SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

THE ADOLESCENT WHITE-COAT HYPERTENSION AND THE CORRELATION WITH CEREBROVASCULAR TARGET-ORGAN DAMAGE

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The Examination takes place at Medical and Health Science Centre
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1. INTRODUCTION

1.1 Adolescent hypertension

The association between hypertension in puberty and adulthood is well known: suffering from hypertension in puberty makes susceptible to become diseased later as well. According to the American guidelines the estimated prevalence of the disease is 1-3 % whilst in Hungary it is 2.53 % based on the „Debrecen Hypertension Study".

The demonstrable connection between adolescent hypertension, atherosclerosis, left ventricular hypertrophy and the intimal thickness of the carotid artery makes the adolescent hypertension exceptionally remarkable. Follow-up studies confirmed the relationship between the severity of the disease and cardiovascular mortality.

1.2 White-coat hypertension

White-coat hypertension means having abnormally high blood pressure when taken in a clinic, while it is in the normal range when checked at home. The phenomena which is called white coat effect is caused by an increased sympathetic activity during stress situation.

Performing the measurement in line with the recommendations the high blood pressure results in the estimated 20 percent of the cases is influenced by the white coat effect. Although the phenomena was thought to be a false positive result, it turned out in the last decade that it makes one susceptible to have medical problems in the future.

1.3 Adolescent white-coat hypertension

Based on the different criteria the prevalence of white-coat hypertension is 1-41 percent in puberty. Several studies demonstrated the connection between white-coat hypertension and endothel dysfunction and positive correlation was found with left ventricular mass and the intimal thickness of the carotid artery. The cardiovascular risk of an adolescent having white-coat hypertension is lower than the risk of a patient with hypertension but higher than the risk of a healthy one.

2. OBJECTIVES

The aim of this study to perform a more detailed research of the adolescent white-coat hypertension comparing data from patients with normal blood pressure and patients who have raised blood pressure proven by ABPM monitoring. The following parameters were examined:

-anthropometric values

-random and ABPM blood pressure results

-laboratory data (serum glucose, lipids, nitric oxide, homocysteine)

-cerebral end organ damage (intimal thickness of carotid artery, cerebrovascular reactivity)

-relationship of homocysteine and intimal thickness

The aim was to clarify if the white-coat hypertension is a harmless phenomena or it can cause subclinical end organ damage like real hypertension.

3. PATIENTS AND METHODOLOGY

3.1 The “Debrecen Hypertension Study”

Our working group performed a population-based screening test in the 15-18 age group – under the name “Debrecen Hypertension Study”.

From the 26 high schools of Debrecen 10,359 adolescents (5,262 boys and 5,097 girls, mean age: 16.6 ± 1.0 years) were involved in the epidemiological study. We assigned the percentiles of the systolic and diastolic blood pressure in the age, sex and height divided subgroups.

If the systolic and / or diastolic blood pressure of the teenager exceeded the 90 percentile value of the sub-group, then in two different dates 3-3 additional blood pressure measurements were performed. Based on 3x3 times casual blood pressure measurements, we diagnosed adolescent hypertension in 216 patients: they mean blood pressure was higher than the 95th percentile for the age, gender and height specific subgroups.

3.2 The examined individuals

Among 216 hypertensive adolescents, we had the opportunity for further evaluation in 133 cases. In 8 cases we found secondary reason for hypertension. In 5 cases the data of the ambulatory blood pressure monitoring were technically impossible to evaluate.

In the present study, we performed the further examination of 120 individuals with adolescent hypertension (63 boys and 57 girls). Among them we tried to confirm the diagnosis of hypertension. We compared the manifest and white-coat hypertensives with a normotensive (59 adolescents: 29 girls and 30 boys) control group.

3.3 24-hour blood pressure monitoring

Ambulatory blood pressure monitoring was performed by ABPM-04 (Meditech Ltd. Budapest, Hungary) oscillometry device, validated earlier according to the protocol of the British Hypertension Society and the Association for the Advancement of Medical Instrumentation. In cases where systolic and/or diastolic daytime and / or nighttime average of the ABPM-measured blood pressure reading exceeded the 95th percentile value of the sex- and height-matched control values, the patients were considered to have sustained hypertension. If neither systolic nor diastolic average BP exceeded the 95th percentile BP of the subgroup, the patients were classified as having white-coat hypertension.

3.4 Laboratory tests

The determination of the routine laboratory parameters, nitric oxide and homocysteine happened with validated and standardized methods. The measurement of the active nitric oxide (NO) was carried out by determining the nitric oxide ratio (NO = NO2 + NO3). We used the modified method of Green.

