Thrombosis Research 173 (2019) 91–95

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Family history of venous thromboembolism in the paediatric population: The need for a standardized definition

Anna Hau[a,*], Eric Wegener[b], Vera Ignjatovic[c,d], Shoshana Revel-Vilk[e], Paul Monagle[f,c,d]

[a] John Hunter Children's Hospital, Newcastle, NSW, Australia
[b] Calvary Mater Hospital, Newcastle, NSW, Australia
[c] University of Melbourne, Melbourne, VIC, Australia
[d] Murdoch Childrens Research Institute, Melbourne, VIC, Australia
[e] Pediatric Hematology, Sharee Zedek Medical Center, Affiliated with Hadassah - Hebrew University Medical School, Jerusalem, Israel
[f] Royal Children's Hospital, Melbourne, VIC, Australia

ARTICLE INFO

Keywords:
Family history
Paediatric
Venous thromboembolism
Risk factor

ABSTRACT

Positive family history is known to be an independent risk factor for venous thromboembolic (VTE) that may or may not reflect an underlying hereditary disorder. However, there is no clear standardized definition of what constitutes a positive family history for VTE in children. We aimed to assess the current published definitions of positive family history as a risk factor for VTE in children and ascertain if any consensus exists.

Methods: We conducted a literature review through two major databases PUBMED and EMBASE (1969–June 2018). Three different search statements were used for each database to maximize the number of relevant results, giving rise to 1050 non-duplicated papers.

Results: Of the 1050 papers, 32 articles demonstrated 18 separate definitions on what constitutes a positive family history in paediatric studies. Variations in definitions were related to the closeness of kinship (first or second-degree relatives), whether thrombosis was provoked or unprovoked, the age of presentation of thrombosis in the kinship, and clinical vs. laboratory definition of positive family history. Of the definitions, 1st degree relative/s developing VTE at any age whether provoked or unprovoked was most commonly described.

Conclusion: According to this literature review, the definition of a positive family history in paediatric populations is non-standardized amongst current published papers. To enable accurate comparisons across studies and improve clinical risk assessment, we therefore propose the need for a standardized definition of what constitutes a positive family history.

1. Introduction

Family history is a widely used variable when assessing thrombosis risks in both adults and children, and extensively studied in the adult population. The consensus is that a positive family history is an independent risk factor for development of venous thromboembolism (VTE) regardless of additional identified non-genetic or genetic factors [1–3].

The incidence of paediatric thrombosis is far fewer than adult thrombosis, with reported incidence ratios of VTE ranging from 0.7 to 4.9 per 100,000 person-years [4–6]. Naturally with such relative low incidence, there is correspondingly scarce data and research in comparison to adult studies. To date, much of current paediatric management of VTE has been extrapolated from adult studies [7,8].

However, research indicates that paediatric VTE is significantly different from adult VTE in its epidemiology, frequency and natural history [9,10]. A large meta-analysis found statistically significant odds ratios between all currently identified inherited thrombophilic defects (Protein C deficiency, Protein S deficiency, Antithrombin deficiency, Factor V G1691A, Factor II G20210A, Lipoprotein, > 2 combined genetic traits) and first onset of VTE in paediatric patients [11].

So far, research has generally been focused on assessing the benefits of screening children with a positive family history of VTE for inherited thrombophilia [11,12]. The results have mostly demonstrated that family history is a poor predictor of inherited thrombophilic genetic defects [3,5,13–16]. In fact, an adult study shows the 5 major identified inherited thrombophilic defects (Protein C deficiency, Protein S deficiency, Antithrombin deficiency, Factor V Leiden mutation,

Abbreviations: VTE, venous thromboembolism; ATE, arterial thromboembolism

* Corresponding author.
E-mail address: anna.hau@hnehealth.nsw.gov.au (A. Hau).

https://doi.org/10.1016/j.thromres.2018.11.016
Received 30 September 2018; Received in revised form 12 November 2018; Accepted 15 November 2018
Available online 16 November 2018

