Hypertension in childhood

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Hypertension is a growing health problem in children, and it is an important parameter of cardiovascular risk for adults. It is classified as primary (influenced by obesity, sedentary lifestyles and poor-quality food) or secondary to underlying causes. The AAP 2017 guidelines recommend measuring blood pressure every year from the age of three and in children under the age of three only if they have known risk factors. The measurement of infantile hypertension is relatively complicated and instable and, for this reason, ambulatory blood pressure monitoring (ABPM) and multiple office BP measurement (mOBPM), especially in infants who are not collaborating are indicated. High blood pressure may have an adverse effect on the heart, the vessels, the kidney, and the central nervous system so it is important recognize it and act promptly. Hypertension is initially treated with lifestyle changes such as weight loss, a healthy diet, and regular exercise, but, if non-pharmacological interventions have failed, a pharmacological treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics and/or beta blocker may be indicated.

Definition

Hypertension (HTN) is a relevant clinical problem in pediatrics because it is an alarming cardiovascular risk factor. In adolescents and adults, HTN is defined as blood levels > 140/90 mmHg according to European guidelines, while according to 2017 AHA guidelines it is defined as blood levels > 130/80 mmHg (1). In children, definitions that categorize BP values have been modified by the 2017 AAP guidelines, taking into account two age groups: 1) In children between 1 and 13 years of age - **normal BP** is defined when both Systolic BP (SBP) and diastolic BP (DBP) are < 90th percentile (matched by age, gender, and height); **elevated BP**: SBP and/or DBP > 90th percentile but < 95th percentile; - **stage 1 HTN**: SBP and/or DBP ≥ 95th percentile; - **stage 2 HTN**:

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SBP and/or DBP ≥ 95th percentile + 12 mmHg. 2) For children ≥ 13 years of age, - **normal BP**: BP < 120/80 mmHg; - **Elevated BP**: SBP 10-129 mmHg and DBP < 80 mmHG; - **stage 1 Hypertension**: BP between 130/80 to 139/89 mmHg; - **stage 2 Hypertension**: BP ≥ 140/90 mmHg (2, 3).

Epidemiology and risk factors

The prevalence of hypertension in pediatric age is 1.5-5% (4). The incidence of HTN is approximately 10.4% in well-fed children, but if it is associated with obesity or being overweight, or a diet rich in salts and fats and a sedentary lifestyle, this percentage can raise up to 68%. The Hispanic race and black children have an increased risk of developing hypertension, as well as children of hypertensive parents (5).

Maternal pre-pregnant BMI and maternal hypertension in pregnancy was positively correlated with infant weight gain during the perinatal period (6), in particular, with abdominal obesity and, therefore, with pediatric hypertension and cardiovascular risk (7, 8). The risk of childhood hypertension increases rapidly with puberty and could be associated with hormonal changes.

Etiology

Even in children and adolescents, hypertension can be classified as primary (essential) or secondary. Primary hypertension is the predominant diagnosis for children and adolescents older than 6 years of age who have a positive family history of HTN, are overweight or obese and do not have symptoms or signs suggestive of a secondary HTN. Some chronic conditions, such as coarctation of the aorta, Cushing syndrome, hyperthyroidism, excess mineralocorticoids (congenital adrenal hyperplasia, aldosterone-secreting tumors), pheochromocytoma, disorders of sleep (i.e. obstructive sleep apnea, night snoring, sleep fragmentation), chronic renal disease as renal vascular hypertension (RVH) and parenchymal renal disease, rheumatological disorders and drugs such as contraceptives, steroids, sympathomimetics / stimulants can be related to secondary childhood HTN.

A previouse study supported the hypothesis that inherited variations of the CART gene could influence the development of obesity and complication in Italian children (9).

Increased levels of aldosterone may be responsible for hypertension and for cardiovascular complications associated with obesity (10).

From measurements to diagnosis

Unlike the 2016 European Hypertension Society guidelines that recommended screening every two years from the age of three years, the American Academy of Pediatrics (AAP) 2017 guidelines recommend measuring blood pressure every year from the age of three. Children and adolescents with risk factors (i.e. those who are obese; who have kidney disease, aortic arch obstruction, diabetes mellitus, or who are taking a drug known to increase blood pressure) should have measured the BP at each health check.

High-mobility group protein B1 (HMGB1) takes part in numerous medical conditions, including pregnancy (11, 12). It plays an important role in the inflammatory process associated with childhood obesity. HMGB1 can be passively secreted from damaged or necrotic cells (13), it is one of the most important DAMP molecules, initiating and perpetuating immune responses both in non-infectious and/or infectious inflammatory processes (14, 15). HMGB1 serum levels may therefore represent a predictive marker of disease in pregnant women (16) and it may be an important diagnostic marker for obesity-related complications (17) like hypertension.

In children under the age of three, blood pressure should be measured if they have the same risk factors as older children or if they are premature, if they have a family history of congenital kidney disease, a history of organ or bone marrow transplant malignancy, elevated intracranial pressure or systemic diseases known to increase blood pressure (2).

