Craniomandibular dysfunction in children treated with total-body irradiation and bone marrow transplantation

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The prevalence of pain and dysfunction in the stomatognathic system was studied in a group of 19 long-term survivors after pediatric bone marrow transplantation (BMT), conditioned with total-body irradiation (TBI). Compared with the control group, the children and adolescents in the BMT group had a significantly reduced mouth opening capacity. A reduced translation movement of the condyles was diagnosed in 53% of children treated with TBI, compared with 5% in the control group. Signs of craniomandibular dysfunction were found in 84% of children in the BMT group, compared with 58% in the control group. Both irradiation and chemotherapy induce long-term alterations in connective and muscle tissues resulting in inflammation and eventually fibrosis. These changes in tissue homeostasis and concomitant growth retardation may lead to the observed malocclusion and reduced mobility of the temporomandibular joint, with subsequent muscle pain and headaches, which were found in this study. □ *Bone marrow transplantation; child; headache; radiotherapy; temporomandibular joint syndrome*

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The introduction of bone marrow transplantation (BMT) has made it possible to cure a substantial number of children with malignant disease who otherwise would not have survived (1, 2). The high-dose chemotherapy and total-body irradiation (TBI) used for conditioning before BMT, however, do cause considerable morbidity, including cataract formation, gonadal failure, hypothyroidism, and growth failure (3–5). A high incidence of growth disturbances and growth hormone (GH) insufficiency has been reported in children treated with cranial irradiation and TBI (6). In this connection the age of the patient at the time of treatment has also been pointed out as a factor of importance (7).

All children treated with BMT and conditioned with 10 Gy of TBI before 12 years of age show severe disturbances in dental and craniofacial development, and the condylar growth in the temporomandibular joint (TMJ) is reduced. The dental abnormalities include tooth agenesis, arrested root development, microdontia, and enamel disturbances (8). The impaired root development results in a reduced alveolar bone growth, which adversely affects the vertical development of the mandible and the lower third of the face (9).

A relatively high prevalence of mild to severe functional disturbances and disease of the stomatognathic system has generally been found in children and adolescents. Facial pain, recurrent headaches, sounds from the TMJ, and tenderness of the temporomandibular muscles are reported in these studies (10–12).

Irradiation to the head and neck in children is very rare, and the irradiation fields are variable, which make studies in this patient group difficult to perform. Therefore, studies on disturbances of the craniomandibular complex in children after irradiation are not available. The aim of the present investigation was to study the prevalence of pain and dysfunction in the stomatognathic system in a group of long-term survivors after TBI and BMT.

Materials and methods

Patients and treatment

All children treated with TBI before BMT at Huddinge University Hospital between 1980 and 1989 who were long-term survivors (>3 years) and alive in 1992 were selected for this study. The diagnoses were acute lymphoblastic leukemia (ALL) in nine patients, acute myeloid leukemia (AML) in five, Gaucher's disease in two, and others in three. Seven boys and 12 girls with a mean age of 14.2 ± 4.2 years (range, 6.2–19.9 years) had received allogeneic bone marrow transplants from related sibling donors. The mean age at BMT was 6.5 ± 3.2 (range, 1.5–10.4) years, and the mean follow-up period 7.9 ± 2.7 (range, 3.0–12.0) years. The conditioning before BMT varied with the diagnosis. Children with leukemia were given cyclophosphamide (CY), 60 mg/kg/day, for 2 days and TBI in one fraction (13). The TBI was delivered by a linear accelerator at a mean dose rate of 0.04 Gy/min in a total dose of 10 Gy. The lungs were shielded to receive no more than 9 Gy. Methotrexate (MTX) or cyclosporine (CSA) was given alone or combined (14) to all patients as prophylaxis against graft-versus-host disease (GVHD). Children with leukemia also received intrathecal injections of MTX. Acute GVHD was treated with prednisolone in combination with azathioprine or CSA.

For every child in the BMT group an age- and sex-matched control patient was selected from patients receiving their regular dental check-ups at the Department of Paediatric Dentistry, Karolinska Institutet.

Methods

All 38 children were interviewed, and a clinical examination was performed in connection with their annual dental visit. Answers to questions about head and facial pains were registered.

The number of occlusal contacts in intercuspal position (IP) during light biting was counted to assess the occlusal stability. The degree of anterior open bite was registered in accordance with Tegelberg & Kopp (15). The intermaxillary relationship in the permanent dentition was determined on the basis of the anteroposterior relation between the upper and lower first molars and canines. Deviations from neutral occlusion exceeding one half cusp were diagnosed as mesial or distal occlusion.

