

The impact of replacement therapy on dental health in haemophilia

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Abstract: *Aim.* To evaluate the dental health status and its relationship with the replacement therapy in persons with haemophilia (PwH).

Material and methods. In this descriptive non-interventional cross-sectional study we included a number of 47 patients, divided in 2 distinct age groups: 12 patients under- and 35 above 18 years of age. Demographic information, laboratory findings and dental health status were recorded in a standard form. Dental health was evaluated by means of the decay –missing- filling teeth (DMFT) index and plaque index (PLI); these parameters were correlated with the quality of replacement therapy and compared to a matched control group.

Results and discussions. The image offered by our descriptive cross-sectional study revealed a dental status in hemophilic children comparable with that of the children from the matched control group. On the contrary, adult PwH have a dismal DMFT and PLI indexes; they are in significant correlations with the quantity and frequency of replaced coagulation factors.

Conclusions. The findings highlight the need of comprehensive oral examinations including preventive dental treatment and follow-up care in the PwH connected to an adequate replacement therapy.

Key Words: pharmacologic replacement therapy, coagulation factor VIII and IX concentrates, haemophilia, dental health, DMFT index, PLI index.

INTRODUCTION

Haemophilia is an inherited disorder, result of genetic alterations that cause deficiencies in clotting

factors VIII (haemophilia A) or IX (haemophilia B), hindering the process of hemostasis and predisposing the persons with haemophilia (PwH) to spontaneous or posttraumatic bleedings, therefore requiring a life-

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long expensive replacement therapy with clotting factor concentrates. It is defined by a reduced factor VIII (F VIII) or factor IX (F IX) activity under 40% of normal level, from the point of severity being identified: severe forms with < 1 %, moderate with 1-5% and mild with 5-40% factor activity level, respectively. Prophylaxis is the norm of all severe/moderate deficiency statuses; consequently the only cost-efficient treatment in these diseases is the prophylactic replacement of the missing factor (F VIII in haemophilia A or F IX in haemophilia B), with a dosage and intervals between administrations depending on the severity of the disease and therapy regimen [6, 8].

Due to the impressive advances in medicine registered in the therapy of haemophilia and allied disorders in the last decades, the life expectancy of PwH has increased from about 19 years of age in 1930 to 71 in 2001, assuring an almost normal quality of life. But all these significantly improved results are due to a generous therapy, in the frame of a regular prophylactic treatment. Lack of medication, under-dosage and late introduction of coagulation factors have disastrous clinical consequences. They not only impact the life expectancy, but at the same time its quality. According to the fact that quality of life (QoL) is specifically related with health and disease, health-related quality of life (HRQoL), a multi-dimensional concept, is a preoccupying objective of patients and care-givers. One of the aspects of HRQoL is the oral health related to the dental status. Oral health could have a physical, but at the same time a psychological influence on the individual's life. It could generate unpleasant oral bleedings and pain, simultaneously interfering with feeding, affecting self-confidence, psychological well-being and social life.

As haemophilia is a very rare disorder, such studies usually have relatively small sizes, thus the low number of included patients and inter-individual variations might hinder statistical evaluations. Multi-center studies with high number of patients would be advisable. Unfortunately, according to our knowledge, there are only very limited number of studies dedicated to this topic in hemophilic cohorts in the world and there is not sufficient information in this context. Hence, wishing for more information in that field, we focused our attention on the oro-dental condition of our patients, considering our specific situation: in our country, haemophilia therapy started very late, after 1997, when the National Health Program for haemophilia has been countrywide introduced. But, the average consumption of FVIII was low and though with a stumbling increase along the years, it was maintained for a long time under IU/capita/year, synonymous with a very low availability of adequate therapy. Thus, until very recently, only on demand replacement was accessible, regular prophylactic therapy being started only in 2014, and short term prophylaxis in 2015-2016. In this context, we had the opportunity to analyze oral health in connection with

different treatment modalities: lack of factor concentrates, very low dosage or appropriate treatment regimen.

Even though, there are several studies which have evaluated oral health and periodontal status of PwH in different countries, the relationship between treatment and dental indices, like decay- missing -filling teeth (DMFT) or plaque index (PLI) scores showing conflicting findings among societies. Some investigations reported that the prevalence of carries were lower among children and adults with bleeding disorders, while there are also other investigations reporting similar or higher DMFT index scores (11,13). These challenging data motivated us to conduct this study.

