Timing of menarche in Chinese girls with and without adolescent idiopathic scoliosis: current results and review of the literature

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Abstract Age at menarche is closely related to scoliosis progression during adolescence. Current data concerning the timing of menarche between scoliotic and non-scoliotic girls in the literature are conflicting, with inconclusive results. The aim of this study was to investigate the distribution difference of age at menarche for adolescent idiopathic scoliosis (AIS) girls and normal control population and to subsequently elucidate the menarche age difference through literature reviewing. Moreover, menarche age of AIS girls with Cobb angle $<40^\circ$, $40\text{--}60^\circ$, $>60^\circ$ were compared to estimate its association with curve severity. Menstrual status data were available for 6,376 healthy female adolescents and 2,196 AIS girls. We notice that less than 10% of healthy Chinese girls experienced onset of menses before 11.38 years, and approximately 90% of healthy Chinese girls were menstruating by 13.88 years, with a median age of 12.63 years. As for AIS girls, less than 10% started to menstruate before 11.27 years, and approximately 90% were menstruating by 14.38 years, with a median age of 12.83 years. Average menarche age in AIS (12.83 ± 1.22 years) was significantly later than that of normal control girls (12.63 ± 0.98 years) ($p < 0.001$). Age at menarche for AIS affected girls was significantly greater

than that of normal control girls at 75%, 90% of whom had attained menarche ($p = 0.001$, $p < 0.001$). Proportion of girls starting to menstruate after 14 years was significantly higher in AIS population compared with normal controls (16.3 vs. 8.1%, $p < 0.001$). In addition, AIS girls with Cobb angle $>60^\circ$ experienced onset of menses at an average age of 13.25 years, which was significantly later than AIS girls with Cobb angle $<40^\circ$ (12.81 years, $p < 0.05$) and marginally significantly later than AIS girls with Cobb angle between 40 and 60° (12.86 years, $p = 0.053$). In conclusion, a tendency of delayed onset of menarche was observed in Chinese idiopathic scoliotic girls in this large sample study, especially for girls with Cobb angle $>60^\circ$, which is supported by multiple previously established positive linkages on AIS etiology studies. Accordingly it is believed that late menarche may contribute importantly to abnormal pubertal growth and subsequently modulate curve behavior in AIS.

Keywords Adolescent idiopathic scoliosis · Age at menarche · Curve behavior

Introduction

Adolescent idiopathic scoliosis (AIS) is generally taken as a disorder of growth, with tight association between maturity and curve behavior [1]. Maturation, however, is multidimensional and has various components. Menarche, in particular, is a commonly used, readily identifiable maturity indicator, indicative of the remaining growth potential and reliably associated with decelerated growth velocity [1]. Previous studies revealed that risk of curve acceleration of AIS was appreciably higher before menarche than after menarche [2–4]. Age at menarche was also

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proposed to be related to prevalence of scoliosis. As Grivas et al. reported, late age at menarche is parallel with higher prevalence of adolescent idiopathic scoliosis [5, 6]. Thus, it is hypothesized that adjustment of menarche age may contribute to predisposition and curve progression potential of idiopathic scoliosis. In addition, potential difference of menarche age compared with normal control population may be correlated with hormonal disturbance involving estrogen, melatonin, and leptin [5–10], thus contributing to abnormal pubertal growth, which may be responsible for curve onset and progression of AIS. Such hypothesis, first and foremost, warrants menstrual status data supportive of abnormal menarche age with respect to general population. In the literature, the age at menarche in AIS has been reported as early, normal, and delayed [5, 11–13]. Such controversy still exists currently, with no conclusive results.

The objective of the present study was to estimate the distribution of age at menarche for AIS girls and normal controls with large sample size, and subsequently to explore the potential menarche age difference and elucidate it through literature reviewing, so as to investigate the possible role of menarche in AIS.

