

Original Article

The Effect of Methylphenidate on Cervical Vertebral Maturation and Dental Age in Patients with Attention Deficit Hyperactivity Disorder

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Chronological Age;
Skeletal Age;
Attention Deficit Hyperactivity Disorder;
Methylphenidate;

ABSTRACT

Statement of the Problem: It is postulated that attention deficit/hyperactivity disorder (ADHD) with or without medication has an inhibitory effect on the children's growth and development.

Purpose: This study aimed to assess the dental age and cervical vertebral maturation (CVM) stage in ADHD patients with or without medication.

Materials and Method: This cross-sectional study evaluated the pretreatment panoramic and lateral cephalograms of 129 patients (70 males, 59 females aged 8-14 years). Demirjian index and Baccetti's CVM index were used to determine the dental age and CVM stage, respectively. The subjects were evaluated in two groups of ADHD (case, n=59) and healthy individuals (control, n=70). The ADHD patients were divided into two groups of AWT (ADHD with Treatment, n=43) and AW (ADHD without treatment, n=16) based on the use of methylphenidate. Paired t-test was used to compare the mean dental age between the groups. Linear and ordered logistic regression models were used to detect differences between the groups. The association between dental and chronological age was assessed by using Pearson correlation coefficient ($p < 0.05$).

Results: After age and sex adjustment, the skeletal maturity stage was found to be similar to the control group based on the presence of the disorder or use of medication ($p = 0.711$ and $p = 0.436$, respectively). Similarly, the patients' dental age was similar to the controls in AW and AWT groups ($p = 0.180$ and $p = 0.421$, respectively). The correlation between dental age and chronological age was 0.79 in AWT, 0.88 in AW, and 0.88 in control group ($p < 0.001$ for all the three).

Conclusion: After age and sex adjustment, the dental and skeletal age of ADHD patients with or without Methylphenidate treatment do not manifest a significant delay compared with the controls.

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Introduction

Attention-deficit/hyperactivity disorder is the most common childhood neurodevelopmental disorder with a

high rate of psychological comorbidities. [1] It is accompanied with numerous social malfunctions that often continue into older ages. [2] The number of school-

age children who meet the criteria for ADHD in some regions has been reported to be significantly more than its worldwide prevalence, which is 5.9-7.1%. ADHD prevalence is said to be 8.6% in the capital city of Iran. [3] Considering an updated systematic review on the ADHD prevalence, the main reason for the variability in ADHD prevalence estimates is the methodological procedures of the studies. [4-5]

ADHD may be associated with a poorly regulated growth pattern in affected children. [6-9] Many studies have reported faster growth rate in untreated prepubertal ADHD patients. [10] Furthermore, review of the current literature shows that ADHD can be controlled by medications like methylphenidate (Ritalin®) and dexamphetamine, which decrease the level of hyperactivity and increase attentiveness.

Methylphenidate is among the most widely prescribed medications for ADHD. [11] However, concerns exist about the side effects of stimulant medications on skeletal maturation and growth rate of the involved patients. [8, 12-13] The studies conducted on this issue were mostly focused on the patients' height, weight, and BMI as the indicators of short-term drug effects. [4, 14]

Many studies reported the obvious weight loss and growth deceleration as the frequent collateral effects of the medications, especially in the first year of treatment. It goes on with a progressive normalizing trend over 2-3 years of treatment when administrated properly with careful titration and follow-up dosage adjustments. [11, 13-17] In contrast, some studies reported a continuous inhibitory effect of prolonged medication use on the skeletal growth rate, particularly during puberty. Thus, the clinicians are recommended to maintain the lowest possible dosage. [18-19]

The major postulated mechanism responsible for the reported growth deceleration effect of the stimulants is related mostly to the altered dopaminergic pathways that play a major role in growth hormone secretion. [20] Decreasing the dopamine reuptake reduce the growth hormone secretion, which directly restricts the postnatal growth. [20]

On the other hand, orthodontic treatment timing and planning obligate the clinicians to estimate the children's growth and development status accurately, so that they can provide early prevention and interception

of dentofacial deformities. [21] Many physical characteristics such as height, weight, skeletal maturation, and dental developments can be used in diagnostic procedures for assessment of growth and development. Accordingly, several methods have been developed to assess the children's dental and skeletal maturity that helps the dental clinicians as well as the pediatricians and endocrinologists. [22]

Considering the limited cross-sectional studies for precise evaluation of growth potentials in patients with ADHD, it is difficult to determine the physical developmental status of these patients with or without stimulant medications. One approach to address this and clarify the scope of growth impairment in ADHD may be through the assessment of dental age and skeletal maturity stage in these patients. To date, there is no study assessing the bone and dental maturity in ADHD patients. Hence, the aim of this study was to assess the dental age and the cervical vertebral maturation (CVM) stage in 8-14 year-old ADHD patients with or without methylphenidate use in comparison with healthy controls.