Serum homocysteine was measured using colorimetric enzyme assays.

3.5 Determining the intima-media thickness of the common carotid artery

The common carotid artery intima-media thickness measurement was performed using a 7.5-MHz linear array probe (Hewlett-Packard Sonos 2000, USA).

3-3 measurements were made in both common carotid arteries at end-diastole. We calculated the average lumen-intima and media-adventitia distance.

3.6 Transcranial Doppler measurements

The middle cerebral artery of both sides was insonated by a fixed probe through the transtemporal window, using Rimed Digilite Transcranial Doppler sonograph

(Rimed Ltd, Israel). During the Breath-holding tests, repeated measurements were made after 30 s breath hold. We investigated the mean blood flow velocity changes.

3.7 Calculation of cerebrovascular reactivity

Effect of the provocation test (the breath-holding) the blood flow velocity of the middle cerebral artery changes. Cerebrovascular reactivity was defined as the percent change of the mean blood flow velocity.

CVR = (MCAVtest - MCAV rest) / MCAV rest x 100

Where mean blood flow velocity (MCAV) rest is resting mean blood flow velocity in the middle cerebral artery, and MCAV test is middle cerebral artery mean blood flow velocity as measured after breath holding.

3.8 The methods of statistical assessment

We used the Statistica for Windows (Statsoft, Tulsa, USA) program for data analysis. We defined the average values and the standard deviations for every parameter. Then by using normality test (Shapiro-Wilk test supplemented with visual examination) we identified if a parameter follows normal- (Gauss) or non-normal distribution. Normally distributed parameters were compared using *t* -test, and those with non-normal distribution with the appropriate Kruskal – Wallis tests.

By the comparison of gender differences Chi2 tests were used. Spearman correlation was applied for the assessment of the relationship between homocysteine and intima-media thickness.

Comparison of the parameters measured by transcranial Doppler was performed using one-way ANOVA test. Bonferroni correction was used for multiple comparisons. A $P < 0.05$ was accepted as a level of significant difference.

4. RESULTS

4.1. Grouping of young hypertensives

We separated the manifest hypertensives from white-coat hypertensives by using 24-hour blood pressure monitoring. ABPM confirmed 61% of the hypertension diagnosed by repeated manual blood pressure measurement, while 39% were considered white-coat hypertensives. In the two examined groups, we registered significant difference between the blood pressure values measured by ABPM. Systolic blood pressure of the manifest hypertensive group was 5-6 mm Hg higher than in the white coat hypertensive group. In true hypertension the average 24-hour blood pressure was 130.8 ± 9.5 mmHg, while in white-coat hypertension the average systolic blood pressure was 125.2 ± 9.3 mmHg ($p < 0.01$). Similar differences were observed in the daytime (137.2 ± 10.0 mmHg vs. 131.3 ± 9.1 mmHg, $P < 0.001$) and nighttime average blood pressure (118.7 ± 11.1 mmHg vs. 112.3 ± 9.8 mmHg, $p < 0.01$) also.

The 24-hour, daytime and night-time average diastolic blood pressure values and heart rate did not differ in the two groups. Adolescent hypertension confirmed by ABPM was more common among boys (44 boys, 29 girls), while white-coat hypertension was more common in girls (28 girls, 19 boys).

4.2 Anthropometric characteristics

Henceforth we compared the results of the 47 white coat-hypertensives and 73 manifest hypertensive adolescents to normotensive controls (30 boys, 29 girls). The three groups had similar mean age (15.8 ± 0.6 years vs. 16.3 ± 1.1 years vs. 16.5 ± 1.0 years; p = NS). The manifest hypertensives were heavier and taller than the white coat hypertensives and normotensives. We registered significant difference in the case of body mass index also. The BMI was the highest in the manifest hypertension

(23.4 ± 4.2 kg/m2), which is significantly higher than in the white-coat hypertension (21.8 ± 3.25 kg/m2) and the control group BMI (20.2 ± 2.7 kg/m2; $p<0.001$). The difference between BMI also was statistically significant in the latter two groups ($p<0.001$).

4.3 Repeated manual blood pressure measurement blood glucose and blood lipid values

The repeated office systolic- and diastolic blood pressures values in both hypertensive groups were significantly higher than in the control group. During the repeated manual blood pressure measurements were observed 6.5 mmHg systolic blood pressure difference (138.3 ± 11.4 mm Hg vs. 144.8 ± 11.1 mm Hg; $p=0.002$) between the two hypertensive group, the difference was significant. The average diastolic blood pressure was the same in the manifest and the white-coat hypertension. Fasting glucose levels and lipid parameters were similar in the three groups.

