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Tooth abnormalities in pediatric patients submitted to antineoplastic treatment for central nervous system neoplasms

Anormalidades dentárias em pacientes pediátricos submetidos a tratamento antineoplásico para neoplasias do sistema nervoso central

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ABSTRACT

Objective: The aim of this study was to evaluate the frequency of tooth abnormalities in pediatric patients treated for central nervous system neoplasms. **Material and methods:** This cross-sectional study assessed thirty-one patients, median age 14.2 years (range 5 - 25), who were off therapy for at least one year, comparatively with a control group of thirty-one healthy patients matched for age with the study group. Tooth abnormalities were evaluated by panoramic radiographs. **Results:** There was no statistical significant evidence that patients of the study group (age range 5 - 25 years) have more frequency of tooth abnormalities comparatively with controls. However, in children who were diagnosed before five years of age, microdontia was the most common abnormality with statistically significant difference (P = 0.037). Root shortening grade III was observed in patients over 10 years of age at the time of radiographic examination, also with statistical significance (P = 0.046). **Conclusions:** There was no difference in the frequency of tooth abnormalities in pediatric patients treated for central nervous system neoplasms, comparatively with the control group. However, the findings of this study highlight the importance of giving parents and patients orientation about maintenance of good oral hygiene and proper treatment.

KEYWORDS

Central nervous system neoplasms; Drug therapy; Pediatrics; Radiotherapy; Tooth abnormalities.

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a frequência de anormalidades dentárias em pacientes pediátricos tratados para neoplasias do sistema nervoso central. **Material e Métodos:** Este estudo transversal avaliou trinta e um pacientes, com média de idade de 14,2 anos (entre 5 – 25 anos), que estavam fora de terapia há pelo menos um ano, comparativamente com um grupo controle composto por 31 pacientes saudáveis pareados por idade com o grupo de estudo. As anormalidades dentárias foram avaliadas por meio de radiografias panorâmicas. **Resultados:** Não houve evidência estatisticamente significante de que pacientes do grupo de estudo (entre 5 – 25 anos) apresentam maior frequência de anormalidades dentárias quando comparados aos pacientes do grupo controle. No entanto, em crianças diagnosticadas antes dos cinco anos de idade, microdontia foi a anormalidade mais comumente encontrada, com diferença estatisticamente significante (P=0.037). Encurtamento radicular grau III foi observado em pacientes com mais de 10 anos de idade ao exame radiográfico, também com significância estatística (P=0.046). **Conclusão:** Não houve diferença na frequência de anormalidades dentárias em pacientes pediátricos submetidos a tratamento antineoplásico para neoplasias do sistema nervoso central, comparativamente ao grupo controle. No entanto, os achados deste estudo ressaltam a importância de reconhecer os efeitos dentários tardios do tratamento antineoplásico em crianças com câncer e deste modo orientar pacientes e responsáveis sobre cuidados de higiene bucal e sobre opções de tratamento apropriado.

PALAVRAS-CHAVE

Neoplasias do sistema nervoso central; Quimioterapia; Pediatria; Radioterapia; Anormalidades dentárias.

INTRODUCTION

Central nervous system (CNS) neoplasms are the most frequent solid tumors in pediatric patients, accounting for 20% of all malignancies in children under 15 years of age [1]. Treatment modalities include surgery, radiotherapy and chemotherapy. The conventional radiation dose regimen is 54 Gy (gray) in 30 daily fractions of 1.8 Gy. Chemotherapy is used in association to radiotherapy or previously in children younger than 3 years in order to delay radiation exposure and to avoid neurocognitive sequelae [2]. Modern diagnostic techniques and advances in antineoplastic treatment have contributed significantly for improvement of survivor rate in children with cancer. However, acute and late effects of treatment can affect multiple organs and tissues, especially those in development [3,4].

CNS neoplasms are classified according to histological origin and the most frequent types include astrocytoma (20.9%), medulloblastoma (16.8%) and ependimoma (7%). Astrocytomas, the most common CNS neoplasms, are found in the cerebellum and in the optic pathway. Most cases of medulloblastoma affect the cerebellum and projects to the IV ventricle. Patients with medulloblastoma at high risk present evidence of dissemination to cerebrospinal fluid at diagnosis. Ependimomas are found in the ependimal line of the IV ventricle and the standard treatment consists of radiotherapy, which improves survival rates [2].

