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Impact of Hematopoietic Stem Cell Transplantation on Dental Development

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A B S T R A C T

To investigate dental development in patients treated with a hematopoietic stem cell transplantation (HSCT), 42 children and young adults who were under 12 years old at time of HSCT were examined for dental agenesis, microdontia, and root-to-crown ratio. Conditioning regimens were total body irradiation (TBI) based in 12 patients, busulfan based in 21 patients, and 9 patients had other chemotherapeutic agents. Sixteen patients were <3 years old, 9 patients were 3 to 6 years old, and 17 patients were 6 to 12 years old at HSCT. Prevalence of agenesis and microdontia of at least 1 permanent tooth were, respectively, 51.3% and 46.2% in the study population, and 76.3% had an aberrant root-to-crown ratio. All these results were highly different from the prevalence in the healthy population. Patients treated before the age of 3 years had more microdontia (76.9%) and agenesis (92.3%) compared with patients treated at an older age. In the subgroup of patients treated after 6 years, there was more microdontia when treated with busulfan (50%) compared with treatment with TBI (0%) ($P = .044$). Patients treated with HSCT had many disturbances in dental development. Age at HSCT and possibly also the conditioning regimen used had an effect on their type and prevalence. Dental follow-up should be incorporated in the multidisciplinary follow-up program of these patients.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is currently the only treatment with curative potential for various malignant and nonmalignant disorders [1]. In preparation for HSCT, patients are conditioned with chemotherapy, irradiation, and/or serotherapy to eliminate residual malignant cells, prevent acute and chronic graft-versus-host disease, and facilitate engraftment. Chemotherapy-based preparative regimens often contain alkylating drugs such as cyclophosphamide or busulfan [1,2]. Total body irradiation (TBI) based preparative regimens are used exclusively in children older than 3 years and only for malignant disorders [1]. The increasing overall survival post-HSCT necessitates the need for a rigorous long-term follow-up care and a profound documentation of late side effects [1-3]. Patients who undergo HSCT during childhood have a risk of at least 60% long-term morbidity of 1 or more organ systems [1-5]. Also, little is known about the impact of a HSCT on dental development [4-9].

An aberrant dental development can be due to genetic and/or environmental factors including chemotherapy or radiation therapy [7,10,11]. Agenesis is the clinical and radiographic absence of 1 or more teeth. Agenesis is a common dental anomaly, with a prevalence of 3% to 10% [7,11,12]. In the general population the lower second premolar and the upper lateral incisor are most frequently agenetic, if the third molars are not included [11]. If environmental factors are at stake, agenesis may occur when the tooth bud is damaged before its calcification process has started. As a rule, the younger the patient at the time of HSCT, the higher the chance of agenesis [7].

The prevalence of microdontia (teeth smaller than normal) is between 1% and 2.5% [7,12]. Microdontia and agenesis share a common etiology and therefore are often seen together. However, in microdontia the tooth bud is not completely destroyed. Generalized microdontia is rare and most often associated with syndromal disorders like ectodermal dysplasia, Down syndrome (trisomy 21), or congenital hypopituitarism [13]. Localized microdontia is more frequent. The tooth most frequently found to be microdontic is the lateral incisor. The microdontic tooth can have a normal or aberrant morphology (eg, peg shaped) [7,12].

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The root-to-crown ratio is the ratio of the length of the root to the length of the crown. After normal tooth development extrinsic factors like external root resorption or dental trauma can cause reduction of the root length [14,15]. However, disturbances of root development can be due to both genetic and extrinsic factors [14,15]. Because root development follows crown development, disturbances of the root development will more frequently be found in patients treated at an older age [5,8,13].

Previous studies mainly investigated the effect on dental development of radiotherapy and chemotherapy in a non-HSCT regimen [16-18]. Cranial irradiation can cause agenesis, microdontia, and shortened roots [16,18]. The younger the patient at the time of treatment, the worse and more detrimental the effect of irradiation or chemotherapy on dental development [16,18-20]. Radiotherapy can destroy proliferating and nonproliferating ameloblasts and odontoblasts and therefore cause agenesis or microdontia depending on the stage of dentogenesis at the time of treatment [16,19,20]. Studies investigating the effect of chemotherapy on dental development show that chemotherapy can affect proliferating odontoblasts and ameloblasts in the susceptible cell cycle phase (depending on the administered agent) [16,19,20]. Nonproliferative cells are not affected by chemotherapy [16,19]. Because of the differences in pathophysiology, irradiation is believed to cause more dental aberrations compared with chemotherapy. Because of the wide variety of administered chemotherapeutic agents, toxicity to dentogenesis of each agent separately is difficult to determine [6,17,19]. The effect of the alkylating agent cyclophosphamide is most frequently studied [16,18]. Administration of cyclophosphamide may result in agenesis, microdontia, and/or an aberrant root-to-crown ratio [16,18]. Studies on dental development after HSCT mainly focused on the effect of TBI versus non-TBI regimens without specification of the chemotherapeutic agents used [6]. Apart from the study of Vesterbacka et al. [4] and preliminary data from Dahllöf et al. [21], the effect of busulfan on dental development remains undetermined.

