Carotid intima-media thickness and inflammatory biomarkers in adolescents with tension-type headache

Agnieszka Cwalińska¹, Anna Mania¹, Katarzyna Mazur-Melewska¹, Paweł Kemnitz¹, Katarzyna Jończyk-Potoczna², Wojciech Służewski¹, Magdalena Figlerowicz¹

¹Department of Infectious Diseases and Child Neurology, Poznan University of Medical Sciences, Poznan, Poland
²Department of Paediatric Radiology, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Introduction: Primary headaches are frequent complaints among adolescents. Tension-type headache (TTH), which causes symptoms influencing the patients' quality of life, can be associated with various medical disorders.

Aim of the study: To research the reason for TTH in adolescents.

Material and methods: The study included 76 patients, aged from 14 to 17 years, diagnosed due to TTH. Patients with the carotid intima-media thickness (cIMT) in the 90th percentile (the cut-off point: 0.42 mm for boys, and 0.41 mm for girls) were included in group 1, and the rest in group 2. All the patients underwent laboratory tests with serum levels of IL-6, IL-10, TNF-α, and sICAM-1. Twenty-six (34%) patients were enrolled in group 1 and 50 (66%) in group 2.

Results: There were no significant differences in age, sex, height, BMI, and systolic and diastolic blood pressure between patients from both studied groups. The mean cIMT value (mean, SD) for all patients from the study group was 0.41 ±0.012 mm: for girls 0.39 ±0.014 mm and for boys 0.44 ±0.016 mm. In 16-year-old adolescents, the cIMT was significantly higher in boys than girls. In 17-year-old patients, cIMT was significantly higher in boys only in group 1. The significantly higher concentrations of IL-6, TNF-α, and sICAM-1 were found in patients from group 1. Whereas the IL-10 level was significantly higher in the control group. In over one-third of patients (34%) with TTH, the cIMT was in the 90th percentile, despite having normal BMI, blood pressure, and lipid profile in serum.

Conclusions: The inflammatory process in the vascular wall could be considered as the reason for the higher cIMT value and/or TTH in adolescents.

KEY WORDS:

biomarkers, adolescents, carotid intima-media thickness, tension-type headache.

INTRODUCTION

Primary headaches, including migraine and tension-type headache (TTH), are frequent complaints among adolescents [1, 2]. The prevalence of headaches is estimated to be 27-32% at the age of 13-14 years, increasing with age [2, 3]. TTH cause symptoms influencing patients' quality of life, school attendance, and daily activity.

TTH can be associated with various medical disorders, chronic psychiatric, and neurological diseases (for example sleep disorder, anxiety, depression, epilepsy, attention deficit, and hyperactivity disorders) as well as...
Atherosclerosis could be the cause of the latter. Atherosclerosis is known to be associated with a higher level of low-density lipoprotein as well as total cholesterol in the blood, impaired glucose tolerance and diabetes, obesity, hypertension, and tobacco smoking [7]. It has also been proven that chronic inflammation contributes to accelerated atherogenesis and plays an essential role in all stages of the process, from fatty streak formation, through atheroma progression, to the development of thrombosis, as well as plaque rupture [8]. When the disease is still in a subclinical stage, the presence of atherosclerosis can be identified by several methods ranging from B-mode ultrasonography, intravascular ultrasonography, and coronary angiography to computed tomography and magnetic resonance imaging. Several studies have shown that the measurement of the common carotid artery intima-media thickness (IMT) represents a perfect marker of subclinical atherosclerosis [9–11]. Other studies have proven that IMT is very weak predictor of cardiovascular events [12] and progression of IMT does not predict cardiovascular events. According to some studies, IMT and atherosclerosis are biologically and genetically determined [13–15].

One of the causes of atherosclerosis could be a progressive inflammatory process in the vascular wall, which provides signals for leukocyte and macrophage infiltration [9]. Additionally, the cytokines released as a part of the inflammatory cascade stimulate the production of interleukin 1 (IL-1) and interleukin 6 (IL-6), which in turn lead to the excessive output of other acute reactants such as tumour necrosis factor α (TNF-α). Moreover, it is well known that serum concentration of the soluble form of intracellular adhesion molecule (sICAM-1) is associated with many cardiovascular disease risk factors including body mass index (BMI), blood pressure, and lipid disorders [8].

