Craniofacial growth in children treated for malignant diseases

Göran Dahllöf
Department of Pediatric Dentistry, School of Dentistry, Karolinska Institutet, Huddinge, Sweden

Dahllöf G. Craniofacial growth in children treated for malignant diseases. Acta Odontol Scand 1998;56:378–382. Oslo. ISSN 0001-6357.

With the improving cure rate in childhood malignancies, increasing interest has been focused on the long-term survivors of childhood cancer and the quality of their life. The severity of long-term disturbances in dental and craniofacial development is dependent on the age of the child at diagnosis, if chemotherapy is combined with radiation or not. With regard to craniofacial development combination chemotherapy has no effects compared with healthy controls, whereas children treated cranial irradiation before 5 years of age exhibit a reduced growth of the mandible. Conditioning before bone marrow transplantation with total body irradiation results in a significantly reduced growth of the craniofacial skeleton. The mandible was four times more radiosensitive compared with the maxilla. With attention to the dental and craniofacial development, occlusion and craniomandibular function, children in risk groups should be followed, and given prophylactic treatment and intervention at appropriate times to reduce the consequences of the disease itself and the therapy given. □ *Cancer; chemotherapy; children; malignant diseases; radiation therapy*

Göran Dahllöf, Department of Pediatric Dentistry, School of Dentistry, Karolinska Institutet, P.O. Box 4064, S-141 04 Huddinge, Sweden

Pediatric and adolescent cancer represent about 1% of all cancer cases. In Sweden about 275–300 new cases occur annually. The improvement in survival has been dramatic and achieved over the course of two decades, with the oldest survivors now young adults. It is projected that, in the year 2000, 1 in every 900 adults will be a survivor of childhood cancer (1). With the improving cure rate in childhood malignancies, increasing interest has been focused on the long-term survivors of childhood cancer and the quality of their life.

In some studies disabilities have been detected in as many as 40% of the survivors of childhood cancer (1). Cardiac dysfunction after anthracycline administration and radiation therapy is well known (2). Second cancers are also a significant cause of morbidity and mortality among this population (3). During treatment of leukemia the growth rate generally declines. Soon after therapy the normal growth rate is resumed, or there may even be a catch-up growth. After CNS radiation, however, the final height of female patients is less than expected, owing to early onset puberty and a pubertal growth spurt of subnormal magnitude (4). After bone marrow transplantation (BMT) with total body irradiation (TBI), the children show a continuing growth impairment (5, 6). Bone mineral density is often reduced in long-term survivors of childhood malignancies (7). Low bone mineral density at a young age may lead to significant clinical problems of osteoporosis and fractures (8).

Children treated for childhood cancer also exhibit both acute and long-term complications in the oral cavity and in dental and craniofacial development (9–15). Although life-threatening systemic infections can develop from the oral cavity, more frequently the acute oral complications cause severe discomfort that interferes with oral hygiene and proper nutrition and may delay completion of cancer therapy (11).

The focus of this review is the long-term effects of antineoplastic therapy in childhood on craniofacial development, the interplay between disturbances in dental and craniofacial development, and the consequences with regard to occlusion and TMJ function.

Effects on dental development

Mineralization

A high incidence of disturbances in dental development can be diagnosed in children after different forms of antineoplastic therapy. In studying a group of long-term survivors after chemotherapy treatment for malignancies during childhood, Purdell-Lewis et al. (16) reported that 80% of the children exhibited some type of opacity. In a comparison between children treated with chemotherapy protocols for malignant diseases and children conditioned with 10-Gy TBI prior to BMT, Näsman et al. (17) found that 4.1 ± 5.0 teeth were affected by disturbances in enamel mineralization. In the TBI group 4.6 ± 4.6 teeth were affected, both counts being significantly higher than those of the healthy control group: 0.7 ± 1.4 ($P < 0.05$). White/cream colored opacities were most commonly diagnosed in all three groups, followed by yellow/brown opacities. Twelve percent of the children treated with TBI exhibited hypoplasia, compared with 8% in the chemotherapy group.

Cytotoxic drugs have a short half-life in the human body, and the drugs are metabolized or excreted from within 24 h up to a few days. Thus, the effect on fully differentiated cells such as ameloblasts and odontoblasts will be only transient, and undifferentiated surviving cells will continue to differentiate.

