Evaluation of carotid intima-media thickness and carotid arterial stiffness in children with adenotonsillar hypertrophy

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Background: **Adenotonsillar hypertrophy can produce cardiopulmonary disease in children. However, it is unclear whether adenotonsillar hypertrophy causes atherosclerosis. This study evaluated carotid intima-media thickness and carotid arterial stiffness in children with adenotonsillar hypertrophy.**

Methods: **The study included 40 children with adenotonsillar hypertrophy (age: 5-10 years) and 36 healthy children with similar age and body mass index. Systolic blood pressure, diastolic blood pressure, and pulse pressure were measured in all subjects. Carotid intima-media thickness, carotid arterial systolic diameter, and carotid arterial diastolic diameter were measured using a high-resolution ultrasound device. Based on these measurements, carotid arterial strain, carotid artery distensibility, beta stiffness index, and elasticity modulus were calculated.**

Results: **Carotid intima-media thickness was greater in children with adenotonsillar hypertrophy (0.36±0.05 mm *vs.* 0.34±0.04 mm, *P*=0.02) compared to healthy controls. Beta stiffness index (3.01±1.22 *vs.* 2.98±0.98, *P*=0.85), elasticity modulus (231.39±99.23 *vs.* 226.46±83.20, *P*=0.88), carotid arterial strain (0.17±0.06 *vs.* 0.17±0.04, *P*=0.95), and carotid artery distensibility (13.14±3.88 *vs.* 12.92±3.84, *P*=0.75) were similar between children with adenotonsillar hypertrophy and the healthy controls.**

Conclusions: **The present study revealed increased carotid intima-media thickness in children with adenotonsillar hypertrophy. The risk of subclinical atherosclerosis may be higher in children with adenotonsillar hypertrophy.**

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Key words: **adenotonsillar hypertrophy; carotid artery stiffness; carotid intima media thickness; subclinical atherosclerosis**

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Introduction

Adenotonsillar hypertrophy (ATH) is commonly observed in young children and is the leading cause of obstructive sleep apnea (OSA) for this group. ATH causes cardiopulmonary disease in children and can also produce hypoxia, hypercapnia, pulmonary hypertension, cor pulmonale, ventricular hypertrophy, and systemic hypertension.[1,2] Furthermore, children with ATH may exhibit decreased quality of life, somatic growth retardation, decreased school performance, behavioral problems and attention/hyperactivity disorder.[2,3] Clinical OSA diagnosis is reliable; however, the optimum evaluation method is overnight polysomnography. OSA associated with ATH is treated with adenotonsillectomy, one of the most commonly performed surgical procedures in children.[4]

OSA in children is commonly caused by ATH, whereas OSA in adolescents and adults is typically caused by obesity.[5] Patients with OSA may exhibit increased oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, and metabolic dysregulation, all of which may contribute to systemic hypertension and atherosclerosis.[6] Many studies report increased carotid intima-media thickness (CIMT) in adult patients with OSA, and a correlation has been found between CIMT and inflammatory markers.[7-9] Leukotrienes play an important role in atherosclerosis development, and OSA increases the production of leukotriene B4 and

cysteinyl leukotrienes, demonstrating an activation of the leukotriene pathway.[10] Children with ATH also exhibit the activation of the leukotriene pathway and the increase of serum leukotriene concentration.[11] In adults with OSA, the risk of atherosclerosis and cardiovascular events is increased, but the same risk for children with ATH is unknown.[12]

CIMT is increasingly used as a surrogate marker for atherosclerosis based on its ability to predict future clinical cardiovascular end points.[13] Similarly, arterial stiffness also has a considerable predictive validity for future cardiovascular events and atherosclerotic diseases.[14] CIMT and arterial stiffness represent different vessel wall properties, and combined measurements give optimal results.[15] The aim of this study was to evaluate CIMT and carotid arterial stiffness in children with ATH.

Methods

Study population

This prospective study included 40 patients with ATH (23 males and 17 females) and 36 healthy controls (18 males and 18 females) matched for age and body mass index. The study was approved by the Hospital Ethics Committee, and conducted in accordance with the *2000 Helsinki Declaration*; informed consent was obtained from the subjects and their parents. The researchers evaluated all patients admitted to the ear, nose, and throat (ENT) clinic with reports of snoring, mouth-breathing, noisy breathing, pauses in breathing during sleep, or chronic adenotonsillar infection. Patients suffering from upper respiratory tract obstruction for at least 6 months were included in the study.