**MATERIAL AND METHODS**

The study included 76 patients (n = 76), aged 16.48 ±1.52 years, 40 girls (53%) and 36 boys (47%), diagnosed due to TTH. Prior to inclusion in the study diagnostic procedures were conducted, and as a result persons with psychiatric and neurological diseases, heart defects, acute infection caused by cytomegalovirus and Epstein-Barr virus, and laboratory evidence of lipid disorders were excluded. In all patients, blood pressure (BP) and carotid intima-media thickness (cIMT) were measured. Body mass index (BMI) was calculated basing on the formula: body weight (kg)/body height (m²). Carotid ultrasound was performed with a Philips Healthcare IU 22 scanner, using a 10-MHz linear transducer, according to the cIMT measurement scheme published in 2006 at the Mannheim Intima-Media Thickness Consensus [9]. cIMT measurements were performed on both sides of the common carotid artery (2 cm below the bifurcation), the carotid bulb, and in the internal carotid artery. The study was carried out on the patient in supine position with two access method: front with a slight head-to-back, and posterolateral next to the sternomastoid muscle. The transducer plane was oriented parallel to the course of the vessel so that the ultrasonic beam was perpendicular to the artery wall. In the 2D presentation, a distal wall was seen, within which cIMT assumed the distance between the first linear hyperechogenic vascular structure, starting from its light, and the median separating line from the adductor (Fig. 1). The obtained results (10 measurements in each section on each side) are presented as the arithmetic mean for all projections. The group was divided into two subgroups according to the cIMT value. The 90th percentile was adopted as the cut-off point: 0.42 mm cIMT for boys and 0.41 mm cIMT for girls. Patients with a cIMT value of 90th or higher were included in group 1, and the rest in group 2 (control group). All the patients underwent laboratory tests including serum levels of IL-6, IL-10, TNF-α, and sICAM-1.

Continuous variables were expressed as mean ± standard deviation (SD). For comparison of the continuous variables, the Mann-Whitney U test was used, and the chi-square or Fisher’s exact test was used for comparison of categorical data. Pearson’s correlation coefficient method was used to assess the correlation between cIMT and IL-6, IL-10, TNF-α, and sICAM-1. Statistical analyses were performed using Statistica 8.0, StatSoft. The study was approved by the local Bioethical Committee.

**RESULTS**

The studied group comprised 40 (53%) girls and 36 (47%) boys with TTH. Based on a cIMT value higher than the 90th percentile (cIMT was determined for the studied group, cut-off points for male 0.42 mm and for female 0.41 mm), 26 (34%) patients were enrolled in group 1: 15 boys, and 11 girls. Other patients – 50 (66%) adolescents: 21 boys and 29 girls, were included in group 2.
There were no significant differences in age, sex, height, BMI, and systolic and diastolic blood pressure between patients from both studied groups (Table 1).

The mean cIMT value (mean, SD) for all patients from the study group was 0.41±0.012 mm: for girls 0.39 ±0.014 mm and for boys 0.44 ±0.016 mm. There were 14 patients in the age of 14 years (18%), 18 in the age of 15 years (24%), 21 in the age of 16 years (28%), and 23 in the age of 17 years (30%). The mean cIMT value and SD for 14-year-olds patients was 0.37 ±0.015 mm; for 15-year-old patients it was 0.39 ±0.008 mm; for 16-year-old patients it was 0.42 ±0.012 mm, and for 17-year-old patients it was 0.43 ±0.015 mm.

In 14- and 15-year-old patients, there were no statistically significant differences in cIMT values between girls and boys in group 1 as well as group 2. In 16-year-old adolescents, the cIMT value was significantly higher in boys than in girls, both in group 1 (p = 0.036) and in group 2 (p = 0.022). In 17-year-old patients, cIMT values were significantly higher in boys than in girls only in group 1 (p = 0.011) (Table 2).