MATERIALS AND METHODS

Study design and data collection

This descriptive non-interventional cross-sectional study was conducted on 47 PwH, all males (42 with haemophilia A, 5 with haemophilia B) referred from all over the country to our center; all patients had a severe form of disease; patients with moderate/mild form of haemophilia or the lack of ability for participating in this study were not included. A matched control group of 47 persons, with similar demographic characteristics (age, sex) and without bleeding disorders was used for interpreting the significance of findings and of potential differences. The examination and interview were performed by a dentist, each participant having an intraoral examination by using mouth mirror. The participant's age and sex have been also registered. The study protocol was approved by the Institutional Medical Ethics Committee and an informed consent was obtained by all the patients.

Physical examination scores for dental health evaluation

For examining the oral health status a DMFT and PLI index were performed. The DMFT index was obtained as the sum of decay (D), missing (M) and filling (F) teeth indexes, according to the criteria suggested by World Health Organization (WHO). In addition, for each patient we recorded some laboratory data (residual coagulation activity and inhibitors anti-Factor VIII or IX). The history of replacement therapy was recorded for the correlation with dental results [1, 10, 16].

Statistical analyses

Statistical analyses were performed for the frequency distribution of selected demographic and clinical variable using univariate assessments; Student t-tests, as appropriate were used. The analyses were performed using IBM SPSS Statistics 14 software; p values <0.05 were considered statistically significant and Pearson - r coefficient >0,4 corresponded to a reasonable degree of correlation.

RESULTS AND DISCUSSION

A total of 47 patients agreed to participate in this study; we divided them in accordance to their age in two groups: group I consisting of 12 children with age <18 years and the other group II of 35 patients with the age > 18 years. The first group had, even in lower dosage and only on demand, access to coagulation factor concentrates replacement in frame of a global usage of F VIII < 1 IU/capita /year until year 2014; afterwards these patients have been included in an optimal regular prophylactic treatment regimen. The second group didn't have during its childhood or adolescence any access to specific therapy, even after 2014 receiving only on demand therapy. For an adequate interpretation of the results 47 persons without haemophilia were included in our study, with a similar age and sex distribution as that of PwH.

The results of the performed dental evaluations in the control group are presented in the Table 1 and those of PwH in the Table 2. The image offered by our descriptive

cross-sectional study revealed a deleterious dental status in the control group, of both, children and adults; all the indexes performed are higher than those reported in the European population, fitting to the conclusions of WHO that in Eastern and Central Europe dental status remains still a public health problem [13]. Not astonishing, the situation in PwH is worse for the majority of the parameters, both in children and adults (Tables 3, 4). In hemophilic children comparable with that of the children from the matched control group (Table 3) there are significant differences regarding the D index and PLindex ($p=0.04$, $p=0.01$), proportionally with the age ($r>0.4$). Unfortunately, despite of a higher D index in haemophiliacs the F index, proving a real dental care, is significantly lower ($p=0.003$). Concerning the domain of decayed teeth in children we observed the existence of an age correlation ($r=0.47/0.81$), unfortunately with a lowering appeal for dental care in children with haemophilia, the F index (0.2 ± 0.4) being decreased compared to the children from control group (2.2 ± 2.2), with significant difference ($p=0.003$).

Table 1. Average \pm standard deviation (SD), p value in the control group, children vs. adults

	Average \pm SD		p value
	Children control group	Adults control group	
Age	9.2 \pm 3.7	38.2 \pm 8.5	<0.001
Total no of teeth	24.7 \pm 3.7	32 \pm 0	<0.001
Decayed	1.7 \pm 1.4	4.4 \pm 2.7	0.002
Missing	0	3.5 \pm 4.5	0.01
Filled	2.2 \pm 2.1	8.3 \pm 3.5	<0.001
DMFT	3.8 \pm 3.2	16.2 \pm 6.3	<0.001
Plaque	0.8 \pm 0.7	1.9 \pm 0.7	<0.001

Table 2. Average \pm standard deviation (SD), p value in Patients with Hemophilia (PwH), children vs. adults

