What adult nephrologists should know about childhood blood pressure

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Introduction

A common assumption in cardiovascular medicine is that high blood pressure and other risk factors identified in adult populations only affect the elderly. However, there is increasing evidence that even the blood pressure level attained in childhood has significant short and long term impacts on cardiovascular health. This article reviews the definition, causes and consequences of paediatric hypertension and highlights the relevance of paediatric hypertension for adult cardiovascular health.

Hypertension in childhood

In contrast to adults, most hypertensive children suffer from secondary forms of hypertension, with renal parenchymal disease accounting for at least 75% of cases. Less common forms of secondary hypertension in children are renovascular disease, coarctation of the aorta, endocrine disease and monogenetic inherited forms of hypertension. In practice therefore, hypertensive children are almost exclusively treated by paediatric nephrologists, even if they suffer from essential hypertension. The proportion of essential hypertension varies from 2 to 75% in reported series, depending on region and age. As nearly all pre-pubescent children have an identifiable underlying cause, age is a much more reliable clue towards essential hypertension than overweight [1,2]. However, routine blood pressure measurements are still rarely performed by general paediatricians and the prevalence of essential hypertension in children may be grossly underestimated, simply because of diagnostic neglect.

Due to the very low mortality, the long time lag to cardiovascular complications and the significant co-morbidity of most hypertensive children, it is impossible to define cut-off values for hypertension in children based on clinical outcomes; instead, a population-based approach is required. This approach is complicated by the marked physiological increase of blood pressure with age and body size during childhood. Since height is the closest covariate of blood pressure among the different measures of body size, the 95th percentile of blood pressure at a given height is used to define arterial hypertension in children. In analogy to adult guidelines, any blood pressure above 90th percentile for height has recently been termed 'pre-hypertension' and values >5 mmHg above the 99th percentile define stage 2 hypertension [3]. Children may be hypertensive at absolute blood pressure values that may not seem high in adult dimensions. For example, 120/75 mmHg constitutes severe stage 2 hypertension in a 2-year-old, stage 1 hypertension in a 7-year-old and pre-hypertension in a 11-year-old of average height. In addition to age, stature plays an important role in what constitutes normal blood pressure. Figure 1 gives the upper
End-organ damage from childhood hypertension

Due to infrequent screening in the general paediatric population, severe complications at first presentation, e.g. congestive heart failure and encephalopathy, are common when the underlying disease is not previously known [10]. Approximately 50% of children suffer from hypertensive retinopathy at the time of diagnosis [11]. Severe hypertension is particularly common in infants with renal parenchymal disease [2].

While cardiovascular disease is encountered rarely in the general paediatric population, morbidity and mortality from cardiovascular causes is very real in paediatric end-stage renal disease (ESRD). In under 19-year-olds with ESRD, cardiac disease is responsible for 22 deaths/1000 patient years, accounting for 16% of all deaths in whites and 26% in blacks with ESRD. This represents an up to 1000-fold increase in risk when compared with the general population [12]. Hypertension may be a major contributor to this risk, as more than three quarters of children entering ESRD are either hypertensive or on anti-hypertensive therapy [13].

In terms of long-term cardiovascular outcomes, hypertension has been linked to a number of important markers of cardiovascular disease in children. LVH and increased intima media thickness (IMT) have been demonstrated not only in hypertensive children with chronic renal failure, in whom alterations of mineral metabolism and volume overload are important superimposed risk factors [14–16], but also in children with early essential hypertension [17] and even in children with ‘masked hypertension’, i.e. normal clinic but elevated ambulatory blood pressure [6].

Tracking of blood pressure — do hypertensive children become hypertensive adults?