The levels of analysed cytokines and sICAM-1 were established and compared between both groups (Table 3). Significantly higher concentrations of IL-6, TNF-α, and sICAM-1 were found in patients in group 1 (respectively, p < 0.001, p < 0.001, and p < 0.001), whereas the IL-10 level was significantly higher in the control group (p < 0.005). In whole studied group of patients, the correlation between cIMT values and the concentration of cytokines were established for: IL-6 $r = 0.7398$, TNF-α $r = 0.7623$, sICAM-1 $r = 0.7825$, and for IL-10 $r = -0.5869$ (Fig. 2). No correlation was found between cIMT and: severity of TTH, BMI, weight, or blood pressure.

**DISCUSSION**

In the whole group of 76 patients with TTH girls slightly predominated, but without significant statistical differences. The number of adolescents who were diagnosed because of TTH increased with age, from 14 persons at the age of 14 years, to 23 persons at the age of 17 years. According to a study conducted on a larger population, sex differences were not observed before puberty (only a slight male predominance). Conversely, later, after puberty, a meaningful increase in the frequency of TTH in girls is noticed (with ratio 2.5 : 1). The tendency for

### TABLE 1. General characteristics of the study population (n = 76)

| Characteristic | Group 1 (cIMT ≥ 90th percentile) | Group 2 (cIMT < 90th percentile) | p* |
|---------------|---------------------------------|---------------------------------|----|
| No. of subjects | 26 | 50 | |
| M | 15 | 21 | 0.578 |
| F | 11 | 29 | 0.546 |
| Age, years M | 15.83 ±1.14 | 16.34 ±1.66 | 0.534 |
| F | 15.25 ±2.75 | 16.14 ±1.20 | 0.485 |
| Height, cm M | 162.4 ±11.5 | 163.5 ±6.5 | 0.562 |
| F | 162.8 ±7.3 | 165.5 ±6.8 | 0.463 |
| BMI, kg/m² M | 21.5 ±2.0 | 21.4 ±2.5 | 0.676 |
| F | 20.5 ±3.1 | 21.2 ±3.2 | 0.753 |
| Systolic BP, mm Hg M | 118.1 ±7.2 | 117.1 ±7.1 | 0.689 |
| F | 113.1 ±8.3 | 106.5 ±6.8 | 0.724 |
| Diastolic BP, mm Hg M | 59.5 ±4.5 | 59.8 ±7.3 | 0.426 |
| F | 61.2 ±6.2 | 65.2 ±2.4 | 0.527 |

* - analysis of variance with one parameter, p < 0.05

### TABLE 2. Carotid intima-media thickness values in the examined groups depending on the age and sex of patients

| Age* (years) | Sex | n = 26 | cIMT (mean, SD) | $p^\ddagger$ | n = 50 | cIMT (mean, SD) | $p^\ddagger$ |
|--------------|-----|--------|----------------|-------------|--------|----------------|-------------|
| 14 | M | 2 | 0.48 ±0.013 | NC | 4 | 0.34 ±0.012 | 0.524 |
| | F | 1 | 0.46 | | 7 | 0.34 ±0.008 | |
| 15 | M | 3 | 0.49 ±0.006 | 0.528 | 7 | 0.38 ±0.021 | 0.512 |
| | F | 2 | 0.46 ±0.013 | | 6 | 0.34 ±0.003 | |
| 16 | M | 5 | 0.53 ±0.014 | 0.036 | 5 | 0.40 ±0.001 | 0.022 |
| | F | 3 | 0.46 ±0.013 | | 8 | 0.36 ±0.001 | |
| 17 | M | 5 | 0.53 ±0.001 | 0.011 | 5 | 0.40 ±0.001 | 0.501 |
| | F | 5 | 0.48 ±0.013 | | 8 | 0.38 ±0.001 | |

* - age: 14 (≥ 14 < 15), 15 (≥ 15 < 16), 16 (≥ 16 < 17), 17 (≥ 17 < 18), cIMT – carotid intima-media thickness, F – female, M – men, $p^\ddagger$ – cut-off points M = 0.42 mm, F = 0.41 mm, analysis of variance with one parameter, p < 0.05, NC – has not been calculated
A higher prevalence of TTH in older teenagers described in our study is consistent with the observations of various authors [2,3].

