European Journal of Orthodontics 24 (2002) 285–292

The effect of growth hormone therapy on mandibular and cranial base development in children treated with total body irradiation

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SUMMARY The aim of the present investigation was to study craniomandibular development during growth hormone (GH) therapy in nine girls and one boy, aged between 7.3 and 16 years, who exhibited pronounced growth reduction after total body irradiation (TBI) and bone marrow transplantation (BMT). Age- and sex-matched healthy children with normal dentofacial development constituted the control material. The investigation data were based on measurements made on lateral skull radiographs taken at the start and, on average, 6 months after cessation of GH treatment. The control group comprised similar longitudinal cephalographic records.

The results showed that GH therapy in patients who exhibited growth retardation after TBI and BMT had only a minor effect on cranial base dimensions, probably due to the fact that the development of this area is completed at a relatively early age. The effect of GH treatment on mandibular growth was very obvious. The dimensional increase of the mandibular variables in the patients was equivalent to, or in some cases even exceeded, that of the controls. In relation to basion, the mandibular condyles were displaced in a backward/upward direction in the patient group. Displacement in the opposite direction was recorded in the controls. It seems likely that the development seen in the patients is a reflection of a normalization of the condyle–fossa relationship made possible by enhanced condylar growth. This change should be advantageous for the function of the craniomandibular complex.

Introduction

Over the past few decades, bone marrow transplantation (BMT) has become an increasingly successful method of treatment for children with haematological malignancies. With the improved survival of these patients, the possible sequelae produced by preparative regimens such as radiotherapy and chemotherapy have received more attention.

Growth disturbances following therapeutic irradiation of children have been elucidated in a number of articles (e.g. Gonzales and Breur, 1983; Guyuron *et al*., 1983; Wells *et al*., 1983; Robison *et al*., 1985; Moell *et al*., 1988; Sanders, 1991). Studies regarding the adverse effects of irradiation and chemotherapy on the growth of craniofacial skeletal components have been presented (Nwoku and Koch, 1975; Guyuron *et al*., 1983; Jaffe *et al*., 1984; Göz *et al*., 1988; Dahllöf *et al*., 1989; Sonis *et al*., 1990).

Exogenous growth hormone (GH) therapy seems to mitigate the negative effects of irradiation on growth. In a previous study (Dahllöf *et al*., 1991), the development of dentofacial variables in BMT children treated with GH was compared with the average development in healthy children. It was found that administration of GH did not induce catch-up growth in general, but prevented further dimensional loss. An exception to this developmental pattern was the mandibular length (cd-pgn), which increased more in the GH group. The substantial augmentation in mandibular length, however, was not

reflected in a corresponding change in the antero-posterior position of the mandible in relation to the cranial base (angle SNB). The present investigation, which studied the growth patterns of the mandible and the cranial base in children undergoing GH treatment after BMT, was an attempt to find an explanation for this phenomenon.

Subjects

The patient material comprised 10 paediatric children who had been treated with BMT for acute leukaemia or combined immunodeficiency (Table 1). The following preparative regimen was carried out prior to BMT: Cyclophosphamide 60 mg/kg/day for 2 days and total body irradiation (TBI) in one fraction. TBI was delivered by a linear accelerator at a mean dose rate of 0.04 Gy/minute with a total dose of 10 Gy. The lungs were shielded to receive no more than 9 Gy. Cyclosporin A, methotrexate, or a combination of these two agents were also administered as prophylaxis against graft versus host disease.

All patients exhibited low growth rates after BMT. The mean height standard deviation score (SDS) was –0.7 at BMT (mean age 7.7 ± 3.3 years) and –2.0 4.5 years later. GH secretion was examined with a combination of an arginine provocation test and an insulin tolerance test (Frazier, 1974) within a period of 1 year prior to the start of GH treatment. At a mean age of 12.2 ± 3.0 years, GH therapy was initiated with synthetic GH (Genotropin®; Kabi Pharmacia, Stockholm, Sweden), which was administered subcutaneously at 0.1 IU/kg body weight per day (Borgström and Bolme, 1988). The GH therapy lasted for a mean period of 3.6 ± 1.3 years. For each patient, an age- and sex-matched healthy control subject exhibiting normal dentofacial development was selected from the cephalometric material of the Burlington Growth Centre, Toronto, Canada (Popovich and Thompson, 1977).

Method

The present study was based on measurements made on lateral skull radiographs taken at the start of and, on average, 6 months after cessation of GH treatment. In Patients 2, 6, and 7 (Table 1), however, GH treatment was still ongoing when the second radiographic registration was made. The control group comprised similar longitudinal records that matched the BMT patients for age and the time span between the two radiographic registrations ['Follow-up (years)' in Table 1]. Since different cephalostats were used, all linear measurements were corrected for magnification.

