Letter to the Editor

Abnormal Activity of Sympathetic Nervous System in Girls with Adolescent Idiopathic Scoliosis: A Cross-sectional Study

HU Zong Shan[1,2], ZHAO Zhi Hui[2,3], TSENG Chang-Chun[2,3], LI Jie[2,3], MAN Gene Chi-Wai[1,2], LAM Tsz-Ping[1,2], QIU Yong[2,3], CHENG Chun-Yiu Jack[1,2], ZHU Ze Zhang[2,3], and LIU Zhen[2,3,#]

The objective of this study was to characterize sympathetic nervous system (SNS) activity in girls with adolescent idiopathic scoliosis (AIS) and investigate the correlation of such activity with body weight and bone mass. Fifty-eight girls with AIS and 21 healthy controls were recruited. Abnormal growth pattern (lower weight, lower body mass index (BMI), and longer arm span) and significantly increased adrenaline (AD) level, norepinephrine (NE) level, and low-frequency (LF) were found in girls with AIS. Circulating AD level, NE level, and LF power were negatively correlated with body weight and BMI but significantly correlated with bone quality. This correlation suggests that the presence of abnormal SNS activity in girls with AIS might play an important role in the etiopathogenesis of the disease.

AIS is a multifactorial three-dimensional (3D) spinal deformity that arises in healthy children at or around puberty; the etiology of this disease remains unclear[1]. In general, patients with AIS have an abnormal growth pattern, including lower body weight and BMI, and higher corrected height than the healthy controls throughout the peripubertal growth period. Multiple studies have shown a positive association between body weight and bone mass in healthy subjects of all age groups. In addition to lower body weight and BMI, generalized lower bone mass and osteopenia have been widely reported in patients with AIS; however, none of these factors have been correlated with sympathetic nervous system (SNS) activity.

Some authors found that the hyperactivity of the SNS could potentially cause lower body weight and BMI, which are the most common phenotypes in patients with AIS. Plasma noradrenaline and catecholamine levels can be good indices of SNS activity. Leptin is a key modulator in pubertal growth, body build, and energy metabolism and has been recently found to activate the SNS. A marked increase in sOB-R, together with lower BMI and longer arm span, were observed in girls with AIS compared with the controls in our preliminary study[2]. Burwell et al.[3] proposed the concept of Leptin-Hypothalamic-SNS (LHS) that the SNS may be involved and play a key role in the development of scoliosis. Through its hypothalamic neuroendocrine control of puberty, menarche, and skeletal growth, the SNS has provided the physiologic link to a regulatory system controlling bone mass, which was thought to contribute importantly to the pathogenesis of AIS. Thus far, the relationship between SNS activity and bone mass in patients with AIS has not been elucidated yet.

Previous studies suggested that overweight girls have lower catecholamine levels than normal-weight girls, whereas anorexic girls with lower BMI have higher sympathetic activity. However, the role of SNS in regulation of body weight of girls with AIS who were leaner and osteopenic has yet to be reported. In the present study, we hypothesized that girls with AIS had abnormal SNS activity, which might contribute to lower body weight and lower BMC/BMD than the controls. This work aims to characterize the SNS activity in girls with AIS and investigate its correlation with body weight and bone mass.

Our research adopted a cross-sectional design and carried out in girls with AIS and healthy girls. The study was approved by the ethics committees of our institution. From June 2014 to September 2014, girls with AIS who were diagnosed at 11-16 years of age and needed surgical correction in our department were included in this study. Female subjects

doi: 10.3967/bes2018.094

1. Department of Orthopaedics and Traumatology, Faculty of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories 999077, Hong Kong, China; 2. The Joint Scoliosis Research Center of the Chinese University of Hong Kong and Nanjing University, Hong Kong 999077, China; 3. Department of Spine Surgery, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu, China

accompanying the inpatients were recruited as controls by using Adam's forward bending test. All the patients underwent clinical and radiologic examinations by spinal surgeons, who established the diagnosis and excluded alternate diagnoses of congenital and juvenile scoliosis as well as scoliosis secondary to some other disorder (e.g., congenital deformities, neuromuscular diseases, skeletal dysplasia, connective tissue abnormalities, mental retardation, metabolic diseases, cardiovascular disease or other conditions known to affect SNS activity). Scoliosis curve severity was determined by the Cobb angle on standing whole spine.