This study investigates dental status of patients who underwent HSCT during early childhood. Prevalence of agenesis, microdontia, and root-to-crown ratios in this population is calculated, and the possible impacts of age at HSCT and of different conditioning regimens are examined.

METHODS

Patient Selection

Patients who had HSCT from 1988 until 2016 at the Department of Pediatric Hematology/ Oncology and HSCT of the Ghent University Hospital and who were between 1 and 12 years old at the time of HSCT were included in the study. Another inclusion criterion was an interval of more than 1 year between the HSCT and this study. Exclusion criteria were genetic disorders with a possible impact on dental development (eg, Hurler's disease, osteopetrosis, or severe combined immune deficiency). Ninety-five patients were eligible, and 42 of them participated. Main reasons for dropout were nonresponders (n = 31), refusal to participate (n = 6), loss to follow-up (n = 8), speaking a foreign language (n = 2), family history of dental aberrations (n = 2), deceased (n = 2), and other reasons (n = 2).

This study was approved by our institutional ethical committee (B670201525400) and carried out in accordance with the principles of the Declaration of Helsinki.

This study investigated the impact of age and conditioning regimen as possible risk factors for dental abnormalities. The patients in the study were divided into 3 age categories: <3 years old, 3 to 6 years old, and >6 years old. To investigate the impact of the different conditioning regimens 3 treatment categories were made: TBI based, busulfan based, and other chemotherapeutic agents.

Patient Characteristics

Patient characteristics are listed in Table 1. Median age at HSCT was 4 years, and median age at time of dental examination was 14 years.

Table 1
Patient Characteristics (N = 42)

Characteristics	Subcategory	Value
Sex	Male	21
	Female	21
Conditioning regimen	TBI based	12
	Busulfan based	21
	Other chemotherapeutic agents	9
Diagnosis	Primitive neuroectodermal tumor	1
	Acute lymphoblastic leukemia	9
	Acute myeloid leukemia	2
	Juvenile myelomonocytic leukemia	2
	Neutropenia (severe, congenital)	1
	Neuroblastoma	9
	Wilms tumor/nephroblastoma	2
	Anaplastic large cell lymphoma	1
	Juvenile metachromatic leukodystrophia	1
	X-linked adrenoleukodystrophy	2
	Myelodysplastic syndrome	4
	Secondary myelodysplastic syndrome	1
	Chronic myeloid leukemia	2
	Aplastic anemia	2
	Thalassemia major	1
	Hemophagocytic lymphohistiocytosis	1
	Burkitt's lymphoma	1
Age at HSCT, yr	Mean (range)	5.2 (.3-11.5)
	Median	4
Age at dental examination, yr	Mean (range)	12 (3.5-30)
	Median	14
Years between HSCT and dental examination	Mean (range)	8.8 (.9-25)
	Median	7

Allogeneic transplants were carried out in 29 patients, whereas 13 patients underwent an autologous transplant. Myeloablative conditioning was used in nearly all patients, of which 12 were TBI based, 21 were busulfan based, and in 9 used other chemotherapeutic agents. The 12 patients who were given a TBI-based conditioning regimen received a total irradiation dose of 12 Gy to the whole body, given in 2 daily fractions of 2 Gy for 3 consecutive days. The TBI-based preparative regimen was combined with chemotherapy, mostly cyclophosphamide or etoposide. Patients with malignant diseases were treated according to the recommendations of international therapy protocols, and they all had chemotherapy for several months before the transplant procedure. Patients transplanted for nonmalignant diseases (n = 8) did not receive chemotherapy before the HSCT procedure. None of the patients had irradiation to the skull before HSCT.