A modified Coben (1955) analysis was used for evaluation of the cephalograms. The tracing of the films was performed by one of the authors (CMF) according to the following procedure: a co-ordinate system with the Frankfort Horizontal

Table 1 Age and sex distribution, diagnoses, and chronological data relating to the investigation material.

Patient no.	Sex	Diagnosis	Age at BMT (years)	Age at cephalogram 1 (years)	Duration of GH-therapy (years)	Age at cephalogram 2 (years)	Follow-up (years)
1	F	ALL	4.3	9.3	3.4	15.1	5.8
2	F	CID	10.1	13.1	4.0	16.1	3.0
3	F	ALL	10.1	15.2	2.6	18.7	3.5
4	F	AML	8.1	11.1	2.0	15.2	4.1
5	F	AML	3.2	9.2	5.9	15.3	6.1
6	F	CML	2.2	7.3	3.3	10.2	2.9
7	F	AML	8.1	13.3	5.0	17.9	4.6
8	F	ALL	9.9	16.0	3.3	19.9	3.9
9	F	ALL	9.2	12.1	4.7	17.0	4.9
10	M	ALL	11.6	15.6	2.1	18.6	3.0

ALL, acute lymphoblastic leukaemia, AML, acute myeloid leukaemia; CID, combined immunodeficiency; CML, chronic myeloid leukaemia.

(FH, porion-orbitale) as the horizontal axis, and a perpendicular line through basion (BAV) as the vertical axis, was drawn on a tracing film attached to the first radiograph. The outlines of the anterior part of the sella turcica and the anterior cranial base were also traced. These structures and the FH were then copied onto a new tracing film, which was subsequently placed and fixed on the second radiograph, with the contours of sella turcica and cranial base coinciding. Finally basion point was marked and the line BAV drawn.

The reference points and lines used in the study are shown in Figure 1a–c. Antero-posterior measurements were taken parallel to the horizontal axis of the co-ordinate system (Figure 1a). Vertical dimensions were measured as distances between projected reference points on BAV (Figure 1b).

Eight horizontal and four vertical variables were recorded (Tables 2–4). In addition, cranial base angle (nsba), gonial angle (RL/ML), mandibular inclination (ML/NSL), SNB, and mandibular length (cd-pgn) were also recorded (Figure 1c).

In 10 randomly selected subjects, five patients and five controls, all distances and angles were traced and measured twice with an interval of more than 1 month between the first and second measurement. These measurements were made by the same person who carried out the original tracings. The differences between the two observations of each variable were calculated and used for evaluation of the method error (s_i) according to the formula (Dahlberg, 1940)

$$s_i = \sqrt{\Sigma d^2/2n}$$

where d is the difference between the two observations and n is the number of double determinations. The error of method for the angular measurements was found to vary between 0.21 (SNB) and 0.57 (nsba) degrees, and between 0.27 (n-gn) and 0.69 (cdsup-go) mm for linear measurements.

Changes in variable values in the patients were correlated with the corresponding changes in their respective controls. Correlation coefficients were calculated and tested for significance.

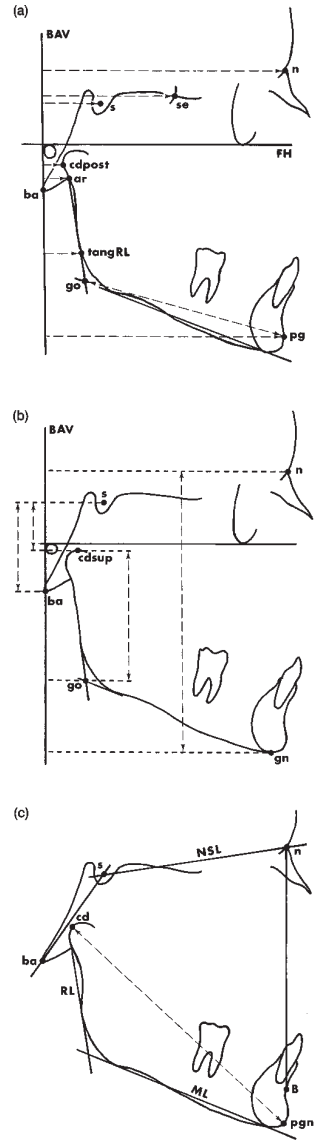

Figure 1 The cephalometric reference points and lines. For definition of points and lines that are not defined below, see Björk (1960). cd, the most supero-posterior point of the condylar head; cdpost, the tangential point between a vertical line, perpendicular to FH, and the posterior contour of the mandibular condyle; cdsup, the tangential point between a horizontal line, parallel to FH, and the superior contour of the mandibular condyle; go, the intersection between the mandibular line (ML) and the ramus line (RL). se, the intersection between the anterior contour of the greater wing of the sphenoid bone and the planum sphenoidale; BAV, the perpendicular line to FH through basion (ba). (a) The horizontal measurements. (b) The vertical measurements. (c) The mandibular and cranial base measurements.

