The Effects of Medroxyprogesterone on Dentofacial Development in Males with Idiopathic Isosexual Precocity

FRANK A. CATALANOTTO, D.M.D.
RAVINDRA NANDA, D.D.S., Ph.D.
DOUGLAS J. MACKO, D.M.D.

The effects of endocrine hormones on development of the craniofacial complex have been studied by many investigators. However, hormonal specificity affecting such development is unclear and conflicting results have been reported in the literature. The clearest evidence of hormonal control of dental development is found in cretins and individuals with acquired juvenile hypothyroidism.[1] Adrenogenital syndrome and precocious puberty, if of prolonged duration, tend to produce advanced dental development, although hormonal specificity is less clear.[2] In all cases of endocrinopathy, skeletal changes are generally more significant than dental changes, if alteration in dental development exists at all.[3]

The specific effects of the sex hormones on craniofacial bone and tooth development have received less attention than have the other endocrine hormones. Animal studies have focused primarily on skeletal changes demonstrating some specific changes in craniofacial form.[4] Alterations of dental development have received less attention. Human studies on individuals with abnormal secretion of sex hormones often demonstrate conflicting results. Most investigators have reported that skeletal development is advanced in children with sexual precocity but there is little or no alteration of dental development.[5] No studies at this time have evaluated the effects of medroxyprogesterone treatment of children with precocious puberty upon oral facial development.

We had the opportunity to study five males with true isosexual precocity treated with medroxyprogesterone. Longitudinal data on somatic growth and cross-sectional data on dental and craniofacial development were obtained. This enabled us to observe the specific effects of both excessive levels of endogenous testosterone and exogenous progesterone on dental and craniofacial development in males.

MATERIALS AND METHODS

The subjects of the study were five males with idiopathic isosexual precocity referred from the Endocrine Clinic at Children's Hospital Medical Center, Boston. Medical history, growth parameters and progesterone treament regimen were gathered from the patient's medical record and are summarized below. An oral examination was performed on each subject. Study casts, panoramic radiographs of the teeth and jaws, lateral cephalometric radiographs and wrist films for all subjects were obtained.

Dental age was evaluated in each subject by assessing tooth emergence and root development. A tooth was considered erupted if at least one cusp had pierced the mucosa. The standards used to assess tooth emergence were based on a population of Boston children similar to these subjects and were obtained from Forsyth Dental Infirmary.[6]

Root development was assessed on panoramic radiographs utilizing all permanent teeth that could be visualized

From the Departments of Pediatric Dentistry and Orthodontics, University of Connecticut Health Center, Farmington, Connecticut 06032.

without significant distortion. Standards for root development were obtained from Moorrees, Fanning and Hunt.[7] Standards for skeletal age based on the wrist films were analyzed using Greulich and Pyle's atlas.[8] Growth and development of the craniofacial skeleton was assessed utilizing a tracing of the cephalometric radiograph which was computer analyzed and compared with age and sex-matched normal subjects using Burstone's standards.[9]

Subjects

1. S.G. was born 12-2-66. At 16 months old his mother noticed a progressive enlargement of the penis which was subsequently followed by growth of pubic hair, deepening of his voice, and an increase in hair on the upper lip. The past medical history and family history were noncontributory. A diagnosis of isosexual precocity was made at 22 months of age and Depo-provera, 150 mg I. M., every two weeks was initiated. At this time it was also noted that he had 16 primary teeth and his bone age, as determined by a hand-wrist film, was 36 months. At the time of this study he was 48 months old and had been receiving Depo-provera for 26 months.

2. B.S. was born 2-26-65. He was first seen at 15 months of age for progressive enlargement of the penis and premature development of secondary sexual characteristics. Past medical history and family history were noncontributory. The bone age was 24 months. After a diagnosis of isosexual precocity, Depo-provera, 150 mg I. M., every two weeks was administered. At the time of this study he was 71 months old and had been receiving Depo-provera for 46 months.

3. D.W. was born 6-17-62. He was first seen at 48 months of age for slight development of secondary sexual characteristics. A diagnosis of isosexual precocity was not made until 74 months old at which time Depo-provera, 200 mg I. M., once per week was started. At the time of this study he was 103 months old and had been receiving treatment for 29 months.

4. C.T. was born on 12-14-61. He was first seen at 52 months of age for enlarged breasts and a large penis. The past medical history and family history were noncontributory except for Von Recklinghausen's disease in the mother. The patient has a fraternal twin who is normal. He had neurofibromatosis, cafe-au-lait spots since birth and, while central nervous system and endocrinological tests were normal, a marked demineralization of the sella turcica was present. At 64 months chronologically (bone age 96 months), treatment with Depo-provera, 100 mg I. M., every two weeks was initiated. At 69 months no change was noted in the rapid growth pattern. At this time his bone age was determined to be 108 months. The dosage of Depo-provera was increased to 200 mg I. M., every 2 weeks. At the time of our examination his chronologic age was 108 months and he had been under treatment for 44 months.

