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The Influence of Oncological Treatment on Tooth Agenesis in Adult Patients after Childhood Chemotherapy and Radiotherapy

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Abstract: Malignant neoplasms are one of the main causes of death in developed countries. Thanks to the multidisciplinary approach and treatments methods (surgical treatment, chemotherapy, radiotherapy) in pediatric oncology, the number of cancer survivors among children is growing. The high survival rate obliges the medical community to monitor the long-term consequences of both the cancer disease and the anticancer treatment used. The incidence and type of complications in oncological treatment vary. Their presence and severity depend on the child's age, the nature of the malignant neoplasm, as well as the specificity and intensity of therapy. Frequent complications of treatment may include serious maxillofacial defects resulting from developmental disorders of bones, soft tissues and teeth. One of the dental complications of both radio- and chemotherapy is tooth agenesis. In this manuscript, we highlight the dental complications of oncological treatment and the need of an interdisciplinary approach in dealing with them.

Key words: Dental complications, dental management, hypodontia, malignant neoplasm.

1. Introduction

Malignant neoplasms, after injuries and poisoning as well as congenital and developmental defects, are one of the main causes of death in children in developed countries [1]. Most of these neoplasms are cancers of the central nervous system (CNS) and leukemias. In recent years, the development of pediatric oncology has resulted in a steadily increasing number of cured patients [2]. This is due to the improved availability of various treatment options [3]. Nowadays, the 5-year survival rate among children with cancer is as high as 80–85% [2]. This translates into a growing population of cancer survivors. The high survival rate obliges the medical community to monitor thethe long-term consequences of both the cancer disease and the anticancer treatment used.

The incidence and type of complications in oncological therapy vary. Their presence and severity depend on the child's age, the nature of the malignant neoplasm, as well as the specificity and intensity of therapy. In the case of recovery from a malignant tumor, oncological therapy has a significant impact on the general health and quality of life of the patient [4, 5]. Frequent complications of treatment may include endocrine disorders (e.g. growth disorders, hypothyroidism, infertility) [4], as well as sensory impairment, problems with education and interpersonal relations [3]. Late complications may also occur in the form of serious maxillofacial defects resulting from developmental disorders of bones, soft tissues and teeth [6].

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2. Discussion

2.1 The Histological Development of the Tooth and Dental Disorders of an Agenesis Nature

During the stages of shaping of the deciduous and permanent tooth in prenatal life, and subsequently

after birth, the germs first increase in volume. In the following stage, their cells differentiate to form enamel, dentin, pulp and periodontium. Enamel and dentin are formed from two tissue types, epithelial and ectodermal, which interact with each other. There are four developmental stages of the permanent tooth: dental plate, bud, cap and bell. Permanent teeth are formed from a secondary lingual dental lamina, in the second row behind deciduous teeth, which arise from the primary lamina. Their mineralization takes place in strictly defined periods. Among permanent teeth, incisors, canines and premolars are initially formed. This happens between the 20th week of gestation and the 10th month after birth. The first molars are formed in the 20th week of fetal life; the third molars are formed at the age of 5 years [7].

One of the most common dental disorders in adult patients with a history of pediatric oncological treatments is tooth agenesis, i.e. the absence of one or more tooth buds. Depending on the number of missing teeth, three types of defect are distinguished: hypodontics, oligodontics and anodontics [8]. Authors of the available publications use different definitions of the above anomalies. Nodal [9] and Sarnäs [10] claim that the basis for the diagnosis of oligodontics is the lack of 4 or more teeth (except wisdom teeth). Sarnas [10] and Schalk van der Weide [11] indicate that only the absence of 6 or more teeth allows the diagnosis of oligodontics. A condition involving fewer missing teeth is defined as hypodontics. Anodontics, i.e. the complete absence of tooth buds, is rarely observed [12]. According to the latest scientific reports, dental agenesis not related to chemotherapy and/or radiotherapy most often affects the third molars, lateral incisors of the maxilla, mandibular second premolars and maxillary second premolars [13-15].

2.2 Effect of Chemotherapy and Radiotherapy on Tooth Tissues

In the case of radiotherapy of the head and neck region in pediatric oncology, complications are associated with damage to organs and cells due to radiation [16]. Cell damage occurs in two ways: direct (the so-called shield effect), through ionization of cell components, e.g. a collision of a radiation particle with the DNA strand, and indirect, as a result of the interaction of water radiolysis products (free radicals) in the cell nucleus containing DNA. This may result in the disturbance of the normal cell cycle, especially of cells with increased mitotic activity. The proportion between the direct and indirect effects of radiation on DNA depends on the type of radiation. In the case of radiation with a low density of ionization, e.g. X-rays, 70–90% of DNA damage is caused by indirect action. With a high density of ionization, caused by neutrons, protons and alpha particles, over 90% of damage to DNA is of direct nature [17].

