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ORIGINAL ARTICLE

Evaluation of carotid intima-media thickness, a marker of subclinical atherosclerosis, in children with cerebral palsy

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Abstract
Background Respiratory and cardiovascular diseases are the most common causes of death in children with cerebral palsy.
Objective To evaluate sonographic carotid intima-media thickness, an early marker of atherosclerosis, in children with cerebral palsy and in healthy controls.
Materials and methods One hundred children with cerebral palsy (65 boys), mean age 6.2 (SD, 2.1) years, and 35 age-matched and sex-matched healthy controls were included. Common carotid artery intima-media thickness was measured sonographically. Differences between patients and controls were evaluated with an independent samples *t*-test.
Results Age, sex distribution and levels of serum lipids were comparable between patients and controls. Average, right and left carotid artery intima-media were thicker in patients compared with controls (mean ± SD, 0.61±0.13 mm vs 0.40±0.03 mm; 0.61±0.14 mm vs 0.40±0.03 mm; 0.61± 0.13 mm vs 0.40±0.03 mm, respectively; all $P<0.001$).
Conclusion Carotid intima-media is sonographically thicker in children with cerebral palsy compared with healthy controls, which may express an increased risk of atherosclerotic diseases.

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Keywords Cerebral palsy · Atherosclerosis · Ultrasound · Carotid intima-media thickness

Introduction

Cerebral palsy is defined as a permanent group of movement and posture disorders that cause limitation of activity due to nonprogressive defects in the brain of the fetus and infant [1]. Although motor defects are often more marked, other symptoms of cerebral dysfunction might also be observed. Musculoskeletal symptoms include walking disorders and contractures. Other problems might also develop, including mental retardation, convulsions, strabismus, urinary and rectal incontinence [2]. Life expectancy is reduced in children with cerebral palsy, and the most common causes of mortality are cardiovascular and respiratory diseases [3]. Chronic respiratory and urinary infections are also quite common in children with cerebral palsy [4]. Chronic infections may contribute to the pathogenesis of atherosclerosis via endothelial dysfunction resulting from vascular inflammation. Studies performed with animal models have demonstrated that, similar to humans, permanently high endothelin concentrations are important risk factors for atherosclerosis [5].

Advanced US has made it possible to demonstrate atherosclerosis in the early phase [6]. One method is by measurement of intima-media thickness (IMT) in the carotid arteries [7]. The intima-media thickness is increased in the artery walls in the early stages of atherosclerosis. This has been observed both in coronary and peripheral arteries. Measurements in the carotid arteries provide an almost perfect representation of the atherosclerotic state of the entire arterial system. Therefore, several studies have considered increased carotid artery intima-media thickness (CIMT) as a predictor of coronary artery disease [8–11].

Our objective was to grade atherosclerosis by measuring carotid intima-media thickness in children with cerebral palsy.

Materials and methods

The study was performed in the Department of Pediatric Neurology of the Medical School of Harran University and in three private physiotherapy and rehabilitation centres in Sanliurfa, Turkey, between 1 January and 28 February 2011. A total of 100 children with cerebral palsy was included in the study. The age-matched controls were 35 children referred to the children's outpatient clinic of the Medical School of Harran University who did not have any neurological deficits or signs of infection. Research ethics approval was obtained from the Ethics Committee of Medical School of Harran University. Written informed consent was obtained from all children/legal guardians. Children who had been diagnosed with hypertension, diabetes mellitus or hyperlipidemia or who had received any corticosteroid medications in the last 1 month were excluded from the study.

Overnight fasting was requested from the patient group, including abstinence from smoking, tea and coffee on the morning. Systolic (SBP) and diastolic (DBP) blood pressure measurements were performed with a standard mercuric sphygmomanometer from the right arm after a 5-min rest in a silent room [12]. Body weight and height were measured without shoes and with light clothes. Body mass index was calculated as BW (kg) divided by height squared (m). Blood glucose (FBG), total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol and C-reactive protein were measured in fasting blood samples using commercially available assay kits. Standard measurement techniques were used in all laboratory measurements.

CIMT measurements were performed using an US device with a broadband, high-resolution 12-MHz probe (Logiq 7; General Electric, Milwaukee, WI, USA). All measurements were performed with the same device by one radiologist (A.Y.) blinded to the clinical and laboratory findings of patients and controls. Recoded data represent the average of three measurements. The right and left common carotid arteries (CCAs) were assessed. All measurements were performed with the child supine, neck in mild extension and head turned to the opposite side. CIMT was measured in the posterior wall in a longitudinal sonogram obtained within the lower third of the neck for the proximal part, and 1 cm caudal to the carotid bulbus for the distal (Fig. 1). Separate right and left and the average right/left CIMT were used in the evaluation of data.