Anthropometric measurements (including body height, body weight, and arm span) were conducted. Height was recorded without shoes, standing against a wall-mounted stadiometer, and measurements were taken to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg in the subjects wearing light clothes without shoes. Arm span was measured by using a wall-mounted tape to the nearest 0.1 cm. As shown by previous studies, the different equations for the correction of height loss caused by the spinal deformity had limitation and might not fit every curve. Therefore, arm span, instead of body height, was used for calculating BMI in the current study.

Peripheral venous blood samples were collected between 8:00 AM and 9:00 AM, after overnight fasting, for biochemical analysis. Plasma adrenaline (AD) and norepinephrine (NE) levels were evaluated by enzyme-linked immunosorbent assay specific for human leptin (Labor Diagnostika Nord, GER) following the manufacturer's suggested protocol. The lowest detection limits for AD and NE were 7 and 35 pg/mL, respectively. The intra-assay coefficient of variations (CV%) for AD and NE were 9.3% and 8.4%, respectively, as established in the authors' laboratory. The inter-assay CV% values for AD and NE were 12.6% and 6.9%, respectively.

Heart rate variability was measured by 24-h Holter (GE healthcare-sight seer, US) monitoring. Examination was performed in all subjects who were asked to avoid caffeine, strenuous exercise, smoking, and alcohol intake 24 h prior to and during the test. All the frequency domain parameters including LF, high-frequency component (HF), and LF/HF ratio were calculated by Superscan™ DCG analysis software. As Task Force of the European Society of Cardiology[4] reported, the increases in the LF component and the LF/HF ratio were interpreted as predominance of sympathetic activity.

The data in this study were presented as mean ± SD. Anthropometric data, AD level, and NE level were compared between girls with AIS and normal controls by using an independent-samples *t* test. Bivariate correlation tests were carried out between SNS activity and different anthropometric data. Statistics software used was SPSS 19.0 for Windows (SPSS Inc., Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

In total, 58 girls with AIS and 21 age-matched healthy girls were included in this study. The mean Cobb angle of girls with AIS was 43.8° ± 3.6° (range 38°-57°). The anthropometric data of girls with AIS versus healthy girls are summarized in Table 1. The BMI of girls with AIS (17.7 ± 0.9 kg/m^2) was significantly lower than that of the controls (20.2 ± 1.1 kg/m^2; $P < 0.001$). The arm span of girls with AIS (157.7 ± 6.0 cm) was significantly longer than that of healthy female controls (153.1 ± 6.7 cm; $P = 0.01$).

Table 1. Physical Characteristics of AIS and Control Girls

Item	AIS (*n* = 58)	Control (*n* = 21)	*t* Test	*P*
Age (y)	13.0 ± 1.2	12.6 ± 1.3	1.43	0.160
Body weight (kg)	44.0 ± 3.79	47.52 ± 4.97	-2.94	0.006**
Body height (cm)	157.1 ± 5.8	158.1 ± 7.6	-0.64	0.520
BMI (kg/m^2)	17.7 ± 0.9	20.2 ± 1.1	-9.78	< 0.001**
Arm span (cm)	157.7 ± 6.0	153.1 ± 6.7	2.72	0.010*
BMC (g)	28.71 ± 2.91	—	—	—
BMD (g/cm^2)	0.88 ± 0.06	—	—	—

Note. BMI calculated by dividing the body weight (kg) by squared arm span (m^2). Symbols indicate significant difference within groups: $^*P < 0.05$ and $^{**}P < 0.01$ between 2 groups (independent-samples *t* test). AIS indicates adolescent idiopathic scoliosis; BMI, body mass index; BMC, bone mineral content; BMD, bone mineral density.

The data related to catecholamine levels and HRV of girls with AIS and healthy girls are summarized in Table 2. The AD in girls with AIS (78.7 ± 7.6 pg/mL) was significantly higher than in normal healthy girls (70.9 ± 9.4 pg/mL; $P = 0.04$). Moreover, girls with AIS had significantly higher NE (289.5 ± 44.0 pg/mL) than normal girls (259.2 ± 20.5 pg/mL; $P = 0.003$). The LF component was also significantly higher in girls with AIS than in controls ($P = 0.045$). The magnitude of HF component and LF/HF ratio showed no significant difference between the two groups.

