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Pediatric hypertension – definition, normative values, epidemiology, screening and treatment

Nadciśnienie tętnicze u dzieci – zarys problemu, wartości referencyjne, wskazania do badań przesiewowych i zasady leczenia

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Keywords
children, arterial hypertension, normative values, prevalence, screening

Słowa kluczowe
dzieci, nadciśnienie tętnicze, wartości referencyjne, występowanie, badania przesiewowe

S u m m a r y

Definition of arterial hypertension in children and adolescents is well known, but there is a lot of controversies regarding use of proper referential values, indications for screening and treatment. In the article we shortly describe history of research on arterial hypertension in children and development of normative blood pressure values. We also discuss the problem of use of referential blood pressure values in childhood, and the prevalence and incidence of arterial hypertension in children. Intermediate phenotype of primary hypertension and the role of life-style in prevention and treatment of primary hypertension in children and adolescents has been discussed. Although there is increasing amount of data indicating that cardiovascular disease starts already in childhood, the population screening of blood pressure in children has been questioned recently. However, it seems that the problem is not "why to measure blood pressure in children" but rather "when to start to measure blood pressure in children".

S t r e s z c z e n i e

Pomimo jednoznacznej pediatrycznej definicji nadciśnienia tętniczego, istnieje wiele kontrowersji dotyczących stosowania właściwych norm ciśnienia tętniczego, wskazań do prowadzenia badan przesiewowych i leczenia nadciśnienia u dzieci i młodzieży. W artykule przedstawiono historię badań nad nadciśnieniem u dzieci, opracowania norm ciśnienia tętniczego oraz zasady leczenia nadciśnienia tętniczego pierwotnego u dzieci i młodzieży. Przedstawiono również kontrowersje związane z zasadnością prowadzenia badań przesiewowych w kierunku nadciśnienia tętniczego w wieku rozwojowym. Zbyt wczesne wprowadzenie badań przesiewowych prowadzi do błędnego rozpoznania nadciśnienia tętniczego, co jest związane z dużą częstością nadciśnienia białego fartucha i efektu białego fartucha. Z kolei zaniechanie badań przesiewowych może prowadzić do zbyt późnego rozpoznania choroby, co ma szczególne znaczenie w przypadku wtórnych postaci nadciśnienia tętniczego. Decyzje o wprowadzeniu powszechnych badań przesiewowych w kierunku nadciśnienia tętniczego w populacji dziecięcej powinny opierać się zarówno na epidemiologii choroby, jej etiologii, jak i znaczeniu efektu białego fartucha w danej grupie wiekowej. Również, zakres działań diagnostycznych w przypadku już rozpoznanego nadciśnienia tętniczego zależy zarówno od wieku chorego, jak i od ciężkości nadciśnienia. Z kolei leczenie nadciśnienia tętniczego musi uwzględniać jego patogenezę, a w przypadku nadciśnienia tętniczego pierwotnego jego fenotyp pośredni.

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For decades, arterial hypertension was regarded as a typical disease of adulthood, strictly related with aging and associated with clinically evident other diseases such as diabetes, ischemic heart disease and/or chronic kidney disease. However, the first measurements of blood pressure in hospitalized children started already 100 years ago when Cook and Briggs from John Hopkins Hospital reported that hospitalized children aged up to 2 years had systolic blood pressure in range from 75 to 90 mmHg and preschool children had systolic blood pressure in the range from 90-110 mmHg. In next decades when strict relations between blood pressure values and cardiovascular risk was documented, blood pressure measurements became routine clinical practice in adults. It is important to note that this analysis was ordered by insurance company Kaiser Permanente and was published in 1925 (1). In Poland, Aleksander Januszkiewicz from Vilnius University stated already in 1922 that "sphygmomanometric measurement of blood pressure" should be routine clinical practice. He also published results of first population study of blood pressure measurements in young adults and adolescents in Poland made in 1920s in Vilnius by Zajączkowski and Łobza (2, 3). They measured blood pressure in 2700 army recruits and 303 male, "non-army" adolescents in age 16-20 years. Blood pressure was measured several times using Korotkov sphygmomanometer, in lying position, at least 1-2 hours after physical exercise. According to Januszkiewicz report, normal systolic blood pressure was in the range of 101-130 mmHg. Systolic blood pressure above 140 mmHg was noted in 10.5% of recruits and in 6.6% of non-army adolescents.