5. C.W. was born on 4-11-59 and is the brother of D.W. The diagnosis of isosexual precocity based upon physical examination was made at the chronologic age of 19 months with a bone age of 24 months. At 108 months of chronologic age, the bone age was determined to be 185 months and treatment was initiated with Depo-provera, 200 mg I. M., once per week. At the time of this study the patient had been under treatment for 32 months and his chronologic age was 140 months.

Results

The comparison between chronologic age and developmental age (as determined by hand-wrist film) is presented in Figure 1. All subjects are above the

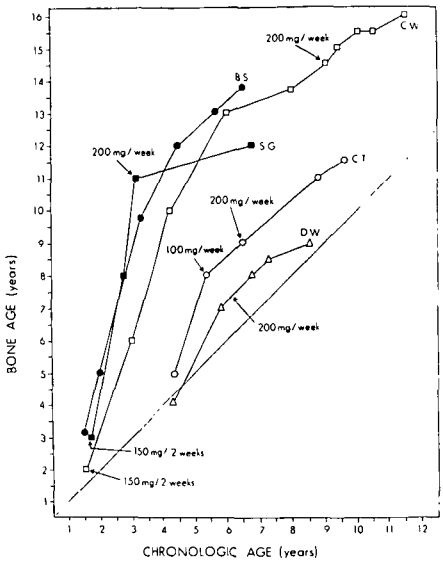

Fig. 1

isodevelopmental line indicating an advancement in bone age. Three subjects (B.S., C.W. and S.G.) were diagnosed at an early age because of rapid onset of symptoms, and concomitantly show the most accelerated advancement of bone age. The remaining two subjects (C.T. and D.W.) were not diagnosed until about 4.5 years of age and seem to have less advancement in bone age. It should also be noted that the three subjects diagnosed at the younger ages received progesterone for a long period of time before we observed them.

Individual tooth root development and the resultant dental ages are presented in Table I. Teeth in which the apex was closed or in which there was too much radiographic distortion to allow accurate analysis were excluded from the analysis. The values for each tooth were averaged to determine the dental age (based on root development). No significant variation in individual tooth scores within each patient was noted. However, D.W. and C.T. showed retardation of development of the mandibular first molars compared with their chronologic age while this was not observed in the other subjects.

The comparisons between chronologic age, bone age, and dental age based on root development and tooth emergence are presented in Table II. All subjects except D.W. showed marked advancement in bone age with the youngest subject, S.G., showing the greatest advancement, 84 months. Dental age based upon root development was highly variable among subjects. The younger subjects, S.G. and B.S., demonstrated markedly advanced root development when compared with their chronologic age. The older subjects showed virtually no difference between root development dental age and chronologic age. Dental age based on tooth emergence was more consistently

TABLE I
Root Development in Males with Isosexual Precocity Treated with Progesterone

Patient	*S.G.*	*B.S.*	*D.W.*	*C.T.*	*C.W.*
Chronologic Age (months)	48	71	103	108	140
Root Development					
Max. Incisors	—	113	102	—	—
Mand. Centrals	—	96	96	—	—
Mand. Laterals	63	108	102	—	—
Mand. Canines	57	96	105	108	156
Mand. First Premolars	63	72	102	114	162
Mand. Second Premolars	52	72	99	114	144
Mand. First Molars	63	72	72	78	—
Mand. Second Molars	60	78	114	114	141
Mand. Third Molars	—	—	—	135	135
Mean Root Dev.	60.5	88.3	99	110.5	147.6

TABLE II

Dental Development in Males with Isosexual Precocity Treated with Progesterone

Subjects	Chronologic Age (months)	Bone Age (months)	DENTAL AGE Root Development (months)	DENTAL AGE Tooth Emergence (months)
S.G.	48	132	60.5	74
B.S.	71	156	88.3	106
D.W.	103	108	99	106
C.T.	108	132	110.5	130
C.W.	140	192	147.6	152
Mean	94	144	101	114

advanced in all subjects except D.W. The younger subjects again showed the most advancement, i.e., 26 months for S.G. and 35 months for B.S., while the older subjects showed moderate advancement, 22 months for C.T. and 12 months for C.W.