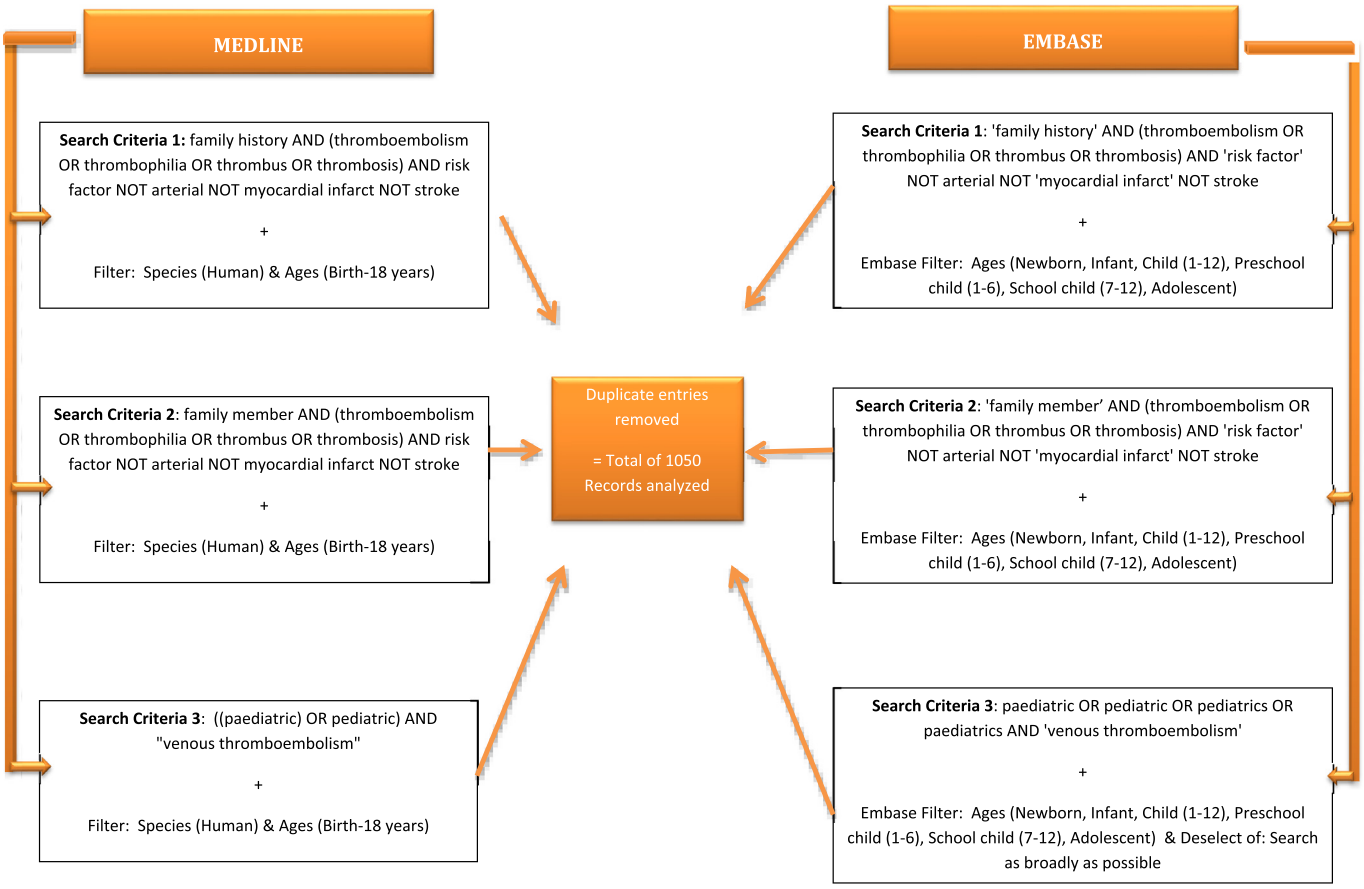

Fig. 1. Search statements used for MEDLINE and EMBASE.

Table 1
Definitions of "family history" reported in paediatric VTE literature.

