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Graduate School

**A STUDY OF CRANIOFACIAL GROWTH IN INFANT
HEART TRANSPLANT RECIPIENTS RECEIVING
CYCLOSPORINE**

by

David G. Niles

**A Thesis in partial fulfillment
of the requirements for the Degree Master of
Science in Orthodontics**

June 1997

Each person whose signature appears below certifies that this thesis in their opinion is adequate, in scope and quality, as a thesis for the degree Master of Science.

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ABSTRACT

A STUDY OF CRANIOFACIAL GROWTH IN INFANT HEART TRANSPLANT RECIPIENTS RECEIVING CYCLOSPORINE

by

David G. Niles

Cyclosporine is an effective immunosuppressive drug that has found widespread application in organ transplantation. However, a few studies have implicated cyclosporine as adversely affecting craniofacial growth in the pediatric population. The purpose of this study was to evaluate the possible untoward effects of cyclosporine long-term on craniofacial growth in a group of infant heart transplantation recipients. A prospective group (n=28) of eighteen Caucasian children (9 female and 9 male, ages 4-10 years) and ten Hispanic children (3 female and 7 male, ages 4-10 years) were evaluated. None of the subjects had undergone orthodontic therapy. All subjects had heart transplantation before six months of age and followed the Loma Linda University International Pediatric Heart Transplantation Immunosuppression protocol. The primary immunosuppression agent was cyclosporine with azathioprine or methotrexate. Rescue therapy for graft rejection consisted of glucocorticoid and/or polyclonal antibody therapy. None of the subjects received the immunosuppressant tacrolimus (FK506). Using lateral cephalometric radiography, seven skeletal angular measurements (SNA, SNB, ANB, GoGn-SN, NA-Pog, ArGoMe, NPog-AB) were examined and compared to

contemporary growth standards. Hand/wrist radiographs were evaluated for bone age. Also, longitudinal height, weight, and head circumference data was obtained and compared to standardized growth and development curves. Descriptive statistics was used to summarize the data. Cephalometrically, 86% (N=24), showed minor deviation from mean normative values. Four subjects (14%) did show cephalometric measures indicative of individuals with a vertical growth pattern. Analysis of the hand/wrist radiographs showed all but one subject to have normal bone age. Height, weight, and head circumference data revealed a wide range of growth percentiles for the entire group with mean percentiles in the range of 25%-50%. The findings of this pilot study indicate that, in general, skeletal growth of the craniofacial complex as well as axial skeletal growth was not significantly altered by the immunosuppressive regimen of cyclosporine over the time period evaluated. Further longitudinal data compiled from this study may shed more light on the possible adverse effects of cyclosporine on craniofacial growth and development.

I. INTRODUCTION

The last decade and a half has witnessed the extension of heart transplantation therapy into the pediatric population. The scope of cardiac lesions which leads to heart transplantation includes children and infants with cardiomyopathies, cardiac tumors, and complex congenital heart disease. The most common cyanotic congenital heart disease is hypoplastic left heart syndrome. Recent actuarial data of infants and children undergoing cardiac transplantation supports a positive prognosis which parallels that of adults.^{1,2,3} Much of this success can be attributed to posttransplantation immunomodulation, surgical experience, improved technology for graft surveillance, and better patient selection.¹ What was once a procedure with high perioperative mortality, is now routine medical intervention for end stage cardiac disease in the pediatric population.⁴

Decreased organ transplantation graft rejection may be attributed to better management of posttransplantation immunomodulation of which several therapeutic regimens have been advocated.^{1,2,3,4,6} The most common immunosuppression therapies are based on cyclosporine or FK506 in combination with adjunctive agents, such as azathioprine and glucocorticoid.^{1,2}

