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Health-Related Quality of Life in Egyptian Children and Adolescents with Hemophilia A

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Quality of life (QoL) in hemophilia is an important area in hemophilia outcome assessment. The Haemo-QoL instrument is a set of questionnaires to measure QoL in those children. The objectives of this study was to assess health-related quality of life (HRQoL) in Egyptian hemophilic children and adolescents using an Arabic version of the Haemo-QoL questionnaire. Sixty patients with severe hemophilia A were recruited from 2 hemophilia treating centers in Egypt. Assessment of quality of life was done using the Haemo-QoL questionnaire. The scores of HRQoL were found to be for all dimensions widely above 50. It was highly significant in the 3 dimensions (physical health–family–treatment) in different age groups, but it was impaired in the dimension of "physical health" for 2 groups, and in the dimension of "family" for the oldest group, whereas the youngest group had highly impaired scores concerning the "treatment." The HRQoL in this study was not affected by the presence of factor VIII (FVIII) inhibitors. The QoL in hemophilic patients in Egypt needs strenuous efforts from hemophilia care–integrated teams of pediatric hematologists and psychiatrists in order to properly assess and improve QoL.

Keywords FVIII inhibitors, Haemo-QoL, hemophilia

Hemophilia A is an X chromosome–linked recessive hemorrhagic disorder that is characterized by impaired factor VIII (FVIII) production [1]. The worldwide incidence of hemophilia A is approximately 1 case per 5000 male individuals, with approximately one third of affected individuals not having a family history. The prevalence of hemophilia A varies with the reporting country, with a range of 5.4 to 14.5 cases per 100,000 male individuals [2].

Quality of life (QoL) of children with chronic conditions, such as hemophilia, has received increasing attention in recent years. It can be defined—in analogy to the World Health Organization (WHO) definition of health—as patient-perceived well-being and function in terms of physical, emotional, mental, social, and behavioral life domains [3, 4].

Before the widespread use of replacement therapy, patients with severe hemophilia had a shortened life span and diminished quality of life that was greatly affected by hemophilic arthropathy [2]. In pediatric hemophilia, research has suggested the

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beneficial quality of life outcomes with prophylaxis and stressed the role of the family for patients' well-being and function. Quality of life research is a relevant area for hemophilia research, which should be pursued further [5]. Four disease-specific measures of health-related quality of life have been developed for hemophilia patients. Two of these were developed for children (the Haemo-QoL and the CHO-KLAT), and 2 for adults (the Haemo-A-QoL and the Hemolatin-QoL) [6, 7].

The Haemo-QoL questionnaire is a quality of life assessment instrument for children with hemophilia; it was developed and tested for psychometric properties in hemophilic children and their parents by the Haemo-QoL Group [8, 9]. The Haemo-QoL is a self-reported questionnaire for children in the age ranges to 4–7 (I: 21 items), 8–12 (II: 64 items), and 13–16 (III: 75 items) years as well as for parent rating containing 9 to 11 subscales (depending on age-group versions) [9].

This study aimed to assess the feasibility of using a translated Arabic version of the Haemo-QoL questionnaire for the assessment of the health-related quality of life in Egyptian children and adolescents with moderate and severe hemophilia. The impact of the factor VIII inhibitor status on QoL was also studied

PATIENTS AND METHODS

Patients

This study was conducted at 2 major centers treating hemophilia in Cairo, Egypt: the Pediatric Hematology Unit, Children's Hospital, Ain Shams University, and the Therapeutic Unit of Hemophilic patients at Vacsera in Cairo. All moderate and severe hemophilia A patients attending both centers in the period from December 31st, 2007, to March 31st, 2008, were included in the study.

They were 60 male children and adolescents with hemophilia A age ranging from 4 to 16 years old. Diagnosis of hemophilia A was based on factor VIII assay in addition to assessment of platelet functions and level of von Willebrand factor (vWF) antigen, which were normal except for low level of factor VIII.