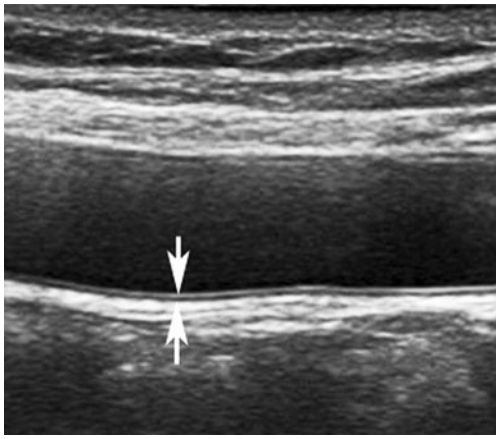

Fig. 1 Longitudinal sonogram of a common carotid artery in a 7-year-old boy with cerebral palsy. There is a thickened intima-media (0.6 mm, compared with the mean thickness of 0.4 mm in the control group)

All data were evaluated using the Statistical Package for Social Sciences 15.0 (SPSS, Chicago, IL). Distribution of data was analysed with the Kolmogorov-Smirnov test. Results were expressed as mean ± SD The independent samples *t*-test or the chi-square test for categorical variables was used in the comparison of patients and controls. The Pearson correlation test was used to determine the relationship between IMT and various variables. $P<0.05$ was considered statistically significant.

A post hoc power analysis was performed using the G power 2 power analysis program (G power 2, Dusseldorf University, Dusseldorf, Germany) based on mean CIMT after assessing 100 children and 35 controls, which showed a power of 0.99 (alpha, 0.05).

Results

Etiological factors for the cerebral palsy group are given in Table 1. In the cerebral palsy group, 84 children were spastic (35 diplegia, 25 quadriplegia, 14 hemiplegia, 10 triplegia), four ataxic, four hypotonic and eight children had mixed motor abnormality. The Gross Motor Functional Classification System (GMFCS) was used to assess the ambulation level for age [13]. Based on GMFCS, seven children were at level 1, 14 at level 2, seven at level 3, 40 at level 4 and 32 children were at level 5. A history of lower respiratory tract infections was reported in all 100 children with cerebral palsy, the number of episodes varying from 1 to 13, with an average of 5.5 episodes. A history of urinary tract infection was reported in 62 of the 100 children with cerebral palsy. The number of urinary tract infection episodes varied from 1 to 4 with an average of 1.4 episodes. Nine of the 100 children with cerebral palsy had asymptomatic bacteriuria.

All variables were normally distributed.

Table 1 Etiological factors in the group of 100 children with cerebral palsy

	n
Maternal and pregnancy factors	
Puerperal infection	15
Preeclampsia	8
Maternal diabetes mellitus	3
Maternal smoking	20
Twin pregnancy	5
Placental insufficiency	10
Perinatal factors	
Prematurity	15
Low birth weight (<2,500 g)	8
Anoxia	8
Kernicterus	5
Postnatal factors	
Convulsion	25
Head trauma	11
Intracranial haemorrhage	7

Patient and control groups were not different for demographic features, total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol or triglyceride levels or blood pressures ($P>0.05$). Height, weight and body mass index were significantly lower, whereas serum C-reactive protein was higher in patients than in controls (Table 2).

Intraobserver variability for CIMT measurement was<5%.

Average CIMT differed between the two groups (mean ± SD, 0.61±0.13 mm in the cerebral palsy group, 0.40±0.03 mm in the control group, $P<0.001$; Table 3). Right CIMT was 0.61±0.14 mm in the cerebral palsy group and 0.40±0.03 mm in the control group ($P<0.001$). Left CIMT was 0.61±0.13 mm in the cerebral palsy group and 0.40±0.03 mm in the control group ($P<0.001$; Table 3, Fig. 2).

No correlations were seen between CIMT and serum levels of LDL cholesterol, HDL cholesterol, triglyceride, age, body mass index, C-reactive protein or fasting blood glucose in children with CP or in controls ($P>0.05$ for all; Table 4).

The post hoc power analysis showed a power of 0.99 at the chosen alpha level.

