CASE REPORT

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Microdontia after chemotherapy in a child treated for neuroblastoma

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Structured Abstract

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Objective – Chemotherapy used on paediatric oncology patients often causes disturbances in dental development. Aim of this case report is to present the late effects of chemotherapy on dental development in a patient treated for neuroblastoma at early age.

Design – Case report.

Results – This paper presents a female patient treated at early age with surgery and chemotherapy for a neuroblastoma (stage IVS) in the right thorax and massive liver metastases. The examination of the patient at age 11.7 years showed microdontia of six teeth. In three of them size and form of the crown were affected, while in the other three the size was reduced but the form was not affected.

Conclusions – Chemotherapy on children treated for neuroblastoma can adversely influence tooth development. This has to be taken into consideration by the dentist when monitoring the development of the dentition and occlusion.

Key words: drug therapy; neuroblastoma; odontogenesis; tooth abnormalities

Introduction

Neuroblastoma is the most common infant malignancy (1) and one of the most common childhood tumours (2,3). It is a solid tumour that arises from neural crest cells, and it can occur primary everywhere in the body but most commonly in the retroperitoneum (4). Most patients have metastases at diagnosis (5). Neuroblastoma shows a great spectrum of clinical behaviour (6–8). This was the reason for the development of a risk-based

classification based on clinical and biological features of the disease [International Risk Grouping System; for details see (9)]. Patients with low-risk disease have a favourable prognosis and usually require minimal therapy using surgery as a primary treatment approach, although some patients will require cytotoxic therapy. Intermediate-risk patients are treated with a combination of surgery and chemotherapy or local radiation in some cases and show also very good prognosis. However, cure rates for patients with high-risk disease are rather low (<50%) in spite of intensive multimodality treatment including induction chemotherapy, high-dose myeloablative therapy followed by stem cell or bone marrow transplantation, minimum residual disease therapy, surgery and in some cases local radiation therapy (7,8). To improve the treatment results in high-risk patients, new approaches like retinoid therapy, immunotherapy, anti-angiogenic therapy and new forms of drug delivery are currently investigated.

The intensive multimodality treatment that is used in patients with neuroblastoma has been shown to have late adverse effects like musculoskeletal abnormalities, cardiopulmonary sequelae, ototoxicity, damage of renal tubule, impairment of gonadal function, endocrine consequences, secondary malignant neoplasms and psychosocial effects (6).

Also disturbances in dental development like tooth agenesis, microdontia and short roots have been reported in a group of patients with high-risk neuroblastoma treated with autologous stem cell transplantation after myeloablative therapy with high-dose chemotherapy and/or total body irradiation (10–12). Total body irradiation was shown to increase the adverse effects (10–12). Similar dental abnormalities have been reported in a small number of neuroblastoma patients treated with bone marrow transplantation after chemotherapy and total body or head/neck irradiation (13,14) and in patients that received head/neck irradiation as local therapy of a metastasis (14).

Little can be found in the literature concerning the effects on dental development in patients with neuroblastoma treated only with chemotherapy. Kaste *et al.* (14) reported dental abnormalities in 37 of 44 children who received chemotherapy according to a variety of treatment protocols, while Goho (13) in his case series presented one patient with neuroblastoma treated with chemotherapy, who had affected primary dentition when evaluated at 4.5 years of age.

Aim of this case report is to present the late effects of chemotherapy on dental development in a patient treated for neuroblastoma at early age.

Case report

This female patient visited the Department of Orthodontics and Oral Biology, Radboud University Nijmegen Medical Centre at the age of 11.7 years seeking orthodontic treatment.

Anamnestic history

At the age of 3 months, the patient was diagnosed with a neuroblastoma stage IVS according to the International Neuroblastoma Staging System (INSS), with a primary tumour in the right thorax and massive liver metastases [For description of the INSS, see(15,16)].

After a non-radical thoracotomy, she received one course of chemotherapy with cyclofosfamide (150 mg/m^2, q.7) and doxorubicine (50 mg/m^2, q. 1). At the age of 11 months, she developed a local relapse in the scar of the thoracotomy, which was treated with six courses (q. 4 weeks) of carboplatin 200 mg/m^2, d. 1, teniposide 100 mg/m^2, d. 2, cyclofosfamide 150 mg/m^2, d. 2–6, doxorubicine 30 mg/m^2, d. 6.

Rethoracotomy revealed no macroscopic tumour, but microscopic invasion of the muscle and subcutis with mature ganglioneuroma was present. At follow-up, she remained in complete remission, but had a mild scoliosis.

Physical examination

The following data were obtained from the physical examination at the start of the orthodontic treatment. The length of the patient was 152,6 cm (−1 SD) and the weight was 40 kg. Skull circumference was 53,5 cm (−0.5 SD). The patient had a slightly long face without evident dysmorphology. Both the thorax and the abdomen showed no abnormalities. The patient wore a brace because of thoracic scoliosis. The patient's right leg was found to be 1 cm longer than the left one; a syndactily of digit II and III was present. No abnormalities on the skin and hairs could be found.

Fig. 1. Lateral view of the occlusion.