Methods

Sample

Research protocols were approved by the University and Hospital Ethic Committee. Subjects for normal control girls were selected from a large cross-sectional anthropometric survey conducted in 2008, which aimed to investigate pubertal linear growth in East China. Disabled students and students from institutes of physical education were excluded from this study. Children and adolescents were also screened with Adam's Forward Bending Test to rule out scoliosis. If scoliosis was suspected, standing whole spine postero-anterior radiographs were taken to confirm the diagnosis. Those affected with scoliosis or diseases causing growth disturbance were excluded from this study. Menstrual status data were collected by inquiring of female participants or their guardians about the age when their periods or menstrual cycles started. 6,376 of the 13,047 female participants experienced onset of menses by the time of investigation, with their menarche data available. As for AIS affected girls, those prescribed with conservative treatment (follow-up at periodic interval or bracing treatment) or correction surgery in our hospital since 2002 were recruited, with their menarche data recorded either at their initial clinical visit or in the follow-up period. AIS patients surgically treated also had pre-operative MRI to exclude the possibility of central system disorders of cerebrum and

spinal cord. Finally 2,196 girls met the diagnosis criteria of AIS with their menstrual status data available. The sample sizes in the present study were large enough for reliable estimation for the total population [14].

Data analysis

Statistical analysis was performed using the SPSS statistical software (version 13.0, Chicago, USA) to calculate proportions of girls reaching menarche at an age. Distribution of age at menarche was subsequently plotted. Probit analysis was used to calculate the median menarche age and estimate ages at menarche at which 10, 25, 50, 75, and 90% of the girls attained menarche. The fiducial limits of these estimates were computed to indicate the level of precision for these estimated ages from the probit analysis. The narrower the range, the higher the precision of the estimated age. Probit plots for age at menarche were made for AIS affected girls and normal controls, respectively. Independent-sample *t* test was used to explore the difference of menarche age between AIS girls and normal controls. Proportion of girls starting to menstruate after 14 years was also compared through χ^2 test among AIS and normal controls. Moreover, mean menarche age of AIS affected girls with Cobb angle $<40^\circ$, $40\text{--}60^\circ$, $>60^\circ$ was compared to investigate its association with curve severity by Independent-sample *t* test. Statistical significance was set at *p* value <0.05 .

Results

Age at menarche for AIS and normal controls

Distributions of age at menarche for AIS affected and normal control Chinese girls are illustrated in Fig. 1. Approximately 40.1% healthy Chinese girls experienced onset of menses at chronological age of 12–13 years, which

Fig. 1 Comparison of distribution of age at menarche between AIS and normal control

accounted for the maximum share in total, and the corresponding proportion is 31.3% in AIS population with the same age range. Proportion of girls starting to menstruate after 14 years was significantly higher in AIS affected population compared with normal controls (16.3 vs. 8.1%, $p < 0.001$). The average age at menarche for healthy Chinese girls and AIS girls is 12.63 ± 0.98 years and 12.83 ± 1.22 years, respectively. This age at menarche in AIS is significantly later than that of normal control girls ($p < 0.001$). Table 1 shows the age at menarche when 10, 25, 75, and 90% of all girls had attained menarche. Probit plot for age at menarche for AIS affected girls and normal control is shown in Fig. 2. Less than 10% of healthy Chinese girls experienced onset of menses before 11.38 years, and approximately 90% of healthy Chinese girls were menstruating by 13.88 years, with a median age of 12.63 years. As for AIS affected girls, less than 10% started to menstruate before 11.27 years, and approximately 90% were menstruating by 14.38 years, with a median age of 12.83 years. The ranges of the fiducial limits were 0.021–0.023 years at 10 and 90% and slightly narrower at 0.01–0.017 years at 25, 50, and 75% of AIS and normal control girls. Age at menarche for AIS affected girls was significantly later than that of normal control girls at 75%, 90% of those who had attained menarche ($p = 0.001$, $p < 0.001$). These case–control differences in the ages where 75 and 90% of the girls had attained menarche are more clearly observed in Fig. 2. Case–control difference in ages at the lower percentages was not significant ($p > 0.05$).

Age at menarche within various curve severity groups

Of the 2,196 AIS girls, 1,748 individuals were recruited in the group with Cobb angle $<40^\circ$, and the corresponding number is 406 and 42 for groups with Cobb angle between 40 – 60° and $>60^\circ$, respectively. The average menarche ages of AIS affected girls with Cobb angle $<40^\circ$, 40 – 60° , $>60^\circ$ were 12.82 ± 1.22 years, 12.86 ± 1.21 years and 13.25 ± 1.43 years, respectively. Significant difference of menarche age was still obvious in AIS girls with Cobb angle $<40^\circ$ compared with normal control ($p < 0.001$). Independent-sample t test revealed that AIS girls with Cobb angle $>60^\circ$

Fig. 2 Probit plot for age at menarche for AIS affected girls and normal controls

experienced onset of menses at a significantly later age than AIS girls with Cobb angle $<40^\circ$ ($p < 0.05$) and marginally significantly later than AIS girls with Cobb angle between 40 and 60° ($p = 0.053$). No significant difference was detected between groups with Cobb angle $<40^\circ$ and 40 – 60° ($p > 0.05$).