Dental abnormalities are commonly observed as late effects of antineoplastic therapy in the oral cavity. Disturbances can affect size of crown and roots, as well as number of teeth [5]. Alterations can occur if radiotherapy and/or chemotherapy are coincident with the time of tooth development. Abnormalities can affect teeth groups at different times, as odontogenesis is a dynamic process and each dental group develops in different moments [6]. The severity of abnormalities depends on the type of treatment and the patient´s age at diagnosis [7-9].

Absence of teeth or changes in crown size result in malocclusion and impairment of orofacial structures [5]. Reduced root surface areas have less periodontal support, leading to rapid progression of periodontal disease and loss of teeth [10]. Therefore, it is imperative that patients have access to preventive care and appropriate treatment in order to minimize the impact on their oral function and quality of life.

The purpose of this study was to evaluate the frequency of tooth abnormalities in pediatric patients treated for central nervous system neoplasms, comparatively with a control group.

MATERIAL AND METHODS

Subjects

In this cross-sectional study, thirty-one patients who underwent antineoplastic treatment for central nervous system neoplasms were selected from the Dentistry Department of Hemato-oncology Service, Clinics Hospital School of Medicine, University of São Paulo (HC-FMUSP) - São Paulo/SP, Brazil. The study was approved by the Research Ethics Committee of the HC-FMUSP. Inclusion criteria were: age under 16 years at the time of diagnosis; children who were off therapy for at least one year; children who underwent chemotherapy, radiotherapy and both concomitant treatments. The control group was composed of thirty-one panoramic radiographs of healthy children selected from the Radiology Department database of São Paulo State University (UNESP), São José dos Campos, São Paulo, Brazil. Controls were matched with the study group according to age at radiographic examination. Panoramic radiographs of the control group were already available at the Radiology Department database and were originally performed for evaluation prior to orthodontic treatment. Therefore, controls were not exposed unnecessarily to radiographic examination only to participate in this study. Inclusion criteria for the control group were: patients without history of cancer and patients without history of diseases that could affect tooth development.

Clinical Examination

Clinical intraoral examination was performed in patients of the study group using a reflecting mirror and an explorer, in order to assess dental condition, to give patients and parents oral hygiene orientation and to refer patients for appropriate treatment if necessary, as part of routine of the Institution´s Dental Department. Dental abnormalities in shape of dental crown (microdontia) and in number of teeth (agenesis) were clinically assessed and confirmed afterwards by radiographic examination. Data such as CNS diagnosis, age at diagnosis, type of treatment, doses and fields of radiotherapy were collected from patient´s medical records.

Radiographic Examination

Panoramic radiographs of the study group were collected from the Oncology-Hematology Service database. Patients who did not have the radiographic exam were able to perform it at the Radiology Institute (INRAD-HC-FMUSP). Radiographs of both groups were randomly enumerated and evaluated by two independent examiners blinded to case and controls. Examiners only had access to patient´s gender, age and date of the exam. Radiographs were visualized in the digital Bitmap (bmp) format. Tooth abnormalities were assessed according to the developmental stage of teeth by Nolla method [11]. To analyze crown abnormalities (microdontia), teeth had to be at least in Nolla´s stage 6, where crown formation is complete. For root abnormalities, teeth should be at least in Nolla´s stage 10, where the root formation is complete and apices are closed. Abnormalities of the third molars were excluded because they often occur in general population. Upper and lower incisors were also not considered due to distortion of this region in panoramic radiographs. The following definitions for crown abnormalities were used (Figure 1): (1) Agenesis - absence of one or more teeth due to developmental failure. (2) Microdontia - tooth with mesiodistal dimension visually smaller when compared to the same tooth of the opposite side, as tooth dimensions vary in general population according to gender, ethnic group and genetics. In case of absence of contralateral tooth, we considered the dimension of the tooth of the same group, on the same side, once dimensions of teeth of the same group are similar [12,13]. Root abnormalities were defined as follows (Figure 2): (3) Short root grade II - shortened roots with dimension greater than 50% of normal root length. (4) Short root grade III - shortened roots with dimension of less than 50% of normal root length [7]. Normal root length was considered as a mean crown-root ratio of 2 [14].

