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HYPERTENSION IN CHILDREN AND ADOLESCENTS

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Introduction

The incorporation of blood pressure (BP) measurement into routine paediatric healthcare and the publication of norms for BP in children [1] has not only enabled detection of significant asymptomatic hypertension secondary to a previously undetected disorder, but it has also confirmed that mild elevations in BP during childhood are more common than was previously recognized, particularly in adolescents.

The roots of hypertension in adulthood extend back to childhood. Indeed, childhood BP has been shown to follow into adulthood. That is to say, children with elevated BP are more likely to become hypertensive adults [2–4], an observation emphasizing the importance of BP control in children and adolescents. Importantly, both the use of repeated measurements (aimed at the reduction of measurement error) in the identification of those children with elevated BP [2], as well as the assessment of co-morbidities (in particular obesity) and family history of cardiovascular disease, critically improve the accuracy of the prediction of hypertension later in life.

Diagnosis

Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define hypertension, as done in adults.

Extensive paediatric normative data on auscultatory clinic measurements have been provided for the United States, based on more than 70,000 children [5]. Blood pressure percentiles have been calculated for each sex and age group, and for seven height percentile categories (www.pediatrics.org/cgi/content/full/114/2/S2/555). Height percentiles are based on the growth charts of the Center for Disease Control and Prevention (www.cdc.gov/growthcharts). According to the criteria of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [5], criteria shared by the ESH Guidelines in Children, normal BP in children is defined as systolic and diastolic BP < 90th percentile for age, gender, and height, while hypertension is defined as systolic and/or diastolic BP persistently ≥ 95th percentile, measured on at least three separate occasions with the auscultatory method. Children with average of systolic or diastolic BP ≥ 90th but < 95th percentiles are classified as having high-normal BP. Adolescents with BP ≥ 120/80 mm Hg even if < 90th percentile are also considered as having high-normal BP (Table 1).

The diagnosis of hypertension should be based on multiple office BP measurements taken on separate occasions over a period of time. Office BP measurement has provided the basis for the present knowledge of the potential risk associated with hypertension [6] and has guided patient management for many years. Although office BP should be used as a reference, BP values obtained out of office may improve the evaluation in untreated and treated subjects.

Ambulatory BP measurement (ABPM) is now increasingly recognized as being indispensable in the diagnosis and management of hypertension [7], and it has contributed significantly to our understanding of hypertension by "unmasking" BP phenomena that were not readily apparent using office BP: the non-dipping patterns of nocturnal BP [8], white-coat [9], and masked hypertension [10]. Recommendations for the use of 24-hour ABPM are: *during the process of diagnosis* (confirm hypertension before starting antihypertensive drug treatment, type 1 diabetes, chronic kidney disease, or renal, liver, or heart transplant); *during antihypertensive drug treatment* (evaluation of refractory hypertension, assessment of BP control in children with organ damage, symptoms of hypotension); *clinical trials; and other clinical conditions* (autonomic dysfunction, suspicion of catecholamine-secreting tumours). Concerning home BP measurements, the evidence in children and adolescents is promising but limited.

Table 1. Definition and classification of HTN in children and adolescents (modified from: Task Force on High Blood Pressure in Children and Adolescents [5])

Class	SBP and/or DBP percentile
Normal	< 90th
High-normal	≥ 90th to < 95th
	≥ 120/80 mm Hg even if below 90th percentile in adolescents
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mm Hg
Stage 2 hypertension	> 99th percentile plus 5 mm Hg

Evaluation

Several steps should be followed, from screening to confirmation, to rule out secondary causes of hypertension, if indicated. The proposed diagnostic algorithm is found in Figure 1 [11].

Once hypertension is confirmed, organ damage evaluation should include the heart and kidney due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease. Subsequently, the evaluation is useful not only as an assessment for cardiovascular risk, but also as an intermediate endpoint for monitoring treatment-induced protection.