Dental Examination

Each patient was examined at the department of Pediatric Dentistry of the Ghent University Hospital. A medical history of dental care and a clinical and radiographic examination focusing on dental agenesis, microdontia, and root-to-crown ratio was performed by 2 independent investigators (a final year dental student and a pediatric dentist). In addition, an orthopantomogram (OPT; Planmeca ProMax 2D, Location: Department of Dentistry at the Ghent University Hospital, Manufacturer: Planmeca, Planmeca Oy Asentajankatu 6 FI-00880 HELSINKI Finland) was taken. Finally, medical history focusing on relevant diseases and medication use, family history of dental aberrations, oral hygiene, caries and fillings, eruption, and occlusion were evaluated. Third molars were excluded for all analyses, and only permanent teeth were taken into account.

Knowledge of the mineralization process of the permanent teeth was of crucial importance for this research. Figure 1 shows the chronology of the dental mineralization of the permanent dentition [13]. The first molars start their calcification mineralization around birth, the permanent incisors and canines during the first year of life, and the permanent premolars and second molars during the second and third year of life [13]. Except for the third molars, development of the crown ends around the fifth to seventh years of

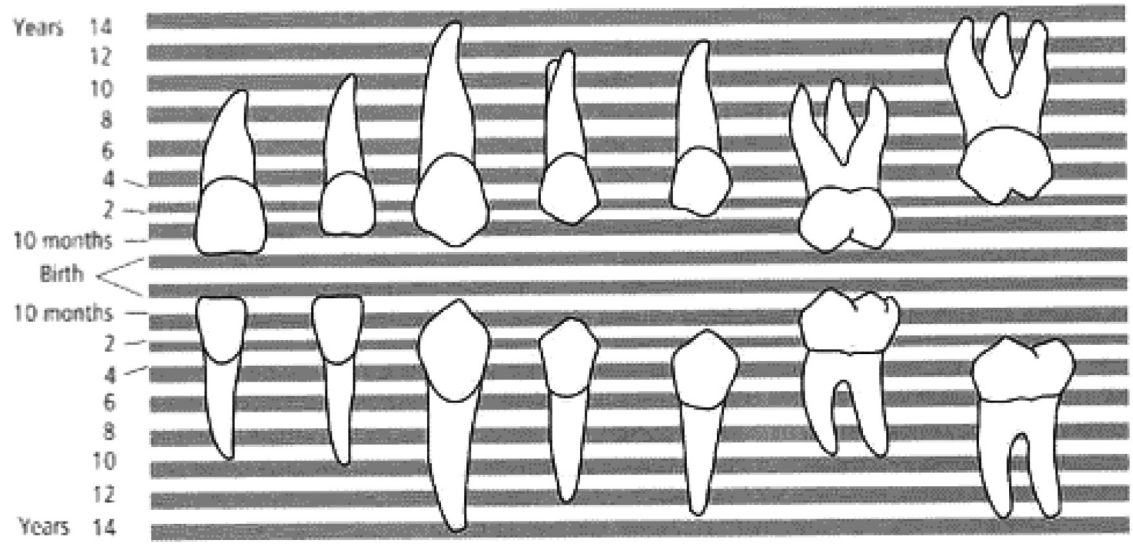

Figure 1. Chronology of permanent dental mineralization [13].

life [13]. Development of the root has a duration of 6 to 7 years. Individual variation should be considered [13].

Agenesis was diagnosed based on the clinical and radiologic examination. Clinically, all teeth should be present in the oral cavity at ages 12 to 14 [13]. Diagnosis of agenesis can be made earlier based on radiographic examination [7]. At 6 years all permanent teeth (except the third molars) should have started calcification mineralization and should therefore be visible on an OPT [7,13].

Because tooth size depends on many different factors like ethnicity, there is no strict definition of microdontia and no clear limits to help regarding measurements as normal [7,12]. Diagnosis of microdontia is therefore made when the size of the affected tooth is clearly smaller in comparison with its healthy counterpart. One way to diagnose this is by direct measurement in the mouth when the tooth is erupted or on radiograph before the eruption [7,12]. Another way to diagnose microdontia is measuring and comparing the crown size on dental models. Here also the teeth should be fully erupted. In this study the first method was used.

The root-to-crown ratio was measured by 2 blinded investigators on the OPT using (Image J is an open source Java image processing program. National Institutes of Health and the Laboratory for Optical and Computational Instrumentation at the University of Wisconsin). This software allows precise measurements. Reference points are the cement–enamel junction and the crest of the alveolar bone for, respectively, the anatomic and the clinical root-to-crown ratio [22]. The cutoff for measurements was .5 mm. To counteract any vertical deformation, the modified Lind method was used (Figure 2) [14,15,23]. Both researchers measured each tooth independently. To test the reliability of this method, a calibration was performed on normal OPTs. Mean Pearson correlation coefficients for inter- and intracorrelation were, respectively, .78 and .71. Therefore, this method was found to be reliable. Root-to-crown ratios that differed > 1 mm between both investigators were excluded from our results, and this was done in <5% of the cases. Immature teeth with an open apex and teeth with unclear reference points, abnormal root curvature, history of dental trauma or signs of attrition, abrasion, or erosion were excluded (<5% of cases) [14,15,22].

