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Research Article

Xerostomia in Childhood Cancer Survivors: A Late Effect of Antineoplastic Treatment?

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Received: January 16, 2023; **Published:** January 27, 2023

Abstract

Objective: This retrospective cross-sectional study aimed to assess the effect of antineoplastic treatment on salivary indices of childhood cancer survivors. Further objective was to correlate patient-reported xerostomia with objective hyposalivation.

Methods: Seventy children and adolescents, aged 5 - 21 years, that have been treated for any type of malignancy up to age of 10 years and are in remission were enrolled. Saliva was collected to determine stimulated salivary flow rate and buffer capacity. Patient-reported xerostomia was evaluated using xerostomia inventory questionnaire.

Results: Mean salivary flow rate was 1.56 ml/min, with only 5% of participants having very low. Most participants (71%) had high buffer capacity while 4% had low. Univariate ordinal regression analysis revealed a significantly higher incidence of low and very low flow rate in patients with fewer post-treatment years. Patients with longer post-treatment periods showed 1.21 times greater risk of developing altered buffer capacity. Multivariate analysis confirmed that years since the end of treatment were the only variable associated with altered salivary function. Only 13% of the participants reported xerostomia, which was not significantly associated with hyposalivation.

Conclusion: Xerostomia should not be considered a late effect of antineoplastic treatment, as it does not persist for many years after treatment completion.

Keywords: *Salivary Flow Rate; Xerostomia; Hyposalivation; Antineoplastic Treatment; Childhood Cancer Survivors*

Introduction

Xerostomia is defined as the subjective sensation of dry mouth, resulting from reduced salivary flow most often due to induced hypofunction of the salivary gland and is usually associated with a change in the composition of saliva [1]. It is one of the most common and significant complications of antineoplastic treatment [2].

Sensitivity of the major salivary glands to radiation, causes dysfunction with a gradual decrease to less than 10% of the initial flow rate during the first week of therapy [3]. Ionizing radiation may equally affect the secretory cells, the blood supply to the gland, and the nerves [4]. It is not clear though whether radiation damage to the glands is caused by the direct effect on secretory and ductal cells or it is caused by injury to the fine vascular structures. From experiments in non-human primates, it was concluded that gland impairment is caused by radiation-induced serous acinar cell death rather than by vascular injury [5].

Radiation therapy has a dose-dependent effect to the salivary tissues, with doses < 30Gy having a reversible effect while more permanent damage being caused with cumulative doses of ≥ 50Gy [5,6]. The severity of the effect increases further if the radiation field involves one of the major salivary glands, causing severe and permanent xerostomia [5]. The amount of xerostomia is reduced if the contralateral gland is excluded from the radiation field [7].

The effect of chemotherapy has not yet been clarified, as in many cases it is used in combination with concomitant radiation therapy and its independent effect cannot be determined. It has been reported that 50 - 60% of patients undergoing chemotherapy experience xerostomia, with only cyclophosphamide being directly associated with this effect [8]. In a study by Hsieh., *et al*. [9], it was shown that participants that received cyclophosphamide had a 12.4 higher risk of having very low salivary flow rate as compared to those that had not received it. In the same study, no other chemotherapeutic agent was significantly associated with reduced salivary flow rate.

In the literature it has been shown that salivary function of affected glands rarely recovers completely, but the dryness of the mouth tends to diminish few months after the end of treatment, partly due to hypertrophy of unirradiated glands that have a compensatory effect [10]. Nemeth., *et al*. [4] demonstrated that unstimulated salivary flow rate of childhood cancer survivors was normal, supporting that the recorded decrease in the salivary flow rate cannot be attributed to the damage caused to the major salivary glands, as this seems to be compensated by the function of the minor salivary glands. Initially, hyposalivation was considered as a short-term side effect of antineoplastic treatment. Even in cases of irradiation in the head and neck region, where immediate organ toxicity was reported, patients felt improvement after 4 - 12 months [10]. Lee., *et al*. [11] though supported that even if salivary secretion improves, it never reaches pre-treatment levels while Nemeth., *et al*. [4] concluded that it can be considered as a late effect solely of chemotherapy treatment.