The unique action of cyclosporine on T-cell immunosuppression without myelosuppression has established it as a first line therapy for graft maintenance.⁶ However, the adverse effects of cyclosporine, including nephrotoxicity, lymphoproliferative disease, hypertension, gingival hyperplasia, and hypertrichosis are well documented in the literature.^{5,6,7,8,9,10} In

addition to these side effects, studies by Reznik *et al* linked cyclosporine to abnormal facial growth in pediatric renal transplant patients. Initial investigations by Reznik *et al*. (1987), revealed thickening of the nares, lips and ears, puffiness of the cheeks, prominence of the supraorbital margins, and mandibular prognathism. The changes in facial appearance resembled those seen with phenytoin therapy.¹¹ A follow-up study by Reznik *et al*. (1989), evaluated the effects of cyclosporine on facial bone growth. The results showed a relative shortening of the posterior face height, an increase in anterior face height, a steep mandibular plane angle, an absolute shortening of the mandibular body and mandibular retrognathia. These characteristics are often seen in patients with long face syndrome.¹⁴ These findings have raised some important questions concerning possible dysmorphic craniofacial growth and has been the impetus for this study.

The purpose of this paper is twofold. Firstly, it is to initiate the formation of a longitudinal study to evaluate the effects of long-term cyclosporine immunosuppression on craniofacial growth in the pediatric heart transplanted patient treated in the International Pediatric Heart Transplantation Program at Loma Linda University's Childrens Hospital. Secondly, it is a pilot study with the intent to gather initial patient data and compare this with normative growth study data.

II. MATERIALS AND METHODS

A prospective group of twenty-eight pediatric heart transplantation patients currently on maintenance cyclosporine based immunosuppression therapy were evaluated. Inclusion criteria for this study was limited to pediatric patients who required a heart transplantation at Loma Linda University before six months of age and who were 4 years of age or older at the beginning of the study. Children with associated genetic problems, hormonal deficiencies, major organ failures, and other related syndromes were excluded from this evaluation in an effort to minimize confounding variables. The composition of the study group was as follows: eighteen subjects were Caucasian of European ancestry (9 female and 9 male, ages 4-10 years) and ten were of Hispanic decent (3 females and 7 males, ages 4-7 years). Age groups were determined by including in each age interval, radiographs taken six months before a birth month through five months after a birth month.¹⁵

All patients followed the Loma Linda University International Pediatric Heart Transplantation immunosuppression protocol. The primary posttransplantation immunosuppression agent was cyclosporine with decreasing doses of azathioprine or methotrexate. Target radioimmunoassay (RIA) whole blood levels of cyclosporine were maintained at therapeutic doses of 150-350 ng/dl. The use of adjunctive agents such as polyclonal antibody therapy and/or pulse glucocorticoids was limited to severe or chronic graft rejection. None of the patients received the immunosuppressive agent tacrolimus (FK506).

Data was gathered on each patient in an effort to conduct a craniofacial growth analysis. Each child had a lateral cephalograph, panoramic

radiograph, hand/wrist radiograph, and a standard orthodontic photographic series (frontal, frontal smiling, profile, and intra-oral). In addition, height and weight data was obtained from age three until the time of study initiation. Head circumference data was also recorded until the age of three.

Cephalographs were obtained by the Broadbent cephalometric technique which positions the subject's head in a cephalostat oriented to the Frankfort horizontal plane. An anode-to-object distance of five feet was used.¹⁶ The object-to-film distance was standardized at 13cm which produces a consistent 9% enlargement factor. Standard anatomical landmarks from each cephalograph were identified and traced on standard 0.003 inch acetate matte tracing paper by the principal investigator. Each landmark location was reviewed by at least one other investigator before computer digitization. The cephalometric analysis was completed using the *Quick ceph image pro* software program.

The following *landmarks* were identified on each lateral x-ray film (Fig 1): sella turcica (S), nasion (N), point A (A), point B (B), pogonion (Pog), gnathion (Gn), gonion (Go), menton (Me), and articulare (Ar).

The definitions for these landmarks have been widely published.^{15,20} Various angular measurements have been derived from these landmarks which have been described in the classic literature.^{17,18,19} The *skeletal angular parameters* examined in this study were as follows: Fig. 2. SNA, SNB, ANB, GoGn-SN, Angle of Convexity (NAPog) and Fig. 3. Gonial angle (ArGoMe), A-B Plane (NPog-AB). Descriptive statistics were used to compare the acquired cephalometric data with normative non-medically compromised subject data.