4.4 Nitric oxide levels

Compared to normotensives (38.8 ± 7.6 mmol / l), both white-coat hypertensive (30.6 ± 11.0 mmol / l) and sustained (28.7 ± 22. 4 mmol / l) hypertensive adolescents had significantly lower nitric oxide levels ($p<0.001$). There was no difference in the nitric oxide levels between the hypertensive groups.

4.5 Homocysteine levels

We observed significantly ($p<0.05$) higher homocysteine levels in adolescent white-coat hypertension (11.6 ± 6.8 mmol / l) and adolescent sustained hypertension (12.1 ± 7.0 mmol / l) compared to normotension (9.8 ± 3.1 mmol / l). Homocysteine levels did not differ in the two hypertensive group.

4.6 Intima-media thickness of the common carotid artery

IMT was higher in both white-coat (0.056 ± 0.001 cm) and sustained hypertensive adolescents (means 0.054 ± 0.001 cm) compared with controls (0.048 ± 0.001 cm). Not significant difference was observed in the two hypertensive group.

4.7 Comparison of IMT and serum homocysteine

In the two hypertensive groups between serum homocysteine levels and carotid artery intima-media thickness a significant positive correlation was observed ($r = 0.43$; $p < 0.01$), while in normotensives we found a loose tendency-like, not significant correlation ($r = 0.2$, $p = 0.06$).

4.8 Transcranial Doppler results during rest and breathing-holding test

We determined the blood flow velocity in the middle cerebral artery using transcranial Doppler examination. Resting cerebral blood flow velocity was significantly ($p=0.05$) higher in the sustained hypertensive group (77.3 ± 4.4 cm / s, $p<0.001$) compared to white coat hypertensives (70.2 ± 5.3 cm / s) and controls (64.4 ± 4.8 cm / s). After thirty seconds breath-hold, blood flow velocity increased in all groups. During this test we registered the highest blood flow velocity in sustained hypertensives (84.6 ± 5.4 cm / s), which significantly exceeded the blood flow velocity measured in the white-coat hypertensive (73.9 ± 6.9 cm / s; $p<0.001$) and the control group (72.3 ± 6.6 cm / s, $p<0.001$). After the breath-holding test white-coat hypertensive and normotensive group cerebral artery blood flow velocity did not differed.

4.9 Cerebrovascular reactivity

During breathing-holding test the cerebral artery blood flow velocity increased in all studied group. The cerebrovascular reactivity is the percent change in middle cerebral artery mean blood flow velocity after 30 s of breath holding, which express

the adaptability of the blood vessels. CVR was 12.1 ± 2.2% among healthy adolescents. The percent increase in middle cerebral artery mean blood flow velocity after 30 s of breath holding was lower both in WCH and SH (5.3 ± 3.1% and 9.5 ± 2.6%) groups, indicating lower vasodilatory reactivity compared to healthy adolescents. In both cases the difference was significant ($p<0.001$). The CVR of the white-coat hypertensive group was the lowest.

5. DISCUSSION

We investigated whether there is noticeable difference between adolescent white coat hypertension and normotension. We examined risk factors, co-morbidities and target-organ damages.

5.1 Anthropometric characteristics and laboratory tests

Body mass index of white coat hypertensives exceeded that of normotensives. The highest BMI was observed in sustained hypertension. Fasting glucose levels and lipid parameters were similar in the three groups.

5.2 24-hour blood pressure monitoring

In adolescent hypertensives - diagnosed by repeated casual blood pressure measurements - we performed 24-hour blood pressure monitoring confirming the diagnosis. Hypertension was clearly confirmed in 61% of cases, while 39% were considered as white coat hypertensives. Our results were similar to various international studies, where the prevalence of adolescent white coat hypertension was between 1-41%. Systolic blood pressure of the manifest hypertensive group exceeded the values measured in the white coat hypertensive group. We did not register any significant difference in diastolic blood pressure.

5.3 The importance of nitric oxide

We found significantly lower nitric oxide levels both white coat and sustained hypertensive adolescents groups comparing to normotensive controls. There was no difference in nitric oxide level between the two hypertensive groups. Nitric oxide is an endothelial vasodilator substance, and is the key element of developing vascular tone. In the background of the lower level of nitric oxide may be impaired endothelial function.