Tenderness and irregularities in movement of mandibular condyles were assessed by lateral palpation of the TMJs. The muscles palpated were the masseter (superficial and profound) and the anterior part and the insertion of the temporal muscle. The palpation was carried out bilaterally. Reduced condylar mobility during maximal opening of the mouth was recorded if one or both temporomandibular joints showed a reduced palpable translation movement. TMJ sounds like clicking or crepitation were also recorded. The pattern of mandibular movement was examined in front of the child, who was requested to open and close the mouth repeatedly. Irregularities in the opening and closing paths exceeding 2 mm were recorded. The size of the lateral movement was measured in millimeters with a steel ruler with aid of these marks. Maximal mouth opening capacity was measured as the distance between incision superius and its horizontally marked projection on the buccal surface of the lower jaw incisors.

Dysfunction index

On the basis of these observations, a modified version of Helkimo's dysfunction index (16), as used by Mohlin et al. (17), was calculated. The index comprised scores for 1) impaired movement: a) maximal opening points of $\geq$40 mm = 0, 30–39 mm = 1, and $\leq$30 mm = 2; b) maximal protrusion points of $\geq$7 mm = 0, 4–6 mm = 1, 0–3 mm = 2; and impaired movement scores (a + b): 0 points = 0, 1–2 points = 1, $\geq$3 points = 2;

Table 1. Distribution of extension of anterior open bite

Degree of open bite	BMT* group ($n = 19$) Right, n	Left, n	Control group ($n = 19$) Right, n	Left, n	Sign†
Occlusal contacts on incisors and canines	11	13	18	18	$p < 0.05$
Occlusal contacts missing anterior to 2nd premolar	6	5	1	1	
Occlusal contacts missing anterior to 1st molar	2	1	—	—	

* BMT = bone marrow transplantation.
† Chi-squared test.

2) scores for impaired TMJ function: no impairment = 0, any sounds or deviations = 1; 3) scores for muscle pain: no pain = 0, pain in 1–2 muscle sites = 1, pain in 3 muscle sites = 2; and 4) TMJ pain scores: no tenderness to palpation = 0, tenderness on either side = 1. The dysfunction index was calculated as the summation of score groups 1–4, with minimum = 0 and maximum = 6 scores.

Roentgenologic examination

In children diagnosed clinically to have a reduced translation movement of the condyle, transcranial radiographs were taken. The position of the condyle was classified as anterior, central, or posterior of the fossa in postural position and as anterior of the tubercle, on the tubercle, or posterior to the tubercle in maximal opening position.

Statistical analyses

Student's t test was used for comparisons of continuous variables. The chi-square test and the Mann–Whitney U-test were used to determine the significance of differences between the two groups when data consisted of frequencies in discrete categories.

Table 2. Temporomandibular joint (TMJ) function, muscle tenderness, and frequency of headaches

Variables	BMT* group ($n = 19$) n	%	Control group ($n = 19$) n	%	Significance†
TMJ function					
Deviation on opening	8	42	0	0	**
Tenderness on palpation of joint	1	5	0	0	NS
Palpable joint sounds	3	16	1	5	NS
Reduced translation movement of the condyle	10	53	1	5	**
Muscle tenderness					
M. masseter	6	32	1	5	NS
M. temporalis anterior	8	42	3	16	NS
M. temporalis insertion	4	21	2	11	NS
Headache (>once/week)	6	32	2	11	NS

* BMT = bone marrow transplantation.
† Chi-square test; NS = not significant; ** = $p < 0.01$.

