Haemophilia

Haemophilia (2012), **18**, e297–e301 DOI: 10.1111/j.1365-2516.2011.02665.x

ORIGINAL ARTICLE *Paediatrics*

Significance and causes of abnormal preoperative coagulation test results in children

A. SAMKOVÁ,* J. BLATNÝ,† V. FIAMOLI,† P. DULÍČEK‡ and E. PAŘÍZKOVÁ*

**Department of Pediatrics, University Hospital, Charles University, Hradec Kralove; †Department of Pediatrics Hematology, Children's University Hospital, Masaryk University, Brno; and ‡Department of Clinical Hematology, University Hospital, Charles University, Hradec Kralove, Czech Republic*

Summary. To prevent bleeding related to adenoidectomy and tonsillectomy, coagulation screening tests were, until recently, performed routinely in the Czech Republic for all paediatric patients. The aim of this study was to evaluate benefit of preoperative coagulation screening tests in children. We retrospectively analysed laboratory and clinical data of children referred for abnormal preoperative coagulation test results (aPTT, PT) to the outpatient haematology clinic. A total of 274 paediatric patients were retrospectively evaluated due to abnormal preoperative coagulation tests results. In 140 of 274 patients (51.1%), coagulation tests were normal on repeated testing in a specialized haematology clinic. Ten patients had decreased factor XII. Five patients had a suspected bleeding disorder which was confirmed in two of them. One patient had low levels of von Willebrand factor, and one patient had mild factor VII deficiency. Both these patients had positive personal and/or family history of bleeding. Each case history was taken individually, without use of standardized questionnaires. Bleeding complications were not observed, and coagulation factor replacement was not needed perioperatively in our cohort. The majority of abnormal findings in aPTT and PT appeared only transiently. All the bleeding disorders found in our cohort of patients were mild in nature. Our findings provide supportive evidence for the current national Czech recommendation: laboratory coagulation screening should be performed only in patients with positive family and/or personal bleeding history.

Keywords: bleeding, children, coagulation, disorder, preoperative

Introduction

Selected ENT (ear- nose- and throat) surgeries are associated with an increased risk of bleeding. Bleeding complications after adenoidectomy (AT) occur with an incidence of less than 1% [1], whereas tonsillectomy (TE) is associated with significant bleeding in about 3% of cases [2–4]. To identify patients with impaired haemostasis and to prevent potentially life-threatening bleeding, coagulation screening tests may be routinely performed on all paediatric patients prior to these surgical interventions. Preoperative screening was managed in a similar fashion in the Czech Republic until 2010. However, at this time, revised guidelines from the Czech society of Otorhinolaryngology and Head and Neck surgery recommended that the routine preoperative coagulation screening could be replaced by a bleeding questionnaire. We aimed to review the benefit of coagulation screening tests in children undergoing ENT surgery, as we are of the opinion that the bleeding is often caused by local and/or surgical conditions rather than coagulation disorders, and thus, the coagulation screening tests provide information of low clinical specificity and significance (especially the aPTT) in asymptomatic children. In addition, the benefit of bleeding history taken during the preoperative interview was evaluated. According to Licameli *et al.*, [5] a positive preoperative bleeding questionnaire followed by coagulation tests has a good ability to predict bleeding tendency. The aim of our study was to evaluate the ability of preoperative coagulation screening tests to predict bleeding complications as well as to identify the most frequent causes of prolonged aPTT and PT in our cohort of patients.

Correspondence: Aneta Samková, Department of Pediatrics, University Hospital, Sokolska 581, Hradec Kralove, 50005 Czech Republic.
Tel.: 00420495833752; fax: 00420495832100;
e-mail: anetasamkova@atlas.cz