Left ventricular hypertrophy remains to date the most thoroughly documented form of end-organ damage caused by hypertension in children and adolescents. The role of microalbuminuria assessment in paediatric essential hypertension, however, has gained ground. Consequently, echocardiography and a test for microalbuminuria should be performed in all hypertensive children and adolescents. The assessment of carotid-intima media thickness is not recommended for routine clinical use. The presence of organ damage is an indication to initiate or to intensify antihypertensive therapy.

Preventive measures

As most cases of high normal blood pressure and hypertension in childhood are now known not to be cases of secondary hypertension to be detected and specifically treated, efforts should be made to understand the conditions necessary to return BP to within the normal range or to prevent high normal BP in childhood developing into full hypertension in adulthood.

Considerable advances have been made in recent years in identifying conditions often associated with, and considered responsible for, high BP in children and adolescents while more limited evidence has been accumulated on the results of corrective interventions.

Overweight is probably the most significant condition associated with elevated BP in childhood [12] and accounts for more than half the risk of developing hypertension [13–15]. Fatter children are known to be more likely to remain fat, and adiposity is the most powerful risk factor for higher BP. In addition to body mass index, waist circumference (abdominal obesity) has been shown to play a role [16]. Birth size and postnatal growth have also recently been implicated in the development of high blood pressure and adult cardiovascular disease [17–19]. Finally, dietary habits early in life, and particularly high salt intake, have been implicated as factors favouring higher BP values [20, 21].

Data about BP reduction from randomized intervention trials for reducing weight are limited. Lifestyle trials are currently underway in many

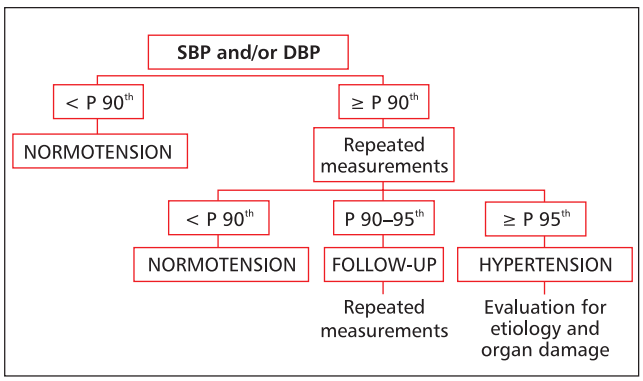

Figure 1. Diagnostic algorithm of hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure; P — percentile

settings, but until these are finished, evidence-based recommendations are limited [11]. Most, however, are obvious and based on common-sense. From the reviews, it appears that "40 minutes of moderate to vigorous aerobic-based physical activity 3–5 days/week is required to improve vascular function and reduce BP in obese children" [12].

Thus, any interventions which not only reduce energy intake but also increase physical activity in these children are likely to be helpful in keeping BP lower. In general, such interventions should be global policy in schools and should also take the form of 'advice' to parents, not just advice directed at individual children. Group activities, a whole new ethos of outdoor lifestyle promotion, wherever and whenever possible, as part of school curricula, and regular vigorous activity sessions for boys and girls are regarded as essential components in helping children and parents (re-)learn that these are the foundations of what we currently know about how to keep BPs low throughout childhood and adolescence.

Evidence for therapeutic management

Cardiovascular end-points such as myocardial infarction, stroke, renal insufficiency, or heart failure are extremely uncommon in childhood and their rarity has so far prevented event-based randomized therapeutic trials. Despite this, clinical experience shows that reduction of high BP in life-threatening conditions, such as acute heart failure, hypertensive encephalopathy, and malignant hypertension, improves survival and reduces sequelae in children. Because of the rarity of events, most of the limited evidence available so far is based on the use of organ damage markers including left ventricular hypertrophy and increased urinary albumin excretion as surrogate endpoints.