Craniofacial skeletal analysis of all individuals was performed using cephalometric head films for Burstone's[9] computerized analysis. The measurements obtained were compared with those of normally growing children of similar chronologic age (Table III). The anterior (S-N) and posterior (S-Ar) cranial bases were found to be significantly larger in all individuals except subject D.W. where only the posterior cranial base was larger. The cranial base flexure angle (NS-Ar) was within normal range in all subjects. The length of maxilla (PNS-ANS and PNS-A) and length of mandible (Ar-Pg, Go-Ar and Pg-Go) were significantly larger compared with the normal standards. The facial height (N-Me) was increased in all individuals except subject D.W. who did not show any significant difference compared with the normal standard. The major contributor of this increase was found to be lower facial height where the deviation from the standard measurement in ANS-Me dimension ranged from + 14.9 mm to 21.1 mm in four subjects. The mandibular plane angle (MP-FH) was within the normal range in all individuals except subject D.W. The facial profile (N-A-Pg) was found to be within the normal range. An analysis of the anteroposterior position of maxilla and mandible as compared with nasion using the Frankfort horizontal plane as the coordinate showed that in all subjects, points A, B, and Pg were situated significantly anteriorly. This indicated a prominence of both

TABLE III

Craniofacial Growth Parameters in Males with Isosexual Precocity Treated with Progesterone

Subjects / Cephalometric Measurements	*S.G.*	*B.S.*	*D.W.*	*C.T.*	*C.W.*
	Measurements ± Deviation from Chronologic Age				
S-N mm	71.4 + 7.1	73.8 + 9.3*	69.5 + 3.0	71.7 + 4.6	79.6 +11.0*
S-Ar mm	39.6 +11.5*	37.3 + 8.7*	35.6 + 5.9*	37.1 + 6.4*	39.0 + 6.7*
N-ANS mm	47.1 + 4.3	50.0 + 6.8*	50.1 + 4.9	50.0 + 3.4	53.8 + 5.0
ANS-Me mm	69.5 + 15.3*	75.5 + 21.1*	62.0 + 5.5	72.9 + 15.7*	74.2 + 14.9*
N-A-Pg°	12.6 + 4.3	11.7 + 2.7	5.3 — 3.1	12.0 + 5.0	6.7 + 0.4
ANS-PNS mm	61.1 + 12.8*	56.9 + 8.1*	51.9 + 2.1	56.1 + 5.3*	56.0 + 3.5
Go-Ar mm	56.2 + 19.2*	47.6 + 10.5	42.6 + 3.5	46.9 + 6.8*	48.7 + 6.8*
Pg-Go mm	79.6 + 16.8*	76.1 + 12.4*	76.3 + 9.4*	88.7 + 19.7*	85.5 + 13.2*
Ar-Pg mm	18.2 + 28.9*	109.8 + 19.9*	122.4 + 26.1*	105.0 + 11.1*	121.7 + 21.5*

* $Z > 2.00$

jaws in a profile view. In all subjects, dental analysis of the cephalometric films did not show any consistent pattern in the relationship of maxillary and mandibular incisors to each other and to the supporting bones.

We also compared the cephalometric analysis of the five subjects with normal standards based upon their developmental age (as determined by the hand-wrist films). This comparison demonstrated that the bone-age matched norms were more representative of the experimental subjects but differences were still observable in certain measurements such as lower vertical dimension and over-all length of the mandible.

Discussion

The results of this study demonstrate that males with isosexual precocity treated with medroxyprogesterone demonstrate significant advancement in bone development age, variable advancement in dental root development (with younger subjects displaying more advancement than older subjects), marked advancement in dental eruption (with younger subjects again displaying more advancement than older subjects), and significant changes in craniofacial development as observed on lateral cephalometric radiographs.

The diagnosis of precocious puberty is limited to those cases manifesting significant development of the secondary sexual characteristics before the ages of 8.5 years in girls and 10 years in boys.[10] Girls frequently show breast development, sexual hair, development of the labia majora and minora, periodic menstruation, urinary estrogens clearly elevated to the range of normal adult females, and vaginal smears demonstrating cornification. In males, there is an increase in pubic, axillary and facial hair, acne, and testicular and phallic enlargement. The 17-ketosteroids are only slightly elevated but testosterone is significantly elevated. True or idiopathic precocious puberty is always isosexual in nature and indicates not only precocity of the secondary sexual characteristics but also an increase in the size and activity of the gonads. There is no known cause of true precocious puberty in 80-90 percent of females and 50 percent of males. The disease is also far more frequent in females than in males. In spite of the early advancement in sexual development, osseous maturation and growth, the increased rate of ossification results in early closure of the epiphyses so that the ultimate stature is often less than would be otherwise.

Medroxyprogesterone has been used to treat both males and females affected with idiopathic isosexual precocious puberty.[11] In females, the hormone results in cessation of menses and regression of breast development. Testosterone levels are depressed in males. On the other hand, growth and skeletal maturation usually continue unaffected. The side effects include suppression of the pituitary-adrenal axis, cushingoid manifestations and alterations of testicular histology.[12]

The early literature on dental development in patients with sexual precocity is poorly documented and controversial. Various authors have combined all cases of sexual precocity together and reported various results including premature eruption, early dentition, normal dental age and slight advancement in dental age.[13-15] Seckel,[5] in a lengthy review and detailed evaluation of six children with precocious sexual development of various etiologies, concluded that dental age was not generally advanced compared with chronologic age but that facial growth was advanced. This was in contrast to a markedly advanced bone age.