All patients underwent a complete ENT examination including flexible nasopharyngoscopy. The Brodsky scale was used to grade tonsil hypertrophy as follows: grade 1 (tonsils in the tonsillar fossa, barely visible behind the anterior pillars), grade 2 (tonsils easily visible behind the anterior pillars), grade 3 (tonsils extended three-fourths of the way to the midline), and grade 4 (tonsils completely obstructing the airway). Furthermore, adenoid hypertrophy was graded according to the severity of airway obstruction, as follows: grade 1 (<25%), grade 2 (25%-50%), grade 3 (50%-75%), and grade 4 (>75%) airway obstruction.[16-18] Adenoid hypertrophy was defined as obstruction of more than 50% of the nasopharyngeal airway. Patients with grade 3 or 4 adenoid or tonsillar hypertrophy were included the study. Patients with grade 1 or 2 tonsillar hypertrophy, congenital or acquired cardiac anomalies, rheumatologic disorders, obesity, acute and chronic liver disease, kidney insufficiency, diabetes mellitus, hypertension, and dysrhythmia were excluded from the patient group.

Patients referred to the outpatient clinics of pediatric cardiology due to cardiac murmur who were found to have no cardiac disorder based on physical examination, electrocardiography, and echocardiography and diagnosed with an innocent murmur were included in the control group. Patients with congenital or acquired cardiac anomalies, rheumatologic disorder, obesity, acute and chronic liver disease, kidney insufficiency, diabetes mellitus, hypertension, dysrhythmia, adenotonsillar disease, respiratory tract infection, and systemic and local infections were excluded from the control group.

Age, weight and height measurements were conducted for all patients. Body mass index was calculated by dividing body weight in kilograms by the square of height in meters. In addition, systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were obtained in all patients, and pulse pressure (PP) was calculated.

Echocardiographic examination

Two-dimensional, M-mode, pulsed and color flow Doppler echocardiographic examinations (Vivid 7 pro, GE, Horten, Norway, 3-MHz transducer) were performed in all subjects by a cardiologist who was blinded to the clinical details and to the results of the other investigations conducted in the patients and controls. During echocardiography, one-lead electrocardiographic measurements were recorded continuously. The systolic function of the left ventricle was evaluated using M-mode echocardiography in the parasternal long-axis view.[18]

Measurement of carotid intima media thickness

Following a resting period of 10 minutes prior to ultrasonography, CIMT measurements were obtained under conditions of stable temperature and silence. An experienced pediatric cardiologist who was blinded to the patient and control groups performed all measurements. A 12-MHz transducer was used with a Toshiba (Xario, Toshiba Medical Systems Corp., Tochigi, Japan) echocardiography device for ultrasonographic evaluation. Measurements were obtained with mild extension of the head and in a supine position in the opposite direction of the carotid artery of interest. Measurements were obtained in the distal part of the right common carotid artery 1-cm proximal to the bifurcation to evaluate the posterior wall of the vessel. During measurements, the vessel was imaged longitudinally. For CIMT, the hypoechogenic area between the echogenic lines of the innermost two

layers of the arterial wall was measured.[19] The mean values of three measurements were calculated.

Measurement of carotid artery stiffness

SBP and DBP values were measured and recorded using a Dinamap Pro100 (Critikon Inc., GE Medical systems, US) automatic sphygmomanometer from the right brachial artery after the participants had rested for 15 minutes in a supine position. The mean values were calculated from three measurements. PP was calculated as PP=SBP-DBP. The best acoustic window was identified with the jugular vein above the common carotid artery, and a series of images were acquired over a 20-second period. On average, 5-6 cardiac cycles were used for the estimation of carotid diameters. The carotid artery luminal diameter 1-cm proximal to the common carotid artery bifurcation was measured in both systolic and diastolic phases of the cardiac cycle using a high-resolution B-mode ultrasonographic system (Xario, Toshiba Medical Systems Corp., Tochigi, Japan) equipped with a 7.5-MHz real-time B-mode scanner and pulsed-Doppler mode scanner.

Formulae including the carotid arterial systolic diameter (D_s), carotid arterial diastolic diameter (D_d), SBP, DBP and PP were used to calculate carotid arterial strain (CAS). Pressure strain elastic modules (Ep), beta stiffness index (βSI) and carotid artery distensibility (CAD) were used as carotid artery stiffness parameters. The formulae were as follows: $CAS=(D_s-D_d)/D_d$; $\beta SI=[\ln (SBP/DBP)]/strain$; $Ep=(SBP-DBP)/strain$; $CAD=2\times[(D_s-D_d)/D_d]\times PP$.[19-21]

Statistical analysis

The Statistical Package for the Social Sciences for Windows 17 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses in the present study. The Kolmogorov-Smirnov test was used to assess whether the samples exhibited a normal distribution. An unmatched Student's *t* test was used to compare the mean values of the samples showing a normal distribution, and the Mann-Whitney *U* test was used to compare the mean values of the samples showing a non-normal distribution. Pearson's correlation coefficient test was used to assess the correlations between quantitative data. Data were expressed as means±standard deviation. A *P* value <0.05 was considered statistically significant.