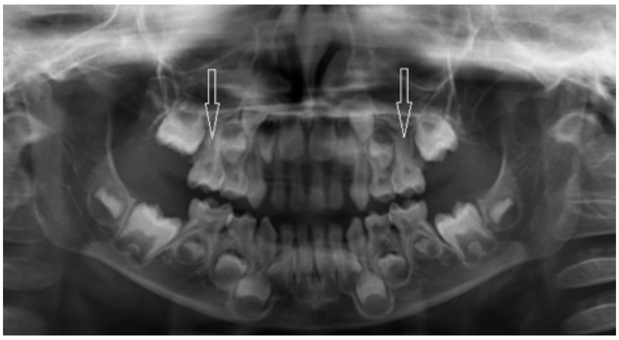

Figure 1 - Agenesis. Panoramic radiograph of a 5.5-year-old patient, diagnosed with CNS neoplasm at the age of 2 years. Notice the absence of tooth buds (agenesis) of upper second premolars (arrows).

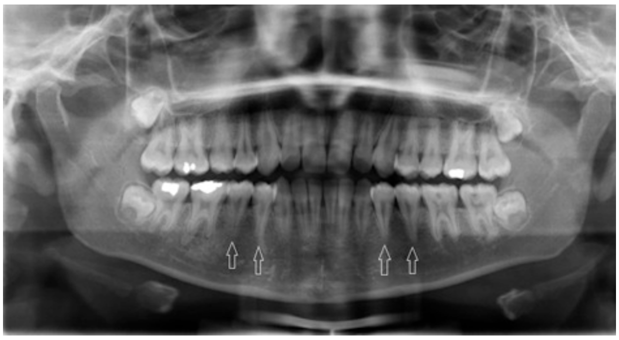

Figure 2 - Short roots. Panoramic radiograph of a 17-year-old patient, diagnosed with CNS neoplasm at the age of 7 years. Notice short root of lower first and second premolars (arrows).

Statistical Analysis

Fisher´s exact test was used to compare abnormalities between groups, age at diagnosis, age at radiographic examination and type of diagnosis. After collection, data calculations were performed with R 3.1.1 software (R Core Team, 2014). The power calculation was 80% and the level of significance was 5%.

RESULTS

The characteristics of patients and controls are detailed in Table 1. Of the 31 patients of the study group, 17 were male. Mean age at diagnosis of CNS neoplasms was 7.3 years ± 3.9 (range 2-15) and mean age at radiographic examination was 14.2 ± 5.7 (range 5-25). The most frequent CNS neoplasm was medulloblastoma (58.1%), followed by astrocytoma (25.8%) and ependymoma (3.2%). Most patients of the study group (77.4%) underwent chemotherapy combined with radiotherapy (Table 2). The field of radiotherapy was the craniospinal axis and total doses of irradiation ranged from 36 to 54 Gy.

Table 1 - Characteristics of patients and controls

Gender	Study group (n=31)	Control group (n=31)
Male	17	20
Female	14	11
Age at diagnosis (years)	7.3 (3.9)*	-
Age at radiographic examination (years)	14.2 (5.7)*	14.2 (5.7)*

NOTE: *mean (standard deviation)

Table 2 - CNS diagnosis and type of treatment - study group

CNS diagnosis	Study group (n=31)
Medulloblastoma	18 (58.1)
Astrocytoma	8 (25.8)
Ependymoma	1 (3.2)
Others	4 (12.9)
Type of treatment	
Radiotherapy	4 (12.9)
Chemotherapy	3 (9.7)
Radiotherapy + chemotherapy	24 (77.4)

NOTE: Value expressed in numbers (%)

Comparisons of tooth abnormalities (in at least one tooth) between patients and controls are shown in Table 3. There was no statistical significant evidence that patients of the study group (age range 5 - 25 years) have more frequency of tooth abnormalities comparatively with controls. The most frequent tooth abnormality in both groups was short root grade III, 16.1% and 9.7% in patients and controls, respectively.