Definitions	References using definition
1st degree relative	[17,18,19,20,21,22,23,24,25,26,27,28]
1st and/or 2nd degree relatives with VTE	[29,30,31,13]
1st and/or 2nd degree relatives with VTE, before age 55	[12]
1st degree relative with VTE/stroke < 40 years	[32]
1st degree relative with VTE, before age 45	[33]
1st degree relatives with VTE and/or arterial TE, before age 50 years	[10]
1st degree relative with VTE, before age 55	[34]
1st degree relative with VTE or bleeding diathesis	[35]
1st degree relatives with thrombosis or cerebrovascular disease before age 50	[36]
1st and/or 2nd degree relatives with thrombosis, before age 45	[37]
1st and/or 2nd degree relative with DVT, pulmonary embolism, myocardial infarct or stroke < 40 years, recurrent abortions (> 3) and/or laboratory diagnosis of inherited thrombophilia	[38]
1st and/or 2nd degree relatives with history of Perthes disease, blood clots, stroke, myocardial infarction, thrombosis of the lower limbs, and pulmonary embolism, before age 55	[39]
Myocardial infarct or Cerebral Vascular Attack (CVA) before age 55	[40]
1st degree relatives with antithrombin-, protein C-, or protein S-deficiency carriers, or in cases of combined inherited thrombophilia	[41]
Confirmed family history of higher risk prothombotic defects, such as Antithrombin (AT), protein C or protein S deficiency	[42]
Family history of young thrombosis, habitual abortion, foetal/neonatal hydrocephalus and consanguineous marriages	[43]
1st and/or 2nd degree relatives with VTE, before age 50	[44]
Family history of VTE, stroke, or myocardial infarction in a first- or second-degree relative < 50 years old	[45]

Prothrombin 20210A mutation) contribute to only ~30% of family history [1]. This is significant as it implies that there are unmeasurable familial factors or unknown genetic factors that have been accounted for by a positive family history.

To our knowledge, there is no current consensus of what constitutes a positive family history of VTE in regards to the paediatric population. As a variable with such potential to risk stratify and affect management, it is vital to have a uniform definition of what constitutes a positive family history. Our objective is to assess current published definitions of positive family history as a risk factor for VTE in the paediatric population and ascertain if any consensus exists.

2. Methods

We conducted a literature review on June 30, 2018 through two major databases MEDLINE and EMBASE. Three different search statements were constructed in order to obtain high yield and specific results (Fig. 1). The search results where then uploaded to the program

EndNote to manage the database and delete duplicate results.

Inclusion criteria: English language literature; paediatric cohort 0–18 years; family history as a risk factor for VTE.
Exclusion criteria: family history not identified as a risk factor for VTE; non-human; grouped data sets with mixed adult and paediatric populations; articles that did not differentiate between ATE and VTE. Our reasoning behind this is due to arterial and venous thrombus originating from two different pathologies.

Given this review aimed to assess current published definitions of positive family history as a risk factor for paediatric VTE, the statistical significance of the article was not a factor in our consideration for inclusion.

1050 non-duplicated articles were analyzed from the search terms. Only 32 articles gave definition of a positive family history in regards to being a risk factor for paediatric thrombosis (Table 1). The remaining articles either did not meet the inclusion criteria or did not give a formal definition of what constitutes a positive family history.

Our review of the literature yielded 18 definitions of a positive family history. Variations in definitions were related to:

1) Closeness of kinship (e.g.: first or second degree relatives)
2) The age of presentation of thrombosis in the kinship
3) The type of thrombosis (e.g.: arterial vs. venous)
4) Clinical diagnosis versus laboratory evidence of inherited thrombophilia (e.g.: DVT/PE vs. AT deficiency)

The most common definition of a positive family history was a 1st degree relative developing VTE at any age (12/32 or 37.5%) followed by 1st and/or 2nd degree relative with VTE (4/32 or 12.5%). Table 1 lists the definitions in descending order of frequency.

3. Discussion

The aim of this study was to investigate whether a consensus exists in published literature for what defines a positive family history as a risk factor for VTE in the paediatric population. Our finding of 18 separate definitions confirmed that there is currently no consensus in published literature on the definition of a positive family history.

This supports a previous observation that family history was not a well-defined variable in the context of assessing children for risk of thrombophilia [46].

In adult clinical practice, family history has long been used to risk stratify VTE, particularly as a tool to distinguish between sporadic and inherited thrombophilia, to validate extensive testing for prothrombotic genetic traits for individuals or families [15].