Results

Clinical characteristics and M-mode echocardiographic findings of ATH patients and healthy controls were compared (Table 1). The study and control groups were similar in age (7.32±1.52 *vs*. 7.27±1.46 years, *P*=0.90), body mass index (15.77±1.25 *vs*. 15.83±1.29, *P*=0.93), interventricular septal wall thickness (diastolic), left ventricular posterior wall thickness, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular posterior wall thickness (systolic), interventricular septal wall thickness (systolic), and ejection fraction. Furthermore, the ATH patients were similar to the healthy controls for SBP (96.67±6.81 *vs*. 95.27±6.17 mmHg, *P*=0.28), DBP (59.20±5.29 *vs*. 58.47±3.70 mmHg, *P*=0.39) and PP (37.47±6.74 *vs*. 36.80±4.45, *P*=0.59).

CIMT and the parameters of carotid artery stiffness were compared in the children with ATH and healthy controls (Table 2). CIMT (0.36±0.05 mm and 0.34±0.04 mm, *P*=0.02) was significantly greater in the children with ATH than in the healthy controls. However, the two groups were similar in βSI (3.01±1.22 *vs*. 2.98±0.98, *P*=0.85), Ep (231.39±99.23 *vs*. 226.46±83.20, *P*=0.88), CAS (0.17±0.06 *vs*. 0.17±0.04, *P*=0.95) and CAD (13.14±3.88 *vs*. 12.92±3.84, *P*=0.75).

Correlation analysis revealed that patient age was correlated with CIMT (*r*=0.52, *P*<0.01), carotid arterial systolic diameter (*r*=0.83, *P*<0.01) and carotid arterial diastolic diameter (*r*=0.80, *P*<0.01). In addition, CIMT was correlated with body mass index (*r*=0.35, *P*=0.02), SBP (*r*=0.40, *P*=0.01) and DBP (*r*=0.35, *P*=0.02).

Discussion

ATH is the most common cause of OSA because tonsil enlargement during preschool years reduces pharyngeal

Table 1. Clinical characteristics and M-mode echocardiographic parameters

Variables	ATH (*n*=40)	Controls (*n*=36)	*P* value
Age (y)	7.32±1.52	7.27±1.46	0.90
BMI (kg/m^2)	15.77±1.25	15.83±1.29	0.93
SBP (mmHg)	96.67±6.81	95.27±6.17	0.28
DBP (mmHg)	59.20±5.29	58.47±3.70	0.39
IVSd (mm)	8.12±1.47	7.83±1.57	0.48
LVIDd (mm)	35.92±4.26	35.11±4.95	0.34
LVPWd (mm)	7.82±1.48	7.55±1.68	0.31
IVSs (mm)	10.25±2.19	10.00±2.00	0.67
LVIDs (mm)	21.85±2.86	21.41±3.00	0.50
LVPWs (mm)	11.35±1.88	11.11±2.05	0.62
EF	68.30±5.06	69.05±4.96	0.50

ATH: adenotonsillar hypertrophy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; IVSd: interventricular septal wall thickness (diastolic); LVIDd: left ventricular internal dimension (diastolic); LVPWd: left ventricular posterior wall thickness (diastolic); IVSs: interventricular septal wall thickness (systolic); LVIDs: left ventricular internal dimension (systolic); LVPWs: left ventricular posterior wall thickness (systolic); EF: ejection fraction.

Table 2. Carotid artery stiffness parameters and carotid intima media thickness

Variables	ATH (n=40)	Controls (n=36)	P value
PP (mmHg)	37.47±6.74	36.80±4.45	0.59
D_s (mm)	4.20±0.55	4.29±0.60	0.56
D_d (mm)	3.58±0.53	3.65±0.54	0.50
CAS	0.17±0.06	0.17±0.04	0.95
βSI	3.01±1.22	2.98±0.98	0.85
Ep	231.39±99.23	226.46±83.20	0.88
CAD	13.14±3.88	12.92±3.84	0.75
CIMT (mm)	0.36±0.05	0.34±0.05	0.02

ATH: adenotonsillar hypertrophy; PP: pulse pressure; D_s: carotid systolic diameter; D_d: carotid diastolic diameter; CAS: carotid arterial strain; βSI: beta stiffness index; Ep: pressure-strain elasticity modulus; CAD: carotid artery distensibility; CIMT: carotid intima media thickness.