Up to date the evidence on the effect of antineoplastic therapy on salivary glands is limited, with most studies concentrating on the reported prevalence of resulting hyposalivation/xerostomia. Therefore, the study aimed to assess the late nature of the effect of antineoplastic treatment on major salivary glands through estimation of salivary flow rate and buffer capacity of childhood cancer survivors. A further objective was to associate subjective xerostomia, through a patient-reported xerostomia inventory, with clinically measured hyposalivation.

Materials and Methods

It is a retrospective cross-sectional study in children and adolescents diagnosed with any type of malignancy and treated with various protocols early in life.

Sample

Seventy children and adolescents that have been treated for various types of malignancy and are in remission were randomly selected from the Pediatric Hematology-Oncology Unit, First Department of Pediatrics (Medical School, National and Kapodistrian University of Athens). The sample was the most possible convenient and its size was calculated mainly based on the total number of childhood cancer survivors attending the Department per year.

Inclusion criteria were patients aged 5 - 21 years old, that have been treated at ages 0 - 10 years old for any type of malignancy and have completed antineoplastic treatment at least one year before the day of the examination. Exclusion criteria were young adults, chil-

dren and adolescents with active disease or patients under treatment, and survivors that have completed treatment less than a year before the day of the examination.

The research was performed according to the Declaration of Helsinki (WMA 2013) and the protocol was approved by the Ethics Committee of the Dental School, National and Kapodistrian University of Athens (N363, approved on 22/6/2018) and all eligible patients who accepted to participate were asked to sign a written informed consent.

Data collection

Participants were initially examined in the Post-graduate clinic of the Pediatric Dentistry department of the Dental School of the National and Kapodistrian University of Athens, by one calibrated pediatric dentist ($k > 0.80$).

For saliva evaluation, participants were seated in an upright position and were asked to chew a piece of paraffin gum for 5 minutes, expectorate and then collect the accumulated saliva into a marked calibrated vessel, avoiding swallowing. The volume of the saliva was read off the vessel, after the removal of the foam on the top, and the stimulated salivary flow rate (ml/min) was then recorded [12]. Stimulated flow rate was chosen against unstimulated given the young age of the patients in the sample and the difficulty in their perception and co-operation.

The salivary buffer capacity was then determined from the stimulated saliva samples. A drop of saliva was taken using a pipette, was placed in the paper of the colorimetric test, and left for 5 minutes (CRT buffer, Ivoclar Vivadent AG, Schaan, Lichtenstein). The color of the test corresponds to different predetermined capacities. Blue refers to a pH between 5.6 and 7.0 and indicates a high buffer capacity, green a pH between 4.6 and 5.5 and medium capacity of saliva, and yellow a low capacity with a $pH < 4.6$.

Xerostomia inventory

The patients were asked to complete, the Greek Version of the short version of the Xerostomia Inventory, with the help of their parents/guardians when required [13]. The questionnaire asks patients to rate the frequency of specific symptoms related to skin, mouth, eyes dryness felt for the past 15 days. For each of the 11 symptoms, they give a value from 0 to 5, with 0 indicating never and 5 very often. Each item score is added, and the sum corresponds to the final score ranging from 0 to 55, with higher scores representing greater levels of xerostomia. Values greater than 30 indicate severe xerostomia.

Before the initiation of the study, the applicability and validity of the questionnaire in our population was tested in a pilot sample of 10 childhood cancer survivors, that were not included in the final sample.

Statistical analysis

Salivary variables were presented using charts and frequency tables. Univariate ordinal logistic regression analysis was performed to associate the dependent variables (salivary flow rate and buffer capacity) with the continuous independent variables (disease and treatment characteristics). Comparisons were also performed, to explore significant differences in gender, age at examination, radiation dose and site, and administration of different chemotherapeutic agents. Multivariate ordinal logistic regression analysis with backward elimination of nonsignificant predictors (deletion criterion $p > 0.05$) was also performed to identify possible risk factors for the development of deviations in physiological salivary flow rate and buffer capacity of childhood cancer survivors.

In order to associate subjective xerostomia and clinically quantitated hyposalivation calculated values were converted to dummy variables, in which xerostomia is considered when the value of the index is above 14 and hyposalivation was considered when stimulated salivary flow was below 0.7ml per minute [1]. McNemar exact test was used to compare hyposalivation as recorded through the stimulated salivary flow, and subjective xerostomia as reported through the xerostomia inventory.