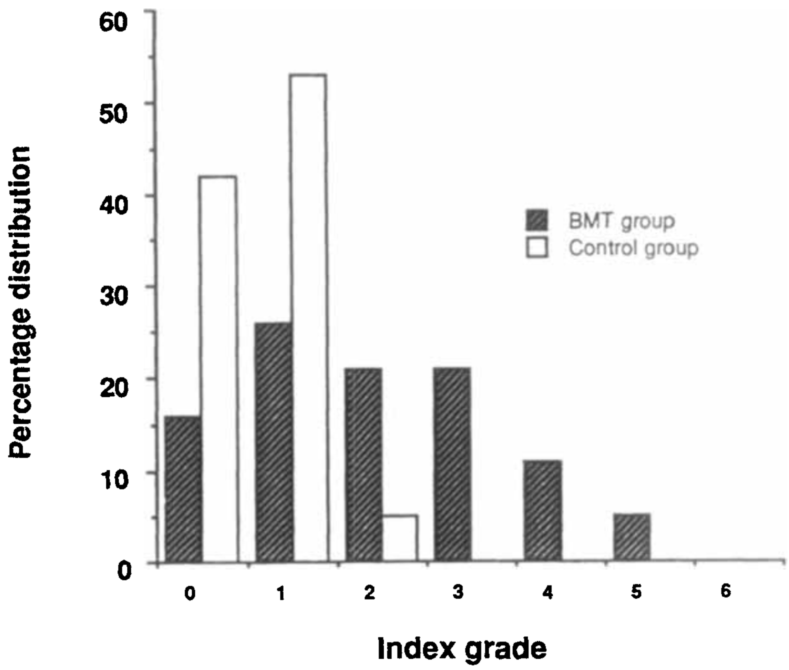

Fig. 1. Percentage distribution of the temporomandibular dysfunction score (see Methods). Filled bars=bone marrow transplantation (BMT) group; open bars=control group.

Results

In the BMT group 56% of the patients had neutral and 44% distal occlusion. In the control group the corresponding values were 72% and 28%, respectively. The number of occlusal contacts was 12.9 ± 4.1 in the BMT group, which was significantly less than in the control group (18.6 ± 6.3) ($p < 0.01$). As can be seen in Table 1, anterior open bite was significantly more frequent in the BMT group ($p < 0.05$).

Children and adolescents in the BMT group showed a significantly reduced opening capacity, 46 ± 8 mm, compared with 51 ± 6 mm in the controls ($p < 0.05$). Six children in the BMT group had an opening capacity of less than 40 mm. Such low values were not found in the control group. The BMT children also showed a reduction in lateral movements of the mandible and protrusion, although the difference did not reach statistical significance. According to the dysfunction index, 57% of the children in the BMT group had an impaired movement capacity, compared with 32% in the control group.

Ten children in the BMT group (53%) showed evidence of impaired TMJ function compared with one (5%) in the control group ($p < 0.01$). Deviation of 2 mm or more on opening movements was found in 42% of BMT children compared with none in the controls ($p < 0.01$) (Table 2). A reduced translation movement of the condyles was diagnosed in 53% of the children treated with TBI, compared with 5% in the control group ($p < 0.01$). Tenderness of the masticatory muscles on palpation was found in 42% of the BMT children, compared with 32% in the control group. Tenderness was most often found in the anterior temporal muscle. Thirty-two per cent of the children in the BMT group reported that they had headache more than once a week, compared with 11% in the control group. Children reporting headaches more than once a week had tenderness to palpation of the anterior

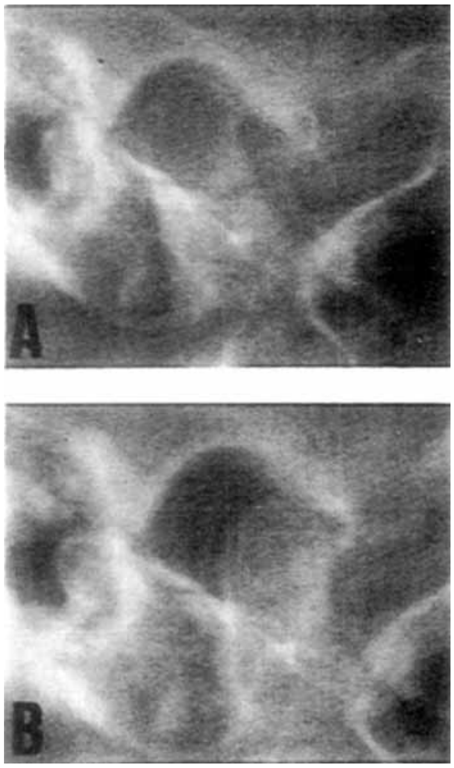

Fig. 2. Transcranial radiograph showing the right condyle in a 19-year-old girl treated for Gaucher's disease at 9 years of age. 2A. In postural position; 2B Maximal opening position. Note the reduced translation movement.

temporal muscle significantly more often ($p < 0.05$).

The distribution of severity of dysfunction on the basis of the modified Helkimo index is presented in Fig. 1. Signs of dysfunction were found in 84% of children in the BMT group, compared with 58% in the control group ($p < 0.05$). Only one child (5%) among the children in the control group had an index score exceeding 1, compared with 58% of the children in the BMT group ($p < 0.001$). In the BMT group low age at transplantation was associated with high value of the dysfunction index. The association between these variables was not statistically significant, however.

