Original article

https://doi.org/10.6065/apem.1938164.082
Ann Pediatr Endocrinol Metab 2020;25:92-96

Annals of Pediatric Endocrinology & Metabolism
apem

Prevalence of idiopathic scoliosis in girls with central precocious puberty: effect of a gonadotropin-releasing hormone agonist

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Purpose: Adolescent idiopathic scoliosis (AIS) is the most common form of scoliosis and occurs in children between 10 to 18 years old, during periods of growth spurts and puberty changes. In patients with central precocious puberty (CPP), due to early growth spurt, AIS is expected to develop before 10 years of age. Both AIS and CPP are more common in girls than in boys. The aim of this study was to determine the prevalence of AIS in girls with CPP and to evaluate the effect of treatment with gonadotropin-releasing hormone (GnRH) agonists on progression of scoliosis in these patients.

Methods: We retrospectively reviewed medical records of 553 girls, 338 with CPP and 215 without CPP. Scoliosis angle was measured on the standing frontal radiograph of each patient according to the Cobb method. Patients with a Cobb angle of 10° or more were diagnosed with scoliosis. For girls with CPP, follow-up spine radiographs were collected 1 year after treatment with GnRH agonists. Progression of scoliosis before and after treatment was compared in terms of Cobb angle changes.

Results: AIS was more prevalent in girls that were affected by CPP compared to controls without CPP (11.5% vs. 6.0%, CPP girls vs. non-CPP girls, respectively, P=0.031). The peak serum luteinizing hormone level positively correlated with Cobb angle (R^2=0.015, P=0.023) in the CPP group. No progression of scoliosis was observed in CPP girls after one year of GnRH agonist treatment. Additionally, the prevalence of scoliosis decreased in CPP girls after 1 year of the treatment.

Conclusion: We report that the prevalence of AIS is higher in girls with CPP than in non-CPP patients. A regular follow-up schedule for spine radiographs should be considered to reduce the risk of progression. Furthermore, GnRH agonist treatment for CPP may have a suppressive effect on progression of AIS.

Keywords: Central precocious puberty, Gonadotropin-releasing hormone agonist, adolescent idiopathic scoliosis, peak LH

Received: 7 October, 2019
Revised: 22 November, 2019
Accepted: 28 November, 2019

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Introduction

Adolescent idiopathic scoliosis (AIS) is the most common form of scoliosis, affecting approximately 2% to 4% of adolescents.[1-4] The prevalence of AIS in the Korean population is 3.26%, but a recent report showed that the incidence is progressively increasing.[4] Patients with a severe form of AIS may develop adverse long-term health outcomes in later adulthood, including pulmonary disorders, disability, back pain, psychological effects, cosmetic issues, and a reduced quality of life.[5] Therefore, early identification and effective intervention of mild scoliosis could slow or stop disease progression before skeletal maturity, thereby improving long-term outcomes in adulthood.

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

AIS occurs in children between 10 and 18 years of age, usually during periods of growth spurts and puberty changes.[6] The spinal curve progression in AIS is related to growth, skeletal maturity, and sexual maturity, especially during the Tanner sexual characteristics stage II.[7] Maximal progression of the scoliosis curve was observed during peak height velocity in adolescent girls affected by AIS.[8,9]

AIS is 2–10 times more common in females than in males, and a similar frequency is observed in central precocious puberty (CPP).[8,10] In patients with CPP, growth spurts start earlier than in their peers. At diagnosis, the mean growth velocity ranges from 8 cm to 10 cm/yr, roughly between +2 and +4 standard deviations (SDs) of the population distribution of the same age, resulting in increased height, between +1.5 and +2.5 SD of the same age population, on average.[11] In patients with CPP, AIS is expected to develop before the age of 10, especially in girls.

The aim of the present study was to determine the prevalence of AIS in girls affected by CPP and to evaluate the effect of gonadotropin-releasing hormone (GnRH) agonist treatment for CPP patients to suppress progression of scoliosis.