In children, as in adults, the decision to initiate antihypertensive treatment should not be taken on BP levels alone, but should also take into consideration the presence or absence of target organ damage, other risk factors or diseases such as obesity, renal diseases, and diabetes [11]. In children with proven secondary hypertension, specific treatment of the underlying disease must be initiated immediately after detection. In children with primary hypertension, antihypertensive therapy should first target the risk factors for BP elevation (i.e. overweight, increased salt intake, low physical activity).

Non-pharmacological therapy should be continued even after starting pharmacological therapy as it can improve the overall cardiovascular risk profile in hypertensive children.

In the absence of prospective long-term studies linking children BP levels to cardiovascular outcomes, paediatric BP targets are commonly defined in relation to the distribution of BP in the normal population. The 95th percentile is commonly used as a cutoff for defining hypertension in children and adolescents. This provides a rationale for targeting children and adolescents with essential hypertension to a BP below the 95th age, sex and height specific percentile, but it is probably wiser and safer to aim at a BP below the 90th percentile [11].

In children with chronic kidney disease, there is preliminary evidence from the prospective randomized ESCAPE trial that strict BP control aiming for a 24-hour target below the 50th percentile of mean arterial pressure by the addition of other antihypertensive agents to ACEI inhibitor therapy results in a better 5-year renal survival, despite a return of proteinuria toward pretreatment values [22]. Analysis by achieved BP levels shows similar renal outcomes with any 24-hour BP below the 75th percentile, contrasting with significantly reduced 5-year renal survival in patients exceeding this cutoff level. A poorer renal survival is associated with an attained 24-hour BP above the 90th percentile. Proteinuria appears to be an important modifier of the renoprotective efficacy of intensified BP control. Despite the dissociation in time of the renoprotective and antiproteinuric effects, an improved renal survival is associated with targeting BP to lower levels only in children with even mild baseline proteinuria, whereas no benefit of more intense BP lowering is found in children with non-proteinuric disease.

Therapeutic strategies

It should be reiterated here that lifestyle measures should not only precede but also accompany pharmacological treatment.

Monotherapy

It is reasonable that in children treatment should be started with a single drug, administered at a low dose, in order to avoid rapid fall in BP. If BP does not decrease sufficiently after a few weeks, usually 4 to 8, an increase to the full dose should be initiated. When BP does not respond adequately or significant side effects occur, switching to another antihypertensive drug of a different class is recommended. This procedure allows the patient's best individual response to the drug to be found in terms of efficacy and tolerability. Since the response rate is often not sufficient in single drug treatment, particularly in moderate or severe hypertension, combination therapy is often necessary.

As in adults, the choice of antihypertensive agents can include ACE-inhibitors, angiotensin receptor antagonists (ARB), calcium antagonists, β-blockers, and diuretics. Results from a few placebo-controlled studies are available, but there are almost no head-to-head studies directly comparing the efficacy and safety of different antihypertensive drugs in children or adolescents.

Combination therapy

In children with renal disease, monotherapy is often not sufficient to achieve adequate BP control. Therefore, early combination therapy is required. Early dose combination of antihypertensive agents is more efficient and has a lower rate of adverse drug reaction compared to that of high dose monotherapy. Antihypertensive drugs of different classes have complementary effects, resulting in a higher degree of BP reduction and a lower rate of adverse drug reaction. The best choices of antihypertensive drug combinations are those recommended in the ESH 2009 Reappraisal of Guidelines [23]. Fixed-dose combinations of two drugs are rarely used in children since individual-based contributions are preferred, but fixed combinations may have a place in the treatment of adolescents to improve compliance.

Conclusions

It is clear that paediatric high BP will further contribute to the current epidemic of cardiovascular disease unless it is given the attention it deserves by policy makers, health care providers, schools, parents, caregivers, and society as a whole. The role of learned societies, particularly the European Society of Hypertension, is crucial not only for spreading the guidelines all over European Countries, but also for obtaining their acceptance by national hypertension societies and leagues.

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