Discussion

Cerebral palsy is characterised by permanent but changeable movement, tonus and posture disorders resulting from non-progressive damage to the brain early in life when anatomical and physical development have not been completed [14]. Several studies have been performed on the causes of death and life expectancy in patients with cerebral palsy [15–18]. Life expectancy is markedly shortened, particularly in patients with severe forms. Respiratory and cardiovascular diseases are the most common causes of death. The most common cause of death in patients with cerebral palsy is respiratory diseases [3]. The frequencies of chronic respiratory and urinary infections are also significantly increased [4]. Though high frequencies of infections were reported in children with cerebral palsy in our study, we could not find any association between CIMT and presence, frequency or type of infections.

Death due to cardiovascular causes is also significantly more common in patients with cerebral palsy compared with the general population. Previous studies have suggested that this may be secondary to the reduced rate of physical activity in patients with cerebral palsy [3]. Atherosclerosis is accepted as an inflammatory disease and the persistent low-degree inflammation determined in patients with

Table 2 Comparison of demographic, clinical and laboratory features between children with cerebral palsy (CP) and controls

	Children with CP mean ± SD (n=100)	Controls mean ± SD (n=35)	P[a]
Age (years)	6.16±2.13	6.21±2.14	0.530
Male/female (n)	65/35	23/12	0.710
Systolic blood pressure (mmHg)	104 ±8.5	107.3±10.8	0.620
Diastolic blood pressure (mmHg)	65.4±9.1	69.5±6.7	0.514
Height (cm)	104.31±14.12	116.40±17.56	<0.001
Weight (kg)	18.32±3.41	24.01±4.21	<0.001
Body mass index (kg/m^2)	16.45±1.71	19.40±2.10	<0.001
Fasting blood glucose (mg/dl)	81.5±12.14	82.5±11.03	0.610
Total cholesterol (mg/dl)	105.65±24.53	107.12±22.51	0.640
LDL cholesterol (mg/dl)	57.02±24.27	58.74±23.54	0.790
HDL cholesterol (mg/dl)	36.54±5.31	35.55±4.24	0.748
Triglyceride (mg/dl)	140.28±55.30	137.54±66.40	0.576
C-reactive protein (mg/dl)	4.84±2.92	1.01±0.54	<0.001

[a]Independent samples *t*-test or chi-square test

Table 3 Comparison of carotid intima-media thickness between children with cerebral palsy (*CP*) and controls

	Children with CP (n=100) mean ± SD	Controls (n=35) mean ± SD	P[a]
Right common carotid artery (mm)	0.61±0.14	0.40±0.03	<0.001
Left common carotid artery (mm)	0.61±0.13	0.40±0.03	<0.001
Average of the two common carotid arteries (mm)	0.61±0.13	0.40±0.03	<0.001

[a]Independent samples *t*-test

atherosclerosis and individuals at risk for atherosclerosis is considered to play a key role in the pathogenesis [19]. Local or systemic exacerbation of the inflammatory process at intervals might lead to acute clinical events. Endothelial injury is the main point of onset in atherosclerosis and is associated with disruption of the balance between autocrine and paracrine parameters of endothelial cell functioning [20]. The endothelial imbalance secondary to inflammation results in secretion of adhesion molecules from the endothelial surface, binding of ligands to inflammatory cells, infiltration to vessel wall, secretion of chemokins, synthesis of cytokines and secretion of procoagulant factors [21]. Several molecules activated by endothelial activation are considered to cause the transformation of monocytes into macrophages and migration of smooth muscle cells to beneath the endothelium [22–24]. Although there is a well-known association of infection-inflammation and atherosclerosis, we could not show association of CIMT with either the inflammatory marker (C-reactive protein) or presence, frequency or type of infections.