The cIMT measurements of common carotid arteries have found a well-established place in estimating the risk of premature atherosclerosis in both adults and children [11, 16, 17]. These values increase with the patient’s age (approximately 0.01-0.02 mm/year) and are slightly higher in boys than in girls of the same age [18–20]. In our study, the mean cIMT value increased from 0.37 mm in 14-year-old to 0.43 mm in 17-year-old patients with TTH. During the observation period the mean cIMT val-

### TABLE 3. Serum cytokines levels in patients with carotid intima-media thickness ≥ 90th percentile and < 90th percentile

| Cytokines     | Group 1 (cIMT ≥ 90th percentile) | Group 2 (cIMT < 90th percentile) | p*   |
|---------------|---------------------------------|---------------------------------|------|
|               | n = 26                          | n = 50                          |      |
| IL-6 (pg/ml)  | 14.1 ±7.5 (6.4–18.5, 5.1)       | 9.8 ±4.3 (0.0–12.2, 2.3)        | < 0.001 |
| (mean, SD)    | (range, median)                 | (range, median)                 |      |
| TNF-α (pg/ml) | 29.5 ±8.4 (2.8–4.5, 14.8)       | 10.2 ±8.4 (0.0–28.1, 15.3)      | < 0.001 |
| (mean, SD)    | (range, median)                 | (range, median)                 |      |
| IL-10 (pg/ml) | 8.2 ±2.8 (0.0–12.2, 5.0)        | 10.3 ±4.3 (0.0–12.1, 6.8)       | < 0.005 |
| (mean, SD)    | (range, median)                 | (range, median)                 |      |
| sICAM-1 (ng/ml)| 363.2 ±53.4 (130.2–428.3, 130.0) | 205.0 ±44.3 (0.0–301.0, 84.5) | < 0.001 |
| (mean, SD)    | (range, median)                 | (range, median)                 |      |

cIMT – carotid intima-media thickness, IL-6 – interleukin 6, TNF-α – tumour necrosis factor α, IL-10 – interleukin 10, sICAM-1 – soluble intracellular adhesion molecule, * analysis of variance with one parameter, p < 0.05

![Figure 2](image-url)
ue in boys increased by 0.09 mm (from 0.38 to 0.47 mm) and in girls by 0.05 mm (from 0.36 to 0.41 mm).

In a multicentre study of a healthy paediatric population, Doyon et al. confirmed the occurrence of a difference in cIMT values according to the sex of children aged 15-18 years. The cIMT values of the 50th percentile in a six-year-old was 0.37 mm, regardless of the child’s sex, but increased to 0.39 mm for girls and 0.41 mm for boys aged 18 years [10]. In the current study, the mean cIMT value in all studied adolescents was higher in boys than in girls, and it rose by 0.44 mm and 0.39 mm, respectively. The differences according to sex were statistically significant in 16- and 17-year-old patients in group 1 and in 16-year-old patients in group 2.

Statistically significantly higher amounts of IL-6, TNF-α, and sICAM-1 were observed in patients from group 1 compared to the control group, while the inverse relationship was obtained for IL-10. Levels of the concentration of the cytokines were correlated to cIMT values in the whole group of tested children. Moreover, a positive correlation between cIMT value and the levels of IL-6, TNF-α, and sICAM-1 and a negative correlation between cIMT and the levels of IL-10 were found. These results could indicate that in examined patients with TTH the reason for the higher cIMT value was the inflammatory process in the vascular wall, which showed that proinflammatory cytokines such as IL-6, TNF-α, and sICAM-1 were involved.

Besir et al., in a study of young adult migraine patients, showed similar results: a relationship between atherosclerosis and inflammation. In their study the patients had higher cIMT values and sICAM-1 levels than the healthy controls [21]. Some authors present endothelial dysfunction as the reason for higher values of cIMT, migraine headache, and syncope in children and young adults [22, 23].

CONCLUSIONS

TTH in adolescents is present in both sexes, with a slightly higher prevalence in girls. The cIMT was higher in boys than in girls. Moreover, the presented results indicate that the inflammatory process in the vascular wall could lead to the higher cIMT values and/or to TTH in adolescents.

DISCLOSURE

The authors declare no conflict of interest.

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