Fig. 1. Cephalometric landmarks used

Fig. 2. Cephalometric planes and angles

Fig. 3. Cephalometric planes and angles

Caucasian subjects were analyzed against the normative standards from the Michigan growth study.¹⁵ This comparative database was compiled in Ann Arbor and involved a typical non-medically compromised group of normal growing children including those with mild and moderate malocclusions. The Hispanic subjects were analyzed against crosssectional data obtained through research at the University of Texas at Houston.^{12, 21} All children of this group had normal profiles and Angle Class I occlusions. This sample, although not typical of a random population represents an adequate database for comparison and is one of the largest databases available.

A standard right hand carpal index was taken with hand and wrist of each subject in full contact with the film cassette with no focusing grid in place. This produces a less than measurable amount of magnification. Each hand/wrist radiograph was compared to Greulich and Pyle's Radiographic Atlas of Skeletal Development of the Hand and Wrist and analyzed for axial skeletal growth deviations by a pediatric radiologist from the Loma Linda University Medical Center.²²

Height and weight data was gathered from the age of three to 27 of the 28 subjects. The last measurements were used for percentile ranking. Head circumference measurements were recorded at about 36 months of age. Data for the entire group was plotted and analyzed against standard prepubescent growth and development statistics percentiles data from the National Center for Health Statistics.²³

III. RESULTS

The cephalometric skeletal angular parameter values for individuals of the Caucasian and Hispanic groups are recorded in Tables 1 and 2, respectively.

Tables 3 and 4 shows the descriptive statistical data and mean normative values for each cephalometric parameter recorded. Table 3 indicates that the difference between the Caucasian mean norms and the recorded mean values range from 0.0 to 0.5 degrees for six of the seven parameter measurements, with the Gonial angle value differing by 3.9 degrees. Table 4 lists the above mentioned statistical measurementst for the Hispanic group. The difference between the mean norms and recorded mean values in this group range from 0.8 to 3.7 degrees. The mean and median values for both groups were quite close with a difference ranging from 0.1 to 0.9 and 0.1 to 1.7 degrees, respectively.

Table 5 indicates the distribution of individuals in each of the two groups studied within 1, 2 and greater than 2 standard deviations for each angular parameter value measured. The majority of the subjects were within 2 standard deviations of the norm for each measurement. These findings would suggest a relatively normal pattern of facial growth for the majority of this sample. The most common cephalometric measurements greater than 2 standard deviations from the norm were GoGn-SN, Gonial angle, and ANB angle. However, only four subjects (#5,#7,#8, & #13) exhibited a pattern of growth similar to those implicated in Reznik's investigation, that of steep mandibular plane angle and mandibular retrognathia.¹⁴

Table 1. Caucasian lateral cephalometric data.

Subject	SNA	SNB	ANB	GoGn-SN	Angle of Convexity	Gonial Angle	A-B Plane Angle
1	76.7	72.6	4.0	48.4	8.9	142.6	-5.4
2	85.8	80.1	5.7	37.4	12.4	128.4	-6.5
3	82.0	75.5	6.5	38.9	12.8	135.3	-8.0
4	78.3	74.8	3.5	28.5	6.4	127.8	-5.7
5	80.3	72.6	7.8	43.9	18.8	138.4	-9.0
6	86.4	80.4	6.0	43.2	14.4	143.5	-6.9
7	80.8	71.1	9.7	46.9	20.6	139.1	-8.7
8	84.9	77.1	7.8	44.3	18.5	139.5	-5.4
9	84.0	81.8	2.2	34.2	4.0	135.2	-3.1
10	84.3	81.0	3.4	36.9	7.9	137.4	-4.2
11	80.9	75.1	5.9	33.9	10.7	130.3	-7.0
12	80.0	74.8	5.2	33.0	4.3	119.7	-9.3
13	83.0	73.2	9.8	44.4	22.0	138.4	-10.6
14	78.6	77.2	1.4	41.2	2.5	130.6	-2.1
15	79.0	71.6	7.4	43.4	14.7	130.8	-9.6
16	82.1	79.4	2.7	35.0	4.0	128.6	-4.4
17	79.2	73.6	5.5	40.2	11.6	127.2	-8.1
18	82.9	79.6	3.3	37.9	8.0	141.9	-2.4

Table 2. Hispanic lateral cephalometric data.