In girls with AIS (Table 3), BMI was found to correlate with AD ($r = -0.849$, $P < 0.001$), NE ($r = -0.843$, $P < 0.001$), and LF ($r = -0.864$, $P < 0.001$). An inverse correlation was also observed between body weight and SNS parameters, such as AD ($r = -0.44$, $P = 0.001$), NE ($r = -0.343$, $P = 0.008$) and LF ($r = -0.417$, $P = 0.001$). In addition, negative correlations were detected between AD, NE, and LF and BMC/BMD.

In the study reported by Enslein and Chan[5], the SNS activity in girls with AIS was significantly higher than the controls, as assessed by a questionnaire survey, which was inadequate for evaluation. The sympathetic innervation in patients with idiopathic scoliosis was significantly different between both curve sides, leading to abnormal blood supply to the vertebrae and anterior chest wall and development of scoliosis. Several methods (such as Valsalva maneuver, deep breathing, orthostatic test, and heart rate variability test) are currently available for evaluating autonomic function. Plasma catecholamines can be good indices of SNS activity. As Task Force of the European Society of Cardiology reported[4], the increases in the LF component and the LF/HF ratio were interpreted as predominance of sympathetic activity. The increase in the HF component and the reduction in the LF/HF ratio were interpreted as predominance of parasympathetic activity. In the current study, we evaluated SNS activity by measuring the levels of plasma AD and NE and calculating the HRV parameters in the frequency domain. The results showed that girls in the AIS group possessed higher AD and noradrenaline levels and higher LF component and LF/HF ratio, all of which suggested that girls with AIS have higher SNS activity.

Table 2. Plasma AD and NE Levels and HRV Parameter of AIS and Control Girls

Item	AIS	Control	*t*	*P*
AD (pg/mL)	78.7 ± 7.6	70.9 ± 9.4	2.12	0.040*
NE (pg/mL)	289.5 ± 44.0	259.2 ± 20.5	3.03	0.003**
LF (ms^2)	631.36 ± 191.65	540.14 ± 165.81	2.07	0.045*
HF (ms^2)	570.65 ± 27.89	576.76 ± 40.48	-0.76	0.450
LF/HF ratio	1.11 ± 0.36	0.95 ± 0.32	1.95	0.058

Note. AD, indicates adrenaline; NE, norepinephrine; HRV, heart rate variability; LF, low frequency; HF, high frequency; ms^2, milliseconds squared. $^*P < 0.05$ and $^{**}P < 0.01$.

Table 3. Correlations between Circulating Catecholamine Levels, LF Power and Growth Related Parameters in AIS Girls

Item	AD		NE		LF	
	r	*P*	*r*	*P*	*r*	*P*
Age	-0.238	0.072	-0.222	0.095	-0.209	0.115
Body weight	-0.440	0.001**	-0.343	0.008**	-0.417	0.001**
Body height	-0.180	0.894	0.050	0.710	0.004	0.974
Arm span	-0.080	0.552	-0.014	0.914	-0.088	0.513
BMI	-0.849	< 0.001**	-0.843	< 0.001**	-0.864	< 0.001**
BMC	-0.442	0.001**	-0.362	0.005**	-0.416	0.001**
BMD	-0.311	0.020*	-0.342	0.009**	-0.360	0.005**

Note. AIS indicates adolescent idiopathic scoliosis; BMI, body mass index; AD, adrenaline; NE, norepinephrine; LF, low frequency. $^*P < 0.05$; $^{**}P < 0.01$.

Mauro et al.[6] noted that NE has a positive effect on longitudinal bone metabolism and that SNS activity is a regulator of linear skeletal growth. Pagony et al.[7] found that guanethidine-induced sympathectomy caused a negative balance of bone metabolism, leading to decreased bone mass and BMD during bone modeling and remodeling. Several studies[8] have reported that the hyperactivity of the SNS could contribute to low BMD and long extremities, which are the most common phenotypes in patients with AIS. The SNS could be the link between the hypothalamus and the peripheral bone tissue and could be responsible for the negative effects of leptin on bone mass. In line with previous studies[9], girls with AIS were found to have significantly lower BMD and longer arm span than female controls in the current series. This finding matches our observation on the changes in the SNS activity in girls with AIS.