	Average \pm SD		p value
	Children with Haemophilia	Adults with Haemophilia	
Age	9.4 \pm 3.8	34.8 \pm 9.8	<0.001
Total no of teeth	24.3 \pm 3.6	32 \pm 0	<0.001
Decayed	3.3 \pm 3.2	8.7 \pm 5.6	0.003
Missing	0	6.4 \pm 7.6	0.006
Filled	0.2 \pm 0.4	3.6 \pm 4.6	0.01
DMFT	3.5 \pm 3.5	18.7 \pm 8.3	<0.001
Plaque	1.5 \pm 0.5	2 \pm 0.9	0.07

Table 3. Average \pm standard deviation (SD), p value in children with haemophilia vs. children in the control group

	Average \pm SD		p value
	Children with Haemophilia	Children control group	
Decayed	3.3 \pm 3.2	1.7 \pm 1.4	0.04
Missing	0	0	-
Filled	0.2 \pm 0.4	2.2 \pm 2.2	0.003
DMFT	3.5 \pm 3.5	3.8 \pm 3.2	0.47
Plaque	1.5 \pm 0.5	0.8 \pm 0.7	0.01

Table 4. Average \pm standard deviation (SD), p value in adults with haemophilia vs. adults in the control group

	Average \pm SD		p value
	Adults with Haemophilia	Adults control group	
Decayed	8.7 \pm 5.6	4.4 \pm 2.8	<0.001
Missing	6.4 \pm 7.7	3.5 \pm 4.5	0.06
Filled	3.6 \pm 4.6	8.3 \pm 3.5	<0.001
DMFT	18.7 \pm 8.3	16.2 \pm 6.3	0.10
Plaque	2 \pm 0.9	1.8 \pm 0.7	0.44

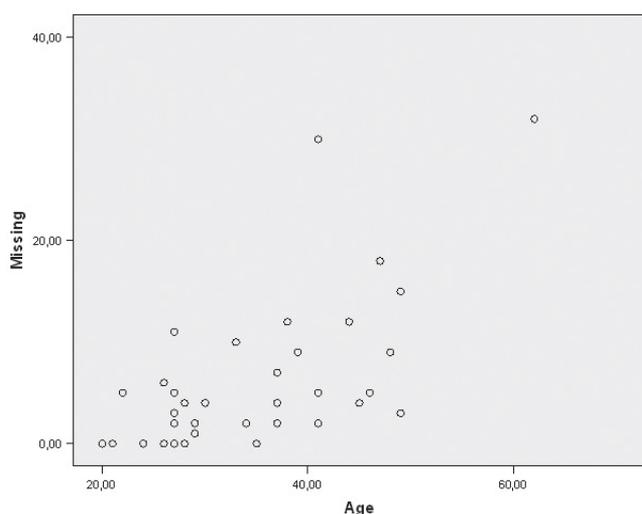
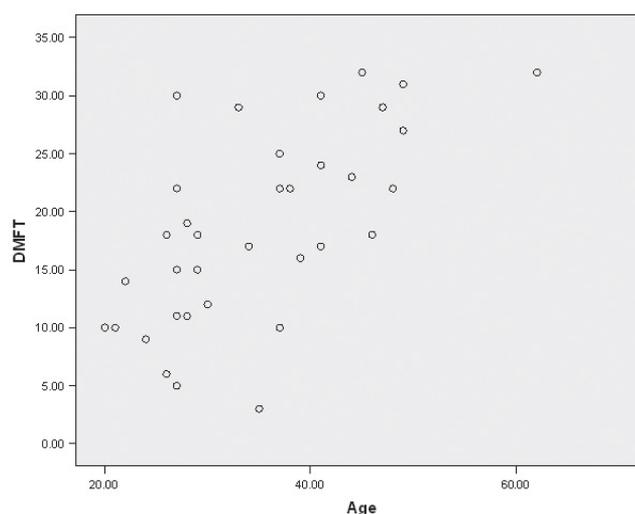
Table 5. Age correlation (r) with Decayed, Missing, Filled, DMFT, Plaque indexes

	Age correlation (r) with				
	Decayed	Missing	Filled	DMFT	Plaque
Children with Haemophilia	0.47	-	-0.02	0.43	0.41
Children control group	0.81	-	0.47	0.67	0.48
Adults with Haemophilia	-0.08	0.63	0.21	0.65	0.19
Adults control group	0.05	0.33	0.06	0.29	0.27