Table 2 Mean differences between patients and controls at the start (d_1) and end (d_2) of GH treatment.

	(d_1)	SE	(d_2)	SE
Age (years)	0.3	0.17	0.2	0.26
Horizontal variables (mm)				
BAV-n	–0.2	2.61	–1.1	3.05
BAV-se	–0.5	2.00	–0.7	2.14
BAV-s	0.2	1.82	–0.2	1.94
BAV-cdpost	3.6	0.92	2.2	1.25
BAV-ar	1.6	0.73	0.9	1.07
BAV-tangRL	0.9	0.48	–0.1	0.60
BAV-pg	1.1	1.97	0.6	2.23
go-pg	–2.2	1.46	–2.2	1.89
Vertical variables (mm)				
n-gn	–4.2	2.18	–5.2	2.68
s-cdsup	1.1	1.03	0.2	1.16
s-ba	–0.5	1.02	–0.3	0.94
cdsup-go	–4.17	1.28	–2.0	1.51
Other variables				
nsba (degrees)	1.2	2.23	0.1	2.30
RL/ML (degrees)	1.1	2.89	–0.9	2.54
ML/NSL (degrees)	–0.6	1.77	–2.5	1.57
SNB (degrees)	0.2	0.48	0.5	0.52
cd-pgn (mm)	–5.4	1.63	–5.2	2.25

SE, standard error; $n = 10$.

Table 3 Correlation (r) between age at BMT and difference in variable size between patients and controls at the first radiographic registration.

	r	$P <$	Significance
Horizontal variables			
BAV-n	0.88	0.001	***
BAV-se	0.78	0.01	*
BAV-s	0.87	0.001	***
BAV-cdpost	0.80	0.01	**
BAV-ar	0.69	0.05	*
BAV-tangRL	–0.40	0.25	NS
BAV-pg	0.51	0.13	NS
go-pg	0.27	0.45	NS
Vertical variables			
n-gn	0.39	0.27	NS
s-cdsup	0.37	0.30	NS
s-ba	–0.22	0.53	NS
cdsup-go	0.24	0.50	NS
Other variables			
nsba	0.79	0.01	**
RL/ML	0.36	0.31	NS
ML/NSL	0.10	0.78	NS
SNB	–0.54	0.11	NS
cd-pgn	0.38	0.27	NS

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 4 Median growth changes in patients (M_{GH}) and controls (M_{CTR}) and the level of significance (α) for differences between the groups.

	M_{GH}	M_{CTR}	α	r	$P <$	Significance
Horizontal variables						
BAV-n	0.85	1.85	NS	0.56	0.09	NS
BAV-se	–0.40	0.70	NS	0.25	0.49	NS
BAV-s	0.25	0.95	NS	0.06	0.88	NS
BAV-cdpost	–0.40	0.80	**	–0.04	0.91	NS
BAV-ar	–0.25	0.35	NS	0.05	0.89	NS
BAV-tangRL	3.45	4.10	*	0.63	0.05	*
BAV-pg	4.95	2.60	NS	0.79	0.01	**
go-pg	3.95	2.45	NS	0.52	0.13	NS
Vertical variables						
n-gn	4.40	5.40	NS	0.87	0.001	***
s-cdsup	–0.50	0.35	*	0.27	0.46	NS
s-ba	0.55	0.45	NS	0.70	0.05	*
cdsup-go	6.10	2.90	***	0.77	0.01	**
Other variables						
nsba	–0.20	0.65	NS	–0.43	0.21	NS
RL/ML	–2.65	–0.35	*	–0.46	0.18	NS
ML/NSL	–2.25	–0.10	**	–0.47	0.17	NS
SNB	0.80	0.50	NS	0.00	0.99	NS
cd-pgn	6.70	5.45	NS	0.83	0.01	**

r, correlation between changes recorded in patients and controls.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Differences in the developmental pattern between the patients and controls were tested with the Wilcoxon signed ranks test.