In the same time i.e. in years 1928-1932, normative values of blood pressure in adolescents and adults were published in United States. It was found that systolic blood pressure values rise with age and until age of 30 years are higher in males than in females. In 1924 Stocks published normative values of blood pressure including children below 10 years of age. He reported blood pressure values in age strata from 5 to 39 years in two-year intervals (4). Interestingly, these values are similar to normative values used nowadays. Stocks made few interesting observations and noted that systolic blood pressure rises from adolescence until 39th year of age and that diastolic blood pressure is relatively stable. Thus, it leads to increase of pulse pressure. In Poland, the first pediatric report on blood pressure is from 1925 when Matylda Biehler in her handbook "Principles of diagnosis of pediatric diseases" cited results of the study by dr Nobécourt, who measured blood pressure in children with Riva-Rocci method (5). In the same handbook she also noted that in children in age below 4 years "blood pressure is difficult to estimate, is elevated during crying and lowered during sleep". Biehler proposed also an algorithm to calculate blood pressure in relations to age: blood pressure = 80 + (2 x X); where X is the age in years.

The next step in understanding character of blood pressure distribution in pediatric population is from reports published in 1952 by Hamilton et al. They published referential values of blood pressure based on measurements done in patients, including children from 10 years of age, who were referred to departments of dermatology, orthopedics and because of venous atheroembolic disease (6). Although blood pressure measured in hospitalized patients cannot be regarded as source data for construction of normative referential values, this study gave few important results. First, they found that in every age strata, including children, blood pressure values have normal distribution and there is no strictly defined threshold dividing normal and abnormal blood pressure values. Second, it indicates that those subjects who have highest blood pressure will suffer in future from hypertensive disease. However, those who have normal blood pressure will have normal blood pressure in future or risk of increase of blood pressure will be lower. Third, Hamilton et al. made in 180 subjects second blood pressure measurements after 3 weeks to 4 months. They found that mean blood pressure values were significantly lower than those obtained during first measurement and the difference was higher the higher was first blood pressure measurement. These historical reports which evidence normal distribution of blood pressure in population gave arguments for advocates of polygenic etiology of arterial hypertension in discussion with advocates of monogenic origin of arterial hypertension.

In the next decade first reports of normative blood pressure values expressed as percentile charts were published. In 1966 Londe published normative values of blood pressure based on measurements done in 1473 healthy children and adolescents in age range 4-15 years and presented values of 80th and 90th percentile for systolic and diastolic blood pressure (7). In the same time, in Poland Mira Pyżuk and Napoleon Wolański published percentile charts of systolic and diastolic blood pressure for children and adolescents in age from 3 to 18 years (8, 9). However, the percentile charts were combined both for girls and boys because, as authors claimed "the differences between blood pressure values in boys and girls were statistically negligible".

The important step in description of the pediatric hypertension was done in 1970s when the first report of the US Task Force for Blood Pressure in Children and Adolescents was published. In this publication known as "The First Report", pediatric blood pressure normative values based on data obtained in population studies were published and definition of arterial hypertension in childhood based on percentile distribution and cut-off of 95th percentile was proposed. Because of white coat effect, it was proposed to define arterial hypertension when elevated blood pressure was found on three independent measurements. Since then, the next Task Force Reports were published in 10 years intervals. The last, the 4th Task Report was published in 2004 (10). Task Force Reports include both normative blood pressure values and guidelines for the diagnosis and management of blood pressure in children and adolescents. The normative values of blood pressure presented in the Task Force Reports are based on results obtained in NHANES studies. The next, 5th Task Report is prepared to be published in 2016.