Given the lack of similar paediatric data that shows significant correlation between inherited thrombophilia and VTE development [14], the current recommendation to avoid over screening and causing undue distress to the child and family members is to perform thrombophilia testing on an individual basis after counseling the family of the potential risk benefits of testing [47]. Furthermore, the 7th American College of Chest Physicians (ACCP) Conference on Antithrombotic and thrombolytic therapy concluded that due to the unclarified relationship between known genetic factors and occurrence of paediatric VTE, screening children with VTE for prothrombotic genetic risk factors was of unproven benefit, regardless of any acquired risk factors [7]. Furthermore, testing for thrombophilia is complicated by the concept of developmental haemostasis, a term coined by Dr. Andrew, describing the evolving age-dependent process of haemostasis, which continues throughout life. Most marked changes happen during childhood, and are evident by the distinct physiological concentration differences of prothrombotic proteins [48].

Family history still plays an important role in everyday practice, even though as a stand-alone tool, it is a weak instrument to determine who to screen for thrombophilia. Despite Rudd et al. [13] showing a weak association between positive family history of venous thrombosis and certain well known genetic traits; it should be noted that multiple adult studies [1,2,49,50] have found family history to be an independent risk factor regardless of known genetic or environmental risk factors.

However, family history becomes unhelpful given there is no consensus on its definition. As observed in our findings, the various definitions encompassed both clinical and laboratory definitions of a positive family history. The definitions based on laboratory findings are often unhelpful as the risk of having a relative with a VTE is quite different from the risk of having an asymptomatic relative with a known inherited thrombophilic trait.

We believe family history can be utilized more effectively as an independent risk factor if it is further subdivided. Several recent adult studies have sought to differentiate the strength of this risk factor by examining factors such as number of relatives affected; provoked vs. unprovoked VTE; age of first onset of VTE in relatives [2,50]. In order to use family history as a reliable risk factor in the paediatric population, there is an urgent need for similar studies examining paediatric data.

In our literature review, we have minimized any language bias by including articles in foreign languages if they have an English abstract that satisfies the inclusion criteria. However if the information from the abstract was insufficient to determine eligibility, it was marked as unable to be analyzed. We were unable to analyse 9 out of the 1050 articles. Assuming these 9 articles to be eligible for inclusion, a 0.8% exclusion error is present. Our strict inclusion criteria excludes several studies exploring gender, familial and age variants with familial transmission of VTE [1,2,51]; however, their findings would not have altered our results as their definitions of a positive family history were included in our findings. Additionally we included poster abstracts in our search to ensure relevant grey literature was maximised.

4. Conclusion

Our review has found no consensus exists in published literature on what defines family history in paediatric VTE. The most commonly used definition was that of first degree relative with VTE, but did not include information such as provoked or unprovoked nor age of VTE, nor number of affected relatives. There is an urgent need for more quantitative research in order to come to a consensus of positive family history, given its significance as an independent risk factor for paediatric VTE. In the interim, all papers reporting family history as a risk factor for paediatric VTE, should include the specific definition of family history that was applied to their patient population, so rates and significance of family history can be appropriately compared throughout the available literature.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] I. Bezemer, F. Van der Meer, J. Eikenboom, F. Rosendaal, M. Doggen, The value of family history as a risk indicator for venous thrombosis, Arch. Intern. Med. 169 (6) (Mar 23 2009) 610–615. Available from: http://archinte.jamanetwork.com/ (Internet, cited 2016 Apr 21).
[2] B. Zoller, X. Li, J. Sundquist, K. Sundquist, Age – and gender – specific familial risks for venous thromboembolism, Circulation 124 (Aug 8 2011) 1012–1020, https://doi.org/10.1161/CIRCULATIONAHA.110.965020 (Internet, cited 2015 Jun 12).
[3] S. Noboa, G. Gal, K. Lacut, B. Mercier, C. Leroyer, E. Nowak, D. Mottier, E. Oger, Family history as a risk factor for venous thromboembolism, Thromb. Res. 122 (Feb 20 2008) 624–629, https://doi.org/10.1016/j.thromres.2007.12.026 (Internet, cited 2015 Jun 12).
[4] M. Andrew, M. David, M. Adams, K. Ali, R. Anderson, D. Barnard, M. Berstein,

L. Brisson, B. Cairney, D. DeSai, R. Grant, S. Israels, L. Jardine, B. Luke, P. Massicotte, M. Silva, Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE, Blood 83 (9) (Mar 1 1994) 1251–1257 http://dx.doi.org.ezp.lib.unimelb.edu.au/ (Internet, cited 2015 Jun 12).