Our study group previously demonstrated negative relationship between nitric oxide levels and carotid intima-media thickness. Nitric oxide inhibits the endothelin-1 production as well. The NOx/endothelin-1 imbalance and the increased vasoconstriction accelerates the atherosclerotic process. Some studies observed different nitric oxide and endothelin-1 levels in white coat hypertension, but these were less pronounced difference as registered in sustained hypertension. We confirmed decreased NO levels in white coat hypertension as well. The nitric oxide levels were similar to the figures recorded in the sustained hypertensive group.

5.4 The importance of homocysteine

In our study, we found that serum homocysteine level is elevated not only in sustained hypertensive adolescents, but also in case of white coat hypertension. The correlation between homocysteine and atherosclerosis has already proved. Our study confirms the relationship between homocysteine and hypertension. Furthermore, we were also able to confirm that not only the sustained, but also the white coat hypertensives have higher homocysteine levels. Previously, higher serum levels of homocysteine were known only in adults. Homocysteine levels did not differ in the two hypertensive group. This suggests that elevated homocysteine in adolescent hypertension either independently may increase the cardiovascular risk.

5.5 Intima-media thickness of the common carotid artery

Intima-media thickness of the carotid arteries has been considered by some authors as a marker of subclinical atherosclerosis, which predicts the occurrence of cardiovascular events. Only a few studies have examined the intima-media thickness in adolescent hypertension, where a greater thickness was observed. In our study, intima-media thickness was higher in both white coat and sustained hypertensive adolescents compared to controls. Not significant difference was observed in the two hypertensive group.

5.6 Comparison of serum homocysteine and intima-media thickness

Authors have found that in adulthood homocysteine level is an independent risk cardiovascular risk factor of carotid intima-media thickness, while other studies could not confirm this perception. Litwin and colleagues examined adolescents with primary hypertension compared to healthy controls. They found positive correlation between homocysteine and carotid IMT, but after the regression analysis the prognostic effect of homocysteine was not significant. However, they observed predictive effect in the case of femoral artery. We proved positive correlation between serum homocysteine levels and carotid artery intima-media thickness in the two hypertensive groups.

5.7 Blood flow velocity in the middle cerebral artery

We studied blood flow velocity in the middle cerebral artery by transcranial Doppler device. Resting cerebral blood flow velocity in the middle cerebral artery was significantly higher in the sustained hypertensive group compared to white coat hypertensives and controls. For the normal cerebrovascular function, the constant blood flow is necessary. The blood flow is mainly controlled by smooth muscle constriction and dilation. The middle cerebral artery blood flow velocity depends from the capaciousness of the artery and from the diameter of peripheral blood vessels. In

hypertension, because of the higher systemic blood pressure, the blood vessels react with vasoconstriction.

The increased blood flow - observed in sustained hypertensive adolescents - is because the vasoconstriction of the larger blood vessels.

5.8 Cerebrovascular reactivity

The vasodilatory effect of carbon dioxide expressed in brain blood vessels is a well-known phenomenon. Carbon dioxide-induced effect occurs through chemoregulation. The produced nitric oxide effects vasodilatation in the vascular smooth muscles. During breath-holding test we have registered reduced cerebrovascular reactivity in both hypertensive groups compared to healthy subjects. The vasodilatation of the white coat hypertensive group was similar to sustained hypertensive group.

Among adult hypertensives the cerebrovascular reactivity is lower than in normotension. In borderline hypertension studies found less powerful decrease in vasodilatation. Sharma and colleagues examined children with hypertension and demonstrated decreased cerebrovascular reactivity.

In the background of the carbon dioxide-mediated vasodilatation, the rate of NO produced by endothelial cells and the NO produced by neuronal cells is not fully clarified. Recent results suggest the importance of endothelial NO is pronounced.

Primarily the endothelial dysfunction may be in the background of reduced cerebrovascular reactivity in white-coat hypertensive group.

5.9 The importance of adolescent white coat hypertension

The harmful effect of elevated blood pressure is evincible in adolescent white coat hypertension already: the synthesis of nitric oxide reduced, the endothelin-1 level is increased. Partly because of this, the endothelial-influenced cerebrovascular

reactivity is worsening. The increase in homocysteine level accelerates the extent of atherosclerosis. In addition to functional impairment, structural damage is also shown by the increase in carotid intima-media thickness.

Adolescent white coat hypertension is associated with increased cardiovascular risk status. Patients suffering from white coat hypertension requires further follow-up.

6. SUMMARY

Adolescent hypertension diagnosed by repeated casual blood pressure measurements was confirmed by ABPM in 63% of cases. We compared the data of 47 adolescent white coat hypertesives to 73 sustained hypertensives (proven by ABPM) and 59 normotensive individuals.