Materials and Method

This cross-sectional study was performed on 129 Iranian patients (70 males and 59 females), out of which, 70 were healthy controls (mean chronological age: 10.97 ± 1.80 years) and 59 had ADHD. The case group was subdivided into two subgroups, 43 were allocated to the group of ADHD with methylphenidate treatment (AWT; mean chronological age = 10.12 ± 1.61 years) and 16 were allocated to the group of ADHD without methylphenidate treatment (AW; mean chronological age = 10.20 ± 1.82 years).

The sample size was determined based on the Tabachnick and Fidell's (1996) model for testing multiple correlations ($k=4$; age, sex, ADHD and medication). Considering the possibility of 20% attrition, 139 patients were enrolled. The ADHD patients were mainly recruited from the pre-registered ADHD patients at psychological centers who referred to the Orthodontics Department of Shahid Beheshti University of Medical Sciences.

The patients' demographic data were recorded and documented via interviewing the parents. Written informed consent was obtained from the parents for the

entire process of the study including radiographic examinations. The study protocol was approved by the Ethical Committee of Dental Research Center of Shahid Beheshti University of Medical Sciences.

The ADHD diagnosis as per DSM-IV of the patients was made according to the WHO Questionnaire in addition to precise clinical examination by expert psychologists. The ADHD patients were divided into two separate groups considering the medication status. In order to address the drug type bias in this study, ADHD patients under methylphenidate (Ritalin®) for a minimum of 1 and maximum of 3 years were included in AWT group.

Patients who had been taking methylphenidate less than 6 months and longer than two years or any other kind of medication like amphetamines were excluded. The dosage of methylphenidate was between 10 and 40 mg per day, with a mean dose of 16.36 mg per day. Taking into account the inclusion and exclusion criteria, 70 children (30 boys and 40 girls) among patients referring to the Orthodontics Department were selected through random cluster sampling method.

The exclusion criteria were other congenital, systemic, or concomitantly diagnosed serious medical conditions, history of dental trauma, previous orthodontic treatment, or permanent tooth extraction. Those whose radiographs lacked visibility at the 2nd, 3rd and 4th cervical vertebra, those with significantly distorted radiographs, crowding of teeth, unclear roots and those with bilaterally missing teeth in the mandible were also excluded. In the case of a unilaterally missing permanent tooth, the contralateral tooth was assessed.

The original panoramic and lateral cephalograms of all the three groups were obtained with the same digital X-ray unit (Cranex-D; SOREDEX, Helsinki, Finland) at the same distance and using the same exposure settings (70-85 kVp at 10 mA). All radiographs were exported and saved in JPEG format by using the Digora software, ver. 2.8®. The digital radiographs were then visualized and analyzed via Adobe Photoshop CS (San Jose, CA, USA). Aa zoom of up to 150% was applied

when necessary.

The images were evaluated by Demirjian and Baccetti's methods for dental age and skeletal maturity stage estimation, respectively. All the lateral cephalograms were taken in natural head position and the reviewers used the cropped version of the radiographs limited to the cervical area (not the traced version). The children's chronological age was calculated and recorded by subtracting the birth date from the date on which the radiographs were taken.

To assess the dental age of the subjects, seven left permanent mandibular teeth were scored from "A" to "H" depending on the stage of calcification. Standards were given for each sex separately and the sum dental maturity scores was converted to dental age by using a conversion chart. The scores used in this study were the revised scores published by Demirjian and Goldstein. [23]

The patients' skeletal maturation was determined based on the modified version of Baccetti's CVM method. [24] In this method, two sets of variables were used including presence or absence of concavity at the inferior border of C2, C3 and C4 and the morphological shape of the body of cervical vertebrae C3 and C4 (trapezoid, rectangular horizontal, square and rectangular vertical). According to these two series of variables, the patients were allocated to six stages of skeletal maturation from CS1 to CS6. [24] All radiographs were scored by two calibrated examiners trained for this staging and blinded to the chronological age of the patients. The disagreements were resolved by debate and consensus.