[5] C. Van Omen, H. Heikboer, E. Van den Dool, B. Hutten, M. Peters, Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome, J. Thromb. Haemost. 1 (12) (Oct 6 2003) 2516–2522, https://doi.org/10.1046/j.1538-7836.2003.00465.x (Internet, cited 2015 Jun 12).

[6] P. Stein, F. Kayali, R. Olson, Incidence of venous thromboembolism I infants and children: data from the national hospital discharge survey, J. Pediatr. 145 (4) (Oct 12 2004) 563–565, https://doi.org/10.1016/j.jpeds.2004.06.021 (Internet, cited 2015 Jun 12).

[7] P. Monagle, A. Chan, E. Chalmers, A. Michelson, Antithrombotic therapy in children: The Seventh ACCP Conference on antibthrombotic and thrombolytic therapy, Chest 126 (3) (Sept 2004), https://doi.org/10.1378/chest.126.3_suppl.645S (Internet, cited 2015 Dec 16, 645S-87S).

[8] P. Monagle, A. Chan, N. Goldenberg, R. Ichord, J. Journeycake, U. Nowak-Göttl, S. Vesely, American College of Chest Physicians, Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, Chest 141 (2 Suppl) (Feb 2012) e737S–801S, https://doi.org/10.1378/chest.11-2308 (Internet, cited 2016 Jan 26).

[9] P. Monagle, V. Ignjatovic, H. Savoia, Hemostasis in neonates and children: pitfalls and dilemmas, Blood Rev. 24 (2) (Mar 2010) 63–68, https://doi.org/10.1016/j.blre.2009.12.001 (Internet, cited 2016 Jan 16).

[10] R. Tuckuviene, A. Christensen, J. Helgestad, S. Johnsen, S. Kristensen, Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study, J. Pediatr. 159 (4) (Mar 24 2011) 663–669, https://doi.org/10.1016/j.jpeds.2011.03.052 (Internet, cited 2015 Jun 12).

[11] G. Young, M. Albisetti, M. Bonduel, L. Brandao, F. Chan A Friedrichs, N. Goldenberg, E. Grabowski, C. Heller, J. Journeycake, G. Kenet, A. Krumpel, K. Kurnik, A. Lubetsky, C. Male, M. Manco-Johnson, P. Mathew, M. Monagle, H. van Ommen, P. Simioni, P. Svirin, D. Tormene, U. Nowak-Gottl, Impact of inherited thrombophilia on venous thromboembolism in children, Circulation 118 (Jul 11 2008) 1372–1382, https://doi.org/10.1161/CIRCULATIONAHA.108.789008 (Internet, cited 2015 Jun 12).

[12] M. Calhoon, C. Ross, E. Pounder, D. Cassidy, M. Manco-Johnson, N. Goldenverg, High prevalence of Thrombophilic traits in children with family history of thromboembolism, J. Pediatr. 157 (3) (Sept 10 2010) 485–489, https://doi.org/10.1016/j.jpeds.2010.03.031 (Internet, cited 2015 Jun 23).

[13] E. Rudd, H. Holmstrom, F. Brosstad, F. Wesenberg, Diagnostic value of family histories of thrombosis to identify children with thrombophilia, Pediatr. Heatol. Oncol. 22 (6) (Sept 2005) 453–462, https://doi.org/10.1080/08880010591002224 (Internet, cited 2015 June 13).

[14] D. Tormene, P. Simioni, P. Prandoni, F. Franz, P. Zerbinati, G. Tognin, A. Girolami, The incidence of venous thromboembolism in thrombophilic children: a prospective cohort study, Blood 100 (7) (Oct 1 2002) 2403–2405, https://doi.org/10.1182/blood-2002-04-1186 (Internet, cited 2015 June 13).

[15] W. Briet, F.J. van der Meer, F.R. Rosendaal, J.J. Houwing-Duistermaat, H.C. van Houwelingen, The family history and inherited thrombophilia, Br. J. Haematol. 87 (2) (June 1994) 348–352 (Internet, cited 2015 June 10).

[16] G.L. Van Sluis, M. Sohne, D.Y. El Kheir, M.W. Tanck, V.E. Gerdes, H.R. Buller, Family history and inherited thrombophilia, J. Thromb. Haemost. 4 (10) (Oct 2006) 2182–2187 (Internet, cited 2015 June 10).