Statistical Analysis

The prevalence of agenesis, microdontia, and aberrant root-to-crown ratio found in our study was compared with the prevalence within a normal population as mentioned in the literature [7,11,12,15]. Fisher's exact test was used with the significance level of $P < .05$. Bonferroni correction for multiple testing was used when relevant. Logistic regression was used to compare the impact of age at HSCT with the impact of conditioning regimen on dental development.

RESULTS

Prevalence of Dental Aberrations

Prevalence of agenesis of 1 or more teeth was 51.3% (95% confidence interval, 36.2% to 66.1%) in the study population. The lower second premolar (29.5%) and the upper second premolar (27%) were found to be the most agenetic in this study population. The upper and lower first molar and the lower canine showed no agenesis.

Prevalence of microdontia of 1 or more teeth was 46.2% (95% confidence interval, 31.6% to 61.4%) in the study population. The lower first premolar (14.3%) and the upper second molar (13.4%) were most affected by microdontia in this study population. The upper first molar was not, and the lower first molar was only affected by microdontia in 2.6% of patients.

An aberrant root-to-crown ratio was seen in 76.3% (95% confidence interval, 60.8% to 87%) of patients.

Impact of Conditioning Regimen on Dental Development

There was no significant difference for agenesis in the different conditioning regimen groups ($P = .409$). Most agenesis was found in patients treated with busulfan (63.2%) compared with TBI (41.7%) and other chemotherapeutic agents (37.5%).

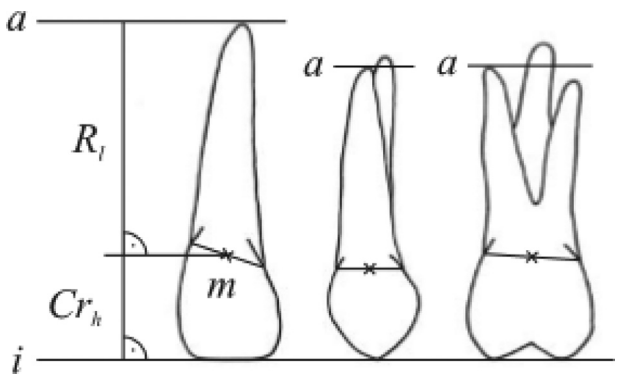

Figure 2. The modified Lind method [15]. *Reference line i*: occlusal or incisal plane. In molars and incisors this is determined by the connecting line between the buccal cusps or by the course of the incisal edge. In canines and premolars reference line i is determined by the tangent to the incisal or buccal cusp that is perpendicular to the axis of the tooth. *Reference line a*: tangent line to the apex of the tooth, parallel to reference line i. *Reference point m*: center of the connection line between the mesial and distal root-to-crown border. Cr_h: crown height measured from point m perpendicular to reference line i. R_l: root length measured from point m perpendicular to reference line a. Palatal roots were omitted, and in teeth with 2 buccal roots, the longer 1 was measured. (From [14,15,22,23].)

There was a significant difference for microdontia in the different conditioning regimen groups ($P = .023$). Pairwise testing showed that this difference was found between patients treated with busulfan (68.4%) and TBI (25%) (Figure 3). After Bonferroni correction for multiple testing, the difference in microdontia between the busulfan and the TBI group became nonsignificant ($P = .087$). There was no significant difference for root-to-crown ratio aberration in the different conditioning regimens (TBI, 72.7%; busulfan, 78.9%; other chemotherapeutic agents, 75%).

When comparing the total effect (agenesis and/or microdontia and/or aberrant root-to-crown ratio) of conditioning regimen on dental development, there was no significant difference between the 3 conditioning regimens ($P = .252$). Busulfan (94.7%), TBI (75%), and other chemotherapeutic agents (75%) had a comparable effect on dental development.

Impact of Age at HSCT on Dental Development

Age had a strong effect on agenesis ($P < .001$), and this was significant between the different age categories (Figure 4). After Bonferroni correction for multiple testing, the difference in agenesis between ages < 3 years and 3 to 6 years remained strongly significant ($P = .003$).

Age had a very strong significant effect on microdontia ($P < .001$). Pairwise comparison of the different age categories showed a significant difference between ages < 3 years (76.9%) and >6 years (11.8%; $P < .001$) and 3 to 6 years (66.7%) and >6 years ($P = .008$) (Figure 5). After Bonferroni correction for multiple testing, these results remained significant.