Data were analyzed using the Statistical Package for Social Sciences (SPSS v. 17.0®) and statistical significance was set at $p < 0.05$.

Results

The sample consisted of 70 children and adolescents with a mean age of 11.2 years. Almost half of the participants (46%) were males, the most common diagnosis was leukemia (45%) and the overall mean age at diagnosis was 4.17 years. More than two-thirds (71%) of the participants had undergone only chemotherapy and the mean time since the end of antineoplastic treatment was 5.48 years. Among the participants that have undergone radiotherapy, 42% received high doses of > 50Gy and 68% received radiation in the head and neck region. Regarding the type of the chemotherapeutic agents, most participants received one alkylating agent (64%), antimetabolites (68%), steroids (68%), and vincristine (90%).

Salivary indices

The mean salivary flow rate was 1.56 ml/min, with a minimum value of 0.2 ml/min and a maximum of 7 ml/min. Stimulated flow rate being almost equally divided between physiological (1.5 - 2 ml/mn) (46%) and low (49%) (0.8 - 1.4 ml/mn) while only 5% of participants had very low (< 0.7 ml/mn). Regarding buffer capacity, most of the participants (71%) had high, 1/4 (25%) had medium and only 4% had low.

The distribution of salivary flow rates in different groups according to various patients and treatment characteristics reveals that the physiological flow rate is equally distributed (Table 1). Differences can be seen when age is considered with younger patients having an increased incidence of low flow rate. Increased incidence of very low salivary flow rate was also evident in patients with a diagnosis other than Acute Lymphoblastic Leukemia, that have undergone combination treatment modalities and for whom fewer years since the end of treatment have elapsed.

	Very Low SSF N (%)	Low SSF N (%)	Physiological SSF N (%)
Gender			
Male (n = 32)	2 (7)	16 (50)	14 (43)
Female (n = 38)	2 (4)	18 (48)	18 (48)
Age at examination			
<11.2 yrs (n = 35)	1 (4)	22 (70)	12 (26)
>11.2 yrs (n = 35)	3 (6)	12 (35)	20 (59)
Diagnosis			
Acute Lymphoblastic Leukemia (n = 31)	0 (0)	18 (59)	13 (41)
Other (n = 39)	4 (9)	16 (43)	19 (48)
Age at diagnosis			
<4.17 yrs (n = 42)	1 (3)	22 (53)	19 (44)
>4.17 yrs (n = 28)	3 (8)	12 (44)	13 (48)
Treatment			
Chemotherapy alone (n = 49)	2 (3)	25 (52)	22 (45)
Combination (n = 21)	2 (11)	9 (42)	10 (47)
Years since end of treatment			
<5.48 yrs (n = 41)	4 (10)	21 (51)	16 (39)
>5.48 yrs (n = 29)	0 (0)	13 (45)	16 (55)

Table 1: *Distribution of stimulated salivary flow rate (SSF) according to patient and treatment characteristics.*

Similarly, the distribution of buffer capacity among various groups (Table 2) revealed that patients with low buffer capacity were older females, treated with combination protocols and presenting more years after antineoplastic treatment completion. Greater differences in the distribution of medium buffer capacity were seen when age at diagnosis and time since the end of treatment were considered. Patients diagnosed at younger age and those with more years after the end of treatment had increased incidence of medium buffer capacity. This difference was reversed in the distribution of high buffer capacity, with the incidence being higher in patients that have been diagnosed at older ages and for whom less time has elapsed.

	Low N (%)	Medium N (%)	High N (%)
Gender			
Male (n = 32)	0 (0)	7 (21)	25 (79)
Female (n = 38)	2 (7)	11 (29)	25 (65)
Age at examination			
< 11.2 yrs (n = 35)	0 (0)	8 (24)	27 (76)
> 11.2yrs (n = 35)	2 (6)	10 (27)	23 (68)
Diagnosis			
Acute Lymphoblastic Leukemia (n = 31)	0 (0)	10 (32)	21 (68)
Other (n = 39)	2 (5)	8 (22)	29 (73)
Age at diagnosis			
< 4.17 yrs (n = 42)	1 (3)	15 (36)	26 (62)
> 4.17 yrs (n = 28)	1 (4)	3 (12)	24 (84)
Treatment			
Chemotherapy alone (n = 49)	0 (0)	14 (28)	35 (72)
Combination (n = 21)	2 (10)	4 (20)	15 (70)
Years since end of treatment			
< 5.48 yrs (n = 41)	0 (0)	8 (20)	33 (80)
> 5.48 yrs (n = 29)	2 (7)	10 (31)	17 (62)