Statistical analysis

All data were statistically analyzed by STATA software, version 12.0 (Statacorp LP; College Station, Texas, USA). Having assessed all the radiographs, a random subset of 40 radiographs were re-examined after 2 weeks to estimate the methodological error by means of percentage of absolute intra-observer agreement and Cohen's Kappa coefficient. The mean Kappa was 0.89±0.03 (least amount of 0.62 for the second molar) for determination of tooth calcification stages and 0.96±

Table 1: Distribution of cervical vertebral maturation stage in AWT, AW, and control groups

	CS1	CS2	CS3	CS4	CS5	CS6
AW	4 (25.0%)	6 (37.5%)	5 (31.2%)	1 (6.2%)	0 (0%)	0 (0%)
AWT	16 (37.2%)	17 (39.5%)	5 (11.6%)	4 (9.3%)	1 (2.3%)	0 (0%)
C	17 (24.9%)	15 (21.4%)	24 (34.2%)	11 (15.7%)	3 (4.2%)	0 (0%)

AW, patients without medication use, AWT; patients with medication and C, the control group

Table 2: The percentage distribution of calcification of each tooth at each dental stage from A to H in the three groups

	C			D			E			F			G			H		
	AWT	AW	C	AWT	AW	C	AWT	AW	C	AWT	AW	C	AWT	AW	C	AWT	AW	C
M2	0 (0%)	0 (0%)	1 (1.4%)	9 (20.9%)	5 (31.2%)	12 (17.1%)	17 (39.5%)	5 (31.2%)	22 (31.4%)	11 (25.8%)	5 (31.2%)	16 (22.8%)	4 (9.3%)	1 (6.2%)	14 (20.0%)	2 (4.6%)	0 (0%)	5 (7.1%)
M1				6 (13.9%)	4 (25.0%)	3 (4.2%)	12 (27.9%)	4 (25.0%)	17 (24.2%)	16 (37.2%)	6 (37.5%)	22 (31.4%)	8 (18.6%)	1 (6.2%)	15 (21.4%)	1 (2.3%)	1 (6.2%)	13 (18.5%)
PM2				1 (2.3%)	1 (6.2%)	2 (2.8%)	12 (27.9%)	6 (37.5%)	11 (15.7%)	15 (34.8%)	3 (18.7%)	17 (24.2%)	11 (25.2%)	3 (18.7%)	19 (27.1%)	4 (9.3%)	3 (18.7%)	21 (30.0%)
PM1						7 (16.2%)	5 (31.2%)	5 (7.1%)	21 (48.8%)	3 (18.7%)	18 (25.1%)	10 (23.2%)	6 (37.5%)	17 (24.2%)	5 (11.6%)	2 (12.5%)	30 (42.8%)	
C									0	1 (0%)	2 (6.2%)	7 (2.8%)	5 (16.2%)	9 (12.8%)	36 (83.7%)	10 (62.5%)	59 (84.2%)	
LI													0	2 (0%)	4 (12.5%)	43 (5.7%)	66 (87.5%)	
CI																		

AW: patients without medication use; AWT: patients with medication; C: the control group

0.05 for cervical maturation. The results revealed that the reproducibility of the diagnosis in our reviewers were approximately perfect.

Furthermore, the inter-examiner reliability was measured between the raters. For dental stage estimation, the percentage of inter-observer agreement varied from 86.11% to 100%, with a mean of 95.24%. The Kappa coefficient varied from 0.47 to 1 with a mean of 0.841, which is considered to be a high degree of agreement. The intra-examiner agreement of incisors and first molars was about 100% following natural near-to-complete development of these teeth at or before the age 8 years.

For CVM stage estimation, the percentage of intra-observer agreement varied from 81.33% (determination of C3 shape) to 100%, with a mean of 91.67%. The Kappa coefficient varied from 0.69 to 1, with a mean of 0.88, which is considered as high degree of agreement. The difference between both scores did not exceed one stage for any tooth or cervical maturation stage.

The mean dental age was compared between the groups by using t-test. The linear regression model was used to compare the dental age after adjustment for age and sex. Considering the ordinal type of CVM stage variable, the ordered logistic regression model was used to compare the skeletal stage after adjustment for age and sex. Pearson’s correlation coefficient was used to assess the correlation between the dental and chronological age within each group. $p < 0.05$ was considered to be statistically significant.

Results

Descriptive data

The radiographs of 139 participants (age range 8-14 years; mean age= 10.43) were studied. Ten of them were excluded; eight because of unclear cephalometric radiographs and two because of bilateral missing of mandibular second premolars.