Materials and methods

1. Subjects

We reviewed the medical records and radiographs of 553 girls, 338 CPP patients and 215 control subjects that were not affected by CPP, that visited the pediatric endocrinology clinic of Korea University Medical Centers between March 2014 and September 2018. The CPP diagnosis was made based on the following criteria: onset of breast development before 8 years of age and a pubertal response to an exogenous GnRH stimulation test (peak serum luteinizing hormone [LH] ≥ 5.0 IU/L), in the absence of any identifiable adrenal or gonadal pathology. Administration of GnRH agonists was initiated after initial diagnosis. Non-CPP girls between 8 to 9 years old who visited the same centers to assess growth and development were selected as the control group. We excluded from the study CPP girls with an identified etiology, such as brain tumor or cranial irradiation, and girls with any chronic diseases, such as chronic nephrosis, asthma, and epilepsy.

2. Measurement methods

Angle of scoliosis was measured on the standing frontal radiograph of each patients using the Cobb method. Patient data, including CPP status, were unknown during Cobb angle measurement. Moreover, to reduce any confounding bias, each radiograph for the measurement of Cobb angle was randomly selected. Each Cobb angle was measured 3 times, consecutively, and the average was calculated. Curves with a Cobb angle of 10° or more were diagnosed as scoliosis.[12] For girls with CPP, follow-up data were collected 1 year after the treatment, including spine radiographs, measurement of the new Cobb angle, and a comparison with the initially measured Cobb angles.

For the GnRH stimulation test, a standard dose of 100μg GnRH was administered as an intravenous (IV) bolus. An IV cannula was inserted and blood samples were obtained immediately before injection and at 15, 30, 45, 60, 90, and 120 minutes after injection.

Age, height, weight, body mass index (BMI), and bone age were collected for all subjects. Peak serum LH, follicle stimulating hormone, and estradiol levels were collected only for girls with CPP.

3. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Continuous variables are expressed as mean±SD. The differences between continuous variables in the 2 groups were evaluated by the Student *t*-test. Categorical variables were evaluated by the chi-square test. The correlations between the Cobb angle and other factors, such as age, height, weight, BMI, height standard deviation score (SDS), weight SDS, BMI SDS, and bone age, were assessed using Pearson correlation analysis. Multivariable logistic regression analysis was also performed for CPP status, age, height, weight, BMI, height SDS, weight SDS, and BMI SDS. Follow-up data for girls with CPP were analyzed using the paired Student *t*-test and the chi-square test. A *P*-value <0.05 was considered statistically significant for all the tests.

Results

Girls with CPPs (n=338) were age-matched to non-CPP girls (n=215) (mean±SD, 8.3±0.7 years vs. 8.4±0.3 years). Height, weight, and height SDS were statistically different in the 2

Table 1. Baseline characteristics and prevalence of adolescent idiopathic scoliosis in central precocious puberty (CPP) girls

Characteristic	CPP (n=338)	Control (n=215)	*P*-value†
Age (yr)	8.3±0.7	8.4±0.3	0.130
Height (cm)	132.6±6.6	129.2±5.0	<0.001
Weight (kg)	30.9±5.6	29.4±5.8	0.002
Body mass index (kg/m^2)	17.5±2.3	17.5±2.6	0.948
Height SDS	0.8±0.9	0.1±0.9	<0.001
Weight SDS	0.6±1.0	0.5±1.2	0.115
BMI SDS	0.3±1.0	0.3±1.1	0.993
Bone age (yr)	9.9±0.8	9.2±0.7	<0.001
ALP (IU/L)	302.6±78.9	242.5±5	<0.001
Cobb angle (°)	4.6±3.9	4.3±3.6	0.486
Scoliosis (Cobb angle >10°)	39 (11.5)	13 (6.0)	0.031‡

Values are presented as mean±standard deviation or number (%).
SDS, standard deviation score; BMI, body mass index; ALP, alkaline phosphatase.
†*t*-test. ‡Chi-square test.

groups. Bone age at diagnosis was significantly higher in the CPP group (9.9±0.8 years) than in the non-CPP group (9.2±0.7 years) (P<0.001). Alkaline phosphatase was significantly higher in the CPP group (302.6±78.9 IU/L) at diagnosis than in the non-CPP group (242.5±5 IU/L) (P<0.001). The difference of mean Cobb angle between the groups was not significant (Table 1).