The measurement of infantile hypertension is relatively complicated and blood pressure values are unstable and change according to the size of the cuff, the level of activity and anxiety, the intake of substances such as caffeine or cocoa, some drugs, the day or night hours and to the positioning of the child (18). The measurement is performed with the auscultatory method or an oscillometric (automatic) device. The bracelet must be applied on bare skin and

its width must be at least 40% of the circumference of the arm, while the length between 80 and 100% of the circumference of the arm. It is preferable to use the right arm for the measurement since on the left arm the measurement can provide erroneously low readings if coarctation of the aorta coexists. Regardless of the initial method used, an initial high blood pressure reading should be followed with at least two other auscultatory blood pressure measurements to avoid false positive cases.

To identify patients with *white coat* hypertension and those with *masked hypertension*, ambulatory blood pressure monitoring (ABPM) is indicated, in which BP is measured throughout the day and night at intervals varying between 20 and 60 minutes A minimum of 1 records for hour for a 24-hour period is considered necessary for a correct interpretation of the data and to correctly distinguish patients with normal pressure, or those with "white coat hypertension" or "masked hypertension",

Table I. *Etiologies of hypertension and suggestive findings in children and adolescents*.

Etiology	Hystory	Physical examination	Laboratory and other test
Primary hypertension			
	Adolescent age, diet high in fat and salt, family history of essential hypertension or early cardiovascular disease or diabetes, obesity and dyslipidaemias, limited physical activity	Acanthosis nigricans (insuline-resistance), diabetes and obesity	Hyperlipidemia Impaired glucose tolerance or type 2 diabetes
Secondary hypertension			
• ***Parenchimal renal disease*** (glomerulonephritis, polycystic kidney disease, congenital anomalies of the kidneys and urinary tract and CDK)	Enuresis, family history of renal disease, age <6 y, recurrent urinary tract infections	Abdominal mass, edema gross hematuria, growth retardation	Abnormal blood urea nitro¬gen, creatinine, anemia, urinalysis or urine culture, abnormal renal ultrasonography
• ***Renal artery stenosis*** (fibromuscular dysplasia and Takayasu's arteritis)	Prior umbilical artery catheterization	Epigastric and/or upper abdominal bruit	Ultrasonography, angiography if response to antihypertensive drugs is poor
• ***Coarctation of the aorta***	Hystory of neurofibromatosis, Williams syndrome, Alagille syndrome, or Takayasu arteritis	BP difference in the upper or lower limbs of 20 mm Hg or more, possible difference in BP between right and left arms, a systolic murmur with radiation in the back, diminished femoral pulses	Echocardiography
• ***Glucocorticoid excess*** (Cushing Syndrome, adrenocortical carcinoma)	Family hystory of endocrinopathies, cronic therapy with glucocorticoids	HTN, signs of Cushing syndrome, (acne, hirsutism, striae, moon facies, truncal obesity	Elevated cortisol levels
• ***Mineralocorticoid excess*** (congenital adrenal hyperplasia,	Family hystory of endocrinopathies	Ambiguous genitalia Muscle weakness	Elevated plasma aldosterone levels,

prehypertension, ambulatory hypertension, or severe ambulatory hypertension. Recently, it has been proposed a new method, named multiple Office Blood Pressure Measurements (mOBPM) that provide reliable measurements of BP and likely may be used instead of ABPM, particularly in infancy. This method is a simpler and faster tool than ABPM, especially in infants who are not collaborating (19).

After establishing a diagnosis of high BP or hypertension, it is necesary to identify a possible underlying etiology and any comorbidities. Nutritional history should assess for intake of foods that are associated with high BP such as high salt and caffeine, and low potassium. Physical activity, smoking status, and alcohol intake should also be explored. Patients should be screened for a family history of hypertension, other cardiovascular risk factors, diabetes, obesity, dyslipidaemias and familial renal or endocrine diseases. A sleep disturbance history should be investigated because an association between sleep disorders and hypertension is well documented in adults and it cannot be excluded in children, although on this topic the reports are limited. Screening for kidney, endocrinological diseases, rheumatological, cardiological and taking drugs that can increase blood pressure is indicated (Table I) endovascular techniques, and surgery. We aimed to describe the course of renovascular hypertension (RVH(20, 21).

Consequences

HTN is known to be one of the most relevant factors for the development of atherosclerosis and cardiovascular disease in adults. The most important aspect of the management of hypertensive children is the detection of early changes of "target-organs" and the assessment of the individual cardiovascular risk. Increased carotid intima-media thickness (cIMT), high pulse wave velocity, left ventricular hypertrophy (LVH) and microalbuminuria have been identified as "end organ-effects", expression of injury related to HTN.

Electrocardiography has high specificity but very low sensitivity for identifying children with LVH; for this reason, clinicians should not perform EKG in hypertensive children for evaluating LVH. Echocardiography, instead, is a good tool to assess heart damage secondary to HTN. In particular, it has been documented that height-adjusted left ventricular mass, assessed by echocardiography, is correlated to both body mass index and systolic blood pressure and this has been suggested to be a good indicator of the need for pharmacological terapy in pediatric patients with HTN.