Methods

The Haemo-QoL self-reported disease-specific questionnaire for the quality of life in hemophilia, as supplied by Von Mackensen et al in 2004 [9], was translated into the Arabic language, including the questionnaire for different age groups (child and parent versions). The translation was undertaken by a team of 2 professional pediatric hematologists, a psychologist, and a professional English language expert. Backward and forward translations were carried out to ensure efficient translation. An interview version for smaller children (age group I: 4–7 years) was available with 21 items pertaining to 8 dimensions ("physical health," "feelings," "view," "family," "friends," "others," "sport and school/kindergarten," "treatment"); for the schoolchildren aged 8–12 years (age group II), the self-administered questionnaire consisted of 2 additional domains ("perceived support," "dealing") with overall 64 items; and for adolescents (age group III: 13–16 years), it was expanded with another further additional domain ("future") and consisted of 75 items as well as a questionnaire for parent rating containing 9 to 11 subscales (depending on age-group versions). Because there were different numbers of items between the dimensions and in the different age groups, the values were transformed to a scale from 0 to 100 to allow comparison between the answer patterns across the age groups and to compare the impairments in the different dimensions. High values indicate high impairments in HRQoL. A pilot study was initially performed to verify the terminology and the standardization of the expressions used; and the feasibility of some of the

questions included. After validation of the questionnaire, quality of life was finally assessed and the results were included in the final study results.

The pilot and the final studies were conducted after approval of the Ethical Committee of Department of Pediatrics, Faculty of Medicine, Ain Shams University, and all the included hemophilia A patients or their caregivers had signed ethical consent for the study, before they were subjected to the following:

- Thorough history and clinical examination, especially concerning the frequency of bleeding attacks, sites, severity, and the frequency of administration of factor VIII preparations and the types used. The presence of hemarthrosis, muscle hematoma, target joint, and limitation of the movement of any affected joint was particularly assessed during examination.
- Assessment of the quality of life using the translated Arabic version of the Haemo-QoL questionnaire. In addition, the distribution of quality of life scores, sociodemographic, psychosocial, and medical determinants of quality of life were examined.
- Evaluation of Factor VIII–inhibitory activity by a quantitative Bethesda method [10].

Statistical Analysis

Data were collected; coded, tabulated, then analyzed using SPSS program version 10 computer software using multivariate analysis. Comparisons of numerical variables were performed with unpaired Student *t* test if its assumption was fulfilled; otherwise, Kruskal-Wallis test was used instead. Comparisons of categorical variables were performed by chi-square test. Any difference with P value $<.05$ was considered statistically significant.

RESULTS

The results of the present study are shown in Figure 1, and Tables 1 to 3.