Table 2: *Distribution of buffer capacity according to patient and treatment characteristics.*

Univariate ordinal regression analysis revealed significant differences between post-treatment follow-up time and salivary flow rate (Table 3). An inversely proportional relation was recorded, with children for whom less time has elapsed since the end of treatment presenting increased incidences of low and very low salivary flow rates. Similarly, a directly proportional relationship was seen when age at examination was considered, with salivary flow rate moving from low to physiological as age increases. The same significant relationship was recorded between buffer capacity and time since the end of antineoplastic treatment (Table 4). It is evident that patients with increasing post-treatment periods have a 1.21 times greater risk of developing altered buffer capacity.

Further analysis revealed that neither radiation site and dose nor chemotherapeutic drugs were significantly associated with salivary flow rate and buffer capacity, with p values ranging between 0.1 (for vincristine) and 0.9 (for alkylating agents). These findings were also supported by the results of multivariate analysis, which underlined the significance in the reported difference only for the variable years since the end of treatment (p = 0.03 and p = 0.01 for salivary flow and buffer capacity respectively, data not shown).

	Odds Ratio	95% Confidence Interval	p-value
Gender			
Male	0.86	0.34 - 2.15	0.75
Female	Ref		
Age at examination			
Per year	0.86	0.75 - 0.99	0.04
Diagnosis			
Acute Lymphoblastic Leukemia	0.86	0.34 - 2.15	0.75
Other	Ref		
Age at diagnosis			
Per year	0.99	0.84 - 1.17	0.94
Treatment			
Combination protocols	0.85	0.38 - 3.15	0.63
Chemotherapy alone	Ref		
Years since end of treatment			
Per year	0.85	0.74 - 0.98	0.03

Table 3: *Univariate ordinal logistic regression analysis for the development of low or very low stimulated salivary flow.*

	Odds Ratio	95% Confidence Interval	p-value
Gender			
Male	2.63	0.87 - 7.92	0.09
Female	Ref		
Age at examination			
Per year	1.07	0.92 - 1.24	0.38
Diagnosis			
Acute Lymphoblastic Leukemia	1.03	0.37 - 2.91	0.95
Other	Ref		
Age at diagnosis			
Per year	0.84	0.68 - 1.04	0.10
Treatment			
Combination protocols	1.57	0.52 - 4.77	0.42
Chemotherapy alone	Ref		
Years since end of treatment			
Per year	1.21	1.04 - 1.40	0.01

Table 4: *Univariate ordinal logistic regression analysis for the development of medium and low buffer capacity.*

Patient-reported xerostomia

When xerostomia was estimated through the Xerostomia Inventory, 33 patients (47%) reported that they never faced any of the xerostomia symptoms (score 11 in the index), 28 patients (40%) reported mild symptoms (score 12 - 14) and only 9 patients (13%) reported to have xerostomia (score > 14). The correlation of patient-reported xerostomia and objective hyposalivation (Table 5) showed that only 3% of the patients reporting xerostomia had also measurable hyposalivation, while 14% of patients that did not report xerostomia did have measurable hyposalivation. Most patients did not report xerostomia and did not have hyposalivation, although all the reported differences were not statistically significant.

	Reported Xerostomia			
Hyposalivation	**Yes**	**No**	**Total**	**McNemar test p-value**
Yes	2 (3%)	10 (14%)	12 (17%)	0.64
No	7 (10%)	51 (73%)	58 (83%)	
Total	9 (13%)	61 (87%)	70 (100%)	

Table 5: *Correlation of patient-reported xerostomia and clinically reported hyposalivation.*

Discussion

The present study reported on quantitative hyposalivation and qualitative xerostomia of childhood cancer survivors with a mean follow-up period of 5-year post-treatment, underlying the long-term effect of cancer and its treatment on salivary flow rate and buffer capacity. The mean value for stimulated flow rate and buffer capacity calculated on our cohort was considered normal, although extreme values were seen in cases of shorter post-treatment follow-up periods.

