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Special Invited Articles

What's New in Childhood Hypertension?

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Abstract The pattern of childhood hypertension is changing with a significant increase in the numbers of children with primary hypertension occurring in conjunction with childhood obesity. The phasing out of mercury sphygmomanometry, the problems of identifying an alternative method of blood pressure measurement, the increasing use of ambulatory blood pressure monitoring, the emphasis on systolic hypertension and the recognition of white coat hypertension are modifying the views of what is and what is not hypertension in childhood. Newer investigative techniques and more sophisticated therapeutic manoeuvres, including interventional radiology, are influencing the handling of secondary hypertension and there is an increasing recognition that monogenic forms of hypertension affect children. Anti-hypertensive drug trials are now including children with hopefully in future the availability of newer therapeutic agents for paediatric use.

Key words Blood pressure; Childhood; Hypertension; Mercury; Obesity

Introduction

In recent years it has been accepted that 1-3% of the childhood population have a blood pressure consistently above the upper end of the normal range and that approximately 10% of these have severe hypertension, usually secondary, with renal disease as the most common cause.[1-3] However, although, these figures are probably still relevant there is overwhelming evidence that there is a significant increase in the numbers of children with primary hypertension, a hitherto predominantly adult disorder, and this is closely associated with childhood obesity.[4-7] The pattern is therefore beginning to change and this has also been associated with other factors that have impinged on the identification of high blood pressure in children namely the phasing out of mercury sphygmomanometry,[8,9] the problems of the accuracy and validation of alternative blood pressure measuring devices,[10] the increasing use of ambulatory blood pressure monitoring,[11,12] the need to establish new device specific blood pressure nomograms,[13] the emphasis on systolic rather than diastolic hypertension[14] and the recognition of "white coat hypertension" even though what it means remains uncertain.[15] Of course, secondary hypertension as a cause of severe treatment requiring increases in blood pressure remains a problem for paediatricians but newer investigational tools and better therapeutic options have improved the accuracy of diagnosis and the outcomes in affected children.[1,16] In addition the identification of monogenic forms of hypertension is beginning to help in the understanding of the genetic factors that influence blood pressure[17,18] and the increasing awareness of the importance of providing newer more effective antihypertensive drugs for children has resulted in attempts to undertake trials of agents in children as well as adults so younger patients will not be denied the latest therapy as has been the case in the past.[19-21] An attempt will be made to address some of these issues in this review.

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Phasing Out of Mercury Sphygmomanometry

Concerns regarding potential toxic effects of mercury from sphygmomanometers, inspite of the fact that these

must be minimal compared to environmental pollution, have resulted in recommendations to phase out mercury sphygmomanometry.[8,9] The problem, however, that arises is what are we going to do without mercury? The alternatives are to utilise aneroid devices or oscillometric devices. Aneroid manometry involves pressure being registered by a bellows and lever system that is initially accurate but becomes inaccurate with use and underestimates blood pressure.[22,23] Hence, aneroid devices require very regular calibration and maintenance, and are particularly vulnerable to the day to day trauma of routine clinical use.[24]

Most aneroid manometers are not recommended for adults let alone children on the basis of their accuracy and reliability. However, some devices have recently been shown to fulfill validation criteria allowing recommendation for use in adults and perhaps there is an opportunity for these to be further studied to see if they will also be acceptable for paediatric practice.[25]

Oscillometry, on the other hand, utilises the arterial wall oscillation at the time of pulsatile blood flow through the vessel transmitted to a cuff encircling the extremity to measure blood pressure. Systolic blood pressure is recorded at the point where a rapid increase in oscillation amplitude occurs (the equivalent of K1). Diastolic blood pressure is recorded at a point where a sudden decrease in oscillation amplitude occurs (the equivalent of K5). Early devices tended to overestimate blood pressure in children.[13,24] The ESH (European Society of Hypertension) utilising the AAMI (Association for the Advancement of Medical Instrumentation) and the BHS (British Hypertension Society) validation procedures recommended 2 instruments: the Datascope Accutor Plus and the CAS model 9010 (that had also been tested in neonates).[26] More recently the Welsh Allyn "Vital Signs" monitor also passed AAMI and BHS validation procedures in adults and was strongly recommended for hospital use. It's noteworthy that the Dinamap 8100, often used in paediatric departments, failed and was not recommended.[27]

Inspite of these findings no alternative device to mercury sphygmomanometry has been securely validated for use in children. Furthermore it has to be remembered that all non mercury devices need to be calibrated against mercury and elimination of all mercury sphygmomanometers is a foolhardy step until satisfactory alternatives have been identified and satisfactory non mercury means of calibration have been developed. Two important publications, one from North America and one from Europe, strongly recommend that mercury sphygmomanometers should not be abandoned until satisfactory alternatives have been found.[8,9]

Ambulatory Blood Pressure Monitoring

In recent years ambulatory blood pressure monitoring (ABPM) has become an important additional tool in identifying hypertension and monitoring treatment for it. The advantages are that it allows multiple measurements utilising a consistent device for the purpose, it provides a "truer" picture of blood pressure trends, it provides better blood pressure correlation with cardiac outcome, it identifies "white coat hypertension" and identifies nocturnal hypertension (non dippers).[28] A number of important publications have appeared describing ABPM in paediatric practice and providing blood pressure nomograms, at least for certain devices.[11,12,29,30]

However, there are problems with ABPM monitors and surprisingly some of the most commonly used worldwide have failed the vigorous validation procedures to which they have been subjected.