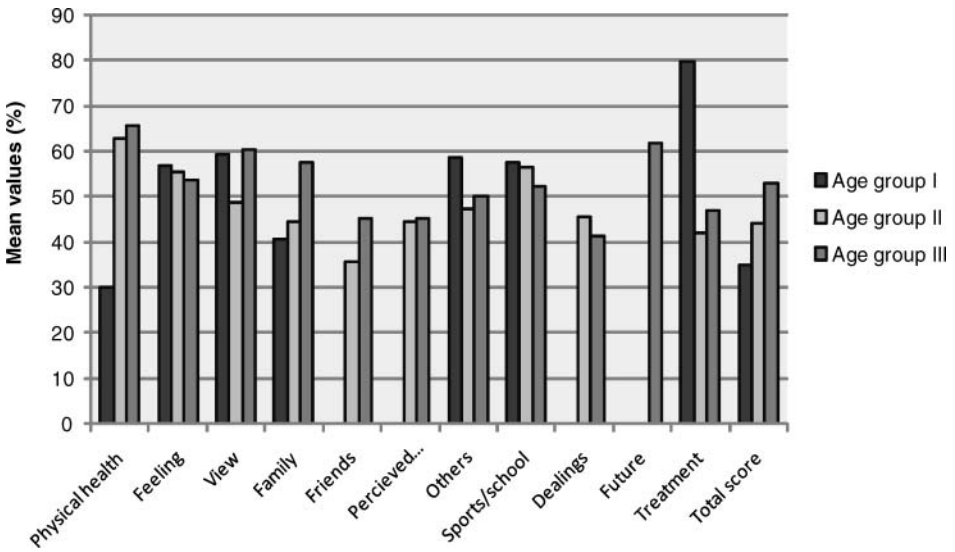

FIGURE 1 Mean values of the Haemo-QoL dimensions score in the 3 age groups. The different dimensions of Haemo-QoL questionnaire within the studied 3 age groups and the mean values were for all dimensions widely above 50, reflecting that the HRQoL was not satisfactory in our study (as high score demonstrates bad HRQoL).

TABLE 1 Clinical Data of Different Age Groups of Hemophilia Patients

Characteristics	Age groups			
	I ($N = 25$) 4–7 years	II ($N = 19$) 8–12 years	III ($N = 16$) 13–16 years	P value
Treatment regimen				
Secondary prophylaxis	32%	31.6%	31.2%	.798
On demand	68%	68.4%	68.8%	
Circumcision bleeding	68%	78.9%	100%	.044*
Epistaxis	24%	63.2%	31.3%	.024*
Gum bleeding	52%	84.2%	68.7%	.079
Bleeding following dental procedure	12%	78.9%	37.5%	>.000**
Previous surgery	4%	31.6%	37.5%	.018*
Intracranial hemorrhage	0.00%	0.00%	6.2%	.247
Hemarthrosis	60%	57.9%	56.3%	.971
Muscle hematoma	36%	63.2%	81.3%	.013*
Target joint	72%	78.9%	100%	.073
Limited joint movement	44%	52.6%	93.8%	.005**

Using Student t test: *significant; **highly significant.

In group III, there was significantly higher frequency of bleeding during circumcision as well as limited joint movement and muscle hematoma. Previous surgery included mainly minor surgeries as tonsillectomy and appendectomy. One third of the patients were on secondary prophylactic treatment but most probably on no constant protocol depending on factor availability (Table 1).

Concerning mucosal bleeding, 39.5% of patients had recurrent epistaxis, significantly more frequently in age group II (63.2%) ($P = .024$); 68.3% had recurrent gum bleeding more frequently in age group II, all the episodes of epistaxis and gum bleeding were preceded by trivial trauma, and 42.8% of the patients reported to have bleeding with recurrent dental procedures, also significantly higher in age group II (78.9%) compared to other age groups ($P > .000$) (Table 1).

Among hemophilia patients, at least 1 target joint was present in 83.3%: 72% in young age group up to 100% in older age group (Table 1).

Regarding movement of the joint, 63.5% of patients had limitation of at least 1 joint movement, which was significantly higher in the older age (group III) compared to other age groups ($P = .005$) (Table 1).

In the current study, only 31.6% of the patients were on prophylactic treatment, receiving it mostly every week but not on constant protocol, just depending on FVIII availability, whereas the majority of the children, 68.4%, receive the treatment on demand, and no differences were found between the 3 age groups.

Only 3 out of 60 patients (5%) were found to be positive for FVIII inhibitors by quantitative Bethesda method. All had severe hemophilia. They were aged 8, 12, and 7 years, respectively. Their inhibitor levels were 16, 13, and 9 BU, respectively.

In both moderate and severe hemophilics, the HRQoL was found to be for most dimensions above 50, which is not satisfactory (as high scores demonstrate bad HRQoL). Regarding the 3 hemophilic patients positive for FVIII inhibitors, the HRQoL was satisfactory in 1 patient, and impaired in 2 patients.

The HRQoL for the dimension "physical health" was statistically significantly higher in severe hemophiliacs compared to moderate hemophiliacs. There was significantly higher scores in the older age group in the bleeding attack scores "suffering," "severity," "strange feeling of the joints before," and "quiet in bed during attack" in the last 4 weeks prior to evaluation; reflecting more disease burden in the older age group (Tables 2 and 3, Figure 1).