Accepted after revision 1 September 2011

Materials and methods

We retrospectively analysed data from 274 consecutive children, who were referred to the outpatient

haematology clinic in two Czech university hospitals (Brno, Hradec Králové) for abnormal preoperative coagulation test results between September 2008 and September 2009. During their visit in the clinic, we also asked parents about the history of bleeding symptoms in their child as well as any family history of bleeding symptoms and/or disorders. No standardized questionnaire was used. With regard to the criteria for positive bleeding history, we evaluated any bleeding disorder in the family or bleeding symptoms except trivial symptoms in the family history (sporadic epistaxis in parents during childhood, which resolved spontaneously). The coagulation tests (aPTT/PT) were repeated in all referred patients, and if the abnormal results were confirmed, we performed specific coagulation factor assays. In patients with prolonged aPTT, levels of factor VIII, factor IX, factor XI, factor XII and ristocetin cofactor activity (vWF:RiCo) were tested. In the case of the latter, we also tested for von Willebrand factor antigen (VWF Ag). In patients with prolonged prothrombin time (PT), levels of factor VII, factor V and factor X were tested. If both screening tests were abnormal, factor V and X activities were assessed. Assay for factor II was not tested in asymptomatic patients due to extreme rarity of this deficiency. In case of confirmed factor deficiency, the factor assay was repeated within 2–20 months. Coagulation tests in University Hospital Hradec Králové were performed using STA-R and STA-Compact (Diagnostica Stago S.A.S., Asnières sur Seine, France) with the following reagents: aPTT – PTT Automate 10 (Diagnostica Stago), mixture studies aPTT – PTT Automate 10 and Coag Norm (Diagnostica Stago), aPTT LA – PTT-LA – with high lupus anticoagulant sensitivity (Diagnostica Stago), PT – DG-PT (Grifols, S.A., Sant Cugat del Vallčs, Barcelona, Spain), factor V – STA Deficient V (Diagnostica Stago), DG-PT (Grifols), factor VII – DG-FVII, DG-PT (Grifols), factor X – STA Deficient X (Diagnostica Stago, DG-PT (Grifols), factor VIII – DG-FVIII (Grifols), C.K. Prest 5 (Diagnostica Stago), factor IX – DG-FIX (Grifols), C.K. Prest 5 (Diagnostica Stago), factor XI – DG-FXI (Grifols), C.K. Prest 5 (Diagnostica Stago), factor XII – DG-FXII (Grifols), C.K. Prest 5 (Diagnostica Stago), vWF RiCo – Ristocetin Cofactor Kit (Helena Biosciences, Gateshead - Tyne and Wear, United Kingdom) and vWF antigen – STA-LIATEST vWF. In University Hospital Brno assessment of aPTT, aPTT with actin and PT was performed on the coagulation automate Amax Destiny Plus with these reagents: PT – TriniClot PT Excel S (Trinity Biotech Trinity Biotech Plc, Co Wicklow, Ireland), aPTT - TriniClot aPTT HS with high lupus anticoagulant sensitivity (Trinity Biotech) and aPTT actin – Actin FS activated PTT Reagent with low lupus anticoagulant sensitivity. VWF:RiCo test was performed using Ristocetin Cofactor Assay Kit (Helena Biosciences). Specific factor assays and von Willebrand factor antigen assay were performed on the automated analyser STA-R (Diagnostica Stago) using the following reagents: factor V – STA Deficient V (Diagnostica Stago), factor X – STA Deficient X (Diagnostica Stago), factor VII – DG-FVII (Grifols), factor VIII – DG-FVIII (Grifols), factor FIX – DG-FIX (Grifols), factor XI – DG-FXI (Grifols), factor XII – FXII Deficient Plasma (Hyphen BioMed SAS, Neuville-Sur-Oise, France) and vWF antigen – STA-LIATEST vWF (Diagnostica Stago). Age-dependent reference ranges were used as appropriate [6]. We used retrospectively collected anonymized data taken from the clinical records of two centres. In accordance with state legal requirements, approval from an ethics committee was neither needed nor requested.

Results

A total of 274 consecutive paediatric patients were tested for abnormal preoperative coagulation tests in two university hospitals in the specified 1-year period. Elective ENT surgery was the most frequent reason for coagulation tests – 272 patients (259 AT, five TE, two AT+TE, two otoplasty, one nasal polypectomy, one lateral cervical cyst excision, one cleft palate surgery and one tympanostomy). Two patients had coagulation tests before excision of a sacral dimple.