The ESH have examined 24 devices utilising AAMI and BHS criteria and amongst these 5 have been evaluated in childhood.[26] The oscillometric Space Labs 9027 passed the AAMI test for systolic BP but failed the diastolic test. It received a C for systolic and a D for diastolic using BHS criteria and was therefore not recommended. The Takoda TM-2421 (also oscillometric) received a C for both systolic and diastolic BP utilising the BHS procedure and was also not recommended. However, the Tycos Quiet Track (Welch Allyn) oscillometric device passed both AAMI and BHS criteria and was recommended.

One of the issues that has arisen in relation to ABPM is the question of the standards used to define population normal blood pressures. Since devices differ in a number of ways and are not necessarily directly comparable, unlike mercury sphygmomanometry, should standards be device specific?[13] This matter remains unresolved at present but will need to be addressed especially as there are a number of devices in paediatric use worldwide but only nomograms prepared utilising one or perhaps two devices available.

Systolic Hypertension

Historically there has been an emphasis on diastolic blood pressure and diastolic hypertension. There has also

been a view that systolic blood pressure and systolic hypertension has been benign and less clinically important. Diagnosis of hypertension used to be based on diastolic blood pressure thresholds but there has been a change of emphasis. There is evidence that systolic hypertension is a clear cardiovascular risk factor in adults.[31] From systolic hypertension treatment trials also in adults, there is clear benefit compared to placebo in terms of myocardial infarction, heart failure and stroke.[32,33]

From a paediatric perspective systolic hypertension is more common than diastolic hypertension in children,[14,34] systolic blood pressure is more closely related than diastolic blood pressure to left ventricular mass (LVM) and left ventricular mass index (LVMI) in normotensive and hypertensive children[35,36] and the risk of left ventricular hypertrophy (LVH) in children is influenced to a greater extent by systolic blood pressure elevation than by diastolic blood pressure elevation.[37] Therefore, systolic hypertension in children should be considered of importance in terms of prognostic influence, trials of anti-hypertensive medication in children should focus on systolic hypertension and therapy for paediatric hypertension should be directed at normalisation of systolic blood pressure even when diastolic blood pressure is within the normal range.[14]

White Coat Hypertension

Is white coat hypertension common and does it matter? The former question is fairly easily answered. Yes it is common as has been shown in a number of studies and has been identified in 53%, 45% and 22% of 115 children referred for evaluation of elevated casual blood pressure who underwent 24 hour ABPM if compared to Task Force criteria, mean BP or BP load respectively.[15] Is it innocuous? This is another matter and the answer presently is not clear. However, it may not be a benign entity and could indicate an early stage of cardiovascular dysfunction.[13,38,39] This might justify individuals classified as manifesting this phenomenon being followed up in the longer term to define whether they eventually develop sustained hypertension.

Primary Hypertension

Hitherto, as mentioned previously, primary hypertension in childhood, compared to adults, contributed a small proportion of the overall hypertensive population where secondary hypertension predominated. However, there is a changing pattern emerging and this is particularly linked to obesity. The prevalence of overweight children in the USA. increased from 5% in the 1960's to 11% in the 1990's[7] and is likely to be 30% or so at the present time if Canadian data are considered.[40] In the USA, the number of overweight children has doubled in the past 2-3 years and in the world it is estimated that there are 22 million children <5 years of age who are overweight.[5]

Obese children are at approximately a 3-fold higher risk for hypertension than non obese children and this is probably the major factor in the increasing numbers of children with primary hypertension.[7]

The mechanisms of hypertension in obese children and adolescents is multi-factorial. The following are considered to play some part:- excess renal sodium reabsorption; insulin resistance; renal structural changes; altered vascular structure and function; renin-angiotensin-aldosterone activity; sympathetic nervous system overactivity and alterations in the hypothalamic-pituitary-adrenal axis.[41]

In addition there are pre-natal influences that appear to be linked to post-natal growth that almost certainly play a part.[42,43] Twenty-five percent of children with low birth weight but high body mass index (BMI) at 12 years have been shown to subsequently develop a high blood pressure compared to 9% of those with a high birth weight and a low BMI.[43] Evidence also supports the view that hypertension originates in slow foetal growth followed by rapid compensatory growth in childhood.[42] It has also been shown that this path of growth has a greater effect on the risk of disease among children who live in poor social conditions.[43] From these studies the primary prevention of hypertension may depend on strategies that promote foetal growth and reduce childhood obesity.