In a study by Avsar., *et al*. [14] unstimulated salivary flow (1.2 ± 0.25) was within the normal range although the stimulated salivary flow rate was significantly reduced. Similarly, unstimulated flow rate has been reported unaffected by other authors, and no significant difference between patients and controls has been shown [15,16]. Dahllöf., *et al*. [17] reported lower values for unstimulated flow rate (0.7 ± 0.5 ml/min) in children who had received combination antineoplastic treatment including chemotherapy and Haemopoietic Stem Cell Transplantation. Previous reports detected hyposalivation (USF ≤ 0.1 ml/min) for more than one quarter (28.5%) of the study population but not for the control group and supported that it can be considered as a late effect of cancer therapy as it persists even 5 years after the end of treatment [18]. These studies though, refer to the unstimulated and not to the stimulated salivary flow that reflects to the initial tissue damage of the major salivary glands [4].

It has been shown that reduction in salivary flow is reversible in most cases and may reflect an increased function of minor salivary glands supported by the overall high buffer capacity of most survivors [4]. This agrees with our report where the cumulative percentage of patients with high buffer capacity was above 70% directly comparable to 80% in the report by Nemeth., *et al* [4]. Nevertheless, there are reports in healthy populations, where patients with reduced salivary flow showed at the same time a reduced buffer capacity [19-21].

Radiation field and dose have been highly associated with xerostomia prevalence [22,23]. Salivary glands, unlike most non-dividing tissues, are extremely radiosensitive and due to their location are often included in the radiation field for most head and neck malignancies [23]. Glandular damage seems to affect the composition of saliva and its physiological function, reducing saliva buffering capacity [24].

The association of chemotherapy with xerostomia though is controversial. Investigators are indicating no significant difference in xerostomia or hyposalivation between exposed to chemotherapy or non-exposed patients [25], while a recent systematic review showed

lower average salivary flow rate in children treated with chemotherapy when compared to controls [26]. Nemeth., *et al*. [4] recognized hyposalivation as a direct consequence of chemotherapy even five years after treatment completion.

In the present study, most patients did not report xerostomia and did not have hyposalivation. Only 3% of the patients reporting xerostomia had hyposalivation, while 14% of the patients that did not report xerostomia had hyposalivation with calculated difference being statistically insignificant. This is attributed to the fact that salivary function returns to normal within 6 - 12 months and all our patients have been off treatment for at least one year [8].

In a systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies in adults, the self-reported prevalence of xerostomia reported by the 79 included studies was 83.5%, two years post-radiation for head and neck cancer [2]. In contrast, childhood survivors with rhabdomyosarcoma, who received radiation in the head and neck region for a median follow-up period of seven years, had a prevalence of only 12% [27]. Similarly, low prevalence was reported in a study by Kaste., *et al*. [28] with the reported xerostomia in survivors being 2.8%, compared to 0.3% in their siblings. The big difference noticed between younger and older survivors may be attributed either to the higher radiation doses used in adults, to greater healing potential of the salivary glands in children or to possible underreported symptoms by children and or guardians [29].

Conclusion

- Most childhood cancer survivors have normal values of stimulated salivary flow rate and high buffer capacity.
- Time that has elapsed from treatment completion was significantly associated with increased incidences of low and very low salivary flow rates.
- Patients with increased post-treatment periods have a 1.21 times greater risk of developing altered buffer capacity.
- Low scores on the xerostomia index were recorded for most participants indicating under reporting of symptoms.
- The correlation between patient-reported xerostomia and hyposalivation was non-significant.
- The above support that xerostomia should not be considered as a late effect of antineoplastic treatment, as it does not persist for many years after treatment completion.

Funding Support

The authors have no relevant financial or non-financial interests to disclose.

Conflicts of Interest

None to declare.

Availability of Data and Materials

N/A.

Code Availability

N/A.

Ethics Approval

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Dental School of the University of Athens (N363, approved on 22/6/2018).

Consent to Participate

All eligible patients who accepted to participate were asked to sign a written informed consent.

Consent for Publication

N/A.

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Volume 22 Issue 2 February 2023