The prevalence of AIS in all subjects was 9.4%. The overall prevalence of AIS was higher in the CPP group (11.5%) than in the control group (6.0%) (P=0.031) (Table 1). The mean Cobb angle for girls with AIS was 12.8°±2.4° in the CPP group and 13.3°±2.8° in the control group; there was no statistically significant difference between the 2 groups (P=0.6).

The linear correlation analysis to examine the association between Cobb angle and anthropometric factors revealed that, in the CPP group only, peak serum LH level had a positive correlation with Cobb angle (R^2=0.015, P=0.023) (Table 2).

The clinical and radiographic factors that were assessed by multivariate analysis to determine predictors for scoliosis showed that the presence of CPP was related to a high Cobb angle (odds ratio [OR], 2.027; 95% confidence interval [CI], 1.055–3.892). In addition, age was associated with a high Cobb angle (OR, 0.643; 95% CI, 0.431–0.960) (Table 3).

One hundred sixteen subjects from the CPP group had follow-up data for spinal radiographs for scoliosis progression after 1 year of GnRH agonist treatment. The average Cobb angle did not change significantly after 1 year of GnRH agonist treatment (5.2°±4.3° at the time of diagnosis and 4.3°±3.2° one year after GnRH agonist treatment) and the prevalence of scoliosis decreased after 1 year of treatment. In the 20 patients affected by scoliosis at the time of diagnosis, 17 improved and 3 were still affected by scoliosis after 1 year of treatment (P<0.001) (Table 4). The height SDS of girls who showed scoliosis improvement was higher than that for the girls whose scoliosis persisted (0.90±0.67 vs. 0.06±0.44). The growth velocity for girls with improved scoliosis was 6.38±1.36 cm/yr and 4.77±0.56 cm/yr in girls with no improvement, which showed a higher growth velocity in girls with improved scoliosis.

Table 2. Correlation of the Cobb angle with anthropometric characteristics and peak LH in CPP group

Characteristic	Total (n=553)	P-value†	CPP (n=338)	P-value†
Age (yr)	-0.044	0.300	-0.019	0.725
Height (cm)	0.010	0.806	0.004	0.947
Weight (kg)	-0.030	0.485	-0.050	0.360
BMI (kg/m^2)	-0.040	0.347	-0.063	0.251
Height SDS	0.038	0.367	0.017	0.758
Weight SDS	-0.008	0.853	-0.066	0.225
BMI SDS	-0.037	0.388	-0.064	0.243
Bone age	0.021	0.615	0.011	0.838
ALP (IU/L)	-0.006	0.896	-0.016	0.771
Peak LH (mIU/mL)	-	-	0.123	0.023
Peak FSH (mIU/mL)	-	-	-0.043	0.432
Estradiol (pg/mL)	-	-	0.102	0.062

LH, luteinizing hormone; CPP, central precocious puberty; BMI, body mass index; SDS, standard deviation score; ALP, alkaline phosphatase; FSH, follicle stimulating hormone.
†Pearson correlation.

Discussion

AIS is one of the most common spinal deformities, yet its etiology is unknown. There are various theories for the etiology of scoliosis, including biomechanical, neuromuscular, genetic, and environmental origins, yet our understanding is still limited.[13-17] The involvement of growth-related factors has been suggested for development of AIS. After observation of girls with AIS, Willner et al.[18,19] proposed that girls with AIS were taller than the normal population, and that growth in the scoliosis group occurred earlier, in the pre- years rather than in later years. Archer and Dickson[20] later reported that, among female scoliosis patients, girls with a more severe spinal curve were taller than girls with a mild curve. Based on these results, it was hypothesized that girls with CPP have the propensity to develop scoliosis at a young age because of their earlier growth spurt. Consistent with this hypothesis, in our study, we observed a higher prevalence of AIS among CPP patients (11.5%) compared with the non-CPP controls (6.0%, P=0.031). Our results also showed a higher scoliosis prevalence compared to the general population between 10 and 16 years of age (0.47%–5.2%), although this age range is higher than that of

