Blood Cells, Molecules and Diseases xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

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

Health-related quality of life in children, adolescents and adults with hereditary and acquired bleeding disorders

Ulrike Nowak-Göttl, MD [a,*,1], Hartmut Clausnizer [a,1], Dorothee Kowalski, MD [a,1], Verena Limperger, MD [a,1,2], Anne Krümpel, MD [b], Maria Shneyder, MD [a,2], Sarah Reinke [a], Angela Rocke, MD [a,1,2], David Juhl, MD [c,2], Dagmar Steppat, MD [c,1], Manuela Krause, MD [d]

[a] Department of Clinical Chemistry, University Hospital Schleswig Holstein, Kiel, Lübeck, Germany
[b] Univ. Childrens' Hospital, Department of Pediatric Oncology and Hematology, Münster, Germany
[c] Center of Blood Transfusion, University Hospital Schleswig Holstein, Germany
[d] DKD HELIOS Klinik Wiesbaden GmbH, Wiesbaden, Germany

ARTICLE INFO

Article history:
Submitted 6 September 2016
Available online xxxx

Keywords:
Hereditary-acquired bleeding disorder
DVT
Quality of life
Children
Adults

ABSTRACT

Background: To better understand self-reported health-related quality-of-life (HrQoL) in children and adults with chronic hemostatic conditions compared with healthy controls.
Methods/patients/results: Group 1 consisted of 74 children/adolescents aged 8–18 years with hereditary bleeding disorders (H-BD), 12 siblings and 34 peers. Group 2 consisted of 82 adult patients with hereditary/acquired bleeding disorders (H/A-BD), and group 3 of 198 patients with deep venous thrombosis (DVT) on anticoagulant therapy. Adult patients were compared to 1011 healthy blood donors. HrQoL was assessed with a 'revised KINDer Lebensqualitaetsfragebogen' (KINDL-R)-questionnaire adapted to adolescents and adults. No differences were found in multivariate analyses of self-reported HrQoL in children with H-BD. In contrast, apart from family and school-/work-related wellbeing in female patients with DVT the adult patients showed significantly lower HrQoL sub-dimensions compared to heathy control subjects. Furthermore, adults with H/A-BD disorders reported better friend-related HrQoL compared to patients with DVT, mainly due to a decreased HrQoL subscale in women on anticoagulation.
Conclusion: In children with H-BD, HrQoL was comparable to siblings and peers. In adults with H/A-BD HrQoL was comparable to patients with DVT while healthy blood donors showed better HrQoL. The friend-related HrQoL subscale was significantly reduced in female compared to male patients.

1. Introduction

Hereditary bleeding disorders (H-BD) encompass a heterogeneous group of diseases with the most frequent clinical entities being von Willebrand disease (vWD) and hemophilia A (HA). In contrast acquired bleeding disorders (A-BD) are based on various underlying chronical medical diseases, the administration of antiplatelet agents or antithrombotic drugs. The incidence of H-BD is overall low but the individual burden of disease remains high despite encouraging advances in secondary prevention including prophylactic factor replacement and enhanced treatment options such as optimized joint disease prevention and improved inhibitor management in children as well as in adults [1–8]. When patients with HA receive optimal medical care and when they are not affected by blood-borne viruses (such as HIV or HCV) they may face a life expectancy similar to that of the general population [9,10]. It remains unclear however, whether quantitative gains in terms of life expectancy are accompanied by qualitative gains in self-reported health-related quality-of-life (HrQoL) and whether these gains are apparent over the life circle, i.e. from pediatric patients to elderly adults. Recent studies in children and adolescents with HA and other H-BD HrQoL reported comparable to or even better than population norms [11–14]. In adolescents and young adults however, Alpkilic et al. [15] compared a group of 71 patients with HA, 14–34 year old, matched for age and gender to healthy controls, and found in five out of eight domains of the SF-36 significantly higher scores in healthy controls compared to the patient group.

To the best of our knowledge few studies have investigated HrQoL in pediatric and adult patients with H/A-BD in comparison with their siblings or with healthy individuals deriving from their social or community based environment.

* Corresponding author at: University of Schleswig-Holstein, Institute for Clinical Chemistry, Arnold-Heller-Straße 3, 24105 Kiel, Germany.
E-mail address: leagottl@uksh.de (U. Nowak-Göttl).
[1] Kiel.
[2] Lübeck.

http://dx.doi.org/10.1016/j.bcmd.2016.11.010
1079-9796/

Table 1
Basic socio-demographic characteristics of all adult study participants with complete adapted KINDL-R questionnaires, n = 1247.

Variable	Patients (n = 236)	Blood donors (n = 1011)	*p*-Value
Female gender (%)	59.3	47.0	<0.001
Age in years, mean ± SD and (range)	51.2 ± 18.4	37.5 ± 14.2	<0.001
Marital status (%)			
Married/with partner	61.2	35.9	
Married, living separated	1.7	1.9	
Unmarried	24.5	55.3	
Divorced	7.0	6.3	
Widowed	5.7	0.6	<0.001
Household size (%)			
1 person	19.6	22.1	
2 persons	49.1	40.7	0.064
>3 persons	31.3	37.2	

KINDL-R = revised KINDer Lebensqualitaetsfragebogen; does not sum up to 100% due to rounding errors.