Discussion

Despite extensive research for decades, adolescent idiopathic scoliosis remains a pathological entity of unknown etiology. However, consensus has been reached that abnormal pubertal growth is tightly associated with curve development and progression. Multiple maturity indicators corresponding with multidimensional aspects of pubertal growth and development have been studied in AIS either for abnormality related to etiology or for its association with curve progression. Menarche, in particular, is an important milestone for determining sexual maturation in adolescent girls. Onset of menarche reveals the status quo of puberty, reliably indicating the slowing of pubertal spurt [12]. Thus, establishment of menarche status for each AIS

Table 1 Ages at menarche in years by probit analysis for selected percentiles of AIS affected and normal control Chinese girls who were menstruating

	10%	Fiducial limits	25%	Fiducial limits	50%	Fiducial limits	75%	Fiducial limits	90%	Fiducial limits
Normal controls	11.378	11.367– 11.390	11.972	11.963– 11.980	12.631	12.624– 12.638	13.290	13.282– 13.299	13.884	13.872– 13.895
AIS	11.272	11.261– 11.282	12.008	12.000– 12.015	12.826	12.819– 12.832	13.643	13.636– 13.651	14.380	14.369– 14.390

The fiducial limits for overall were based on 95% confidence limits

individual would be helpful to estimate height growth potential and scoliosis prognosis. Besides, abnormality of menarche status is also an indicator of potential hormonal disturbance. Current menarche age in AIS is obscure. The present study, based on analysis with large sample size, revealed not only the mean menarche age, but also its exact distribution situation.

Results of menarche age comparison revealed the detailed distribution difference, leading to the conclusion that delayed onset of menarche occurred more frequently in AIS girls. This finding was in line with the study conducted by Lee et al. [13] in Hong Kong, but was not fully supported by other studies in the literature (Table 2). The current study shows that age at menarche for AIS affected girls was significantly greater than that of normal control girls at 75%, 90% of whom had attained menarche, while such case–control difference was not detected in ages at the lower percentages. A significant higher proportion of girls reaching menarche after 14 years was also detected in AIS compared with general population in our study. It is noteworthy that age at which 90% of AIS girls started to menstruate was approximately 0.5 years delayed. In addition, more significant delayed onset on menarche was observed in patients with Cobb angle beyond 60°. These results, to a certain extent, mirror the finding revealed by Grivas [5] that late age at menarche was parallel with higher prevalence of AIS. Warren et al. [15, 16] reported that young ballet dancers with scoliosis, although not typical of general population, possessed a delayed menarche and a taller stature compared with their colleagues without scoliosis, with the observed prevalence of scoliosis being 24%. Goldberg's study on Irish AIS girls revealed late menarche age in progressive idiopathic scoliosis [12]. Paradoxically, a general tendency of early onset of menarche in AIS was also described in his study. Based on the sample size, we believe our results are more persuasive, and meanwhile more logical.

Delayed onset of menarche could be attributed to hormonal disturbance, associated with abnormal pubertal linear growth. Another alternative interpretation is that delayed menarche correlates with delayed skeletal maturity, resulting in lengthened period of rapid growth and the accompanying period of spine vulnerability, while the real

etiological factors are contributing to the development of AIS [5]. Thus, girls with late onset of menarche may be susceptible to scoliosis progression, accounting for easier diagnosis and higher observed prevalence. Hormones contributing to the adjustment of menarche onset are potentially just modifying factors due to the fact that scoliosis prevalence shows a ratio of 1:1 between females and males in prepubertal periods, and the ratio is subsequently adjusted to 8.4/1 (female/male) during puberty, indicating a clear-cut sex-conditioned manifestation of AIS [6, 16].