Radiotherapy of the developing tissues of the head and neck causes osteocyte death, microangiopathies, periosteal damage, marrow fibrosis and tissue hypoplasia [3]. The degree of damage depends on the radiation dose, the patient's age and the type of irradiated tissues. The affected structures include skin tissues, mucous membranes, subcutaneous tissue, bones, muscles and salivary glands. Vascular damage plays a key role, which reduces the viability of irradiated tissues. In the course of radiotherapy, irradiation of normal tissues and the secondary presence of radiation reaction are inevitable.

Abnormal tooth development caused by radiotherapy and/or chemotherapy causes disturbances in amelogenesis (enamel formation), dentinogenesis (dentin formation) and cementogenesis (formation of dental cement) [18]. Animal studies have shown that a dose of 2 to 50 Gy can cause dental anomalies [18]. The minimum dose that can produce such effects in humans is not known; however, there are studies that have confirmed the effect of a 4 Gy dose on late dental abnormalities. Lindvall et al [18] revealed that even the smallest regular dose of radiation causes changes in enamel, but rarely in dentin. The amelogenesis process is more radiosensitive than

dentinogenesis. In addition, it has been found that with an appropriate dose of radiation, odontoblasts (dentinogenic cells) die regardless of the phase of the cell cycle [3]. For radiotherapy, it has been confirmed that enamel always shows morphological abnormalities, regardless of the dose used in the oncological treatment. In the case of dentin, the radiation dose plays a significant role, i.e. the higher the dose, the higher the level of irreversible morphological disorders. Additionally, after radiotherapy, the time of formation of enamel (from preameloblasts) and, to some extent, dentin (from preodontoblasts), is significantly longer compared with non-irradiated dental tissues [18]. In patients, the therapeutic dose is estimated individually. Exposure of the oral cavity and dentition of a child aged < 5 years to an irradiation dose equal to or greater than 20 Gy is associated with an increased risk of dental disorders [3]. The risk of dental disorders in patients who received head and neck radiotherapy was higher in a statistically significant manner than in patients who were treated only with chemotherapy [6]. The use of radiotherapy causes qualitative and quantitative disturbances in enamel and dentin, unlike chemotherapy, which results only in a qualitative disturbance [18, 19]. Chemotherapy is a treatment method that targets rapidly dividing cancer cells. Ameloblasts (cells that create enamel) and odontoblasts (cells responsible for the formation of dentin) are the most sensitive to cytostatics during tooth formation [20].

There are a number of independent studies that show a significant effect of radiotherapy and chemotherapy on the development of dental disorders. A study by Gawade et al [21] showed that people who were treated with radiotherapy and chemotherapy or hematopoietic cell transplantation in childhood showed an increased tendency for dental caries and developmental dental disorders in the oral cavity. Kaste et al [22] analyzed pantomograms of patients who received oncological treatment for rhabdomyosarcoma (RMS) of the head and neck in childhood. The authors showed that as many as 77% of people in the studied group developed dental disorders in adulthood. In addition, they confirmed that chemotherapy for malignant tumors alone can induce dental disorders as well.

There is agreement in the literature as to the influence of the patient's age on the degree of dental disorders [23-25]. The study by Owosho et al [26] confirmed the significant effect of radiochemotherapy on tooth and craniofacial development disorders in pediatric patients treated for RMS. As a complication of the therapy, 9 out of 13 patients developed secondary craniofacial disorders. Significantly, all of these patients were under the age of 7 years. Trismus and xerostomia were the dominant abnormalities in older children.

It is worth noting that in children who have undergone aggressive oncological treatment, the lack of a tooth rarely appears as a single anomaly, more often it is one of many disorders in the oral cavity. A large follow-up study published by Kaste et al [6], which included 9,308 patients treated for malignant tumors in childhood, showed a significant effect of oncological therapy on dental development disorders in this group of patients compared with their healthy siblings. Among many different correlations, that between the treatment history of malignant neoplasms and the occurrence of agenesis was confirmed, with the odds ratio (OR) of 1.7 (95% confidence interval [CI], 1.4–2.0) in the case of hypodontics. The researchers also showed the effect of the total dose of radiotherapy on the degree of disorders. It was noted that more serious side effects were seen in patients treated with higher doses of radiotherapy. It was proven that the risk of developing at least one dental abnormality (hypodontia, microdontia, enamel hypoplasia, root development disorder, more than 6 missing teeth) is related to the dose of radiotherapy in patients undergoing radiotherapy in the mandibular area compared with the group of patients treated with

radiochemotherapy without irradiating the mandible. When a 0–20 Gy dose was used, there was a significant increase in the risk of the above-mentioned disorders – OR: 1.3; 95% CI 1.2–1.5 – compared with the control group. For doses > 20 Gy, the correlation was much stronger – OR: 5.6; 95% CI: 3.7–8.5.