From 9 of the 10 children with a reduced condylar translation movement on clinical examination, transcranial radiographs were obtained (Fig. 2). In postural position three right condyles and five left condyles were diagnosed as being in a posterior position (Table 3). A reduced translatory movement was verified in six patients.

Discussion

The results of this study show that children who are long-term survivors after TBI and BMT show a higher prevalence of signs and symptoms of craniomandibular dysfunction than a matching group of healthy children. Using the modified dysfunction index, Mohlin et al. (16) found that 54% of healthy 12-year-old children had no dysfunction, which is in agreement with the frequency of 42% found in the present study. In the children treated with BMT, 84% showed signs and symptoms of craniomandibular dysfunction. The explanation for the increase in prevalence may be found in long-term complications induced by antineoplastic therapy. Both irradiation and chemotherapy induce long-term adverse effects in connective and muscle tissues, resulting in inflammation and eventually fibrosis (18). These long-term changes in tissue homeostasis and the concomitant growth retardation (19) may lead to malocclusion, reduced mobility of the TMJ, and muscle symptoms and headaches.

Headaches may have various origins, and

Table 3. Radiographic analysis of temporomandibular joint condylar position in bone marrow transplantation patients with clinically observed reduced translation movement

Condyle	Right ($n = 9$), n	Left ($n = 9$), n
Position in resting position		
Anteriorly	3	3
Central	3	1
Posterior	3	5
Position in opening position		
Anterior of tubercle	3	6
Tubercle	3	1
Posterior of tubercle	3	2
Reduced translation movement	6	3

numerous studies have confirmed that headache is a common symptom of craniomandibular disorders. Several studies have shown a connection between headaches and pain in the temporomandibular joints and muscles, a sign that the pain in several cases emanates from these structures (20–22). It seems reasonable to assume, therefore, that the headache symptoms reported by children in the BMT group could at least in some cases be related to mandibular dysfunction.

Headaches were reported more often in the BMT group than in the control group. In the control group 11% of the children had frequently recurring headaches. This is in agreement with Nilner & Lassing (10), who reported 14% in a group of children 7–14 years old. Headaches were associated with tenderness of the anterior temporal muscle, which is in agreement with previous studies (17).

A reduction in mouth opening capacity is rarely found in healthy individuals. Only 1% of children have an opening capacity of less than 40 mm (16). The average mouth opening has been found to be approximately 40 mm plus the age in years for ages 7 through 18 (23). This is in agreement with the results of this study, in which none of the children in the control group had a reduced opening capacity. In the BMT group, on the other hand, 32% of the patients had limited mouth opening capacity. The most probable explanation for the reduced mandibular mobility is fibrosis of the joint and muscle tissue, as a sequel to the chronic inflammatory reaction after irradiation (24). The translatory mobility of the condyle was reduced in 53% of the BMT patients, compared with 5% in the control group. This finding indicates that fibrous adhesions in the joint is a main cause of reduced mandibular mobility. There was also a good agreement between the radiographic assessment of reduced translation movement of the condyle and the clinical assessment. Irradiation also causes endothelial fibrosis and decreased tissue blood flow, which especially impairs the muscle function (25). Muscle tenderness on palpation of 6 muscle sites was found in 32% of the children in the control group, which can be compared with previous studies reporting frequencies varying between 27% and 40% in examination of at least 14 muscle sites (10, 17). In this study the anterior temporal muscle showed the highest prevalence of tenderness to palpation. In previous studies the lateral pterygoid muscle has shown the highest prevalence of tenderness (17). This muscle was not examined because of the well-known methodologic problems with intraoral palpation of this muscle, especially in children (26).

The children in the BMT group had significantly fewer and more distal occlusal contacts than the controls. One reason for this is that retarded growth of the mandibular condyles results in a development of the occlusion which is similar to that occurring in individuals with juvenile chronic arthritis (15). The growth potential of the condylar cartilage is reduced by the therapeutic irradiation and chemotherapy. The severity of the growth disturbance is related to the dose and to the age at treatment (8, 27). Another reason for a reduced number of occlusal contacts is aplasia caused by TBI administered during early stages of tooth formation and loss of teeth due to other developmental disturbances.

Posterior position of the condyle is common in patients with craniomandibular dysfunction but also in healthy individuals and should not be used as a sign of an abnormal condition (28, 29).

In conclusion, the results indicate that children who are long-term survivors after TBI and BMT have a high prevalence of signs and symptoms of craniomandibular dysfunction. When headache or facial pain is reported in this group of children, a thorough examination of the dentition and the craniomandibular functional system as a whole should be performed.

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