Size

Tooth size is reduced as a result of chemotherapy and/or radiation therapy (18, 19). In a study of long-term survivors of childhood cancer, Näsman et al. (19) reported that children treated with cyclophosphamide (CY) and TBI exhibited the most extensive reduction. Compared with a control group, these children showed reductions in tooth size ranging from 19% in the incisors ($P < 0.001$) to 39% in the second molars ($P < 0.001$). The corresponding values in the chemotherapy group were 7% ($P < 0.05$) and 15% ($P < 0.05$), respectively. The measures were taken on mandibular teeth, and previous cranial irradiation performed on a subgroup of the chemotherapy-treated patients did not seem to affect the size of the mandibular teeth examined.

The reduction in tooth size was mainly due to severe disturbances in root development, which was particularly pronounced in the CY/TBI group. The mean reduction ranged from 24% in the incisors ($P < 0.001$) to 46% in the second premolars ($P < 0.001$).

Regression lines were calculated for crown/root ratios to age at TBI or initiation of chemotherapy. A significant correlation was found in the CY/TBI group for all teeth examined ($P < 0.05$), while no correlation was found in the chemotherapy group. These results are partly in agreement with those of Pajari et al. (18), but their study showed no reduction in crown size, probably owing to a slightly older child population.

Disturbances in dental development and particularly in root development after antineoplastic therapy (17, 20) are characterized by arrested root development with short v-shaped roots, arrested root development with premature apical closure, microdontia, and an increased incidence of aplasia (Fig. 1).

Eruption times

No significant difference was observed between chronologic age and dental maturity in 44 children treated with chemotherapy protocols compared with healthy controls (21). With regard to the number of erupted permanent teeth, no significant differences could be found between the two groups.

Effects on craniofacial development

Effects of chemotherapy protocols and cranial irradiation

Twenty-seven children with acute lymphocytic leukemia (ALL) and treated with chemotherapy (CT) and cranial irradiation (CI) (mean age at diagnosis, 8 years) were examined 5 years later (22). Six children receiving mantle field radiation for lymphoma (mean age at diagnosis, 8 years) were also studied 9 years later. The cephalometric mean values were compared with standard reference values. The longitudinal values were reduced by 5%–11% in children given CI. The distances s-A, S-B, and S-Pg (23) exhibited the highest reduction, about 10%. The anterior cranial base length (s-n) was reduced by 11%, and the anterior facial height (n-gn) and the horizontal portion of the mandible (go-pg) were also significantly reduced ($P < 0.05$). In children treated with mantle field irradiation, by which the radiation field can cover the mandible and maxilla below the nose, the longitudinal values were reduced by 2%–7%.

Holtgrave et al. (24) reported a cephalometric study of 60 children, 26 treated with CT protocols for solid tumors and 34 treated with CT and CI, 18 Gy or 24 Gy. They were diagnosed between 3 months and 4.3 years of age and examined 5.3–15.8 years after diagnosis. The cephalometric values were compared with standard reference values. It was found that longitudinal values were reduced by 0.75%–2.91% compared with reference values. S-n, s-pg, s-A, and ar-Pg exhibited the largest reduction, 2.77%–2.91%. The anterior face height (n-gn)

Fig. 1. An 11-year-old girl treated with bone marrow transplantation at 2.2 years of age receiving 10-Gy total body irradiation. The panoramic radiograph shows v-shaped short roots, enamel hypoplasia, microdontia, and multiple missing teeth.

was reduced by 2.13%. All values in the children given CI were reduced, but no significant difference was found between them and children treated for solid tumors.

Sonis et al. (25) studied dentofacial development in long-term survivors of ALL and compared three treatment modalities: 1) combination chemotherapy (CT); 2) CT, intrathecal methotrexate, and 18-Gy CI; and 3) CT, intrathecal methotrexate, and 24-Gy CI. Craniofacial abnormalities occurred in 18 of 20 children (90%) who received 24-Gy CI before 5 years of age. The mean cephalometric values showed significantly deficient mandibular development. In children not receiving CI, the cephalometric values showed no statistically significant difference from normal reference values.