TABLE 2 The Scores of the Haemo-QoL Questionnaire in the 3 Age Groups

Dimensions	Age group	Range	Mean ± SD	*P* value Kruskal-Wallis test
Physical health	I	17–50	30.0 ± 11.3	>.000*
	II	31–86	62.8 ± 19.0	
	III	49–89	65.9 ± 12.5	
	Total	17–89	49.9 ± 22.2	
Feeling	I	33–100	56.8 ± 23.4	.989
	II	29–89	55.3 ± 18.5	
	III	23–90	53.6 ± 17.7	
	Total	23–100	55.5 ± 20.2	
View	I	33–100	59.3 ± 17.4	.151
	II	18–82	48.8 ± 17.6	
	III	24–94	60.4 ± 18.9	
	Total	18–100	56.3 ± 18.3	
Family	I	25–58	40.6 ± 8.1	>.000*
	II	24–64	44.4 ± 13.1	
	III	38–78	57.6 ± 10.4	
	Total	24–78	46.4 ± 12.5	
Friends	I	17–50	30.0 ± 12.3	.079
	II	25–55	35.8 ± 9.3	
	III	20–65	45.0 ± 16.1	
	Total	0–65	37.0 ± 12.5	
Support	I	—	—	.777
	II	20–75	44.5 ± 14.8	
	III	20–65	45.0 ± 16.6	
	Total	0–75	44.7 ± 15.7	
Other people	I	33–100	58.7 ± 24.1	.273
	II	23–77	47.4 ± 17.6	
	III	20–80	50.2 ± 19.1	
	Total	20–100	52.8 ± 21.2	
Sports & school	I	0–100	57.7 ± 34.9	.377
	II	0–88	56.3 ± 23.9	
	III	0–84	52.2 ± 28.7	
	Total	0–100	55.8 ± 29.8	
Dealing	I	—	—	.149
	II	34–54	45.7 ± 5.9	
	III	23–54	41.3 ± 9.2	
	Total	0–54	43.5 ± 7.5	
Treatment	I	33–100	79.9 ± 20.9	>.000*
	II	23–66	42.1 ± 10.7	
	III	20–68	47.2 ± 15.4	
	Total	20–100	59.2 ± 24.3	
Total score	I	20–80	61.6 ± 17.2	.735
	II	20–80	58.0 ± 18.7	
	III	40–100	63.8 ± 18.2	
	Total	20–100	61.0 ± 17.8	

Note. Total mean values and standard deviation for the 3 dimensions (perceived support − dealing) are for age groups II and III only.

*Highly significant.

DISCUSSION

Our study showed that the episode of first bleeding in 82% of the patients was during circumcision, and it was statistically highly significant in the age group III (100%) compared to other age groups ($P = .04$), possibly reflecting improved awareness for screening children for bleeding tendency prior to circumcision in the recent years.

In this study, patients suffered from hemarthrosis, with no differences found between the 3 age groups; but muscle hematoma was significantly higher in age group

TABLE 3 Comparison Between Severe and Moderate Hemophiliacs as Regards Dimensions of Haemo-QoL Questionnaire

	Mean Haemo-QoL score	
Haemo-QoL dimensions	Severe hemophiliacs ($N = 33$)	Moderate hemophiliacs ($N = 27$)
Physical health	87.9*	53.9
Feeling	68.1	62.3
View	71.4	67.8
Family	48.7	49.3
Friends	45.3	42.1
Support	48.1	50.2
Other people	66.2	52.3
Sports & school	76.3	81.6
Dealing	53.4	51.9
Treatment	58.6	62.6
Total score	62.8	57.6

*Significant by t test ($P < .01$).

III compared to other age groups ($P = .013$). von Mackensen et al [9] reported that only few children had joint swelling and fewer children had muscle atrophy, and a loss of motion being more frequent in older children (age group III).

Although at least 1 target joint was present in the majority of the young age group and in all patients of the old age group, Bullinger and von Mackensen [11] reported that only half of the children have a target joint: 61% of the old age group in comparison to 38.9% in young age group.