Subject	SNA	SNB	ANB	GoGn-SN	Angle of Convexity	Gonial Angle	A-B Plane Angle
19	82.2	77.0	5.2	39.6	12.8	125.2	-3.9
20	85.1	76.4	8.6	42.0	20.5	127.8	-8.4
21	82.0	79.6	2.4	40.8	6.4	145.8	-1.6
22	89.0	80.4	8.6	33.4	15.5	136.5	-8.6
23	79.2	76.2	3.1	36.4	8.0	129.5	-3.1
24	80.8	77.3	3.5	36.5	8.2	133.1	-3.5
25	84.2	80.4	3.8	37.4	8.4	130.3	-4.5
26	84.7	80.5	4.2	36.4	10.7	127.2	-5.5
27	85.7	79.9	5.8	37.8	13.5	129.8	-6.0
28	80.5	76.7	3.8	36.4	9.7	132.5	-4.4

Table 3. Caucasian lateral cephalometric measurements and descriptive statistics in degrees (n=18)

MEASUREMENTS	NORMS		PATIENT DATA					
	Mean	SD	Mean	SD	Median	Min.	Max.	Range
SNA	81.3	3.0	81.6	2.8	81.5	76.7	86.4	9.7
SNB	76.0	3.0	76.2	3.5	75.3	71.1	81.8	10.7
ANB	5.4	2.5	5.4	2.5	5.6	1.4	9.8	8.4
GoGn-SN	40.0	4.7	39.5	5.4	39.6	28.5	48.4	19.9
Angle of Convexity	11.3	5.2	11.3	6.0	11.2	2.5	22.0	19.5
Gonial Angle	130.3	4.5	134.2	6.5	135.3	119.7	143.5	23.8
A-B Plane Angle	-6.7	3.4	-6.5	2.6	-6.7	-2.1	-10.6	8.5

Table 4. Hispanic lateral cephalometric measurements and descriptive statistics in degrees (n=10)

MEASUREMENTS	NORMS		PATIENT DATA					
	Mean	SD	Mean	SD	Median	Min.	Max.	Range
SNA	82.3	3.1	83.3	2.9	83.2	79.2	89.0	9.8
SNB	76.4	3.0	78.4	1.9	78.5	76.2	80.5	4.3
ANB	5.8	1.7	4.9	2.2	4.0	2.4	8.6	6.2
GoGn-SN	36.5	5.7	37.7	2.5	37.0	33.4	42.0	8.6
Angle of Convexity	12.2	6.6	11.4	4.3	10.2	6.4	20.5	14.1
Gonial Angle	128.9	6.3	131.8	5.9	130.1	125.2	145.8	20.6
A-B Plane Angle	-1.3	6.4	-5.0	2.2	-4.5	-1.6	-8.6	7.0

Table 5. Distribution of individuals about the normative mean
(Caucasian (C) n=18, Hispanic (H) n=10)

MEASUREMENTS	< 1SD		< 2SD		> 2SD	
	C	H	C	H	C	H
SNA	12	8	6	1	0	1
SNB	8	6	10	4	0	0
ANB	11	4	5	5	2	1
GoGn-SN	8	10	7	0	3	0
Angle of Convexity	13	8	4	1	1	1
Gonial Angle	8	7	7	2	3	1
A-B Plane Angle	13	8	5	2	0	0

Each subjects chronological age was compared with their skeletal age as determined via their hand/wrist radiograph using Gruelich and Pyle's Radiographic Atlas. Table 6 shows that all but one of the individuals analyzed had a normal axial skeletal bone age. Only subject #11 showed a decreased bone age of greater than 2 standard deviations.

Height, weight, and head circumference data was recorded in Table 7. The mean height and weight percentiles for the entire group was in the 25%-50% range at the onset of the study. The mean head circumference percentiles at the age of three for the entire group was also in the 25%-50% range.