Normative values of blood pressure based on sphygmomanometric auscultatory measurements published in the Task Force Reports became the most often used referential data. In 2009 European Society of Hypertension published pediatric guidelines of diagnosis and management of hypertension in children and adolescents and now new, updated European guidelines are prepared to be published in 2016 (11).

BLOOD PRESSURE MEASUREMENTS IN CHILDREN AND ADOLESCENTS: AUSCULTATORY OR AUTOMATIC – THE ROLE OF NORMATIVE, REFERENTIAL VALUES

Although the blood pressure percentile charts published in the Task Force Reports have been accepted as normative referential values for auscultatory, sphygmomanometric blood pressure measurement, the increasing use of automated oscillometric blood pressure devices needs distinct referential values. In addition, several concerns aroused concerning methodology of preparation of normative data. First, Task Force percentile charts have been prepared from data obtained from National Health and Nutrition Examination Survey (NHANES) studies which were collected for forty years. Second, blood pressure percentiles in NHANES studies were constructed using the first (or single) measurements, which are higher than the average of multiple readings – "the average of multiple BP readings is closer to the basal BP levels and is more reproducible, and its use is recommended by many national studies or committees for children as well as adults" (12). The other concern is effect of body weight on blood pressure (13). The obesity epidemic caused the shift of blood pressure values in pediatric population towards right (higher values). It is assumed that increase of blood pressure with height is physiological. However, increased weight and obesity is associated with significant morbidity. Thus increase of blood pressure with excessive weight may not be physiological. The other concern is ban on production of devices containing mercury in European Union. This caused need to prepare blood pressure normative values based on automated, oscillometric measurements and to prepare normative data calculated from results of blood pressure measurements obtained from healthy and lean children, i.e. after exclusion of overweight and obese children and adolescents. Rosner et al. first calculated normative BP values in non-overweight children only (14). They reanalyzed blood pressure data from NHANES studies and excluded all data obtained from children with overweight and obesity. Since then, three studies done in Europe and based on data obtained with automated oscillometric device were published. First, Neuhauser et al. published normative values for blood pressure based on data obtained with automated oscillometric device from representative group of lean children (BMI below 85th percentile) in age 3-18 years from Germany (15). Authors used averaged value of first and second measurement. In 2012 and 2015, data from OLAF and OLA study done in Poland were published. OLAF and OLA study included representative population of 3-18 years old children and averaged values of second and third measurement were used (16). In both German and Polish study, validated oscillometric devices were used. The third study is IDEFICS study where a cohort of 16 937 non-overweight children from eight European countries (Germany, Hungary, Italy, Cyprus, Spain, Estonia, Sweden and Belgium) and in the age 2 to 11 years, were examined (17). Similarly to Neuhauser et al. study, blood pressure values from the first and second measurement were averaged. However, authors calculated 97th and 99th percentile values but not 90th and 95th percentile. It causes that results of IDEFICS study cannot be applied to clinical practice because definition of increased blood pressure in children and adolescent used worldwide is based on cut-off values of 95th percentile. Nevertheless, all these studies indicate that up to 5th-7th year of age systolic blood pressure is higher in girls than in boys. Subsequently the trend is reversed, with higher values in boys than in girls. Importantly, as documented in our study, systolic blood pressure significantly increases during pubertal growth spurt in boys (13.8 year of age in Poland) but not in girls. This elevated blood pressure values in boys and then in males are observed until the 6th decade of life when blood pressure in women increases.