There was no significant difference in effect on root-to-crown ratio aberration between the different age groups ($P = .16$). Prevalence of aberrant root-to-crown ratio was 69.2%, 100%, and 68.8% for the youngest to the oldest age group, respectively. Note that all patients aged 3 to 6 years old had an aberrant root-to-crown ratio of at least 1 tooth, which was correlated to the timing of dental development.

When comparing the total effect (agenesis and/or microdontia and/or aberrant root-to-crown ratio) of age on dental development there was a significant difference ($P = .011$) between the different age groups. It was clear that the oldest age category (70.6%) showed less disturbances in dental development compared with the youngest group (92.3%).

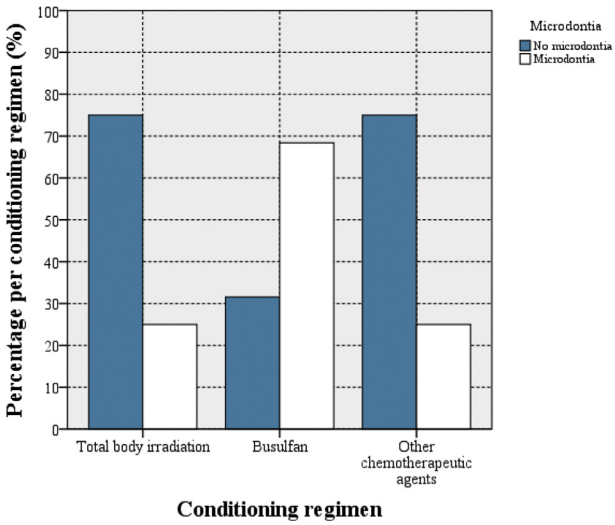

Figure 3. The impact of conditioning regimen on microdontia.

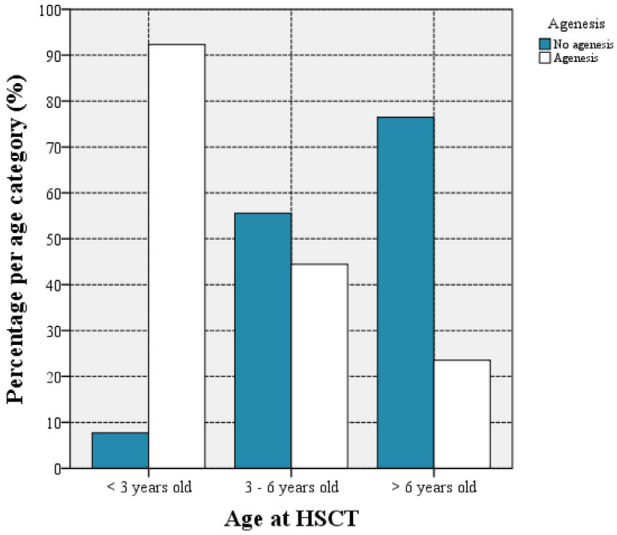

Figure 4. The impact of age at HSCT on agenesis.

Impact of Conditioning Regimen Compared with Impact of Age on Dental Development

Age had a significantly different distribution in the 3 conditioning groups ($P = .002$). TBI-based regimens were not used in patients aged < 3 years (Table 2).

A logistic regression was performed to evaluate the individual impact of both risk factors. Corrected for conditioning regimen, age had a strong significant association with agenesis ($P = .009$) and microdontia ($P = .020$). However, corrected for age, conditioning type was not significantly associated with agenesis or microdontia in the whole group. Our results showed that in the subgroup of patients treated after 6 years of age, there was significantly more microdontia when treated with busulfan (50%) compared with treatment with TBI (0%; $P = .044$).

Clinical Examples

Figure 6 shows the dentition of a patient treated with HSCT for nephroblastoma at age 2 years and 4 months. OPT was taken at 9 years and 4 months of age. An aberrant root-to-crown ratio (1) of the first molars can be seen. The first and second premolars,

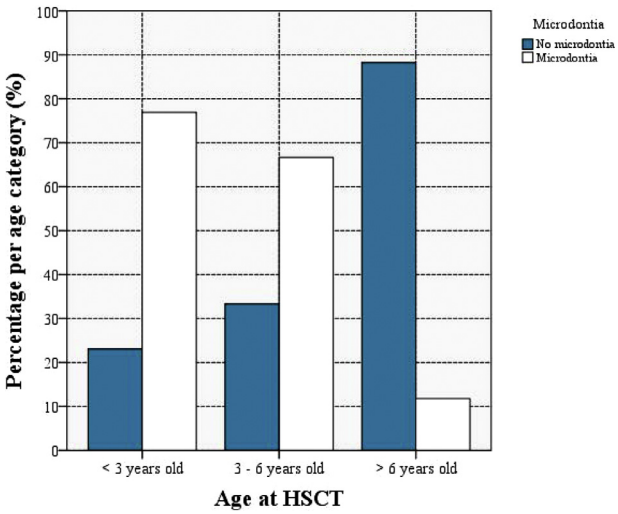

Figure 5. The impact of age at HSCT on microdontia.