[17] J. Dietrich, S. Hertweck, Thrombophilias in adolescents: the past, present and future, Curr. Opin. Obstet. Gynecol. 20 (5) (Oct 2008) 470–474, https://doi.org/10.1097/GCO.0b013e32830ab83f (Internet, cited 2015 Jun).

[18] A. Munck, A. Kheniche, C. Alberti, D. Hubert, R. Martine, R. Nove-Josserand, I. Pin, F. Bremont, R. Chiron, L. Couderc, M. Dalphin, E. Darviot, B. Delaisi, S. Dominique, I. Durieu, A. Fanton, M. Fayon, M. Gerardin, J. Ginies, C. Giraut, D. Grenet, M. Guillot, F. Huet, M. Le Bourgeois, M. Murris-Epin, S. Ramel, A. Sardet, I. Sermet-Gaudelus, F. Varaigne, S. Wanin, L. Weiss, M. Hurtaud, Central venous thrombosis and thrombophilia in cystic fibrosis: a prospective study, J. Cyst. Fibros. 14 (1) (Jan 2015) 97–103, https://doi.org/10.1016/j.jcf.2014.05.015 (Internet, cited 2015 Jun).

[19] B. Zoller, X. Li, J. Sundquist, K. Sundquist, C. Crump, Gestational age and risk of venous thromboembolism from birth through young adulthood, Pediatrics 134 (2) (Aug 2014) e473–e480, https://doi.org/10.1542/peds.2013-3856 (Internet, cited 2015 Jun).

[20] R. Jurcut, D. Coriu, I. Ghiorghiu, I. Calangea, M. Stoian, C. Ginghina, What lies behind venous thromboembolic disease in two young brothers? The impact of thrombophilia testing on management, Exp. Clin. Cardiol. 20 (7) (2014) 822–837 (Internet, cited 2015 Jun).

[21] N. Zitomersky, A. Levine, B. Atkinson, K. Harney, M. Verhave, A. Bousvaros, J. Lightdale, C. Trenor, Risk factors, morbidity, and treatment of thrombosis in children and young adults with active inflammatory bowel disease, J. Pediatr. Gastroenterol. Nutr. 57 (3) (Sep 2013) 343–347, https://doi.org/10.1097/MPG.0b013e31829ce5cd (Internet, cited 2015 Jun).

[22] L. Venkateswaran, J. Dietrich, Gynecologic concerns in pubertal females with blood disorders, J. Pediatr. Adolesc. Gynecol. 26 (2) (Apr 2013) 80–85, https://doi.org/10.1016/j.jpag.2012.07.001 (Internet, cited 2015 Jun).

[23] M. Gokce, I. Altan, S. Unal, B. Kuskonmaz, S. Aytac, M. Cetin, M. Tuncer, F. Gumruk, A. Gurgey, Recurrent pediatric thrombosis: the effect of underlying and/or coexisting factors, Blood Coagul. Fibrinolysis 23 (5) (Jul 2012), https://doi.org/10.1097/MBC.0b013e3283548e39 (Internet, cited 2015 Jun, 434-0).

[24] J. Estepp, M. Smeltzer, U. Reiss, The impact of quality and duration of enoxaparin therapy on recurrent venous thrombosis in children, Pediatr. Blood Cancer 59 (1) (Jul 2012) 105–109, https://doi.org/10.1002/pbc.23396 (Internet, cited 2015 Jun).

[25] S. Savelli, B. Kerlin, M. Springer, K. Monda, J. Thornton, C. Blanchong, Recommendations for screening for thrombophilic tendencies in teenage females prior to contraceptive initiation, J. Pediatr. Adolesc. Gynecol. 19 (4) (Aug 2006) 313–316, https://doi.org/10.1016/j.jpag.2006.05.007 (Internet, cited 2015 Jun).

[26] C.Y. Wang, V. Ignjatovic, P. Francis, T. Cain, F. Babl, R. Kowalski, A. Cochrane, P. Monagle, Risk factors and clinical features of acute pulmonary embolism in children from the community, Thromb. Res. 138 (Feb 2016) 86–90, https://doi.org/10.1016/j.thromres.2015.12.005 (Internet, cited 2018 Jun).