PREVALENCE AND INCIDENCE OF CHILDHOOD HYPERTENSION

It is estimated that the prevalence of arterial hypertension among children and adolescents is 3-5% (18). However, prevalence of arterial hypertension is very low in neonates and infants and increases with age reaching about 10-11% in 18 years old adolescents (19, 20). There are only scanty data on incidence of arterial hypertension in childhood. Most of reports concerned on evolution from prehypertension to sustained hypertension among adolescents and incidence of arterial hypertension in children from risk groups of cardiovascular disease, such as prematurity, type 1 and type 2 diabetes mellitus (DM) and after repair of aortic coarctation (CoA). It is estimated that among adolescents from general population the rate of progression from normotension to hypertension confirmed by 3 measurements on 3 independent visits is 0.3% per year, while the incidence rate among adolescents who were prehypertensive is 1.1% per year (21). The greatest risk of development of arterial hypertension was noted among adolescents in whom blood pressure values were in prehypertensive or hypertensive range before screening and the incidence rate was 1.4% per year, the same as among adults with optimal blood pressure (22). Unexpectedly high incidence rate was found in IDEFICS study. Because in IDEFICS study blood pressure was measured two times on one occasion arterial hypertension could not be diagnosed according to definition. Thus only development of "pre-high normal blood pressure" (preHBP), i.e. blood pressure above 90th percentile and below 95th percentile, and so known "high blood pressure" (HBP) i.e. blood pressure in hypertensive range (above 95th percentile) could be estimated (23). It was found that incidences of preHBP and HBP in hypertensive range per year were: 121/1000 children and 110/1000 children, respectively. Even if incidence rates found in IDEFICS study are overestimated, the important finding is that sedentary behavior and low physical activity were associated with significantly increased incidence of preHBP and HBP.

In prospective study of adolescents with type 2 DM, 11.6% of them were hypertensive at baseline and 33.8% after 3.9 years what gives 4% per year incidence rate of arterial hypertension (24). Elevated blood pressure is one of the main findings in children with CoA. After successful repair, residual hypertension is still present in about 25% of children. However, it was evidenced that 16.7% of children will develop late hypertension after 13 years what gives incidence rate of about 1.3% per year (25).

Although historically the most prevalent form of AH in childhood was secondary hypertension, it changed in last 2 decades. Now, primary hypertension (PH) starts to dominate as the cause of AH in children older than 6 years and its prevalence is at least the same as of secondary hypertension (26). The recent rise in prevalence of PH in childhood and adolescence is strictly associated with the obesity epidemic and the dominant intermediate phenotype of hypertensive adolescent is overweight and metabolic abnormalities typical of metabolic syndrome. The general rule is that the younger child and the more severe hypertension, the greater probability of secondary hypertension. It is why hypertensive prepubertal children and children with stage 2 hypertension irrespective of age need more deep diagnostic investigations (10, 11). However, from public health perspective, the most important problem is primary hypertension which presents usually as stage 1 hypertension during adolescence and is associated with typical metabolic abnormalities.

OBESITY, VISCERAL OBESITY AND PHYSICAL ACTIVITY – NON-PHARMACOLOGICAL TREATMENT OF PRIMARY HYPERTENSION AND CHALLENGES FOR PUBLIC HEALTH

As mentioned previously obesity and especially visceral obesity is the main determinant of blood pressure in general population. Moreover, the dominant intermediate phenotype of primary hypertension in children and adolescents is visceral obesity and abnormalities typical for metabolic syndrome (27). Blood pressure both in children and adults is strongly related to the amount of adipose tissue mass. The adipose tissue is not just simple energy storage but is regarded as endocrine organ interacting with the inflammatory system, the vascular wall and sympathetic nervous system (28). In these interactions body fat distribution plays important role. Intra-abdominal obesity is important risk factor of cardiovascular disease, insulin resistance and dyslipidemic state (29). In a study by Pausova et al. it was found that androgen-receptor (AR) gene is associated with intra-abdominal adiposity, sympathetic modulation of vasomotor tone, and blood pressure in adolescent boys (30). The results showed that boys with a "low" versus "intermediate" or "high" CAG-repeat number in AR demonstrated higher intra-abdominal fat (by 28% and 48%, respectively) but not subcutaneous-abdominal fat and also higher blood pressure. Several epidemiological studies in children and adolescents indicate that waist circumference (as a proxy of visceral adiposity) exhibit stronger correlation with blood pressure compared to body mass index BMI (as a proxy of general adiposity) (31, 32). However in other studies proxy measures of central adiposity (waist circumference, waist-to-height ratio) does not appear to be superior to BMI in predicting increased blood pressure in children and adolescents (33-36). This may be due to the fact that waist circumference may not be an appropriate surrogate for visceral fat, which was shown in a study comparing associations of blood pressure with visceral fat quantified with MRI and waist circumference (37).