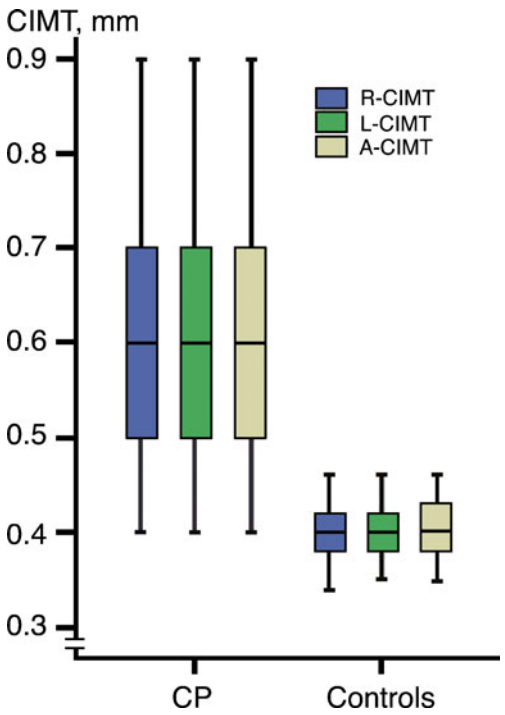

Fig. 2 Comparison of CIMT between children with cerebral palsy and controls. *CP* cerebral palsy, *A-CIMT* average carotid intima-media thickness, *L-CIMT* left carotid intima-media thickness, *R-CIMT* right carotid intima-media thickness

Atherosclerosis is a disease affecting the arterial wall [25]. Several studies have reported that increased arterial wall thickness and, particularly, increased intima and media thicknesses were predictive of development of atherosclerosis [26, 27]. Several comparative studies have demonstrated that IMT is increased in patients with cardiovascular diseases (CVDs) and that the risk of CVD is higher in patients with increased IMT [7, 28, 29]. In a study by Geroulakos et al. [26], carotid intima and media was thicker in patients with angiographic stenosis compared with a group without stenosis, and the thickness of intima-media increased with the number of stenotic vessels [26]. Three large-scale studies—ARIC [24], Rotterdam [27] and Cardiovascular Health Study Collaborative Research Group [7]—showed that CIMT measured non-invasively with B-mode US is predictive of coronary artery disease. Sonographic CIMT has also been reported in clinical studies of children and adolescents [30–35].

We examined CIMT in children with cerebral palsy using B-mode US. CIMT in children with cerebral palsy was compared with that of age, sex, serum lipid, systolic and diastolic blood pressure-matched controls. CIMT in children with cerebral palsy was greater than in controls. This

Table 4 Correlation[a] between average sonographic carotid intima-media thickness, and clinical and laboratory measurements between children with cerebral palsy (*CP*) and controls

	Children with CP (n=100)	Controls (n=35)
Age	r=0.095, P=0.643	r=0.079, P=0.742
Body mass index	r=0.230, P=0.252	r=-0.141, P=0.550
Fasting blood glucose	r=0.129, P=0.531	r=0.224, P=0.342
Systolic blood pressure	r=0.229, P=0.126	r=0.143, P=0.322
Diastolic blood pressure	r=0.020, P=0.888	r=0.204, P=0.155
Total cholesterol	r=0.032, P=0.870	r=-0.241, P=0.310
LDL cholesterol	r=0.310, P=0.123	r=0.012, P=0.965
HDL cholesterol	r=0.150, P=0.465	r=-0.061, P=0.798
Triglyceride	r=0.094, P=0.644	r=0.076, P=0.740
C-reactive protein	r=-0.022, P=0.828	r=0.092, P=0.600

[a] Pearson correlation statistics

suggests that subclinical atherosclerosis may be more common in children with cerebral palsy compared with the controls. The increased CIMT has been suggested associated with chronic infections encountered in patients with cerebral palsy [36].

Similar to the general population [7, 27, 29], increased CIMT in patients with cerebral palsy might be predictive of increased risk of coronary artery disease. However, more extensive prospective studies need to be performed to support this hypothesis. Consequently, the increased CIMT in patients with cerebral palsy compared with controls suggests that patients with cerebral palsy are at increased risk of atherosclerosis and coronary artery diseases. It should be kept in mind that CIMT is a surrogate marker of atherosclerosis. This is based on the fact that atherosclerosis in a vascular territory partially predicts presence and/or severity of atherosclerosis in other vascular territories as the atherosclerotic burden, initiation and progression patterns of atherosclerosis varies widely among different vascular territories.

Certain limitations of the present study should be considered. First, the cross-sectional study design. Second, that we did not perform power analysis to determine the sample size at the time of study planning; however, a post hoc power analysis demonstrated a high power of our sample size (0.99). One should also keep in mind that the CIMT measurement is operator dependent. Generalising findings of the present study might be inappropriate as the data were obtained in a geographically confined region.

Conclusion

Measurement of CIMT with B-mode US is an easy, applicable, inexpensive and noninvasive method for determining the risk of atherosclerosis and cardiovascular disease. Children with cerebral palsy have increased CIMT, possibly expressing increased atherogenesis. Following-up children with cerebral palsy with respect to the development of atherosclerosis might be beneficial as a great majority of these children reach adulthood.

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