In these studies all children treated for hematologic malignancies without CI show cephalometric values within the normal range (25). Studies on dental development show a slight reduction of the tooth size, 7%–15%, without affecting the craniofacial development. Earlier studies (22, 24) show that children given CI exhibit a reduction of the longitudinal cephalometric values up to 11% compared with standard reference values. Sonis et al. (25) showed that children below 5 years of age had significantly reduced longitudinal values, particularly for those variables describing mandibular growth. Children older than 5 years showed no significant changes compared with reference values.

Effects of total body irradiation

Bone marrow transplantation using marrow ablative doses of CT or chemoradiotherapy, followed by an infusion of hematopoietic stem cells, is being used in an increasing number of children as treatment of malignant and non-malignant disorders. The most common regimens use high doses of CY, given alone or in combination with such agents as busulphan or TBI, 10–12 Gy (26). Both CT and irradiation are known to affect neuroendocrine system function and therefore growth and development (5). TBI has the therapeutic goals of destroying malignant cells, providing sufficient immunosuppression to help prevent graft rejection, and allowing normal bone marrow depletion to provide space for the graft.

In a cephalometric study of craniofacial growth in 17 children treated with CY/TBI, all linear values were significantly reduced compared with those of a healthy control group (27). The most pronounced effects were seen in the youngest patients. The anterior cranial base (s-n) exhibited the smallest difference between the two groups ($P < 0.05$). In children treated with TBI after 7 years of age, no significant difference was found. Following a growth spurt during the first year after birth, the adult dimension of the middle (ethmoid) segment of the cranial base is reached at about 7 years of age (28). A significantly reduced length in both the maxilla (pns-sn) and the mandible was recorded in the BMT group at all ages studied. The difference in maxillary length (pns-sn) between the CY/TBI and control groups was approximately 1 mm at 7 years of age; the corresponding difference in mandibular length (cd-pgn) was four times as great. The reduction was more pronounced in the mandible than in the maxilla, owing to the fact that the maxilla lacks enchondral bone formation.

The height of the alveolar processes in the incisor and first permanent molar region was significantly reduced in the BMT group. The older the patient was at the time of TBI, the less difference compared with normal controls. It was concluded that the poor development of alveolar height in the younger BMT patients may be due to the fact that children conditioned with TBI exhibit severe disturbances in dental development, as described above (19). When TBI was given to children 10–11 years of age, only a marginal effect was seen on the alveolar height.

The rate of skeletal growth varies with age and between different regions of the skull. The effect of TBI on growth is therefore dependent on the age of the patient and the craniofacial area studied.

Effects of localized radiation therapy

In a study of 68 long-term survivors of childhood cancer, 45 had received maxillofacial radiation for lymphoma, leukemia, rhabdomyosarcoma, and miscellaneous tumors (29). Dental and maxillofacial abnormalities were detected in 37 of the 45 children (82%). Maxillofacial abnormalities comprised trismus, abnormal occlusal relations, and facial deformities. On clinical evaluation the most severe deformities were diagnosed in children who had received higher doses at an earlier age for rhabdomyosarcoma (median radiation dose, 55 Gy) as opposed to Hodgkin's disease and leukemia (median radiation dose, 35 Gy) ($P < 0.001$). In children with Hodgkin's disease mild mandibular hypoplasia was noted on the side that received radiation. In children with leukemia receiving CI, the roots and crowns of the first maxillary molars showed evidence of developmental disturbances but no facial deformity. The children with rhabdomyosarcoma were treated with radiation doses of 45–65 Gy, using a variety of ports generally involving the nasopharyngeal area. Four of nine patients developed trismus, nasal voice, and extensive caries. Five patients had maxillary and/or mandibular facial deformities.

Late effects after treatment of 20 children with soft tissue sarcomas in the head and neck were reported by Fromm et al. (30). The children had been treated with radiation therapy in combination with CT. The mean age at diagnosis was 6.0 years (range, 7 months–13 years) with a mean follow-up time from diagnosis of 5.5 years. The major problems encountered were related to eyes (xerophthalmia and cataracts), ears (hearing loss), teeth (disturbances in development and eruption), salivary glands (salivary dysfunction), hypothyroidism, and craniofacial deformity. Deformity was found in all 16 patients aged 9 years or younger at diagnosis. Five patients were noted to have a severe cosmetic deformity with severe maxillary hypoplasia. Two of the children developed TMJ fibrosis with limited joint motion. The tumor dose given to these children varied between 40 Gy and 60 Gy.