Radiochemotherapy during childhood causes a number of complex developmental anomalies in the structure of the oral cavity. The lack of dental buds may coexist with bone and soft tissue disorders and other dental abnormalities. The most common bone defects include delays in bone development (facial asymmetry, hypoplasia) and impaired repair processes of bone cells. Soft tissue disorders include, among other, reduced salivation (sialopenia), which develops indirectly, through reduced salivation due to the atrophy of receptors located on the surface of the tongue, and directly, through damage to the cells of the salivary glands. The result is dryness (xerostomia) and recurrent stomatitis and tooth decay. Other soft tissue abnormalities are trismus, dysgeusia (most often a lack of taste due to the destruction of taste buds), severe inflammation or necrosis of soft tissues, scar tissue formation and facial deformity [6]. The effect of radiotherapy on the reduction of the mobility of the temporomandibular joint has also been confirmed [27]. The developmental anomalies coexisting with agenesis after radiotherapy and chemotherapy include: enamel/dentin hypoplasia, anatomical loss/thinning or stunting of the root, premature loss of teeth due to caries, microdontics, taurodontism, delayed loss of deciduous teeth and/or decay of permanent teeth and malocclusion [6]. In the case of treatment with chemotherapy alone, dental redundancy may occur as well [3].

2.3 Dental Treatment

In patients with tooth agenesis after radio- and/or chemotherapy in childhood, a common symptom is unsatisfactory smile esthetics. It is this symptom that usually prompts the patient to visit the dentist. Visual defects in the form of gaps, reduced circumference of the dental arch as well as rotations, migrations or other displacement of teeth [28], which disturb the harmony of the smile, are often noticeable. The above abnormality is most often diagnosed at the age of 6–12 years. Dental examination of a patient who reports this problem should be based on the assessment of functionality, aesthetics and periodontal condition. In order to plan comprehensive dental therapy, thorough diagnostics should be performed. Precise analysis should be based on the systematic collection of information based on the medical history (including the patient's age, specificity and intensity of oncological treatment) and dental interviews, thorough intra- and extraoral examination, careful radiography [28] and intra- and extraoral photography [29]. The basic diagnostic tool used to diagnose hypodontia, oligodontia or anodontics is pantomographic X-ray. The diagnosis of agenesis requires the confirmation of the absence of calcified substances in the tooth in the pantomogram and the absence of evidence of tooth extraction in a clinical examination, as well as interview obtained from the patient [30]. For a broader assessment, a cephalometric image aimed at the apical area, as well as Cone Beam Computed Tomography (CBCT) can be used [14, 28].

Most studies emphasize that dental treatment should be interdisciplinary, conducted in consultation with an orthodontist, prosthetist, dental surgeon, periodontist and pediatrician [14, 29, 31-33]. Treatment of systemic defects following oncological therapy, in which dental agenesis is one of several comorbid complications, should involve physicians of other specialties, such as a pediatrician, hematologist, oncologist, endocrinologist, ophthalmologist, cardiologist, otolaryngologist and psychiatrist. When dental diagnostics requires precise measurements from CBCT, a radiologist should participate in the treatment as well [14]. Regardless of the choice of treatment method, the team of the above-mentioned physicians must be in perfect communication, because

it translates into the future outcome of treatment [33]. It is very important that the dental effect achieved guarantees the best esthetics with the lowest possible invasiveness [31]. When planning dental treatment, it should be remembered that human dentition and the surrounding tissues must be perceived as a dynamic system, subject to continuous changes throughout life [32]. Dentists should recommend regular check-ups to properly conduct comprehensive therapy of these disorders. Patients and their parents should be informed about the multi-stage and long-term nature of dental treatment [33].

3. Summary

Dental agenesis is one of the most common malformations of the dentition. The multifactorial etiology of agenesis should take into account not only the mutation of genes responsible for tooth development, but also environmental causes, which include oncological therapy. Destruction of tooth buds caused by radiotherapy and/or chemotherapy administered to a child at an early stage of development is a rare phenomenon in the daily clinical practice of a dentist. However, the still high incidence of malignant neoplasms among children makes it necessary for dentists to be aware of this problem.

Treatment of dental complications associated with the treatment of cancer, although it is not of primary concern, is one of the most important factors determining the quality of life of the patient after the completion of oncological treatment. Dental management of agenesis of a single tooth or a group of teeth in patients who underwent radiotherapy and/or chemotherapy in childhood should be comprehensive and always individualized [31]. For this reason, physicians in charge of treatment and monitoring of minor patients should inform their parents about the possible dental complications, and in the event of disturbing symptoms, refer the child to competent specialists at reference centers.

Conflict of Interest

The authors declare no conflict of interest.

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