found no difference in the initial management of VTE in those with primary or secondary thrombophilia, except in the rare events of homozygous deficiencies of prothrombotic coagulation proteins. In those cases, the initial treatment should include replacement therapy with FFP or plasma-derived factor concentrate as well as symptomatic anticoagulant therapy [17].We used thrombolytic therapy in two patients of the primary group. It generally follows dosing and monitoring guidelines as for adults because of the limited data for the use of these agents in infants and young children [18].

Two of our studied patients with inherited thrombophilia had an initial presentation by infantile stroke. In both patients the initial management included FFP followed by oral anticoagulation and both experienced thrombosis recurrence despite the use of oral anticoagulant therapy.In previous reports, neonatal stroke was treated acutely with supportive measures only [19]. Antiplatelet therapy and anticoagulation rarely are used,

given the low risk for recurrence; all of the recurrent events were associated with an identifiable prothrombotic or cardiac risk factor which needs to be excluded [20].

In our study, 80% of the patients with cancer related thrombosis received an initial combination of LMWL and oral anticoagulants and were maintained on oral warfarin with recurrence rate of 10 %. In an older report, Lee et al found that dalteparin was more effective in patients with cancer and acute venous thromboembolism than oral anticoagulants in reducing the risk of recurrence without increasing the risk of bleeding, so the practice of shifting patients with cancer and thrombosis to oral anticoagulants needs to be revised [21].

All patients with primary thrombosis presenting by central thrombosis experienced neurological deficit, while 43% of patients with secondary and central thrombosis had neurological sequelae, probably due to earlier age of presentation in primary cases. In a two year follow-up of Swiss children with stroke, neurological outcome was good in 50% and neuropsychological problems were present in 75%. Children suffering from stroke in mid-childhood had the best prognosis [22].

We had recurrent thrombosis in spite of systemic anticoagulation in 5 patients (16.6%)of the total studied group, three of them are from the primary group (30%); Nowak-Gottl et al reported that the risk for recurrence after first episode of spontaneous VTE following completion of 6 months anticoagulation therapy was 21.3% and the presence of prothrombotic defects significantly and independently increased the risk of recurrent VTE [23];yet, they excluded children with cancer or CVL-related VTE.

5. CONCLUSION

We conclude that thrombosis secondary to an acquired risk factor tend to occur at a older age group than in inherited thrombophilias with cancer related thrombosis being the most common acquired risk factor for secondary thrombosis in children. Secondary thrombosis presented most commonly with CNS thrombosis and neurological deficit was the most common residual effect in both primary and secondary thrombosis.

CONSENT

All authors declare that written informed consent was obtained from the parents for enrolment in the study.

ETHICAL APPROVAL

All authors hereby declare that the study was approved by the of ethical committee of the Pediatric Department, Ain Shams University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;1;83(5):1251-7.

2. Wright JM, WattsRG.Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. J Pediatr Hematol Oncol. 2011;33(4):261-4.
3. Goldenberg NA. Thrombophilia states and markers of coagulation activation in the prediction of pediatric venous thromboembolic outcomes: a comparative analysis with respect to adult evidence. Hematology Am Soc Hematol Educ Program. 2008;236-44.
4. Lawson SE, Butler D, Enayat MS, et al. Congenital thrombophilia and thrombosis: a study in a single centre. Arch Dis Child. 1999;81(2):176-8.
5. Goldenberg NA.Long-term outcomes of venous thrombosis in children. Curr Opin Hematol. 2005;12(5):370-6.
6. vanOmmen CH, Heijboer H, van den Dool EJ, et al. Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome. J Thromb Haemost. 2003;1(12):2516-22.
7. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P. Development of the human coagulation system in the full-term infant. Blood. 1987;70(1):165-72.
8. Revel-Vilk S, Chan A, Bauman M, Massicotte P. Prothrombotic conditions in an unselected cohort of children with venous thromboembolic disease. J Thromb Haemost. 2003;1(5):915-21.
9. Athale UH, Chan AK. Thromboembolic complications in pediatric hematologic malignancies. Semin thromb hemost. 2007;33:416-426.
10. Kosch A, Junker R, Kurnik K, et al. Prothrombotic Risk Factors In Children With Spontaneous Venous Thrombosis And Their Asymptomatic Parents: A Family Study. Thromb Res. 2000 ;99:531–7.
11. vanommen ch, Heijboer H, Büller HR, et al. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr. 2001;139(5):676-81.
12. Fullerton HJ, Wu YW, Zhao S, Johnston SC.Risk of stroke in children: ethnic and gender disparities. Neurology. 2003: 22;61(2):189-94.
13. Kenet G, Kirkham F, Niederstadt T, et al. European Thromboses Study Group. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. Lancet Neurol. 2007 ;6(7):595-603.
14. Deveber G, Monagle P, Chan A, et al. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol. 1998;55(12):1539-43
15. Libourel EJ, ten Kate MK, Brouwer JL, et al. Contribution of multiple thrombophilic and transient risk factors in the development of cerebral venous thrombosis. Thromb Res. 2007;121(3):301-7
16. Andrew ME, Monagle P, deVeber G, et al. Thromboembolic disease and antithrombotic therapy in newborns. Hematology Am Soc Hematol Educ Program. 2001:358-74
17. Marlar RA, Montgomery RR, Broekmans AW. Report on the diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the ICTH-Subcommittee on Protein C and Protein S. Thromb Haemost. 1989;61:529–531.

18. Monagle P, Chalmers E, Chan A, et al. American College of Chest Physicians. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).Chest. 2008;133(6 Suppl):887S-968S.
19. Ibrahim SH. Cerebral venous sinus thrombosis in neonates. J Pak Med Assoc. 2006 ;56(11):535-7.
20. Kurnik K, Kosch A, Sträter R, et al. Childhood Stroke Study Group. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. Stroke 2003;34(12):2887-92.
21. Lee AY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;10;349(2):146-53.
22. Pavlovic J, Kaufmann F, Boltshauser E, et al. Neuropsychological problems after paediatric stroke: two year follow-up of Swiss children. Neuropediatrics 2006;37(1):13-9.
23. Nowak-Göttl U, Wermes C, Junker R, et al. Prospective evaluation of the thrombotic risk in children with acute lymphoblastic leukemia carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors. Blood. 1999;1;93(5):1595-9.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=306&id=12&aid=2337