Table 3. Scoliosis predictors selected by the logistic regression model

Predictor	Coefficient value	SE	P-value	OR	95% CI
CPP	0.706	0.333	0.034	2.027	1.055–3.892
Age	-0.441	0.204	0.031	0.643	0.431–0.960
Height	-0.011	0.023	0.629	0.989	0.945–1.035
Weight	-0.044	0.027	0.106	0.957	0.908–1.009
BMI	-0.115	0.065	0.077	0.892	0.785–1.013
Height SDS	0.136	0.151	0.371	1.145	0.851–1.541
Weight SDS	-0.127	0.142	0.372	0.881	0.667–1.164
BMI SDS	-0.251	0.148	0.090	0.778	0.582–1.040
ALP	<0.001	0.002	0.995	1.000	0.996–1.004

SE, standard error; OR, odds ratio; CI, confidence interval; CPP, central precocious puberty; BMI, body mass index; SDS, standard deviation score; ALP, alkaline phosphatase.

Table 4. Change of scoliosis after 1 year of GnRH agonists treatment in CPP patients

Variable	At diagnosis of CPP	1 Year after GnRHa treatment of CPP	P-value
Cobb angle (°)	5.24±4.34	4.30±3.19	0.315†
AIS≥10°	17/116	3/116	<0.001‡

Values are presented as mean±standard deviation.
GnRH, gonadotropin-releasing hormone; CPP, central precocious puberty; AIS, adolescent idiohic scoliosis.
†t-test. ‡Chi-square test.

our cohort.[21] In addition, the prevalence rate of AIS in girls 9 to 10 years of age was reported be 0.24% in Singapore, and the rate for girls 10 to 12 years of age was reported to be 5.57% in Korea, a lower prevalence compare to the prevalence of our CPP group.[4,22]

In this study, we investigated the potential association between degree of spinal deformation with other factors, such as age, height, weight, BMI, height SDS, weight SDS, BMI SDS, bone age, and level of peak serum LH, in the CPP group. Kulis et al.[23] reported that the basal serum LH level in premenarcheal girls affected by AIS was lower than that in their scoliosis-free peers. However, our study showed that the peak serum LH level is positively correlated with degree of scoliosis in the CPP group (R^2=0.015, P=0.023). Because the peak serum LH level showed higher sensitivity and specificity than basal serum LH for diagnosing CPP, peak serum LH level is superior to basal serum LH for representing pubertal status, and correlation between AIS and peak serum LH level is more plausible.[24]

In the neuro-osseous theory, AIS progression is attributed to rapid skeletal enlargement, which is not followed by the autonomic nervous system in the brain and the central nervous system, due to a delayed maturation of posture by the somatic nervous system.[25] The hormonal interruption caused by CPP may cause asymmetric growth of the spine. The results of our logistic regression model indicated that CPP increases AIS (OR, 2.027; 95% CI, 1.055–3.892), which supports the theory. Therefore, progression of AIS may be delayed or interrupted if the patient recovers hormonal balance. Thus, we compared Cobb angle before and after GnRH agonist treatment. We found that the number of patients with scoliosis decreased after 1 year of treatment. Furthermore, progression of scoliosis progression was not observed during treatment (Table 4). GnRH agonists may have a preventive effect on asymmetric growth of the spine. The average height SDS and growth velocity are higher in patients that exhibit improvements for scoliosis, suggesting that GnRH agonists may have a suppressive effect on scoliosis progression in patients with high growth velocity.

There were some limitations to this study. First, no effects on scoliosis could be evaluated prior to treatment due to lack of growth data before CPP diagnosis. Second, our study could only show the association between scoliosis and CPP due to the limitation of the retrospective chart review. Therefore, a prospective longitudinal study with a larger group should be performed and should include serial Cobb angle measurement to identify the effects of GnRH agonist treatment on patients with CPP and scoliosis.

The knowledge that girls affected by CPP have a higher prevalence of idiopathic scoliosis is important for corrective treatment options for clinicians. Although in this study, we observed no scoliosis progression during treatment, scoliosis involves a high risk of progression. Thus, a regular follow-up schedule should be considered. Further longitudinal studies investigating the effects of treatment with GnRH agonists are needed for developing a gold standard for clinical care of CPP patient with idiopathic scoliosis.

Ethical statement

This study was approved by the Institutional Review Board (IRB) of Korea University Hospital (2019AN0031). Informed consent was waived by IRB.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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