The SNS mediates energy metabolism in animals and humans and regulate body growth and development. Some authors found that overweight girls have lower catecholamine levels than normal-weight girls; meanwhile, anorexic girls with lower BMI have higher sympathetic activity. Peterson et al.[8] found that plasma AD and NE were negatively correlated with body fat and BMI. In the current series, approximately 80% of girls with AIS had BMI score < 18.5 and showed marked increases in the levels of AD and NE. These results revealed that girls in the AIS group have lower catecholamine levels. The hyperactivity of the SNS might play an important role in causing lower body mass in girls with AIS.

One primary limitation of the current study was the lack of BMD data available from the healthy girls. Nevertheless, in our previous study, the BMD values was found to be lower in girls with AIS than in normal girls with the same DEXA device[10]. Although the Adam's forward bending test is insufficient for excluding scoliosis of a very small size, it is the only feasible and effective way for scoliosis scanning because a standing spine radiograph is far more unavailable from each healthy subject. The lack of information that if the patients did aerobic exercise or were smokers before recruitment might also be a possible limitation. In addition, the waiting time for surgery may influence the SNS activity of patients and could be a potential confounder of the results.

To our knowledge, this is the first report regarding the role of SNS activity in girls with AIS. The catecholamine levels and LF component were higher in 58 girls with AIS than in healthy girls. The levels of AD and NE were found to be correlated significantly with body weight BMI and BMC/BMD. The results of the current study suggest that increased SNS activity might play an important role in the lower body weight and bone mass in girls with AIS. The present study provides a new perspective on endocrine and neuro-osseous research related to the etiopathogenesis of idiopathic scoliosis. The mechanism for the increased activity of SNS warrants further investigation.

Author Contribution HU ZS designed and performed the experiments, wrote and edited the manuscript. ZHAO ZH designed, performed the experiment, wrote and edited the manuscript. ZHAO ZH, TSENG CC, and LI J performed the experiments. LAM TP, MAN GCW, QIU Y, ZHU ZZ, and CHENG JCY wrote and edited the manuscripts. LIU Z designed the experiments, wrote and edited the manuscript.

Conflicts of Interest The authors declare no conflict of interest.

#Correspondence should be addressed to LIU Zhen, Associate Professor, Tel: 13514001928; E-mail: drliuzhen@163.com

Biographical note of the first author: HU Zhong Shan, male, born in 1989, PhD, specializing in spine surgery.

Received: June 2, 2018;

Accepted: September 3, 2018

REFERENCES

1. Weinstein SL, LA Dolan, JCY Cheng, et al. Adolescent idiopathic scoliosis. Lancet, 2008; 371, 1527-37.
2. Liu Z, EMS Tam, GQ Sun, et al. Abnormal Leptin Bioavailability in Adolescent Idiopathic Scoliosis An Important New Finding. Spine, 2012; 37, 599-604.
3. Burwell RG, RK Aujla, MP Grevitt, et al. Pathogenesis of adolescent idiopathic scoliosis in girls-a double neuro-osseous theory involving disharmony between two nervous systems, somatic and autonomic expressed in the spine and trunk: possible dependency on sympathetic nervous system and hormones with implications for medical therapy. Scoliosis, 2009; 4, 24.
4. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J, 1996; 17, 354-81.
5. Enslein K, DPK Chan. Multiparameter pilot-study of adolescent idiopathic scoliosis. Spine, 1987; 12, 978-82.

6. Mauro LJ, SJ Wenzel, GM Sindberg. Regulation of chick bone growth by leptin and catecholamines. Poult Sci, 2010; 89, 697-708.
7. Pagani F, V Sibilia, F Cavani, et al. Sympathectomy alters bone architecture in adult growing rats. J Cell Biochem, 2008; 104, 2155-64.
8. Peterson HR, M Rothschild, CR Weinberg, et al. Body fat and the activity of the autonomic nervous system. N Engl J Med, 1988; 318, 1077-83.
9. Wang WJ, VW Hung, TP Lam, et al. The association of disproportionate skeletal growth and abnormal radius dimension ratio with curve severity in adolescent idiopathic scoliosis. Eur Spine J, 2010; 19, 726-31.
10. Tam EM, FW Yu, VW Hung, et al. Are volumetric bone mineral density and bone micro-architecture associated with leptin and soluble leptin receptor levels in adolescent idiopathic scoliosis?--A case-control study. PLoS One, 2014; 9, e87939.