Of 41 children given localized radiation to the head and neck during growth, 38 had soft tissue or bony deformities (31). The threshold for harmful effects was calculated to be as low as 4 Gy for the soft tissues and 30 Gy for the craniofacial skeleton.

Children treated with megavoltage external beam irradiation for the treatment of retinoblastoma show orbital and midfacial growth retardation (32). When lateral fields are used in unilateral cases, the contralateral orbit still receives 75%–83% of the tumor dose, 34–35 Gy. Most orbital and midfacial deformities develop and become more apparent during and after adolescence. Radiotherapy was more damaging to the orbital growth in children younger than 6 months than at an older age ($P < 0.01$), and secondary enucleation did not have an additive growth-retarding effect (33).

It is evident from this review that, although few children are treated with localized radiation therapy at a young age, it has a very deleterious effect on craniofacial development. The treatment is often unilateral, creating unilateral bone deformities. Growth should be followed carefully, and reconstructive surgery may be needed for correction of the craniofacial deformity.

Effects of growth hormone treatment

The conditioning therapy with high doses of CY and TBI before bone marrow transplantation results in a reduced growth rate and suboptimal levels of growth hormone (GH) (5). Craniofacial growth was studied in nine children exhibiting growth retardation after BMT (34, 35). They were treated with recombinant GH at a mean age of 12.1 years and evaluated after 3.5 years of treatment. The mean height standard deviation score for standing height was -2.18 at the start of GH therapy and -1.87 at the second evaluation. In the GH-substituted children, no significant differences with regard to growth changes was found compared with normal age- and sex-matched controls. In the CY/TBI group not treated with GH, the mean growth increment was significantly reduced for the variables mandibular length ($P < 0.01$) and mandibular height ($P < 0.05$). The mean growth increment of the length of the mandible was only 30% of that in the recorded in the controls. GH given to children with reduced growth rates after CY/TBI resulted in a mean growth rate similar to that in healthy controls. Although exogenous GH therapy in this group of children did not induce catch-up growth, it appears to have prevented further loss of growth potential.

Consequences for craniomandibular function and occlusion

Children subjected to BMT and conditioned with TBI exhibit a high prevalence of signs and symptoms of craniomandibular dysfunction (36). The number of occlusal contacts was 12.9 ± 4.1 in children treated with CY/TBI, which was significantly lower ($P < 0.05$) than in a healthy control group (18.6 ± 6.3). Thus, anterior open bite was significantly more frequent in the CY/TBI group ($P < 0.05$). Children conditioned with TBI also showed a reduced opening capacity, and a reduced translation movement of the condyles was diagnosed in 53% of children treated with CY/TBI, compared with 5% in the control group ($P < 0.01$). Signs and symptoms of craniofacial dysfunction were found in 84% of children treated with CY/TBI, compared with 54% in a healthy control group. Both irradiation and CT induce long-term adverse effects in connective tissues, resulting in inflammation and eventually fibrosis (37). Chemotherapy as well as irradiation affects the release of both interleukin-1 and tumor necrosis factor-alpha (38, 39). Irradiation also causes endothelial fibrosis and decreased tissue blood flow, which particularly impairs muscle function (40).

Concluding remarks

In conclusion, this review shows that current protocols of combination chemotherapy and radiation therapy induce long-term adverse disturbances in craniofacial development. Children below 5 years of age and those given radiation therapy are at highest risk, along with children given unilateral radiation therapy, which induces an asymmetric growth of the facial skeleton. The growth deficit will often not be fully developed until after the pubertal growth spurt. With attention also to the dental development, development of occlusion, and craniomandibular function, children in risk groups should be followed and given prophylactic treatment and intervention at appropriate times to reduce the consequences of the disease itself and the therapy given.

Acknowledgements.—This study was supported by grants from the Swedish Children's Cancer Foundation, the Patent Revenue Foundation, and the Swedish Medical Research Council.

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