Table 2
Distribution of Age at HSCT in the Different Conditioning Regimen Groups

	Age at HSCT			
Conditioning Regimen	<3 Years	3-6 Years	>6 Years	Total
TBI based	0	4	8	12
Busulfan based	13	4	4	21
Other chemotherapeutic agents	3	1	5	9
Total	16	9	17	42

with exception of tooth 24, are agenetic (2). Tooth 24 is considered to be microdontic (3).

Figure 7 shows the dentition of a patient treated with HSCT for neuroblastoma at age 3 years and 10 months. OPT was taken at 8 years and 5 months of age. An aberrant root-to-crown ratio (1) of the central and lateral incisors and the first molars can be seen. The second premolars are microdontic (3) and the second molars are agenetic (2).

Figure 8 shows the dentition of a patient treated with HSCT for juvenile metachromatic leukodystrophy at age 10 years and 7 months. OPT was taken at 19 years and 8 months of age. An aberrant root-to-crown ratio (1) of the first and second premolars and second molars can be seen.

DISCUSSION

This study investigated the impact of different conditioning regimens (busulfan based, TBI based, and other chemotherapeutic agents) and age at HSCT on dental development in children who underwent HSCT before age 12 years. The impact of head and neck radiation therapy and TBI on dental development has been described in the literature, but little is known about the late effects of non–TBI-based conditioning regimens and more specific busulfan-based regimens.

This study showed that the younger the patient at HSCT, the higher the risk of dental agenesis, with a prevalence of up to 92% for the youngest patients. The chronology of mineralization of the permanent dentition as depicted by Koch et al. defines possible dental aberrations that can be expected at a certain age [7,13]. Our study confirmed that the youngest patients were the most vulnerable for dental agenesis. This finding is in accordance with Hölttä et al. [7] and van der Pas-van Voskuilen et al. [5]. Patients with a known genetic predestination for dental aberrations were excluded from our study. Diseases with a known impact on dental development such as some metabolic disorders (osteopetrosis) were also excluded. Thus, it seems probable that the high prevalence of agenesis can be linked to the exposure to cytotoxic drugs and/or TBI.

In this study we looked at the impact of the procedure of HSCT on dental development, especially the possible impact of chemotherapy-based conditioning regimens and more specifically busulfan-based conditioning regimens. In our study more agenesis was seen in patients treated with busulfan compared with treatment with TBI or other chemotherapeutic agents, but the difference was not statistically significant. Preliminary data of Dahllöf et al. [21] showed significantly more agenesis in patients treated with busulfan compared with treatment with TBI.

The prevalence for microdontia in our study was highest in the youngest age category. This result is in accordance with previous research [4,7].

We noticed that microdontia was more apparent in patients treated with busulfan compared with the other conditioning regimens in our study population. Dahllöf et al. [21] noted a higher prevalence of microdontia in patients treated with busulfan compared with patients treated with TBI (preliminary data). Hölttä et al. [7] found more microdontia in the non-TBI-group versus the TBI-group. However, Hölttä et al. [7] did not specify the different chemotherapeutic protocols in the non-TBI group.

A high prevalence of aberrant root-to-crown ratios in the middle age group was seen, and all 3 different conditioning regimens had a similar effect in this study. In contrast, Hölttä et al. [15] noted a higher prevalence of interrupted root development in the TBI group compared with the non-TBI-group.