Through literature reviewing, we found that estrogen, melatonin and leptin, all of which were previously studied in the etiological research of AIS, were potentially responsible for the predisposition to late menarche in AIS. Estrogen, due to its tight association with menarche, definitely has a role in interpreting the current study results. Lower levels of 17 β -estradiol in blood have been revealed in Esposito's study in AIS population [6], which could interpret the late menarche generally detected in our study. Unfortunately, lower levels of sex steroid are not a constant finding [17]. Age at menarche is also influenced by genetic factors. XbaI polymorphism of estrogen receptor alpha gene was proved to be associated with combined predisposition to AIS occurrence, curve severity, and late menarche, which strongly mirrors the findings of our study [18–20].

Melatonin is another hormone frequently studied in AIS. The intense fluctuation of melatonin level due to artificial lighting or exogenous melatonin injection can modulate the timing of menarche [21–24]. The literature also reported that the prevalence of AIS in girls is generally higher in northern latitude compared with that towards 25–30° (Finland 9.2%–Greece 2.9%) [5, 25]. Coincidentally, late age at menarche was also observed in higher geographic latitude, with its regression curve by latitude similar to that of prevalence of AIS by latitude [5]. Thus, it is hypothesized that sunshine duration varies within different geographic latitude, influencing melatonin secretion and modifying age at menarche, which contributes to the prevalence variation of idiopathic scoliosis. Additionally, the frequency of C allele of promoter polymorphism (rs4753426) of the MT2 melatonin receptor gene (MTNR1B) was confirmed to be higher both in AIS and in areas with short daily sunshine duration [26, 27]. Besides, the prevalence of scoliosis in

Table 2 Menarche ages of AIS affected girls compared with normal controls within different ethnic populations

	Irish ^a	Mediterranean ^a	Hongkongese ^a	Chinese in main land
AIS affected girls	13.13 $\pm$ 1.07 years	11.98 $\pm$ 1.49 years	12.0 $\pm$ 1.1 years	12.83 $\pm$ 1.22 years
Normal controls	13.52 $\pm$ 1.3 years	12.07 $\pm$ 1.35 years	11.8 $\pm$ 1.1 years	12.63 $\pm$ 0.98 years
Sample size	303 versus 2,916	77 versus 476	300 versus 594	2,196 versus 6,376
Study results	Advanced	No difference	Delayed	Delayed

^a Data from Goldberg et al. [12] (Irish), Grivas et al. [11] (Mediterranean) and Lee et al. [13] (Hongkongese)

blind women was reported to be as high as 42.3% [28]. In blind girls, higher melatonin level is indicated and late age at menarche is reported by Segos [29], although controversy still exists [30, 31]. Thus a linkage between sunshine duration, melatonin signaling pathway, late menarche, and AIS prevalence is suspected.

Menarche is also generally related to fat distribution [32, 33]. Girls with higher body mass index and body fat were more likely to have earlier menses, and thin girls tend to mature later [33]. Abnormal growth pattern with higher corrected height, lower weight, and lower BMI has been reported in AIS patients throughout the peripubertal growth period [10, 34–36], indicating late menarche in AIS girls, which is in line with results of our study. Serum leptin level is highly correlated with BMI and body weight, and a marked decrease of circulating leptin level has been confirmed in AIS [10]. Previous studies support the idea that leptin serves as a crucial, permissive but not a causal signal in the timing of the sexual development [37, 38]. Additionally, serum leptin concentrations were observed to increase while approaching the onset of menarche in girls [39, 40], and were inversely related to age at menarche in human females [41], with an increase of 1 ng/ml in serum leptin lowering the age at menarche by 1 month. In all, lower circulating leptin level is observed in AIS affected population with the characteristics of late menarche, lower BMI and body fat, of which late menarche is confirmed in our study.

To our knowledge, the current study covers the largest sample size to analyze the difference of menarche age between AIS and normal population. The results showed not only the general difference of mean menarche age, but also the detailed distribution difference. Late onset of menarche occurred more frequently in AIS, indicating its contribution to AIS predisposition. Further study is warranted to elucidate the predisposition to late onset of menarche in AIS.

Conclusion

Delayed onset of menarche was generally observed in Chinese idiopathic scoliotic girls in this large sample study, with severe AIS girls showing a more delayed menarche age. These results are supported by multiple established positive linkages on AIS etiology studies, indicating definitive association between curve behavior and menarche age.

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Conflict of interest None

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