Coagulation test results

Of the original 274 referred patients, 142 (51.8%) had either normal coagulation tests on repeated testing in the haematology clinic (140 patients – 51.1%) or the haematologist evaluated the initial values as normal for given age and the tests were not repeated (two patients – 0.7%). Eight children with prolonged aPTT were not tested for factor deficiencies as a specific bleeding disorder was unlikely, based on incomplete correction of aPTT in 'mixture studies' as well as on the patient's negative personal and family history, which excluded clinically relevant bleeding disorders. Lupus anticoagulant was suspected in these patients. In the remaining 124 of 274 patients, coagulation factor assays were performed (Fig. 1). A total of 105 (84.7%) of these patients had abnormal aPTT, 13 (10.5%) children had abnormal PT and in 6 (4.8%) of them, both tests were abnormal.

Ninety-nine patients of the 124 (79.8%) children tested for factor deficiency had all investigated coagulation factor activities within the normal ranges. Twenty-five patients (20.2%) had decreased activity of at least one coagulation factor.

One patient had low von Willebrand factor activity (vWF:RiCo: 35.8%; 16%) and decreased von Willebrand factor antigen (30%; 27%). She did not have any bleeding symptoms. Her mother suffered from epistaxis, but had never been tested for von Willebrand disease. One patient had confirmed mild factor VII deficiency

(28%; 39%). He suffered from repeated epistaxis and easy bruising. Epistaxis was also present in his father and grandmother. Both patients were retested, and deficiency of the respective factors was confirmed. The parents of one child with low factor VII (34% of activity) declined our offer to repeat the testing, because the girl currently has no bleeding problems and they did not want to stress the child with repeated blood sampling. Similarly, the parents of another child with low ristocetin cofactor (activity of 11%) preferred not to retest their child. One child with low ristocetin cofactor activity (19%) was lost from further follow-up, and we were not able to repeat the assay (Table 1). No other clinically relevant bleeding disorders were revealed in the cohort of tested patients.

Ten patients had decreased factor XII (0–32%) only, including two children with confirmed severe factor XII deficiency with activity of 0%. The test for factor XII was not repeated in eight patients with mild factor deficiency, because of the low clinical significance of such a coagulation abnormity.

We repeated the factor activity assays in 12 patients with low activity of factors other than factor XII several months (2–20 months) after the initial finding. Seven of those patients had only transient factor deficiency (three Von Willebrand factor, three factor VIII and one factor VII). A further cohort of three patients similarly had only transiently decreased activity of more than one coagulation factor.

All the children with confirmed factor deficiencies underwent the surgery with non-specific prophylactic measures administrated systemically – etamsylate (DICYNONE, Sanofi Winthrop Industrie, Quétigny, France) and/or aminoethylbenzoic acid (PAMBA, Nycomed GmbH, Singen, Germany). No bleeding complications were observed in any of these patients.

Personal and/or family history for bleeding

Twenty-four of 274 children (8.8%) had positive personal or family bleeding history. Two patients of 24 (8.3%) with positive bleeding history had confirmed bleeding disorders. Three patients with suspected, but not confirmed bleeding disorders had a negative bleeding history.

Discussion and Conclusion

Just over half (51.1%) of patients referred for prolonged aPTT and/or PT were not confirmed on repeated testing. This is in accordance with previously published data [7,8]. We can speculate that the reason for this may perhaps be a high incidence of transient non-specific inhibitors or antiphospholipid antibodies in the paediatric population with frequent infections [9]. The influence of preanalytic errors in primary testing also cannot be ruled out. In the vast majority (79.8%) of our patients with confirmed abnormal screening tests, we did not find any factor deficiency. This is consistent with the previous findings of Kitszel and Shaw [7,10].

Most of the identified factor deficiencies were only transient. The frequency with which transient decreases of coagulation factor activity in otherwise healthy persons could cause a significant bleeding tendency remains unclear, but we did not record any peri- or postoperative bleeding complications in such patients. However, these patients have been on supportive pro-haemostatic treatment perioperatively or have been operated after spontaneous correction of factor deficiency. These preventive measures might be responsible for such a favourable clinical outcome, where patients neither needed any specific treatment nor factor replacement therapy.