Therefore the aim of the current investigation was to compare self-reported measures of HrQoL in groups of children and adults with chronic medical conditions leading to bleeding disorders either via hereditary deficiency states or because of A-BD compared to their siblings and to healthy population based controls. Data from own investigations in children with H-BD allowed us to repeat these comparisons between adult patients [16].

Data from an own investigation in children H-BD allowed to repeat these comparisons between adult patients [16].

2. Patients, materials, and methods

2.1. Ethics

The present study was performed in accordance with the ethical standards in the updated version of the 1964 Declaration of Helsinki and was approved by the medical ethics committee of the University of Muenster, Germany. Patients, parents/proxies and healthy control subjects gave their written informed consent prior study entry.

2.2. Inclusion criteria

Pediatric and adult patients with H/A-BD and DVT, aged 8 to 77 years, admitted to three specialized treatment centers in Germany. Patients were recruited during their routine outpatient's visits in Muenster, Lübeck, Kiel and Wiesbaden.

2.3. Exclusion criteria

Patients aged <8 years at the time of completion of the questionnaire, non-German speaking families, patients who were unable to understand and answer the questions due to severe disabilities, and families without written informed consent.

2.4. Study population

Study participants were enrolled between August 2008 and April 2016. Apart from the 74 pediatric patient-sibling/healthy control peers with H-BD recently described in detail [16] the adult H/A-BD cohorts included 82 patients with HA (14), HB (n = 4), vWD (21), factor (F) V (n = 2), VII (n = 5), XIII (n = 2) deficiencies, platelet function disorders (n = 6), acquired inhibitors against F VIII (n = 2) and bleeding due to hepatic dysfunction/reduced coagulation factor production (n = 2), protein Z deficiency (n = 2), hyperfibrinolysis (n = 4). Overall 18 out of 82 patients with H/A-BD showed mucosal bleeding due to antiplatelet therapy. The 198 patients with DVT who were willing to participate in this cross-sectional investigation received oral anticoagulation with either Rivaroxaban or vitamin K-antagonists. The clinical bleeding tendency of this group is described in detail elsewhere [17]. Additionally, data were available from 1011 healthy unrelated blood donors recruited from the same catchment areas as the patients.

Patients completed the questionnaires during a routine ambulatory follow-up visit i) by themselves, or ii) if unable to read and write with the help of a study nurse but not with the help of their parents or other accompanying persons.

2.5. HrQoL outcome

The 'revised KINDer Lebensqualitaetsfragebogen' (KINDL-R) questionnaire [16,18] is a generic instrument to assess HrQoL and was originally developed in German language (www.kindl.org). This 24-item self-administered or proxy-report questionnaire generates a total score (overall well-being) as well as scores for 6 subscales (physical well-being, psychological well-being, self-worth, family-related well-being, friend-related well-being, and school-/work-related well-being). Scores range from 0 to 100, with higher values indicating better HrQoL. In order to be able to repeatedly assess QoL in pediatric and adolescent patients with H/A-BD until their adulthood ("transitional care" [19]), we adapted the KINDL-R instrument—originally validated for the use in healthy children and pediatric patients aged 4 to 16 years—for adolescents >16 years and adults (validation against SF 36/EQ-5D-SL: unpublished data not shown). As recently reported in other chronic conditions, this allows the comparison of HrQoL in patients with chronic coagulation diseases over different age groups both in cross sectional as well as in longitudinal study designs [20–22].

2.6. Statistics

Metric variables are presented as mean ± standard deviation. Multivariate comparisons of HrQoL between patients, siblings and peers and controls were calculated using one-way ANOVA. In case of differences between groups pairwise single comparison were done by Student's *t*-test for independent subgroups. To account for multiple testing (overall

Table 2
Differences in self-reported HrQoL between patients with hereditary bleeding disorders and their siblings respectively peers, measured with the KINDL-questionnaire (overall well-being and all sub-scales); results of hierarchical linear regression models with random intercepts for treatment center (from reference [16]).

KINDL-R-scores	Patients compared with healthy siblings			Patients compared with healthy peers		
	ß$_x$	95%-CI	*p*	ß$_x$	95%-CI	*p*
Overall well-being	−0.3	(−7.3 to 6.6)	0.92	−0.5	(−4.5 to 3.5)	0.81
Physical well-being	−0.1	(−11.9 to 11.8)	0.99	3.3	(−3.8 to 10.4)	0.36
Emotional well-being	0.9	(−7.3 to 9.0)	0.21	0.5	(−4.6 to 5.6)	0.84
Self-worth	−2.4	(−16.4 to 11.6)	0.74	−6.6	(−14.4 to 1.1)	0.09
Family-related well-being	0.7	(−9.0 to 10.4)	0.88	1.7	(−3.9 to 7.3)	0.54
Friend-related well-being	0.4	(−11.4 to 12.2)	0.38	0.3	(−6.8 to 7.4)	0.93
School-related well-being	−1.5	(−13.4 to 10.4)	0.80	0.2	(−6.7 to 7.1)	0.95

KINDL-R = revised KINDer Lebensqualitätsfragebogen; models adjusted for age, gender, number of siblings and school education.

Please cite this article as: U. Nowak-Göttl, et al., Blood Cells Mol. Diseases (2016), http://dx.doi.org/10.1016/j.bcmd.2016.11.010