In our study, more than half of patients had limitation of at least 1 joint movement which was significantly higher in the older age (group III) compared to other age groups ($P = .005$), but Gringeri et al [12] reported that a approximately only one tenth of European patients were suffering from functional joint impairments, with a significant increase in the age group III ($P < .018$).

In the current study, nearly one third of the patients were on prophylactic treatment, receiving it mostly every week but not on constant protocol, just depending on FVIII availability, whereas the majority of the children were receiving the treatment on demand, and no differences were found between the 3 age groups. This is in contrary to Gringeri et al. [12] who reported that about two thirds of patients were on prophylactic treatment, receiving it 3 times a week or more, whereas the remaining third were receiving the treatment on demand.

In the present study, the development of inhibitors in Egyptian children and adolescents with hemophilia A was low (5%), similar to the previous findings of El Alfy et al. [13] who reported 10% prevalence of inhibitors in Egyptian young hemophilics. Ettingshausen and Kreuz [14] demonstrated inhibitor development in 21% of severe hemophilics treated with plasma-derived factor FVIII compared to 36% in patients receiving recombinant FVIII (rFVIII). The low prevalence of inhibitors in our population is possibly related to the prevalent use of plasma-derived cryoprecipitate and intermediate purity factor VIII products as main factor VIII replacement therapy [15]. Also, development of inhibitors is multifactorial and has relation with mutation type and immune status and there may be a racial or human leukocyte antigen (HLA)-related cause for this lower incidence of inhibitors among Egyptian hemophilics [16]. Various incidences of inhibitors have been described in different populations [17–19].

The term "health-related quality of life" refers to the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions (referred to collectively as "perceptions of health") [20].

The measurement of any psychological concept such as QoL is inherently different from measuring a physical concept such as height, and it may therefore be inevitable that we must live with some limitation in any measure [5, 21]. Comparison between different age groups revealed main differences in 3 dimensions (physical health–family–treatment). The dimension of "physical health" was poor in groups II and III; the dimension of "family" was impaired for group III, whereas group I was highly impaired concerning the "treatment" dimension. On the other hand, younger children (group I) showed a higher HRQoL, revealed particularly by the dimension "physical health," and for age groups II and III, higher HRQoL was revealed particularly by the social dimensions such as "perceived support" and "friends" and also in the dimension of "dealing," which concerns personal adaptation to the disease. The 3 age groups were impaired in the dimensions of "feeling," "sports/school," and "view of themselves," and also in the dimension of interaction with "others." Age group III was found to be highly impaired in the dimension of their look to "future."

For the same 3 age groups, Gringeri et al. [12] reported that HRQoL was satisfactory, with scores widely below 50 (in a range from 0 to 100). Age group I was impaired in the dimension "family," which can be related to over protection of the parents, and the same age group was only partially impaired in the interaction with "others," or concerning their "treatment." Children in age groups II and III were perceived not to receive sufficient support from others reported in the dimensions "perceived support" and were impaired in the interaction with their "friends." In addition, older children (group III) had problems in dealing with their hemophilia as reported in the dimension "dealing."

Comparing moderate and severe hemophilics in the different parameters of the Haemo-QoL. The significant difference in HRQoL between severe hemophilics and mild/moderate hemophilics was similarly reported by Miners et al. [22] using the EuroQoL (EQ-5D QoL) utility score.

In conclusion, the quality of life in hemophilic children and adolescents in Egypt needs strenuous efforts for improvement in all dimensions. This needs the efforts of hemophilia care integrated team of pediatric hematologist and psychiatrist to properly assess and improve QoL. The use of the Haemo-QoL questionnaire is easy, applicable, and valuable for the assessment of health-related quality of life in children and adolescents with hemophilia.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Casaña P, Cabrera N, Cid AR, et al. Severe and moderate hemophilia A: identification of 38 new genetic alterations. *Haematologica.* 2008;93:1091–1094.