Because TBI is predominantly used in patients older than 6 years and busulfan can be used in younger patients, age and conditioning regimen may not be independent. Therefore, conditioning regimens were compared within age groups and vice versa. Our study hypothesizes that age at HSCT has a stronger effect on dental development compared with type of conditioning regimen. Nonetheless, more microdontia was noticed in patients older than 6 years and treated with a

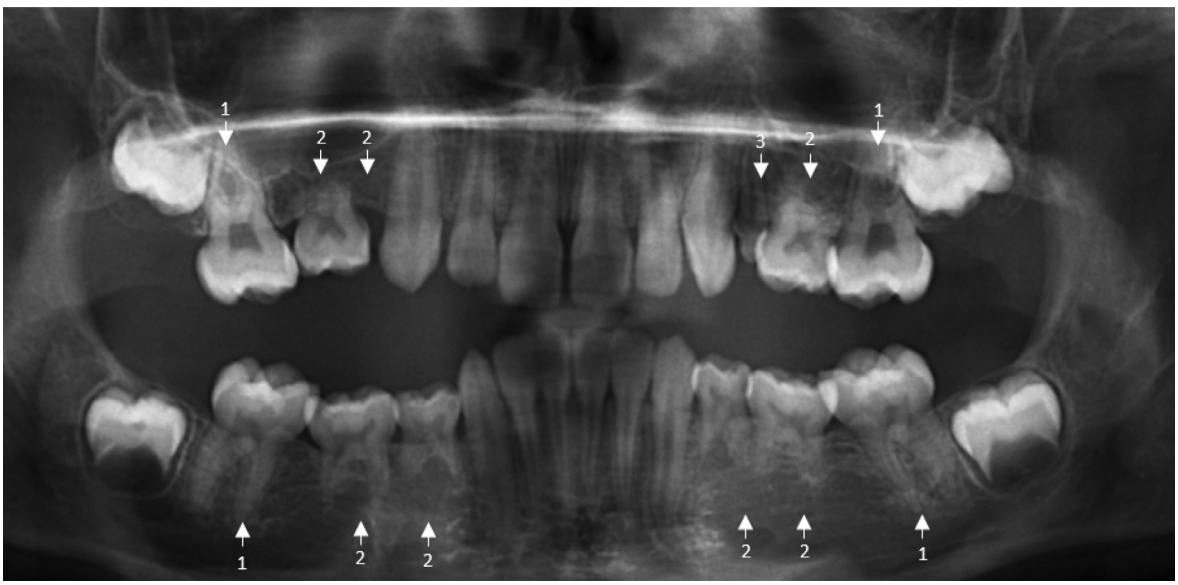

Figure 6. Clinical example of a patient who underwent HSCT as part of therapy for nephroblastoma at age 2 years 4 months.

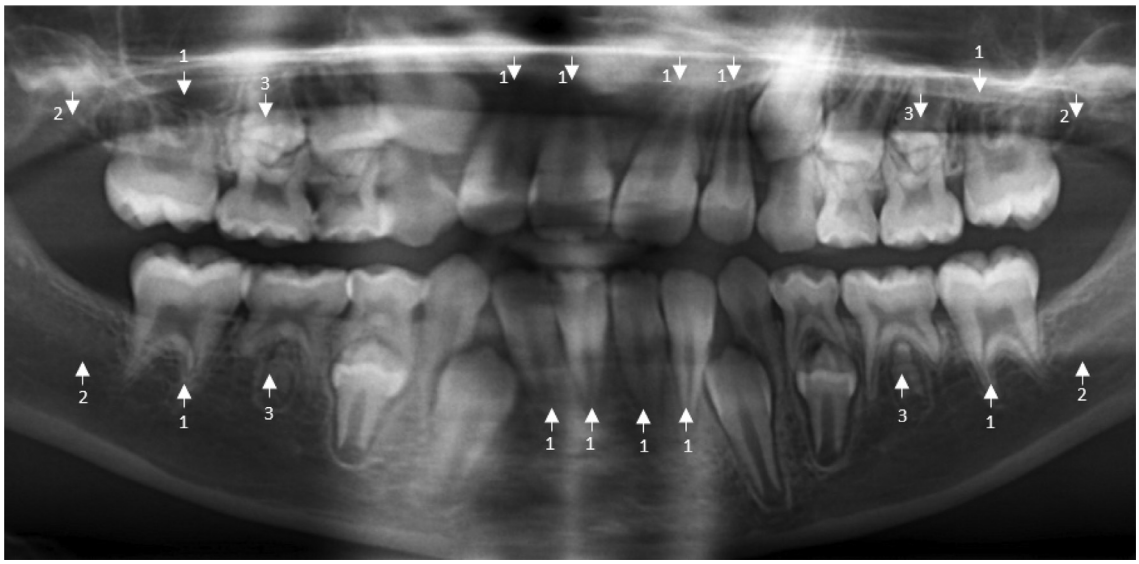

Figure 7. Clinical example of a patient who underwent a HSCT as part of therapy for neuroblastoma at age 3 years and 10 months.

busulfan-based conditioning compared with a conditioning regimen including TBI. Vesterbacka et al. [4] suggested that busulfan is as detrimental as TBI for dental development. Conversely, Näsman et al. [6] concluded there were more disturbances in dental development in patients treated with TBI compared with those treated with a non-TBI regimen. Näsman et al. [6] did not specify the chemotherapeutic agents used in the non-TBI group, and some of these patients received cranial irradiation [6].