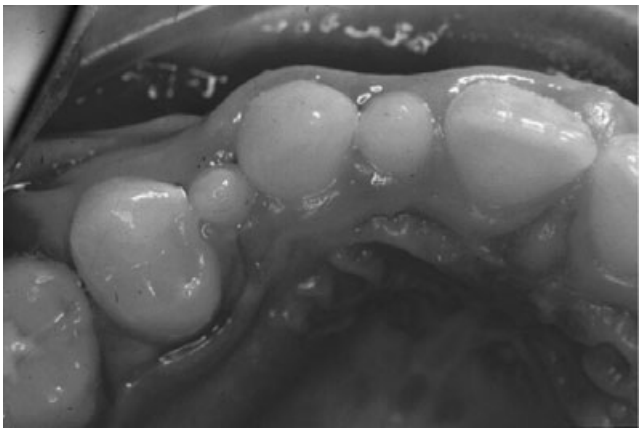

Fig. 2. Teeth 12 and 14 are peg shaped.

Intra oral examination

The intra-oral examination showed a class II/2 malocclusion with a bilateral posterior cross bite (Fig. 1). Three peg shaped teeth: 12 (Fig. 2), 14 (Fig. 2) and 24 (Fig. 3) and three microdentes (with strongly reduced size, but normal crown form): 22 (Fig. 3), 34 (Fig. 4) and 44 (Fig. 5) were present. There was no family history of microdontia.

Fig. 3. Tooth 22 is a microdens and 24 is peg shaped.

Fig. 4. Tooth 34 is a microdens.

Radiological examination

The orthopantomogram shows that all teeth, third molars included, are present (Fig. 6). The root dimensions of the teeth 14, 24 and 34 were more affected than of the teeth 12, 22 and 44.

Discussion

The most striking dental finding on this patient treated for a low-risk neuroblastoma is the microdontia of six teeth. The prevalence of microdontia is generally very low. A recent study on children preparing for bone marrow transplantation reported only

Fig. 5. Tooth 44 is a microdens.

Fig. 6. Orthopantomogram of the patient at age 11.7 years.

4% microdontia (17). On the other hand, very high prevalence of microdontia (78%) was shown in a group of patients with high-risk neuroblastoma treated with autologous stem cell transplantation after myeloablative therapy with high-dose chemotherapy and/or total body irradiation (10). It seems that the younger the patient the higher the risk for agenesis or microdontia (11). Much lower prevalence (38%) reported the study of Kaste et al. (14) on children with neuroblastoma who received chemotherapy according to a variety of treatment protocols (only eight of the 52 children were treated with irradiation, while the remaining 44 received only chemotherapy). In the three patients with neuroblastoma presented as part of the cases series of Goho (13), no presence of microdontia is reported (two of these patients were treated with bone marrow transplantation after chemotherapy and total body irradiation). However, all three patients were examined rather early (4–5 years of age), so that the detection of this anomaly is problematic for several permanent teeth.

Experimental studies have shown adverse effects on the developing teeth of cyclophosphamide and doxorubicin, chemotherapeutic agents that were also administered to the present patient (18–22). Furthermore, reduction of crown dimensions of the rat incisor has been seen in a dose-dependent manner after administration of cyclophosphamide (18). However, the mechanism of developing microdontia during chemotherapy is not known. Chemotherapy may affect tooth development not only through direct toxic effects on the odontogenic cells, but also by disturbing cell communication during tooth development (10,11), since several signal molecules mediate interactions between epithelial and mesenchymal tissues throughout tooth development (23).

In the present patient, treated with chemotherapy in two stages during the first 2 years of life, the lateral incisors were probably affected only by the first chemotherapy at age of 4 months, since their calcification starts on the average at 11 months of age (24) and the second chemotherapy started just after that age.

An interesting observation is that the influence of chemotherapy was not the same on all affected teeth. In three of them both the size and the form of the crown were affected, while in the other three the size was reduced but the form was not affected. It was shown, that the patterning of the tooth crowns is instructed by the enamel knots, signalling centres in the tooth germ epithelium. These signalling centres determine also the location and height of tooth cusps by inducing new, secondary enamel knots at the site of the future cusps (23,25).

Concerning root development adverse effects could be seen only in the teeth that had affected crowns. That is probably due to the fact that the chemotherapy was completed at early age, before root development has started. The adverse effect on the roots of the six affected teeth may be explained as a consequence of the already reduced crown dimensions. The importance of the age of the patient at therapy was shown in a group of patients with various malignancies (including neuroblastoma) treated with autologous stem cell transplantation after myeloablative therapy with high-dose chemotherapy and/or total body irradiation; the worst disturbances in crown/root ratio's were seen in patients aged 3.1–5.0 years, while younger patients were less affected (12).

Besides, the chemotherapy as aetiological factor, it cannot be excluded that the common origin of the teeth and the neuroblastoma might also play a role in the abnormal tooth development, as both teeth and neuroblastoma originate from the neural crest.

Conclusion

Chemotherapy on children treated for neuroblastoma can adversely influence tooth development. This has to be taken into consideration by the dentist when monitoring the development of the dentition and occlusion.

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