[27] M. Hellfritzsch, E.L. Grove, Life-threatening contraceptive-related pulmonary embolism in a 14-year-old girl with hereditary thrombophilia, Am. J. Case Rep. 16 (Sep 29 2015) 667–669, https://doi.org/10.12659/AJCR.894721 (cited 2018 Jun).

[28] B. Zöller, X. Li, J. Sundquist, K. Sundquist, Venous thromboembolism does not share familial susceptibility with retinal vascular occlusion or glaucoma: a nationwide family study, J. Thromb. Thrombolysis 42 (4) (Nov 2016) 505–512, https://doi.org/10.1007/s11239-016-1387-7 (cited 2018 Jun).

[29] P. Pillai, A. Bonny, S. O'Brien, Contraception-related venous thromboembolism in a pediatric institution, J. Pediatr. Adolesc. Gynecol. 26 (3) (Jun 2013) 186–188, https://doi.org/10.1016/j.jpag.2013.02.009 (Internet, cited 2015 Jun 3).

[30] C. van Ommen, H. Heijboer, E. van den Dool, B. Hutten, M. Peters, Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome, J. Thromb. Haemost. 1 (12) (Dec 2003) 2516–2522 (Internet, cited 2016 Jun).

[31] S. Holzhauer, N. Goldenberg, R. Junker, C. Heller, M. Stoll, D. Manner, R. Mesters, A. Krumpel, M. Stach, U. Nowak-Gottl, Inherited thrombophilia in children with venous thromboembolism and the familial risk of thromboembolism: an observational study, Blood 120 (7) (Aug 16 2012) 1510–1515, https://doi.org/10.1182/blood-2012-01-405514 (Internet, cited 2016 Jun).

[32] S. Sabharwal, C. Zhao, M. Passanante, Venous thromboembolism in children: details of 46 cases based on a follow-up survey of POSNA members, J. Pediatr. Orthop. 33 (7) (Nov 2013) 768–774, https://doi.org/10.1097/BPO.0b013e31829d55e3 (Internet, cited 2015 June 15).

[33] A. Samkova, K. Lejhancova, J. Hak, A. Lukes, Venous thromboembolism in adolescents, Acta Medica 55 (2012) 76–82 (Internet, cited 2015 Jun).

[34] N. Goldenberg, E. Pounder, R. Knapp-Clevenger, M. Manco-Johnson, Validation of upper extremity post-thrombotic syndrome outcome measurement in children, J. Pediatr. 157 (5) (Nov 2010) 852–855, https://doi.org/10.1016/j.jpeds.2010.07.003 (Internet, cited 2015 Jun).

[35] N. Goldenberg, R. Knapp-Clevenger, M. Manco-Johnson, Mountain State Regional Thrombophilia Group, Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children, N. Engl. J. Med. 351 (11) (Sep 9 2004) 1081–1088, https://doi.org/10.1056/NEJMoa040161 (Internet, cited 2015 Jun).

[36] B. Bassi, E. Parodi, M. Messina, P. Boffi, B. Bobba, M. Campagnoli, R. Rigardetto, P. Saracco, Screening for genetic and acquired thrombophilia in a cohort of young migrainous patients, J. Headache Pain 4 (Feb 17 2003) 138–145, https://doi.org/10.1007/s10194-003-0048-3 (Internet, cited 2016 Jun).

[37] M. Bonduel, M. Hepner, G. Sciuccati, A. Torres, G. Pieroni, J. Frontroth, Prothrombotic abnormalities in children with venous thromboembolism, J. Pediatr. Hematol. Oncol. 22 (1) (Jan 2000) 66–72 (Internet, cited 2016 Jun).

[38] S. Revel-Vilk, J. Yacobovich, H. Tamary, G. Goldstein, S. Nemet, M. Weintraub, O. Paltiel, G. Kenet, Risk factors for central venous catheter thrombotic complications in children and adolescents with cancer, Cancer 116 (17) (Sep 1 2010) 4197–4205, https://doi.org/10.1002/cncr.25199 (Internet, cited 2015 Jun 3).

[39] D. Yilmaz, L. Karapinar, B. Karapinar, H. Ozturk, K. Kavakli, Evaluation of anticoagulant system in Turkish children with Perthes disease, Pediatr. Int. 47 (1) (Feb 2005) 43–48 (Internet, cited 2015 Jul).