space and promotes airway collapse during sleep in some children. Adenotonsillectomy, the surgical removal of tonsils and adenoids, is the treatment of choice. It is normally well tolerated and, in most cases, leads to OSA symptom resolution. ATH and recurrent tonsillitis are the two most common indicators for treatment with adenotonsillectomy. Children with ATH may also exhibit pulmonary hypertension, right ventricular hypertrophy, cor pulmonale, cardiac failure, and stroke.[1,2,12] OSA in adult patients is usually caused by obesity and less commonly by other upper respiratory tract obstructions, but ATH is the most common cause of OSA in children.[22,23] Adult patients with OSA have a higher risk for the development of atherosclerosis and cardiovascular events.[7-9,12] However, no reports regarding the risk of atherosclerosis and cardiovascular events in children with ATH have been published.

Children with ATH and recurrent tonsillitis may have systemic inflammation, oxidative stress, endothelial dysfunction, and hypoxia, and these combined factors could contribute to atherosclerosis development.[6,24] Recurrent tonsillitis produces systemic inflammation, and increased phospholipase A2 activity has been found in serum. Phospholipase A2 plays an important role in growth regulation, differentiation and inflammation, and in the development of cardiovascular diseases and atherosclerosis.[25-27] Furthermore, T cells are highly proliferative in the tonsils of children with OSA and are associated with increased production of proinflammatory cytokines.[28] The adenosine deaminase enzyme plays an important role in lymphoid cell differentiation, and is also implicated in oxidative stress. In one study, serum and tissue adenosine deaminase activity, oxidant enzyme malondialdehyde, and nitric oxide levels were increased in patients with recurrent tonsillitis, whereas levels of antioxidant carbonic anhydrase and catalase were decreased.[29] ATH is the leading cause of upper respiratory tract obstruction, OSA, and hypoxia in children and can also produce cardiovascular and pulmonary disorders. ATH in children has been linked to atherosclerosis, heart failure, hypertension, cardiac arrhythmias and stroke. In addition, OSA produces endothelial dysfunction, coagulopathy, oxidative and inflammatory stress, elevated sympathetic activity, intrathoracic pressure changes, insulin resistance, and thrombosis.[30-32] Patients with OSA have increased inflammatory responses, which increase levels of C-reactive protein and tumor necrosis factor, and OSA treatment reduces inflammation. Recurrent tonsillitis and OSA are damaging to the cardiovascular system, and untreated OSA increases the risk of cardiovascular disease.[33] Furthermore, activation in the leukotriene pathway and increased serum leukotriene concentrations, both of which contribute to atherosclerosis development, were detected in children with ATH.[11]

In this study, CIMT and risk for subclinical atherosclerosis were increased in children with ATH. However, both groups were similar in βSI, Ep, CAS, and CAD values. Carotid artery stiffness was similar between children with ATH and healthy controls, suggesting no increased risk of cardiovascular events in children with ATH based on this parameter. However, these patients may have a higher risk of cardiovascular events if left untreated. The actual risk of cardiovascular events is not known in adult patients with OSA, although one study reported an increased risk for stroke.[12] In the present study, a correlation between age, SBP, DBP and CIMT was found. Furthermore, the SBP and DBP were higher in patients with ATH, but the difference did not reach statistical significance.

In this study, increased risk of subclinical atherosclerosis was observed in children with ATH. Adenotonsillectomy was performed for the treatment of ATH. However, the tonsils and adenoids also play an important role in humoral and cellular immunity, and the immune system can protect against atherosclerosis.[34] One study reported an increased risk of myocardial infarction in patients who underwent tonsillectomy in childhood. This finding was attributed to certain complex alterations in the immune system after the tonsillectomy procedure.[35] Furthermore, surgical removal of the secondary lymphoid organ, the spleen, was associated with an increased risk of atherosclerosis.[36,37] Various short-term complex alterations may occur in the immune system after tonsillectomy, but this remains a controversial issue.[38-40]

CIMT and carotid arterial stiffness are predictors of atherosclerosis and cardiovascular diseases, respectively.[13,14] In the present study, CIMT was increased in children with ATH, which may indicate an increased risk of subclinical atherosclerosis.

There are some limitations in the present study. This study was conducted in children aged 5-10 years, a group with a naturally lower risk of atherosclerosis and cardiovascular events. Lipid levels were not investigated in the study group, and this is also a limitation. Another limitation is that some markers of systemic inflammation and oxidative stress associated with atherosclerosis risk in children with ATH were not evaluated.

In conclusion, increased CIMT was found in children with ATH in the present study. The increased CIMT is a predictor of atherosclerosis. The risk of subclinical atherosclerosis may be higher in patients with ATH. More comprehensive studies with a longer duration of follow-up are warranted to further investigate the risk of atherosclerosis.

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