Body mass index of white coat hypertensives exceeded that of normotensives. The highest BMI was observed in sustained hypertension. Based on ABPM data systolic blood pressure of sustained hypertensives exceeded that of white coat hypertensives.

The nitric-oxide concentration was lower in both hypertensive groups compared to normotensives. We observed a higher serum homocysteine level in both hypertensives groups than in normotensives. There wasn’t any difference between nitric-oxide and homocysteine in white coat and sustained hypertensives.

Intima-media thickness of white coat hypertensives exceeded that of normotensives and was similar as in sustained hypertension. We found a positive correlation between homocysteine level and carotid IMT.

Resting cerebral blood flow velocity in the middle cerebral artery was significantly higher in the sustained hypertensive group compared to white coat hypertensives and controls. Due to breath holding test the cerebral blood flow velocity increased in all groups. The cerebrovascular reactivity of white coat hypertensives was also damaged.

Adolescent white coat hypertension is not a harmless condition several parameters have a similar aberrations like in sustained hypertension.

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1. **Lengyel, S.**, Katona, É., Zatik, J., Molnár, C., Paragh, G., Fülesdi, B., Páll, D.: The impact of serum homocysteine on intima-media thickness in normotensive, white-coat and sustained hypertensive adolescents.
   Blood Press. 21 (1), 39-44, 2012.
   DOI: http://dx.doi.org/10.3109/08037051.2011.575577
   IF:1.256 (2010)

2. **Lengyel S.**, Szántó I., Katona É., Paragh G., Fülesdi B., Páll D.: A fehérköpeny-hypertonia jelentősége serdülőkorban.
   Hypert. Nephr. 15 (6), 255-260, 2011.

3. Páll, D., **Lengyel, S.**, Komonyi, É., Molnár, C., Paragh, G., Fülesdi, B., Katona, É.: Impaired cerebral vasoreactivity in white coat hypertensive adolescents.
   Eur. J. Neurol. 18 (4), 584-589, 2011.
   DOI: http://dx.doi.org/10.1111/j.1468-1331.2010.03209.x
   IF:3.765 (2010)

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4. Katona, É., Zrínyi, M., **Lengyel, S.**, Komonyi, É., Paragh, G., Zatik, J., Nagy, G., Fülesdi, B., Páll, D.: The prevalence of adolescent hypertension in Hungary: The Debrecen hypertension study.
Blood Press. 20 (3), 134-139, 2011.
DOI: http://dx.doi.org/10.3109/08037051.2010.538987
IF:1.256 (2010)

5. Katona, É., Zrínyi, M., Komonyi, É., **Lengyel, S.**, Paragh, G., Zatik, J., Fülesdi, B., Páll, D.: Factors influencing adolescent blood pressure: The Debrecen Hypertension Study.
Kidney Blood Press. Res. 34 (3), 188-195, 2011.
DOI: http://dx.doi.org/10.1159/000326115
IF:1.5 (2010)

6. Páll D., Komonyi É., **Lengyel S.**, Paragh G., Katona É.: Az antihipertenzív szerek hatása a centrális vérnyomásra.
Hypert. Nephr. 15 (1), 273-279, 2011.

7. Páll, D., Juhász, M., **Lengyel, S.**, Molnár, C., Paragh, G., Fülesdi, B., Katona, É.: Assessment of target-organ damage in adolescent white-coat and sustained hypertensives.
J. Hypertens. 28 (10), 2139-2144, 2010.
DOI: http://dx.doi.org/10.1097/HJH.0b013e32833cd2da
IF:3.98

8. Páll D., Juhász M., **Lengyel S.**, Fülesdi B., Paragh G., Katona É.: Új ismeretek a serdülőkori hypertoniáról.
Hypert. Nephr. 14 (1), 17-21, 2010.

9. Komonyi É., **Lengyel S.**, Juhász M., Katona É., Zatik J., Paragh G., Fülesdi B., Páll D.: Egészséges fiatalok augmentációs indexének napszaki változása.
Metabolizmus 7 (3), 147-152, 2009.

10. Komonyi É., **Lengyel S.**, Juhász M., Katona É., Zatik J., Paragh G., Fülesdi B., Páll D.: Egészséges fiatalok perifériás és centrális vérnyomása.
Hypert. Nephr. 13 (3), 127-133, 2009.

11. Páll D., Juhász M., Katona É., **Lengyel S.**, Komonyi É., Fülesdi B., Paragh G.: Az ambuláns vérnyomás-monitorozás jelentősége serdülőkorban.
Orv. Hetilap. 150 (49), 2211-2217, 2009.
DOI: http://dx.doi.org/10.1556/OH.2009.28732

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