Whilst the great majority of children suffering from cardiovascular disease in childhood have secondary hypertension, there is reason to believe that essential hypertension and mildly elevated blood pressure in childhood also pose significant risks, even if sequelae will be seen with a long time delay. A number of studies have examined the continuity of blood pressure levels from childhood to early adulthood (‘tracking’) in healthy populations. Blood pressure during adolescence clearly tracks at least into early and middle adult age. In the most extended analysis, Beckett et al. [18] showed significant tracking of both systolic and diastolic blood pressure over multiple visits between the ages of 13 and 40 years. In accordance with this large cohort study, the Bogalusa Heart Study found that children in the top quintile of systolic blood pressure were 3.6 times more likely to develop clinical hypertension by age 31 than their peers. In reverse, 48% of hypertensive adults had shown elevated childhood systolic blood pressure [19]. The minimal age at which significant blood pressure tracking into adult life becomes manifest has not been determined.

How are childhood and adult blood pressure linked?

There are a number of possible explanations for the phenomenon of blood pressure tracking. One of the
most controversial issues is the inverse association between birth weight and adult blood pressure. Early findings suggested that with each kg of birth weight, a reduction of adult blood pressure level by 4 mmHg could be expected. On this basis, Barker stated in his ‘fetal origins’ hypothesis of hypertension that malnutrition during critical intra-uterine growth periods leads to life-long programming of the cardiovascular system [20]. Nearly 100 studies examining birth weight and adult blood pressure have been performed to date, and recent meta-analyses have taken a more critical view [21]. However, the inverse association of birth weight and blood pressure remains, even if the size of the effect was probably overestimated in the early studies [22]. Human studies have found smaller nephron number and abnormal renin expression in infants who suffered from intra-uterine growth restriction [23,24]. Animal models suggest that intra-uterine malnutrition affects nephrogenesis, the maturation of the renin-angiotensin system, sodium handling and endothelial function, providing multiple potential pathways that may be involved in the determination of blood pressure in later life [25].

Another intriguing factor that may link adolescent and adult hypertension is uric acid. Johnson et al. [26] have shown that rats with pharmacologically elevated serum uric acid levels develop hypertension; when uric acid is normalized blood pressure drops but the salt sensitivity of blood pressure increases [26]. As hyperuricaemia has also been demonstrated in children with essential hypertension [27], dietary or pharmacological control of uric acid levels may be a useful approach to lowering blood pressure [28]. Furthermore, the animal models suggest that early treatment of hyperuricaemia in adolescence offers a unique window of opportunity, before uric acid independent, salt-dependent hypertension develops.

Besides the influences of early-life environmental factors, the genetics of hypertension have been a focus of attention in recent years. Various observations suggest a genetic susceptibility to high blood pressure and cardiovascular disease. Two population studies have confirmed a predictive power of family history of hypertension (particularly maternal hypertension) on higher blood pressure levels in childhood [29] and overt hypertension in later life [30]. Also, two large studies found increased IMT in young and middle aged adults with a family history of coronary heart disease [31,32]. Several monogenetic forms of arterial hypertension exist, but these account for a very small fraction of hypertensive patients even in childhood. Several gene regions [33,34] and frequent polymorphisms in individual genes have been associated with hypertension (e.g. alpha-adducin [35], CIC-Kb chloride channel [36]), but their individual contribution to blood pressure is relatively small [37]. It may take large-scale whole-genome screening approaches, as currently underway in the Hap Map project, to ultimately define the relative role of genetic factors for blood pressure distribution in normotensive and hypertensive populations, the tracking of blood pressure from childhood to adult life and the apparent association between birth weight and adult blood pressure. Notably, twin studies have not been able to shed significant light on the question of whether the birth weight-blood pressure association is due to genetic or environmental factors [38].