Secondary Hypertension

As has been mentioned already secondary hypertension in childhood is the main type of hypertension that requires treatment and renal disease predominates as the cause. Inspite of the increasing prevalence of primary disease it still remains important to exclude a secondary aetiology before assuming that the hypertension is primary in nature.

There are many transient causes of hypertension in the young and amongst these renal pathology predominates in the form of various types of glomerulonephritis or conditions leading to renal impairment. However,

neurological disorders, drug therapy and various states of salt and water overload, some iatrogenic, contribute to this group of factors.[3] Sustained hypertension, on the other hand, can be considered under a number of headings as shown in Table 1 with again renal causes predominating. The commonest cause of secondary hypertension is some form of parenchymal renal disorder with the coarsely scarred kidneys of reflux nephropathy topping the list followed closely by various glomerulonephritic disorders. Renovascular hypertension contributes approximately 10% of cases but is important since it has the potential for cure by some form of intervention, either transluminal angioplasty or revascularisation surgery. Catecholamine excess hypertension and various corticosteroid excess states or low renin hypertensive states are extremely rare.[44]

Recent advances in terms of imaging have improved the diagnostic skill in identifying the underlying cause of increased blood pressure in childhood including the use of Doppler and computed duplex sonography, colour Doppler sonography and ACE inhibitor renography especially for renovascular disease.[45] However, the sensitivity and specificity of these techniques still remains less than might be hoped for and the gold standard diagnostically for renovascular hypertension is still renal angiography to which might be added renal vein renin sampling to localise sources of excess renin release.[46] Magnetic resonance and CT angiography are utilised at times but the former is still relatively insensitive in picking up intra renal vascular pathology and the latter exposes the child to unacceptably excessive radiation.[47,48]

MIBG scanning, labeled somatostatin scanning, caval catecholamine sampling as well as CT and MRI scanning all have roles in identifying the site of a catecholamine secreting tumour[3,49,50] and newer molecular genetic studies are revolutionising the understanding of some of the rare low renin hypertensive states.[17]

Therapeutically, apart from anti-hypertensive medication that will be dealt with subsequently, what has played a major part in changing the management of renovascular disease has been the development of transluminal angioplasty for amenable renal artery stenosis[51,52] as well as the more sophisticated revascularisation surgical techniques including not only by-pass surgery but also auto transplantation and major vascular reconstruction including the aorta.[53,54] Stenting and embolisation have occasional roles and, of course, nephrectomy still remains a necessity at times. The possibility of gene therapy is also on the agenda especially in the light of knowledge of the various mechanisms involved in angiogenesis and preliminary data from treatment of coronary artery disease.[55] This, however, is not as yet a serious option.

Table 1 Causes of sustained hypertension in children

Coarctation of aorta
Chronic or end stage renal failure
Parenchymal renal disease
Reflux nephropathy
Chronic glomerulonephritis
Congenital or inherited renal disease
Other acquired renal disease e.g. following HUS
Renovascular disease
Renal tumours
Catecholamine excess
Phaeochromocytoma
Paraganglioma
Corticosteroid excess/low renin states
Some congenital adrenal hyperplasias
Cushing's disease/syndrome
Conn's syndrome
Liddle's syndrome
Apparent mineralocorticoid excess
Essential hypertension

Monogenic Hypertension

Amongst the many secondary causes of hypertension some monogenic disorders have been identified[17] including Liddle's syndrome (sodium channel defect), apparent mineralo corticoid excess (11-beta-hydroxy-steroid dehydrogenase defect) and glucocorticoid suppressible aldosteronism (aldosterone synthase defect) that present with hypokalaemic low renin hypertension and require specific therapeutic approaches. These conditions can be suspected by a number of investigative procedures but now specific confirmation is possible by molecular genetic studies.[3,56-58] These findings might throw some light on genetic influences in the aetiology of adult essential hypertension but at present the latter would appear to be a multifactorial and polygenic disorder.

Anti-hypertensive Medication

Paediatricians have in the past been severely handicapped in the management of their patients by the lack of easily available data on hypotensive agents in comparison to their

adult medical colleagues. The result of this has been that children have usually been treated by less modern agents since the pharmaceutical companies have not, in the development of the agents, undertaken trials in children and usually market the product with a "not for use in children" recommendation. Paediatricians have, as a result, undertaken studies themselves or by use developed protocols that have provided dose schedules for their patients, although these have often not been so rigorous as those available in adult medicine. Recently, however, in an attempt to overcome this handicap, new regulations have been introduced by the FDA in the United States in the hope of encouraging pharmaceutical companies to focus on the paediatric end of the age spectrum when developing and marketing their products.[19-21] Needless to say this has involved a financial carrot to the companies by extending the deadline for the discontinuation of their patent rights if they embrace the paediatric age range in controlled trials. This has led to some hastily put together and poorly thought out studies being launched but inspite of this it is a step in the right direction. Hopefully paediatricians will have greater opportunities in the future to prescribe with confidence newer and more focussed therapeutic agents rather than relying on drugs that adult physicians had discarded a decade or so ago.

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