Subjective photographic and panoramic radiographic analysis was also evaluated. The photographic records revealed that many of the patients exhibited mild to moderate hypertrichosis and gingival hyperplasia. Also, it was observed photographically that two individuals (#12,#22) did exhibit facial appearance abnormalities similar to those documented by Reznik.¹³

Upon radiographic analysis there seemed to be an uncommon propensity for missing permanent teeth and to a lesser degree ankylosed primary molars. Eight or 29% of the subjects were suspected of missing either maxillary second bicuspid, mandibular second bicuspid, or maxillary laterals or a combination. Five or 18% of the individuals showed suspected ankylosis of primary molars.

Table 6. Hand/wrist radiographic data and analysis.

Subject	Sex	Age yr.-mo.	Bone age yr.-mo.	S D mo.	Analysis (n)normal (d)delayed
1	m	6-6	7-0	9.7	n
2	m	5-11	5-0	9.3	n
3	m	4-6	4-6	7.8	n
4	m	5-7	6-0	9.1	n
5	f	6-5	5-9	8.6	n
6	f	7-1	5-9	8.3	n
7	f	5-11	5-0	9.0	n
8	m	7-4	7-0	10.5	n
9	m	8-4	8-0	10.8	n
10	f	7-5	7-10	8.5	n
11	m	7-9	5-9	10.8	d
12	f	10-7	8-10	11.0	n
13	m	7-7	7-0	10.6	n
14	m	8-9	8-0	11.0	n
15	f	6-10	6-10	8.3	n
16	f	8-2	8-10	8.8	n
17	f	10-5	-	-	-
18	f	6-0	-	-	-
19	f	5-3	5-0	8.9	n
20	m	4-10	6-0	7.8	n
21	m	6-6	6-0	9.7	n
22	m	5-2	5-0	8.4	n
23	m	6-0	5-0	9.3	n
24	f	5-9	5-9	9.0	n
25	m	6-11	6-0	10.1	n
26	m	5-6	4-6	9.1	n
27	f	6-11	5-9	8.3	n
28	m	7-4	7-0	10.5	n

Table 7. Height(Ht.), weight(Wt.), and head circumference(HC) expressed as a percentile of normative standards for a specific age. Ht. and wt. percentiles were figured from the last recorded entry. The HC percentiles were from the age of three.

Subject	Ht. %	Wt. %	HC. %
1	-	-	-
2	10-25	25-50	50
3	25-50	10-25	75
4	50	25-50	10-25
5	25-50	50-75	5-10
6	50	25-50	25
7	25	25-50	50-75
8	25-50	25-50	5-10
9	10-25	25	<5
10	50-75	90	50-75
11	90	75	-
12	5-10	10	50-75
13	5	10-25	10-25
14	95	50-75	95
15	25	50	50
16	25-50	25-50	25
17	25	<5	50
18	25-50	75	25-50
19	75	>95	50
20	10-25	50	50
21	25-50	75-90	25-50
22	<5	<5	25-50
23	5-10	25-50	10-25
24	5-10	10-25	90
25	5	5	-
26	<5	10	10-25
27	5	5	<5
28	25-50	50	50
Mean%:	25-50	25-50	25-50

IV. DISCUSSION

Dysmorphic craniofacial growth, or the lack thereof, and its relation to a known therapeutic regimen, namely cyclosporine, is the primary interest of this investigation. The effects of cyclosporine have been well documented in the literature.^{5,6,7,8,10} More recently, this agent has been implicated in adversely affecting craniofacial growth in renal transplantation recipients.^{13,14} In order to better understand the long term effects of cyclosporine on growth, we have examined the craniofacial and axial skeletal development of a group of infant heart transplantation recipients and compared them to normative growth data.