Results

The mean differences between the patients and their respective controls at the first and second radiographic registration are shown in Table 2. With the exception of the variables BAV-cdpost, n-gn, cdsup-go, and cd-pgn, the differences recorded were small. Furthermore, apart from the variables BAV-cdpost, cdsup-go, RL/ML, and ML/NSL the differences recorded were also of similar magnitude at the first and second registrations.

It is probable that the differences existing between patients and controls were related to some extent to the age of the patients at BMT. Significant correlations were found for the horizontal variables BAV-n, BAV-se, BAV-s, BAV-cdpost, BAV-ar, and the angle nsba, indicating the existence of a strong association between irradiation therapy at a low age and growth retardation of the skeletal structures related to these measurements (Table 3).

The median growth changes of the variables during the period of GH treatment and the correlations between the changes recorded in the patients and their respective controls are shown in Table 4.

The pattern of change of the variable BAV-cdpost differed between the two groups ($P < 0.01$). In the GH patients, this distance was reduced during growth, whereas the reverse was found in the controls.

There was a significant association between patients and controls as regards changes of the variables BAV-tangRL and BAV-pg ($r = 0.63$ and 0.79, respectively). On average, however, the controls exhibited significantly greater anterior displacement of point tangRL compared with the patients ($P < 0.05$).

The changes in three of the vertical variables were significantly correlated in patients and controls. One of these measurements, posterior mandibular height (cdsup-go), increased significantly more in the patients than in the controls ($P < 0.001$). The measurement which represents the vertical position of condylion in relation to the cranial base (s-cdsup) increased in the controls, but decreased in the patient group. This difference between the groups was statistically significant ($P < 0.05$).

The observation that the variables which indicate condylar position (BAV-cdpost and s-cdsup) exhibited opposite patterns of change in patients and controls prompted a closer analysis of the temporomandibular joints (TMJ). It was then found that the condyle–fossa relationship was almost identical on both head film registrations in the controls. In the patients, on the other hand, the condyle was initially positioned anterior of the glenoid fossa. In some of the youngest patients, the position was almost on the articular eminence. After GH therapy, all patients exhibited a normal condyle–fossa relationship (Figure 2).

Both patients and controls exhibited a similar and substantial increase in mandibular length (cd-pgn, $r = 0.83$, $P < 0.01$, Table 4). The inclination of the mandible (ML/NSL) and the gonial angle (RL/ML) exhibited a significantly greater decrease in the patient group than in the control group ($P < 0.01$ and < 0.05, respectively).

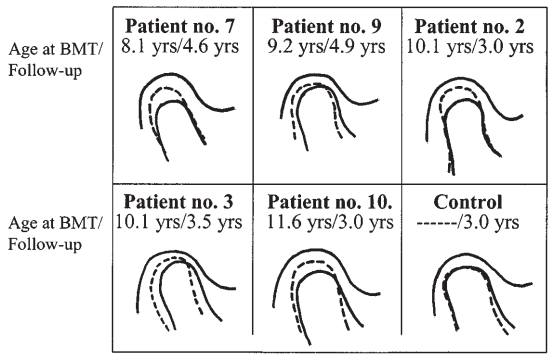

Figure 2 Examples of changes in the condyle–fossa relationship during the period of investigation in five BMT patients and one control. Patient numbers refer to the numbers shown in Table 1. The patients' ages at BMT and the time interval between cephalogram 1 and 2 (follow-up) are also given. Tracings of condyles with solid lines demonstrate condylar position at the start of GH treatment. Broken lines indicate condylar position at the follow-up registration.

Discussion

TBI given as a preparative treatment before BMT adversely affects the dimensional development of the craniofacial complex (Dahllöf *et al*., 1989). In the present study, significant correlation coefficients were found when age at BMT was related to differences between patients and controls in cranial base dimensions at the first cephalographic registration (Table 3). This indicates that irradiation treatment at an early age results in significant growth reduction in the cranial base area. Conversely, irradiation treatment at a relatively older age has only minor, or no effect on the cranial base measurements. Considering the normal developmental pattern of the cranial base, this is a logical result. The most intensive development in this area takes place in the infantile and early juvenile stages (De Coster, 1951; Grossman and Zuckerman, 1955; Ford, 1958; Scott, 1958), and any disturbance in the process of growth during these stages of development will have a marked effect. At approximately 7 years of age, all synchondroses, with the exception of the spheno-occipital synchondrosis, are closed. The formation of the anterior cranial base is complete and, consequently, any factor disturbing the general growth process after 7 years of age will have only minor or no effect on the morphology of this area.