Table 1 displays the frequency distribution of subjects in each stage of CVM from CVMS I to CVMS VI in the three groups. None of the participants was in stage VI. The distribution of dental calcification status in the three groups of AWT, AW and control is shown in Table 2. As it is demonstrated, none of the participants’ teeth was in stage A-C.

Skeletal stage

Logistic regression was used to investigate the correlation between the ADHD and the participants’ age and sex. The results showed that the average chronological age of ADHD participants (AW and AWT) was less than that of the controls (Co.-0.241; 95% CI- 0.45--0.02). Moreover, the percentage of male participants was higher in ADHD compared to the control group (Co. 0.916; 95% CI 0.17- 1.65). Regression analysis revealed that the age and sex were the statistically significant explanatory variables for skeletal stage differences ($p < 0.000$) (Table 3).

Dental age

The patients’ dental age (based on years) was calculated by converting the formula from the overall Demirjian coding of each tooth (Table 4).

Table 3: Ordered logistic regression model analysis for comparison of skeletal stage among the three groups after age and sex adjustments

Parameter	Coefficient	Standard error	z	p Value	95% Confidence interval	
Sex	-1.07	0.358	-3.00	0.000	-1.777	-0.372
Age	0.737	0.117	6.29	0.000	0.507	0.967
Medication	-0.429	0.534	-0.78	0.436	-1.00	0.431
ADHD	0.192	0.520	0.37	0.711	-0.827	1.213

Table 4: Mean and standard deviation (SD) of dental age for AW, AWT and control groups

Groups	Mean±SD	Standard error	95% Confidence interval	
AW	10.73±2.07	0.517	9.62	11.83
C	11.94±2.29	0.274	11.39	12.49
AWT	10.89±2.29	0.275	10.33	11.44

AW: patients without medication use; AWT: patients with medication; C: the control group

The variance ratio test of the groups demonstrated the equality of variances; thus, the t-test was used to compare the groups. The results of t-test demonstrated a significant difference in the mean dental age between the AW and control groups. Hence, the dental age of ADHD patients was significantly less than that of the controls ($p=0.049$). Similarly, the dental age of ADHD patients under Ritalin medication (AWT) was also significantly less than that of controls ($p=0.011$). However, there was no statistically significant difference between AW and AWT groups regarding the patients' dental age ($p=0.769$).

The difference in dental age of AW and AWT patients could be the result of differences in the participants' age and sex. Thus, a linear regression analysis was performed to investigate the differences after adjustment for age and sex (Table 5).

Table 5: Linear logistic regression model analysis for comparison of dental age among the three groups after age and sex adjustments

Parameter	Coefficient	Standard error	t	p Value	95% Confidence interval	
Sex	0.009	0.191	0.05	0.09	-0.369	0.387
Age	1.059	0.053	19.82	0.000	0.953	1.165
Medication	0.245	0.304	0.81	0.421	-0.356	0.847
ADHD	-0.396	0.293	-1.35	0.180	-0.978	0.185

The linear regression analysis revealed that the chronological age was the only statistically significant explanatory variable for dental age differences ($p<0.001$). In contrast to the skeletal stage, sex was not a statistically significant explanatory factor for dental age ($p>0.05$).

Table 6: Correlation and associations between dental age and chronological age in the three study groups

Pearson's correlation coefficient		AWT	AW	C
Chronological age	Dental age	0.79	0.88	0.88
p Value		0.000	0.000	0.000

AW: patients without medication use; AWT: patients with medication; C: the control group

Correlation

In this study, Pearson's Correlation Coefficient between

dental age and chronological age was found to be 0.88 in AW group, 0.79 in AWT group, and 0.88 in control group. These correlations could be considered as statistically significant positive values in all the three groups (Table 6).

Discussion

The current study showed that children with ADHD with or without medication use do not show lower dental and skeletal age than their healthy counterparts do. To the best of our knowledge, this is the first study on ADHD patients to show the effect of the disorder and medication on dental and skeletal development in affected individuals. Many previous studies investigated the growth pattern of ADHD patients with or without medication use through different growth parameters; height is the most frequently evaluated parameter in this regard. [14] However, it remains unclear whether reduction in height in children taking stimulant medications represents any delay in their physical maturation rate. [14]

Many case-control cross-sectional studies investigated the effect of this disorder and its treatment on growth status. Many of them used height measurements as the main growth indicator, but they suffer from inadequate statistical power due to insufficient number of cases to detect the difference between treated and untreated cases and normal controls. [9, 14, 25-27] The number of ADHD patients without treatment evaluated in this study was limited to 16 subjects. The main restriction of finding more cases was that most of ADHD diagnosed patients at psychological centers are assigned to receive pharmacological treatment. In addition, it was not ethical to take radiographs of patients who did not need to be evaluated orthodontically.