Crigler, Cohen and Wittenborg[16] reported that systemic and dentofacial

growth patterns of children with idiopathic or genetic precocity or congenital adrenal hyperplasia were similar in that skeletal maturation was more markedly accelerated than linear growth. In addition, while dental age showed essentially no advancement, analysis of lateral cephalometric radiographs showed advanced growth rates of the craniofacial skeleton.

Wagner, Cohen and Hunt[17] studied dental development in four children with idiopathic sexual precocity and seven children with adrenogenic sexual precocity. They observed no advancement in dental age in the former patients but advanced dental development (based on root development) in the patients with adrenal malfunction. They concluded that sexual-skeletal maturation and dental development are dissociated metabolic activities that respond differentially to increased production of gonadal hormones or 17-ketosteroids.

Garn, Lewis and Blizzard[18] published an extensive review of dental status (root development) in various endocrinopathies. They reported that, in general, children who are advanced or retarded in sexual and osseous maturation are advanced or retarded dentally, but to a less pronounced degree. Their data on twelve subjects with constitutional and nonconstitutional sexual precocity (generally adrenal in origin) demonstrated a 9 percent advancement in dental age as contrasted with a 70 percent of bone age. However, if the four subjects with constitutional isosexual precocity are omitted there is virtually no advancement in dental age in these subjects.

Keller, Sather and Hayles[19] utilized the standards of Moorrees[7] et al. to evaluate dental root development in 179 patients with various endocrine and metabolic diseases. Their data on six females with isosexual precocity treated with medroxyprogesterone and 16 untreated subjects showed a consistent advancement of skeletal age compared with chronologic age in all subjects. In the untreated subjects, dental age was consistently close to chronologic age while in the treated subjects there was a trend toward advanced development.

There are few animal studies on the effects of the sex hormones on craniofacial development. Seipel, van Wagenen and Anderson[20] reported the production of a protrusive open-bite malocclusion in monkeys treated with testosterone, caused primarily by discrepant growth between the maxilla and mandible. They also demonstrated delayed eruption of teeth with abnormal root development. A rather extensive review and experimental protocol reported by Riesenfeld[21] demonstrated the difficulties of studying endocrine influence upon craniofacial growth in animals as he showed marked variation in the effects of various experimental endocrinopathies on craniofacial development.

Based upon this review, most authors have concluded that in true isosexual precocity: skeletal development is markedly advanced over chronologic age; dental age (as measured by root development) is not generally advanced compared with chronologic age; there can be some advancement in craniofacial growth; and treatment of isosexual precocity with progesterone seems to cause some advancement in dental age.

The present findings with respect to advanced bone or developmental age are consistent with observations made in the literature.[10] However, the results of this study related to dental age based on either root development or tooth emergence are not similar to other findings in the literature.[5,13-15] The advancement in root development seen in the younger subjects in our study is prob-

ably related to the earlier onset of the disease in these subjects; this may, in fact, be the source of the variations noted in the literature. However, it may also be related to the longer exposure to medroxyprogesterone treatment, although there is no direct evidence to suport this hypothesis.

The advancement in tooth emergence in isosexual precocity noted in this study is previously unreported and may be a manifestation of the disease itself, or may be the result of medroxyprogesterone treatment. It is interesting to note that eruption age in younger males and females is virtually identical but that just before and during puberty in females (when endogenous progesterone is higher than previous levels), they consistently demonstrate earlier eruption of the permanent dentition than do males.[6,7]

The specific effects of isosexual precocity and/or medroxyprogesterone on craniofacial form as described in this study have not been reported previously. Our findings indicate that the lower face and mandible are most susceptible to these hormonal influences; this may represent the unique developmental characteristics of the mandible as compared with other parts of the craniofacial skeleton.[4,22]

Health Center
Univ. of Connecticut
Farmington, Conn. 06032

ACKNOWLEDGMENTS

Supported in part by U.S.P.H.S. Research Career Development Award 1 K04 DE00012 and N.I.D.R. Grant 5 R 23 DE04130 to Dr. Catalanotto. These data were collected while Dr. Catalanotto was a Postdoctoral Research Fellow in Pediatric Dentistry at Harvard University and Children's Hospital Medical Center and was supported by N.I.D.R. Training Grant 5 T01 DE 00112-08. We wish to thank Dr. John Crigler for referring these patients and Drs. C. F. A. Moorrees and L. Lebret of Forsyth Dental Infirmary for help in evaluating dental development.

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