In obese children waist circumference and/or body mass index and biohumoral and inflammatory parameters can help predict cardiac structural and functional alterations (22). New risk factors, such as homocysteine, lipoprotein (a), apolipoprotein B, adipokines, fibrinolysis and inflammation markers, associated with obesity, insulin resistance and hypertension significantly increase the risk of cardiovascular events in adulthood (23).

Also in obese children and adolescent, screenings for diabetes, steatohepatitis, and dyslipidemia as additional cardio-vascular risk factors are recommended through the evaluation of fasting glucose, hemoglobin A1c, alanine and aspartate aminotransferases, and a fasting lipid panel (24). Abdominal obesity with visceral obesity might be predicting factor for accumulation fatty liver (25).

Vascular lesions in the retina, frequently detected in adults, can also be found in children with severe HTN. Neurological manifestations occur more in hypertensive crisis than in chronic hypertension. Recently it has been reported reduction in cognitive function in children with sustained hypertension (26) untreated hypertension and 75 frequency-matched normotensive controls had baseline neurocognitive testing as part of a prospective multicenter study of cognition in primary hypertension. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed. Parents completed rating scales of executive function and the Sleep-Related Breathing Disorder scale of the Pediatric Sleep Questionnaire (PSQ-SRBD.

Therapy

Accurate identification of secondary hypertension is extremely important because many causes are reversible. The goals of the treatment include achieving a blood pressure level less than the 90th

percentile for age, height, and gender for patients younger than 13 years of age, or less than 130/80 mm Hg for those ≥ 13 years of age. All children with HTN should undertake, first of all, lifestyle changes, such as nutritional intervention dietary (DASH or Dietary Approaches to break down hypertension including poor intake of fat milk products, considerable intake of fruits, vegetables and low salt input) and physical exercise as, at least, 60 min of moderate to vigorous activity, three to five days per week with less than 2 hours of sedentary activity daily.

Despite of the limited availability of studies on pediatric symptomatic hypertension (eg, headache, cognitive changes), if hypertension remains at stage 2, symptomatic or with evidence of "organ damage" after six months of lifestyle changes, it is necessary to choose pharmacological intervention, while if there is normalization of blood pressure, patients can be followed up every 3-6 months.There is no consensus about the best initial antihypertensive drug in children, and there have been no clinical trials of hypertension treatment that evaluate long-term outcomes in children.

First line therapy for hypertension in children is represented by angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers, and thiazide diuretics that are effective, safe, and well tolerated, while beta-blockers are not recommended as initial treatment. Pharmacological therapy should be initiated with single medication at the low end of the dosing range, increasing the dosage every two to four weeks until the blood pressure goal is achieved (BP <90th percentile or <50th percentile if chronic kidney disease). If a single drug is not enough to control BP, a second agent, preferably a thiazide diuretic, can be added to therapy.

Drug choice should take into account the underlying pathophysiology and the presence of comorbidities: ACEi or ARB are the most appropriate first-line agents in the presence of diabetes mellitus and microalbuminuria, CKD and proteinuria and in obese pediatric patients with LVH. Beta-blockers or calcium channel blockers are used in children with hypertension after the surgical repair of aorta coarctation. Beta-blockers are contraindicated in asthmatic or diabetic children, while ACEi and ARB are contraindicated in female adolescents at high risk of pregnancy to avoid potential fetal risks. A close surveillance (every 4-6 weeks) is mandatory in the first months of treatment, while once the BP values are stabilized and the right drug is found at the appropriate dose, controls can be spaced over time.

The recommendations for the treatment of resistant hypertension (persistent hypertension despite the treatment with 3 or more antihypertensive agents of different classes) foresee the reconfirmation of the pressure values with adequate sized caps, the ABPM, the dietary control (27), the identification of secondary causes not diagnosed with hypertension, optimizing current therapy and, if necessary, adding other agents.

Regarding participation in competitive sports, the guidelines recommend that children with stage 2 hypertension be restrict from high-static sports, even in the absence of end organ damage, until their BP normalizes. Children with evidence of target organ damage require an adequate specialist assessment before starting participation in competitive sports (28).

Recent AAP guidelines have reviewed the classification of hypertension and stressed the importance of ABPM for the diagnosis and management of childhood hypertension. Children ≥6 years of age must be advised not to request systematically a thorough investigation into the secondary causes of hypertension if they have a positive family history, are overweight or obese and do not have symptoms or signs suggestive of a secondary HTN.

Adequate strategies are needed to prevent the development of hypertension in children and adolescents: these are mainly based on lifestyle modification, including appropriate diet, regular exercise and obesity treatment. A pharmacological treatment is indicated if non-pharmacological interventions have failed, if hypertension is symptomatic or stage 2 persists and organ damage, such as left ventricular hypertrophy, is present. The main choice of antihypertensives should include acei, arb, long acting calcium channel blocker or thiazide diuretic, while beta blockers should never be used as initial antihypertensives.

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