Table 3 - Tooth abnormalities of patients and controls

Tooth abnormalities	Controls (n=31)		Patients (n=31)		Total (n=62)		p[1]
	N	%	N	%	N	%	
Agenesis	2	6.5	1	3.2	3	4.8	1
Microdontia	0	0	3	9.7	3	4.8	0.238
Short root grade II	1	3.2	4	12.9	5	8.1	0.354
Short root grade III	3	9.7	5	16.1	8	12.9	0.707

[1]Fisher's exact test

Microdontia was more frequent in children who were under 5 years of age at diagnosis (27.3%), with statistical significant difference (p = 0.037), as shown in Table 4. Significant difference (p = 0.046) also was found in short root grade III (19%) in patients over 10 years of age at radiographic examination (Table 5). The analyses according to gender did not reveal any significant difference. One case of tooth agenesis was observed, with significant difference (p = 0.032), in a patient with the diagnosis of ependymoma (Table 6). Patients who underwent chemotherapy combined with radiotherapy showed more frequency of dental abnormalities. However, no significant differences were found in abnormalities according to type of treatment.

Table 4 - Tooth abnormalities according to age at diagnosis

Tooth abnormalities	<= 5 years (n=11)		> 5 years (n=20)		Total (n=31)		p¹
	N	%	N	%	N	%	
Agenesis	1	9.1	0	0	1	3.2	0.355
Microdontia	**3**	**27.3**	**0**	**0**	**3**	**9.7**	**0.037**
Short root grade II	1	9.1	3	15	4	12.9	1
Short root grade III	0	0	5	25	5	16.1	0.133

[1]Fisher's exact test

Table 5 - Tooth abnormalities according to age at radiographic examination

Tooth abnormalities	«= 10 years (n=20)		» 10 years (n=42)		Total (n=31)		p¹
	N	%	N	%	N	%	
Agenesis	1	5	2	4.8	3	4.8	1
Microdontia	1	5	2	4.8	3	4.8	1
Short root grade II	0	0	5	11.9	5	8.1	0.165
Short root grade III	**0**	**0**	**8**	**19**	**8**	**12.9**	**0.046**

[1]Fisher's exact test

Table 6 - Tooth abnormalities according to diagnosis

Tooth abnormalities	Medulloblastoma (n=18)		Astrocytoma (n=8)		Ependymoma (n=1)		Others (n=4)		Total (n=31)		p¹
	N	%	N	%	N	%	N	%	N	%	
Agenesis	**0**	**0**	**0**	**0**	**1**	**100**	**0**	**0**	**1**	**3.2**	**0.032**
Microdontia	2	11.1	0	0	1	100	0	0	3	9.7	0.17
Short root grade II	2	11.1	0	0	0	0	2	50	4	12.9	0.165
Short root grade III	4	22.2	1	12.5	0	0	0	0	5	16.1	0.846

[1]Fisher's exact test

DISCUSSION

Central nervous system neoplasms are the most frequent solid tumors in pediatric patients and represent about 20% of cases in children under 15 years of age [1]. Most studies about late effects of antineoplastic treatment evaluate patients diagnosed with lymphoproliferative tumors, especially acute lymphoblastic leukemia [15,16]. Thus, the present study differs from others, as it evaluates frequency of tooth abnormalities in children treated for CNS neoplasms comparatively with healthy children.

It is known that the severity of dental abnormalities depends on age at diagnosis, type of antineoplastic treatment, dose and field of irradiation [7,9,17-19]. In this study most patients underwent radiotherapy combined with chemotherapy (77.4%). Antineoplastic therapy may affect cells in proliferation during odontogenesis, resulting in changes of crown and root formation [18,20,21]. We found that microdontia was more frequent in children under the age of 5 years at diagnosis, with statistical relevance. Our findings are in agreement with the study of Sonis et al [7]. The authors reported that children treated before the age of 5 years have more serious dental abnormalities because teeth are affected in early stages of dental formation.

The younger the child, the greater the chance of abnormalities during crown formation. Before the age of 5 years, crown alterations may occur in canines, first and second premolars and second molars [6]. In this study, we considered for evaluation canines, first and second premolars and first and second molars, due to less distortion and better visualization of these teeth on panoramic radiographs. Studies about odontogenesis show that until 5.5 years of age those teeth are at Nolla´s stages 3 and 4, with 1/3 and 2/3 of crown formation, respectively [6,11,22]. Therefore, agenesis and microdontia may have occurred in patients whose treatment was coincident with the time of crown formation of these teeth.