We found five children with possible mild bleeding disorder of unclear clinical significance, but we were able to confirm the finding in only two cases. In the other three cases, we cannot exclude a bleeding disorder. The clinical significance of diagnosis of factor VII deficiency in those two patients (FVII around 30%) is still controversial, because levels of 10–15% are thought to be haemostatic in surgery or bleeding episodes [11]. Three patients with possible von Willebrand disease (VWD) underwent surgery on supportive

Table 1. Factor deficiencies.

	Deficiency	Screening test (ratio)	1st factor result (%)	2nd factor result (%)	Personal history	Family history	Surgery	Haemostatic support	Bleed
1	VWF	aPTT 1.5	35.8	16	0	Mother epistaxis	AT	PAMBA, etamsylate*	0
2	FVII	PT 1.49	28	39	Epistaxis	Father epistaxis	TE	PAMBA	0
3	VWF	aPTT 1.31	20	85.8	0	0	AT	PAMBA, etamsylate*	0
4	VWF	aPTT 1.4	35	80	AT bleeding	Mother epistaxis	reAT	PAMBA, etamsylate*	0
5	VWF	aPTT 1.25	26.8	78	0	0	AT	PAMBA, etamsylate*	0
6	FVIII	aPTT 1.56	16	46	0	Mother epistaxis	AT	PAMBA, etamsylate†	0
7	FVIII	aPTT 2.28/1.48	14	44	0	0	AT	PAMBA, etamsylate†	0
8	FVIII	aPTT 1.28	29	162	0	0	AT	PAMBA, etamsylate†	0
9	FVII	PT 1.7	24	47	0	0	LCC	PAMBA, FFP	0
10	FVII	PT 1.47	34		0	0	AT	PAMBA, etamsylate	0
11	VWF	aPTT 1.29	11		0	0	AT	PAMBA, etamsylate*	0
12	VWF	aPTT 1.61	19		0	0	AT	PAMBA, etamsylate*	0

VWF deficient patients, factor results refer to VWF:RiCo assay. FFP, fresh frozen plasma; LCC, lateral cervical cyst excision.
*vWF/FVIII concentrate would be used in case of bleeding (as desmopressin is not registered and is not available in the Czech Republic).
†Surgery was performed after the second factor testing.

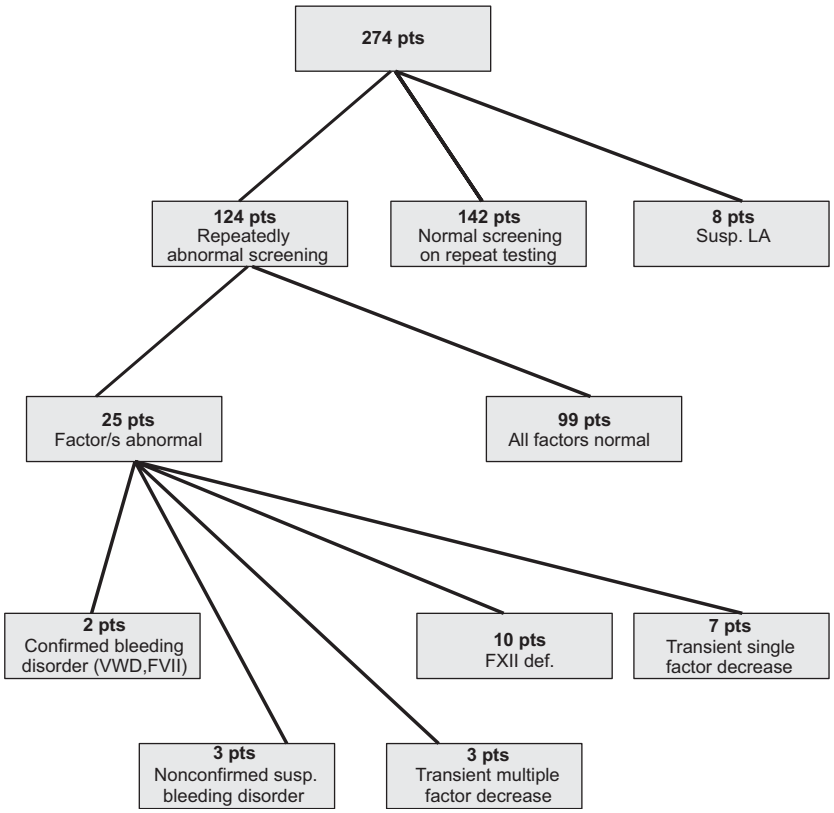

Fig. 1. Coagulation results.