We are aware of possible limitations of the study. It investigated a small group of pediatric HSCT recipients with a large variety of underlying malignant and nonmalignant diseases. Despite the variety of the underlying diseases, the conditioning regimens used were mostly myeloablative, and there was an equal distribution of patients who were heavily pretreated in the different study groups. The cytotoxic treatment before HSCT may have an influence on the high prevalence of dental aberrations reported in this study. Therefore, the reported data must be interpreted with caution, and more investigations are needed to confirm these preliminary results.

Children under 1 year and older than 12 years at HSCT were excluded from this study. At age 12 dental development, excluding the third molar, is complete, and therefore these children have little to no risk for dental disturbances. The inclusion criterion of those < 12 years old at HSCT was also used by Näsman et al. [6] and Vesterbacka et al. [4]. Our study patients were divided into 3 categories: <3 years old, 3 to 6 years old, and >6 years old. Comparable categories were used in previous research: <3 years old, 3 to 5 years old, and >5 years old [5-8]. This small difference in age was done to have proportional groups for statistical analysis. Because this study dealt with small subgroups, individual patients have a large impact. Some of them will be further discussed in future case reports.

Effort was made to exclude confounding variables causing dental aberrations. For example, patients with genetic

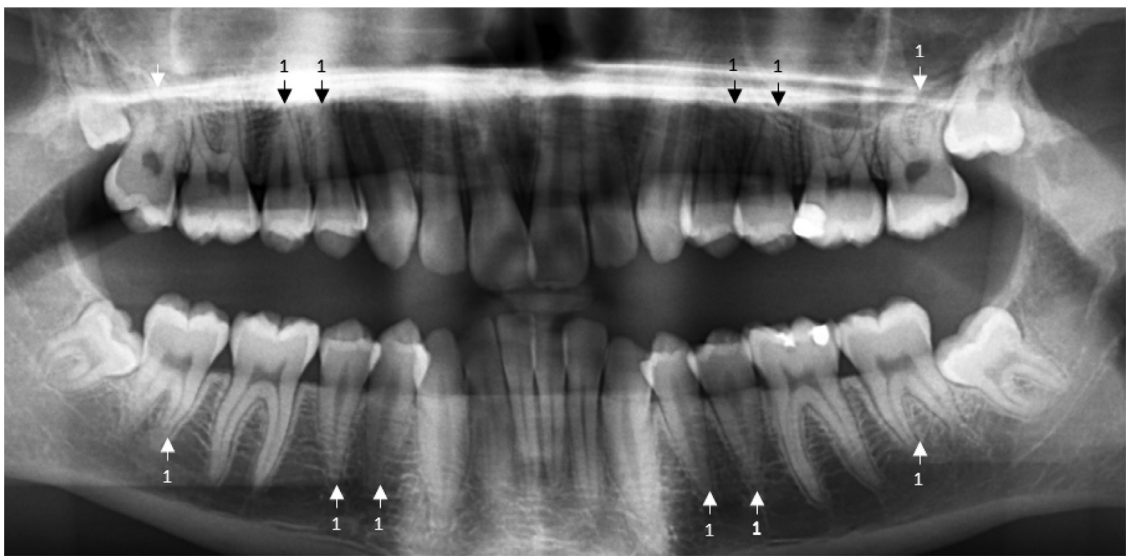

Figure 8. Clinical example of a patient who underwent a HSCT for juvenile metachromatic leukodystrophy at age 10 years and 7 months.

disorders linked to dental disturbances or a family history of dental aberrations were excluded. However, unknown inborn errors responsible for the agenesis or microdontia in patients treated at an older age cannot be excluded from this study.

All examinations were performed by the same 2 independent investigators, which limits the amount of interobserver bias. Considering the inclusion and exclusion criteria of this study, a relatively large group of patients was examined compared with other studies [4-6]. Until now, only Hölttä et al. [7,15] had a larger study cohort. We recommend larger cohorts to confirm the results from this study.

In conclusion, patients treated with HSCT before age 12 had many disturbances in dental development. Age at HSCT and possibly also conditioning regimen used had effects on their type and prevalence. Dental follow-up in a specialized setting is recommended. Additionally, parents and patients should be given adequate information on this topic.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.08.027.

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