[40] J. Dietrich, S. Hertweck, S. Perlman, Efficacy of family history in determining thrombophilia risk, J. Pediatr. Adolesc. Gynecol. 20 (4) (Aug 2007) 221–224 (Internet, cited 2016 Jun).

[41] U. Nowak-Gottl, V. Janssen, D. Manner, G. Kenet, Venous thromboembolism in neonates and children—update 2013, Thromb. Res. 133 (Jan 2013) S39–S41, https://doi.org/10.1016/S0049-3848(13)70019-7 (Internet, cited 2016 Jun).

[42] A. Zia, M. Chitlur, Management of thrombotic complications in acute lymphoblastic leukemia, Indian J. Pediatr. 80 (10) (Oct 2013) 853–862, https://doi.org/10.1007/s12098-013-1158-9 (Internet, cited 2015 Jun).

[43] S. Ohga, D. Kang, T. Kinjo, M. Ochiai, T. Doi, M. Ishimura, Y. Kayamori, M. Urata, J. Yamamoto, S. Suenobu, H. Kanegane, T. Ikenoue, A. Shirahata, T. Hara, Paediatric presentation and outcome of congenital protein C deficiency in Japan, Haemophilia 19 (3) (May 2013) 378–384, https://doi.org/10.1111/hae.12097 (Internet, cited 2015 Jun).

[44] V. Limperger, G. Kenet, N.A. Goldenberg, C. Heller, S. Holzhauer, R. Junker, U.C. Klostermeier, R. Knoefler, K. Kurnik, A. Krümpel, R. Mesters, M. Stach, G. Young, U. Nowak-Göttl, Impact of high-risk thrombophilia status on recurrence among children with a first non-central-venous-catheter-associated VTE: an observational multicentre cohort study, Br. J. Haematol. 175 (1) (Oct 2016) 133–140, https://doi.org/10.1111/bjh.14192 (cited 2018 Jun).

[45] A. Mahajerin, E.C. Webber, J. Morris, K. Taylor, M. Saysana, Development and implementation results of a venous thromboembolism prophylaxis guideline in a tertiary care pediatric hospital, Hosp. Pediatr. 5 (12) (Dec 2015) 630–636, https://doi.org/10.1542/hpeds.2014-0241 (cited 2018 Jun).

[46] L. Raffini, C. Thornburg, Testing children for inherited thrombophilia: more questions than answers, Br. J. Haematol. 147 (3) (Nov 2009) 277–288, https://doi.org/10.1111/j.1365-2141.2009.07820.x (Internet, cited 2016 Jan 18).

[47] C. Thornburg, N. Dixon, K. Paulyson-Nuñez, T. Ortel, Thrombophilia screening in asymptomatic children, Thromb. Res. 121 (5) (2008) 597–604, https://doi.org/10.1016/j.thromres.2007.06.001 (Internet).
[48] M. Andrew, Developmental hemostasis: relevance to thromboembolic complications in pediatric patients, Thromb. Haemost. 74 (1) (Jul 1995) 415–425 (Internet, cited 2015 Dec).
[49] F. Couturaud, C. Leroyer, J.A. Julian, S.R. Kahn, J.S. Ginsberg, P.S. Wells, J.D. Douketis, D. Mottier, C. Kearon, Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism, Chest 136 (6) (Dec 2009) 1537–1545, https://doi.org/10.1378/chest.09-0757 (Internet, cited 2015 June 10).
[50] F. Couturaud, C. Leroyer, C. Tromeur, J. Julian, S. Kahn, J. Ginsberg, P. Wells, J. Douketis, D. Mottier, C. Kearon, Factors that predict thrombosis in relatives of patients with venous thromboembolism, Blood 124 (13) (Sep 25 2014) 2124–2130, https://doi.org/10.1182/blood-2014-03-559757 (Internet, cited 2016 May 1).
[51] B. Zoller, X. Li, J. Sundquist, K. Sunquist, Familial transmission of venous thromboembolism: a cohort study of 80 214 Swedish adoptees linked to their biological and adoptive parents, Circ. Cardiovasc. Genet. 7 (3) (June 2014) 296–303, https://doi.org/10.1161/CIRCGENETICS.113.000341 (Internet, cited 2015 June 10).