Concerning the dental health of the adult non-haemophiliacs, it can be considered very bad: all the indexes D, M and F are high. In comparison, as expected, the dental profile of haemophiliacs is exceptionally dismal. Only 7/35 have a complete denture, 7/35 missing 25% and 3/35 missing more than 50% of their teeth. All the indexes are high, in correlation only in the missing field with the age ($r=0.63$). The D index, M index, F index and DMFT index are all high, significantly higher in the field of D and F than those belonging to the control subjects. It is worth to be mentioned that the F index is significantly higher in the control group than in PwH, proving the lack of preoccupation for dental care in haemophiliacs. All these results, with the exception of Missing teeth and DMFT index ($r=0.63/r=0.65$), seem not to be in strong correlation with the age (Figs 1, 2); that means that even at young and very young age, PwH have a poor dental condition.

Since 1938 the DMF index has become a relevant tool for monitoring dental health caries. The prevalence according to the WHO is dependent on dental care, access to fluoride products, dental hygiene and awareness of the population concerning this topic. Dental carries represent a cumulative life course -related disease, where multiple risk determinants may play an important role (14, 16). In accordance with WHO data, in Eastern and Central European countries, as we mentioned, they remain a public concern. The restructuring of dental health care, years of insufficient preventive actions, lack of promotional oral health campaigns, transition from the paediatric to the adult dental care network, the latter

with a lower cost - support from health insurances are all responsible for the unfavorable situation of dental health in our control group . An associated, life-long disease like haemophilia, risky, with sometimes even life-threatening bleedings could be a serious additional condition for the dismal oral health condition. This absolutely disastrous situation of dental health in PwH, worsening with the age can be connected with the treatment approach of their underlying disease. As a bleeding disorder, with high risk of bleeding in the absence of an adequate replacement therapy, haemophilia is hindering the patients to address the dentist, while the dental care-givers are reluctant to approach these patients. Our results are consistent with those reported in Egypt, Iran or Brasil and very different from those reported in Poland, Germany, Ireland or Lithuania [3, 4, 7, 9, 11-13]. Our patients have a significantly worse condition than those from Northern and Western European countries. The main determinant can be the difference in the quality of coagulation factors replacement. Lack of access to treatment or even only a low consumption, less than 1IU/ capita/year in comparison with 4-8 IU/ capita/ year, especially in young age, can make the difference. We did not find in our casuistry civil litigations and malpractice partly because a sincere communication has been developed and a solid and valid informed consent was obtained. However, such developments are not unknown especially when the informed consent is not fully informed. Legal medicine experts, private or official, does not have to generate a "clame of uniqueness" in their opinions, partly because "uniqueness" is so difficult usually impossible to prove

**Figure 1.** Pearson correlation of age with Missing Index in adult PwH.**Figure 2.** Pearson correlation of age with DMFT Index in adult PwH.

but also because their opinion has to be based on facts only and solid proofs [17].

Medical ethics relationship requires adequate disclosure of the medical data in order to obtain a valid informed consent. Taking into consideration autonomy of the patient is mandatory. Some of the patients however may be desperate and in demanding for medical care including when complications are to be happening. Doctor has to be honest, not to offer guarantees but in the same time to sustain and to offer support and hope for the outcome and to give continuously a specific medical support whenever the patient is in need for treatment or when bleeding.

The main question of our research was to find out if haemophilia poses an additional risk on dental deterioration in PwH and if replacement therapy can influence the oral health and experience. It is certain that improved replacement therapy has a decisive impact on oral health status. But it is not the only solution.

Obviously there is a need for regular dental visits to increase awareness among such patients about the

importance of preventive measures: dental hygiene, regular controls to the dentist, precocious treatment of dental decays. The benefits of prevention of oral diseases has a considerable importance, so that the need for advanced dental treatment could be avoided and minimized. It is important that dental care is accessible for this vulnerable group of patients in the frame of a comprehensive haemophilia care [2, 5].

In conclusion, the worse dental status in PwH is obvious. The long-lasting low availability to an adequate replacement therapy, eventually corrected during the last couple of years, is responsible for the present situation. Our findings highlight, beside the requirement of an optimized replacement therapy, the need for comprehensive oral examinations including preventive dental treatment and follow-up care in vulnerable patients with bleeding disorders. As far as ethical considerations, there are important issues that may be arisen.

Conflict of interest. The authors declare that there is no conflict of interest.

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