pro-haemostatic and antifibrinolytic treatment. The lack of requirement for specific treatment during and after adenoidectomy indicates a mild phenotype of VWD. None of our five patients with suspicious bleeding disorder (FVII deficiency, VWD) experienced clinically significant bleeding during their ENT surgery.

We are aware of the limitations of this study, which is mainly influenced by the design. It is a retrospective study based on analysis of data available from clinical records. We cannot exclude some of the rare deficiencies like factor II, because such a detailed investigation would be beyond the scope of our study. However, according to the clinical outcome of our patients (no bleeding complications), we believe we did not miss any clinically significant disorders.

This study provides more evidence that clinically significant bleeding disorders are very rare among asymptomatic patients with abnormal screening coagulation results. When found that these are usually mild and with no need of specific perioperative treatment.

Our findings support the current Czech recommendations that thorough family and personal bleeding history can replace routine coagulation tests in preoperative screening. Coagulation testing should be performed only in patients with positive bleeding history.

Acknowledgements

AS, JB, VF performed the research. AS, PD, EP designed the study. AS, VF analysed the data. AS, JB wrote the paper. We thank Catherine McGrath for linguistic review.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Schwaab M, Hansen S, Gurr A, Dazert S. Significance of blood tests prior to adenoidectomy. *Laryngorhinootologie* 2008; **87**: 100–6.
2 Windfuhr JP, Chen YS. Hemorrhage following pediatric tonsillectomy before puberty. *Int J Pediatr Otorhinolaryngol* 2001; **58**: 197–204.
3 Windfuhr JP, Chen YS. Post-tonsillectomy and -adenoidectomy hemorrhage in nonselected patients. *Ann Otol Rhinol Laryngol* 2003; **112**: 63–70.
4 Školoudík L, Dufek Z, Vokurka J, Čelakovský P. Krvácení po tonzilektomii. *Otorinolaryng a Foniat* 2005; **54**: 42–6. ISSN: 1210-7867.
5 Licameli GR, Jones DT, Santosuosso J, Lapp C, Brugnara C, Kenna MA. Use of a preoperative bleeding questionnaire in pediatric patients who undergo adenotonsillectomy. *Otolaryngol Head Neck Surg* 2008; **139**: 546–50.
6 Monagle P, Barnes C, Ignjatovic V *et al.* Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost* 2006; **95**: 362–72.
7 Kitszel A, Poznańska M, Krawczuk-Rybak M. Analysis of an abnormal coagulation profile in

children qualified for adenoidectomy/tonsilectomy. *Otolaryngol Pol* 2007; **61**: 158–61.

8 Kang J, Brodsky L, Danziger I, Volk M, Stanievich J. Coagulation profile as a predictor for post-tonsillectomy and adenoidectomy (T + A) hemorrhage. *Int J Pediatr Otorhinolaryngol* 1994; **28**: 157–65.

9 Frauenknecht K, Lackner K, von Landenberg P. Antiphospholipid antibodies in pediatric patients with prolonged activated partial thromboplastin time during infection. *Immunobiology* 2005; **210**: 799–805.

10 Shaw PH, Reynolds S, Gunawardena S, Krishnamurti L, Ritchey AK. The prevalence of bleeding disorders among healthy pediatric patients with abnormal preprocedural coagulation studies. *J Pediatr Hematol Oncol* 2008; **30**: 135–41.

11 Bolton-Maggs PH, Perry DJ, Chalmers EA *et al.* The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004; **10**(5): 593–628.