RELATIONSHIPS BETWEEN BLOOD PRESSURE AND PHYSICAL ACTIVITY

An important element in the prevention and treatment of hypertension is a reasonable, healthy lifestyle, including appropriate levels of physical activity. National and international treatment guidelines for the primary and secondary prevention of hypertension in adults recommend also lifestyle modifications, including regular physical exercise aiming to increase levels of physical activity (38-40). This is due to the fact that numerous research, including also randomized and controlled studies, confirmed inverse association of physical activity and blood pressure in adults (41-45). The mechanism how physical activity positively affects BP is not fully understood but it is postulated that "a reduction in total peripheral resistance is the primary mechanism by which physical activity reduces resting blood pressure. The changes in total peripheral resistance in turn are primarily mediated by changes in blood vessels diameter. A number of neural and local change occur in response to chronic physical activity participation that reduce the vasoconstrictive state of peripheral vasculature and in so doing decrease total peripheral resistance and blood pressure. These changes include less sympathetic neural influence on the peripheral blood vessels and local vasodilator influences on the blood vessels from molecules such as nitric oxide" (46). Exercise improves also endothelial function which may be associated with lowering blood pressure. "Increased physical activity causes increases in blood flow leading to increased shear stress, which is the force acting parallel to blood vessel wall. Enhanced shear stress results in endothelium-dependent, flow-mediated dilation of vessels. Chronic increases in shear stress have been found to improve endothelial function in animal studies as well as in some limited human studies" (47, 48).

In line with the recommendations for prevention of hypertension in adults also US and European guidelines on the management of high blood pressure in children and adolescents recommend maintaining appropriate level of physical activity (10, 11).

However it is worth to note that in the case of general pediatric population the relationships between physical activity and blood pressure are inconsistent. There are evidences that physical activity intervention are associated with reductions in blood pressure levels (49) whereas meta-analysis by Kelley et al. (50) concludes "The results of this study suggest that short-term exercise does not appear to reduce resting systolic and diastolic blood pressure in children and adolescents" and cross-sectional study of blood pressure and physical activity in Greek adolescents by Tsioufis et al. come to conclusion "Intense PA is associated with higher systolic BP" (51). According to the recently published results of longitudinal IDEFICS study children not performing the recommended amount of physical activity (< 60 min/d) have increases risk of high blood pressure (52).

Although there are only few prospective pediatric studies evaluating effects of antihypertensive treatment in children with primary hypertension, both non-pharmacological and pharmacological, it is well documented that increased physical activity and dietary modifications lead to normalization of blood pressure and regression of hypertensive target organ damage (53, 54). It was documented that it is decrease of visceral fat expressed as waist circumference but not decrease of body mass index determined regression of left ventricular hypertrophy and subclinical arterial injury (54). It means that it is not only decrease of fat mass but rather increase of lean body mass what determines regression of target organ damage and decrease of cardiovascular risk.