**Influence of childhood hypertension on adult markers of cardiovascular disease**

Of more practical value than the issue of what generates high blood pressure is the question whether childhood hypertension is a predictor or an actual cause of adult cardiovascular disease. Three large population studies have examined the predictive value of childhood and adolescent risk factors on IMT in young adulthood. While correlations of childhood blood pressure with adult IMT were found in each of the studies, only the Cardiovascular Risk in Young Finns Study found an independent predictive value of adolescent systolic blood pressure on carotid IMT. In addition, childhood low-density lipoprotein (LDL) levels were significant predictors in all three studies and childhood BMI in two studies [39–41]. In the same populations, adolescent blood pressure was also predictive of brachial-ankle pulse wave velocity as a marker of arterial stiffness [41] and brachial flow-mediated dilatation as a marker of endothelial dysfunction [42]. The effect of childhood blood pressure on adult left ventricular mass was only examined in the Bogalusa Heart Study, where the effect of childhood adiposity was greater than that of childhood blood pressure; the latter was only relevant if blood pressure remained elevated from childhood into adulthood [43]. Thus, childhood blood pressure appears to be a significant, but not the only risk factor for later cardiovascular disease.

**Other childhood influences on adult cardiovascular risk**

An important observation is that childhood obesity is related to adult cardiovascular mortality [44]. However, obesity itself seems to track less well than blood pressure and childhood weight does not reliably predict adult blood pressure [45]. Indeed, at the same level of adult obesity, those who were thinnest as children have higher risk profiles [45], suggesting a particularly harmful effect of catch-up growth from under to overweight.

Interestingly, a number of environmental and behavioural factors have also been linked to adult blood pressure and other markers of cardiovascular disease. For example, a correlation of the socio-economic circumstances in childhood with adult blood pressure was described recently [46]. This link appears to be mediated by an elevation of childhood blood pressure tracking into adulthood, rather than by a direct effect of childhood deprivation on adult blood pressure (e.g. via risk-taking behaviour and unhealthy life style habits). However, childhood temperament
Tracking of BP

Blood pressure levels track from adolescence to middle age in normal populations, this may be mediated via ‘programming’ by factors operative during early life (intra-uterine growth restriction, uric acid levels) as well as y genetic influences

Elevated childhood blood pressure is one of several early-life risk factors for later cardiovascular disease

Table 1. ‘Take home’ messages—hypertension in children

<table>
<thead>
<tr>
<th>Measuring BP</th>
<th>BP increases markedly with body size and should be interpreted using age and height adjusted normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension in children</td>
<td>Young children are unlikely to suffer from primary hypertension and deserve thorough investigation for secondary causes</td>
</tr>
<tr>
<td>End organ damage</td>
<td>is often present at first presentation and needs to be excluded regularly during follow-up</td>
</tr>
<tr>
<td>Tracking of BP</td>
<td>Blood pressure levels track from adolescence to middle age in normal populations, this may be mediated via ‘programming’ by factors operative during early life (intra-uterine growth restriction, uric acid levels) as well as y genetic influences</td>
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BP, blood pressure.

predicts adult blood pressure but also multiple cardiovascular risk factors such as smoking behaviour, body mass index and educational status. The predictive power of childhood temperament is so strong that women with childhood hyperactivity have greater adult IMT, even after adjustment for other childhood and adult risk factors [47].

Conclusion

In summary, adult physicians examining blood pressure in children should be aware that values which are considered perfect in an adult may represent serious hypertension in a child, and that childhood hypertension has both immediate and long term risks. Due to the high likelihood of secondary hypertension, children with elevated blood pressure should be referred to an experienced paediatric nephrology service for appropriate diagnostic work-up.

The cardiovascular risk of adults is affected by a large number of factors. Among the factors already operational in childhood, elevated blood pressure is the single most consistent determinant of hypertension and vascular damage in adulthood. In addition, intra-uterine nutrition, birth weight, catch-up growth, adiposity, temperament, socio-economic status and risk-taking behaviour apparently all link to cardiovascular risk factors in adulthood. While the exact contribution of each of these factors is difficult to determine due to multiple interactions and changes over time, there is increasing evidence to suggest that elevated blood pressure in childhood is a treatable condition, that deserves the same diagnostic and therapeutic attention as hypertension in adults.

Conflict of interest statement. None declared.

References