The patients' dental age and skeletal stage have been used as the main indicators of skeletal growth and maturation stage in dental clinics. [28-29] These variables were found to be more valid than the chronological age and assessment of secondary sexual characteristics of patients in clinical setup. [30]

As stated in the literature, a highly significant statistical correlation was found between bone age assessed from hand-wrist radiographs by using Björk's method and bone age assessed from cephalometric radiographs by using the method described by Baccetti *et al.* [31] Therefore, the analysis of cervical vertebrae in

cephalometric radiographs appears to be the most desirable method of bone age assessment. It eliminates the need for additional exposure to X-ray radiation and shortens the duration of examination. [31]

Several dental age estimation techniques have also been developed and applied as an auxiliary tool of age estimation in different populations. The dental age estimation methods of Schour and Massler (S&M), and Demirjian and Goldstien (D&G) were the most applied methods of estimations and are comparable and equally reliable as the skeletal age estimation methods. [32] However, the most appropriate method of dental age estimation is population-specific. [23, 33-35]

Considering the favorable applicability and accuracy of dental age estimation achieved through Demirjian's method demonstrated previously in an Iranian population, this method was applied in the current study. [36-38] In all studies performed in Iran, clinically acceptable dental age overestimation was reported by this protocol for both sexes ranging from 0.3-0.7 years. [36, 39-40] This overestimation highlighted the mildly accelerated dental development in normal population.

To date, dental age and bone age delay have been reported in growth hormone deficient, HIV-positive, underweight, children under oncological treatment and coeliac patients. [28, 30, 41-44] However, dental and bone age acceleration were observed only in obese children. [45-46]

Among a sample of Iranian children suffering from ADHD, the ADHD and ADHD-related symptoms in childhood were found to be related to the male sex. [47] The present study found no difference between the CVM maturation stage and dental age of ADHD patients with or without treatment and the control samples after age and sex adjustment.

As in preventive orthodontic treatments, the clinicians mostly deal with the patients' maturity rather than their absolute growth status; the clinical application of this finding is the lack of necessity of earlier evaluation of ADHD patients for possible preventive growth modification treatments, compared to the normal population.

In this study, the CVM stage was found to be related to age and sex. This result is consistent with other reports. [48-49] As stated in the literature, the mean

chronological age of female patients is less than their male counterparts are when they are diagnosed to be at 1-5 cervical maturation stage. [48] The studies on the growth-effect of this disorder and stimulants are based on the developmental stage of children.

There is a distinction between the magnitude of effect before and after onset of puberty and duration of treatment. The most conflicting time is between 1 to 3 years after the aforementioned period. The age range of individuals in our study was between 8-14 years since most clinical orthodontic preventive treatments are done in this age range. [50] Additionally, CVM stage and radiographic dental age estimation methods have their best accuracy only in this age range when many underdeveloped teeth and rapid growth are observed. [51]

Since most of the dentition is completely developed after the age of 14 years, the accuracy of radiographic age estimation tends to decrease thereafter. [35, 52] In the current study, there was a significant correlation between dental age and chronological age of all three groups ($p < 0.000$). Previous studies also reported the same direct correlation between the chronological age and dental calcification stages. [39]

The samples in this study were derived from more than sixteen psychological centers only patients who needed radiographs for orthodontic purposes were recruited. This inclusion criterion significantly limited the number of available patients for this study. On the other hand, the mean dose of methylphenidate in this study was 16.36 mg with the range of 10 to 40 mg per day. As the growth deceleration effect of this drug is considered dose-dependent, studies using lower doses of this drug might not show a significant effect on growth. [27, 53]

As it is stated in studies, which used height as a growth indicator, the effect of stimulants on growth is less frequently reported at doses not exceeding 20 mg of methylphenidate per day or its equivalent. [14] Further long-term prospective studies are needed to define the children's skeletal and dental development more precisely, relating them to the dose of stimulant medication similar to studies of height in ADHD patients.

Conclusion

The findings suggest that dental age and skeletal stage in

ADHD patients with or without routine methylphenidate medication do not manifest a significant delay in comparison with controls after adjusting for age and sex. Therefore, both indices serve as valuable criteria of the growth status; and it is important to consider both variables in determination of growth retardation in ADHD patients. The clinical application of this finding would be the lack of necessity of any earlier evaluation of ADHD patients for possible orthodontic treatments, compared with the normal population.

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Conflict of Interest

None declared.

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