Beneficial hemodynamic and metabolic effects of physical activity are well known. However, physical activity exerts its effects also on molecular level. In our study we found that adolescents with primary hypertension who were carriers of T allele of endothelial nitric oxide synthase gene T894G polymorphism had greater carotid intima-media thickness in comparison with G allele carriers. Also, in control group – T allele carriers tended to have greater carotid intima-media thickness (55). In another study, it was found that children and adolescents who were TT homozygotes of endothelial nitric oxide synthase gene, had slightly higher blood pressure values in rest compared to GG carriers. However, this difference was found only in adolescents (pubertal and post-pubertal subjects) but not in prepubertal children. Moreover, physical activity modified genetic effect, which was most apparent in inactive subjects (56). Physical activity is important part of non-pharmacological treatment. We analyzed effects of non-pharmacological treatment on expression of genes of renin-angiotensin system and immune system before and after six months of therapy in 23 adolescents with primary hypertension. It was found that non-pharmacological treatment caused not only decrease of blood pressure and normalization of metabolic abnormalities, but also resulted in downregulation of genes involved in renin-angiotensin activation and those engaged in leukocyte responses to adipokines (57). Current knowledge indicates that radical changes of life style including physical activity and dietary modifications is effective both as preventive measures and as non-pharmacological therapy. However, the most important practical problem is acceptance of life style changes.

SCREENING FOR HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS – WHO SHOULD BE SCREENED?

There is no doubt that cardiovascular disease and arterial hypertension develop very early or even may be programmed perinatal. Although there are clear indications for blood pressure screening in children with risk factors (tab. 1), there is hot debate if blood pressure should be screened in general pediatric population to diagnose primary hypertension. Some authors claim that that although there is evidence that elevated blood in children and adolescents is associated with target organ damage and decrease of blood pressure leads to regression of target organ damage, there are still insufficient direct data on relations between elevated blood pressure in childhood, cardiovascular events and efficacy of early treatment (58). Moreover, blood pressure measurements in young children are subjected to large percentage of positively false results what may lead to unnecessary diagnostic procedures, including invasive procedure, and unnecessary treatment (59). Second, there are no firm evidence that antihypertensive treatment of adults with stage 1 hypertension reduces cardiovascular risk and number of cardiovascular events (40).

Table 1. Indications for blood pressure screening in children.

Blood pressure should be measured in every child older than 3 years at least once yearly and during routine medical examination
In children younger than 3 years (< 36 months of age) blood pressure should be measured in: – in premature neonates, children with low birth weight, hospitalized in neonatal intensive care unit, – children with congenital developmental defects, – children with kidney and urinary tract diseases, – children with cancer, – children after solid organ transpantation and after bone marrow transplantation, – children treated with drugs known to affect blood pressure, – children with symptoms and syndromes associated with elevation of blood pressure (neurofibromatosis, tuberous sclerosis, other), children with intracranial hypertension, – hospitalized children

On the other side there is enlarging amount of data on strict relations between elevated blood pressure in adolescence or young adulthood and cardiovascular disease and cardiovascular events in future (60, 61). The other argument is that although there are no firm data on beneficial effects of antihypertensive treatment in young adults with stage 1 hypertension, there is evidence that with time they will develop stage 2 or greater hypertension and their cardiovascular risk will increase. Thus, the practical problem is not "why we should screen for elevated blood pressure in childhood" but "in whom should we screen for elevated blood pressure". As mentioned above, there is no doubt that children with risk factors should be treated as risk group and blood pressure measurements are routine practice. The high percentage of positively false readings of blood pressure in youngest children causes that universal blood pressure screening in every child leads to unnecessary diagnosis, diagnostic procedures and even treatment. The greatest number (up to 40% of false positive results in 1 year of life, 10-20% in children in age up to 3 years of age) of false positive results is observed in children in age below 36 months of life. Thus, guidelines of both 4th Task Report, European Society of Hypertension and Polish Society of Arterial Hypertension do not recommend universal blood pressure screening in children in age below 36 months. However, in children from risk groups blood pressure should be screened.

CONCLUSIONS

Although secondary forms of arterial hypertension dominate in younger children, primary hypertension starts to dominate already in school-age children. It is estimated that about 10% of 18-years old adolescents are hypertensive. Despite many controversies regarding universal population screening towards hypertension, its seems that problem is not "why to screen" but rather "when to start to screen". Early treatment of primary hypertension with both non-pharmacological and pharmacological therapy is effective both in terms of normalization of blood pressure values and regression of target organ damage.

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received/otrzymano: 08.09.2015
accepted/zaakceptowano: 30.09.2015