The cranial base angle, nsba, also exhibited a greater difference between patients and controls in those subjects in whom TBI and BMT had been performed at an early age. Normally the cranial base angle changes insignificantly during growth (Bhatia and Leighton, 1993). The effect of TBI, which is probably particularly unfavourable in areas of cartilagenous growth (Cohen *et al*., 1999), obviously causes a deviating developmental pattern which eventually results in a reduced nsba angle in the youngest patients.

For the majority of the other variables, similar associations between age at BMT and the difference between patients and controls at the first cephalographic registration were also found. None of the correlation coefficients, however, reached the level of significance. For these variables, therefore, it seems that age at irradiation and BMT is of lesser importance as regards the degree of growth retardation; that is, when the BMT was carried out in the age span which was pertinant to the patients studied in this investigation (2.2–11.6 years of age).

The analysis of the effect of GH treatment showed that some variables changed in a similar way in patients and controls (significant correlation coefficients, Table 4), whereas the development of other variables was quite different in the two groups (correlation coefficients near zero).

As regards the mandibular corpus (variables BAV-tangRL, BAV-pg, Figure 1a; and n-gn, Figure 1b), a forward-downward displacement of a similar magnitude occurred in both patients and controls. This resemblance may be assigned to a positive effect of GH treatment on the development in mandibular length (cd-pgn, Figure 1c). In fact, this variable seemed to increase more in the patients than in the controls. The favourable development in the GH treated patients is, in all likelihood, an expression of substantial condylar growth. This change did not, however, seem to have any marked effect on the antero-posterior position of the mandible relative the cranium (SNB angle, Figure 1c) in the patients.

The positional change of the condyles in relation to the basion and sella points was different in patients and controls. During growth, the condyles in the control individuals exhibited a forward-downward displacement in relation to the BAV line and the sella point (Figure 1a,b, respectively), whereas the corresponding changes in the patient group occurred in a backward-upward direction. The explanation for this difference is probably that the growth reduction in the patients after TBI placed the condyles of the mandible in an anterior position on the articular eminence of the temporal bone. The growth following GH treatment had the effect that the condyles moved upwards and backwards into a more central position in the glenoid fossa (Figure 2).

The diverging developmental pattern found in the TMJ area of the patients in combination with the fairly normal development of the SNB angle, may be interpreted as a support for the hypothesis of the functional matrix. This

hypothesis states, as regards growth of the mandible, that the condylar cartilage is not a primary growth centre, but the site of secondary compensatory growth (Moss, 1960, 1969; Moss and Rankow, 1968). Moss (1960) writes that, 'the growth of the facial viscera is by itself primarily sufficient to translate the entire mandible in space. As a consequence, the temporomandibular articulation would be lost as the condyle becomes disengaged. It is to preserve this functionally important joint that secondary cartilaginous growth occurs in the condyle.' This description is directly applicable to the findings in the BMT patients. After TBI, they presumably experienced a considerable reduction in growth of the condylar cartilage. The fact that the SNB angle in TBI/BMT patients does not differ significantly from the SNB angle of healthy children (Dahllöf *et al*., 1991) indicates that the condylar growth reduction does not affect the relocation of the mandible in space following the expansion of the orofacial matrices. During this process, however, the extent of growth of the condylar cartilages is not sufficient to compensate for the downward and forward translation of the mandible and, consequently, the temporomandibular articulation is lost and the condyles become disengaged, as seen on the tracings of the patients' TMJs. The subsequent GH administration stimulates growth of the condylar cartilage (Maor *et al*., 1989), and the superiorly and posteriorly directed adaptive growth of the condyles, which has previously been lacking, will then take place (variables BAV-cdpost, Figure 1a; and cdsup-go, Figure 1b).

The disengagement of the mandibular condyles after TBI and BMT may also be one of the causes of the relatively high prevalence of craniomandibular dysfunction recorded in this category of patients, in whom reduced opening capacity, reduction in lateral movements, and protrusion of the mandible are relatively frequent findings (Dahllöf *et al*., 1994).

Conclusions

It seems that GH therapy in patients who exhibit growth retardation after TBI and BMT has only a minor effect on cranial base dimensions, presumably due to the fact that the development of this area is completed at a relatively early age. The effect of GH treatment on mandibular growth was obvious. The dimensional development of this component in the patients was equivalent to, or in some cases even exceeded that of the controls. In the patient group, the mandibular condyles were displaced in a backward-upward direction in relation to basion during GH treatment. Displacement in the opposite direction was recorded in the controls. It seems likely that the development seen in the patients is a reflection of a normalization of the condyle–fossa relationship made possible by enhanced condylar growth. This change should also be advantageous for the function of the craniomandibular complex.

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