Many factors have been implicated in the disturbance of skeletal and craniofacial growth including, trauma, chronic illness, congenital influences, developmental defects, environmental factors, and teratogens. Moreover, there are recognized at least four major components to the complex phenomenon of craniofacial growth and development. These include the cranial base synchondrosis and the calvarial sutures being influenced by the CNS and other soft tissue growth, the nasal-septal cartilage, the remodeling growth of the maxilla and mandible, and the cartilaginous growth at the temporomandibular condyle.²⁴ Certain etiological factors that affect any or all of these components may cause morphometric changes in craniofacial growth patterns.²⁵

Our cephalometric data revealed that, 86% (N=24), showed minor deviation from mean normative values. Most measures for each subject were within 1 or 2 standard deviations. Four subjects (#5, #7, #8, & #13) did in fact show cephalometric measures indicative of individuals with a vertical growth pattern and apparent mandibular retrognathia as evidenced by an increased

GoGn-SN angle, ANB angle, and Gonial angle. No definitive conclusions could be drawn concerning the specific etiology of the vertical growth pattern seen in these subjects other than normal variations within a given sample. None of these patients were associated with decreased bone age or facial abnormalities. The fact that the mean and median Caucasian Gonial angle measurement was only one standard deviation from the normative mean for this group seemed inconclusive in relation to cyclosporine.

Only one subject (#11) revealed a decreased bone age upon carpal index analysis. The facial and skeletal presentation of this patient appeared within normal limits. This would support the idea of a relatively normal pattern of axial skeletal development for this sample.

Longitudinal height and weight data revealed a substantial range in growth percentiles for the group. Mean height and weight percentiles did suggest a potential decreased stature. In fact, when these subjects are subjectively compared to their non-medically compromised siblings there appears to be a tendency for suppressed statural development. Mean head circumference percentiles at age 3 years were similar to the height and weight data obtained. The potential role of chronic illness, individual genetic variability, and teratogenic influence on general growth and development of this sample is not yet clear.

Clinically, only two individuals (#12, #22) exhibited a facial appearance similar to those reported by Reznik. Neither of these subjects showed any significant skeletal abnormalities and no single variable could be implicated in the dysmorphic presentation seen. However, the long-term use of

prednisone in subject #12 could not be overlooked as a primary etiologic factor in her “cushingoid-like” facial appearance.

It was interesting that eight subjects (29%) were suspected of missing one or more permanent teeth and five subjects (18%) showed ankylosed primary molars. The most commonly found missing teeth were maxillary or mandibular second bicuspid. In light of the fact that the permanent third molars could not be evaluated at this age and that these teeth are by far the most often congenitally missing, one could suspect that it is possible that a higher percentage of subjects could reveal permanent tooth agenesis. This is a significant finding due to the fact that somewhat less than 4% of the general population have one or more teeth congenitally missing.²⁶ There are five principal known causes of congenital absence of teeth: heredity, ectodermal tissue dysplasias, local infections, systemic conditions, and expression of evolutionary changes in the dentition.²⁶ In addition, although primary molar ankylosis is relatively common among the general population it seemed to be more prevalent in our sample, 8% vs. 18%, respectively. No definitive conclusions could be made concerning the primary etiologic factor for these findings. Additional longitudinal data may shed some light on these interesting findings.

Our data seems to support the fact that, in general, craniofacial growth and skeletal development is not affected by the immunomodulatory regimen utilized in this pilot study. It seems to be questionable as to whether the few facial bone “abnormalities” noted are truly dysmorphic features with definitive etiologies. Interestingly, If one was to gather a matched random

sample of children from the general population one may in fact find similar outliers as seen in this preliminary study.

V. CONCLUSIONS

In conclusion, the morphometric analysis of twenty eight cardiac transplanted children treated with long term cyclosporine immunosuppression shows a relatively normal pattern of growth for the vast majority of the sample studied. Our data did not support the findings of previous reports. Due to the tremendous variability of genetic factors as well as individual responses to chronic illness and therapeutic treatments, it makes it quite difficult to implicate any one immunomodulatory agent as a potential divergent to normal growth and development, at least up to this point in time. The possible role of cyclosporine in adversely affecting craniofacial growth over a longer period of time needs to be evaluated further. Continued longitudinal data collection and evaluation is planned for this pilot sample and for a larger sample size.

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