Microdontia may happen during bud and cap stages of tooth development, when size and shape of the crown are being defined. On the other hand, agenesis may occur before the lamina stage, resulting in no tooth formation [22]. Our results show that agenesis may be related to ependymoma, once the only case of this diagnosis was the only patient presenting agenesis. However, other variables may have influenced this outcome. This patient was diagnosed and treated at the age of 2 years, receiving radiotherapy combined with chemotherapy. In this case, absent teeth (agenesis) were left and right upper second premolars. It is known that enamel and dentin matrix formation of premolars has not yet begun at the age of 2 years [6]. Therefore, treatment may have affected precisely these teeth development resulting in agenesis, once it was coincident with the time immediately before tooth bud formation of upper second premolars. Agenesis and alterations in size of the crown (microdontia) can clinically result in malocclusion during the development of the maxillomandibular complex, which reflects in temporomandibular disorders, orofacial pain, respiratory and posture changes. It is important to give patients early orientation so that they can have proper treatment by orthodontics or dentofacial orthopedics, indicated after tumor relapse risk period, which is 5 years on average [23].

Short root grade III was the most common root abnormality found in the study group (16.1%). It is important to highlight that mean age at diagnosis was 7.3 years. At this age, crowns of the evaluated teeth (canines, premolars and first and second molars) are completely developed. However, roots are still being formed, thus susceptible to developmental changes [6,11,24]. Late effects of radiotherapy and/or chemotherapy may result in short, tapered and blunted roots [16,25,26]. We chose to use the parameter of shortened root and measure it in grades II and III [7]. This way, difference between grades is more accurate comparatively with the use of terms such as “tapering” or “blunting”, which reflects a subjective analysis. Moreover, the present study included patients diagnosed with CNS neoplasm until the age of 16 years. Around this period roots of second molars (last teeth considered for evaluation) are completing its formation [6]. Age at clinical and radiographic examination of many patients was greater than 16 years, in order to assess possible changes in root development of the studied teeth.

Our findings showed that short root grade III was only observed in patients who were over 10 years of age at radiographic examination, with statistical difference, 19% versus 0% in patients under 10 years of age. First molars are the only teeth with complete root formation under the age of 10 years. After that, teeth with complete root development may include canines, first and second premolars and second molars. Thus, according to the methodology used in our study, only first molars can be evaluated for root changes at the age of 10 years, since around this time those teeth are the only ones with complete root formation.

Although there was no statistical difference, short roots were more frequent in patients of the study group diagnosed after 5 years of age (grade II - 15% and grade III - 25%). These results are in agreement with Duggal [10], whose study compared root dimensions in 69 long-term survivors of childhood cancer with a control group, using panoramic radiographs. His findings showed that root surface areas of the study group were significantly smaller than those found in controls. Reduced root surface areas have less periodontal support, leading to future oral health impairment of cancer survivors. Therefore, maintenance of good oral hygiene and proper nutrition are important for patients with short roots, since rapid progression of gingival and periodontal inflammation, increased mobility and tooth loss may occur.

Our study compared dental abnormalities according to type of treatment (chemotherapy, radiotherapy or both). Among patients who received only chemotherapy (n=3), one presented short root grade II. Four patients received only radiotherapy and one presented short root grade III. Although not statistically significant, patients who were treated with chemotherapy associated to radiotherapy presented more tooth abnormalities than patients receiving these two treatment modalities separately. According to the results of this study, there was no correlation between type of treatment and tooth abnormalities.

Studies demonstrate that dental abnormalities and treatment with chemotherapeutic agents are dose dependent. Cumulative exposure to alkylating chemotherapeutic agents and radiation doses of more than 2000 cGy (centigray) are associated to increased risk of dental anomalies [27]. Patients who received cumulative doses of cyclophosphamide above 7500 mg/m^2 present more severe dental abnormalities [28]. Our study aimed to analyze the frequency of tooth abnormalities. We did not evaluate the correlation between dental abnormalities and doses of radiotherapy. We believe that such correlation should be performed in future studies with a larger number of subjects, in order to show more consistent results. Our study has the limitation of a small sample size. However, there are not many centers or institutions specialized in multidisciplinary treatment of such specific group of malignancies in our country. We believe that future studies able to relate dental anomalies and specific therapies could contribute to a better understanding of alterations on maxillomandibular complex.

CONCLUSION

There was no difference in the frequency of tooth abnormalities in pediatric patients treated for central nervous system neoplasms, comparatively with the control group.

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