[2] Konkle BA, Kessler C, Aledort L,et al. Emerging clinical concerns in the ageing haemophilia patient. *Haemophilia*. 2009;15:1197–1209.

[3] Bullinger M. Quality of life – definition, conceptualization and implications—a methodologist's view. *Theor Surg.* 1991;6:143–149.

[4] Bullinger M, von Mackensen S. Psycho-social determinants of quality of life in children and adolescents with haemophilia—a cross-cultural approach. *Clin Psychol Psychother.* 2008;15:164–172.

[5] Pollak E, Mu Hlan H, Von Mackensen S,et al. The Haemo-QoL Index: developing a short measure for health-related quality of life assessment in children and adolescents with haemophilia. *Haemophilia.* 2006;12:384–392

[6] Remor E, Young NL, von Mackensen S, et al. Disease-specific quality-of-life measurement tools for haemophilia patients. *Haemophilia.* 2004;10:30–34.

[7] Young NL, Bradley CS, Wakefield CD, et al. How well does the Canadian haemophilia Outcomes-Kids-Life Assessment Tool (CHO-KLAT) measure the quality of life of boys with haemophilia? *Pediatr Blood Cancer*. 2006;47:305–311.
[8] Bullinger M, von Mackensen S, Fischer K, et al. Pilot testing of the Haemo-QoL quality of life questionnaire for haemophiliac children in six European countries. *Haemophilia*. 2002;8:47–54.
[9] Von Mackensen S, Bullinger M, the Haemo-QoL Group. Development and testing of an instrument to assess the Quality of Life of Children with Hemophilia in Europe (Haemo-QoL). *Hemophilia*. 2004;10:17–25.
[10] Dacie JV and Lewis SM. *Dacie and Lewis Practical Hematology*. London: Churchill Livingstone; 2001.
[11] Bullinger M, Von Mackensen S. Quality of life assessment in hemophilia. *Hemophilia*. 2004;10:9–16.
[12] Gringeri A, von Mackensen S, Auerswald G, et al. Health status and health-related quality of life of children with haemophilia from six West European countries. *Haemophilia*. 2004;10:26–33.
[13] El Alfy MS, Tantawy AAG, Ahmd MH,et al. Frequency of inhibitor development in severe haemophilia A children treated with cryoprecipitate and low-dose immune tolerance induction. *Haemophilia*. 2000;6:635–638.
[14] Ettingshausen CE, Kreuz W. Recombinant versus plasma-derived products, especially those with intact VWF, regarding inhibitor development. *Haemophilia*. 2006;12:102–106.
[15] Hay CR. The epidemiology of factor VIII inhibitors. *Haemophilia*. 2006;12:23–28.
[16] Gouw SC, Van Den Berg MH. The multifactorial etiology of inhibitor development in hemophilia: genetics and environment. *Semin Thromb Hemost*. 2009;35:723–34.
[17] Kitchen S, Jennings I, Preston FE, et al. Interlaboratory variation in factor VIII:C inhibitor assay results is sufficient to influence patient management: data from the UK national quality external assessment scheme for blood coagulation. *Semin Thromb Hemost*. 2009;35:778–785.
[18] Oldenburg J, Pavlova A. Genetic risk factors for inhibitors to factors VIII and IX. *Haemophilia*. 2006;12:15–22.
[19] Wang XF, Zhao YQ, Yang RC, et al. The prevalence of factor VIII inhibitors and genetic aspects of inhibitor development in Chinese patients with haemophilia A. *Haemophilia*. 2010;16:632–639.
[20] Manco-Johnson M, Morrissey-harding G, Edelman-Lewis B, et al. Development and validation of a measure of disease-specific quality of life in young children with hemophilia. *Hemophilia*. 2004;10:34–41.
[21] Bergner M. Quality of life, health status, and clinical research. *Med Care*. 1989;27:S148–S156.
[22] Miners AH, Sabin CA, Tolley KH, et al. Assessing health-related quality-of-life in individuals with haemophilia. *Haemophilia*. 1999;5:378–385.