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Low nephron number—a new cardiovascular risk factor in children?

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Abstract There is increasing evidence that primary hypertension, coronary heart disease, and other aspects of the so-called metabolic syndrome that develop in adulthood are primed in fetal life or early postnatally. The identification of this phenomenon, also known as prenatal or fetal programming, and the detailed characterization of the underlying pathomechanisms will greatly influence the understanding of these diseases. The present paper reviews recent experimental and clinical evidence that low nephron number, found in patients with renal dysplasia and low birth weight, is a risk factor for cardiovascular disease in later life. Therefore, it is important to identify children at risk as early as possible in order to treat them early and to prevent the development of end-organ damage. This could be an important goal for pediatrics in the near future.

Keywords Nephron number · Low birth weight · Hypertension · Cardiovascular disease · Nephrogenesis · Prenatal programming

The kidney and essential hypertension

Hypertension is one of the most common diseases in the world with an incidence of 25% in patients older than 45 years. In less than 10% of adult patients hypertension is secondary, i.e., there are specific organic causes leading to an increase in blood pressure. In the remaining group, the origin of hypertension is unknown, or an organic

cause can be excluded leading to the term “essential or primary hypertension”. This group is very heterogeneous and it is fair to assume that different pathomechanisms are involved. About 50% of persons with essential hypertension may have their hypertension explained by genetic factors [1], in the remaining 50% the causes are still unclear. One hypothesis is that the kidney itself may be not only the victim, i.e., the target organ, but also the source of primary hypertension.

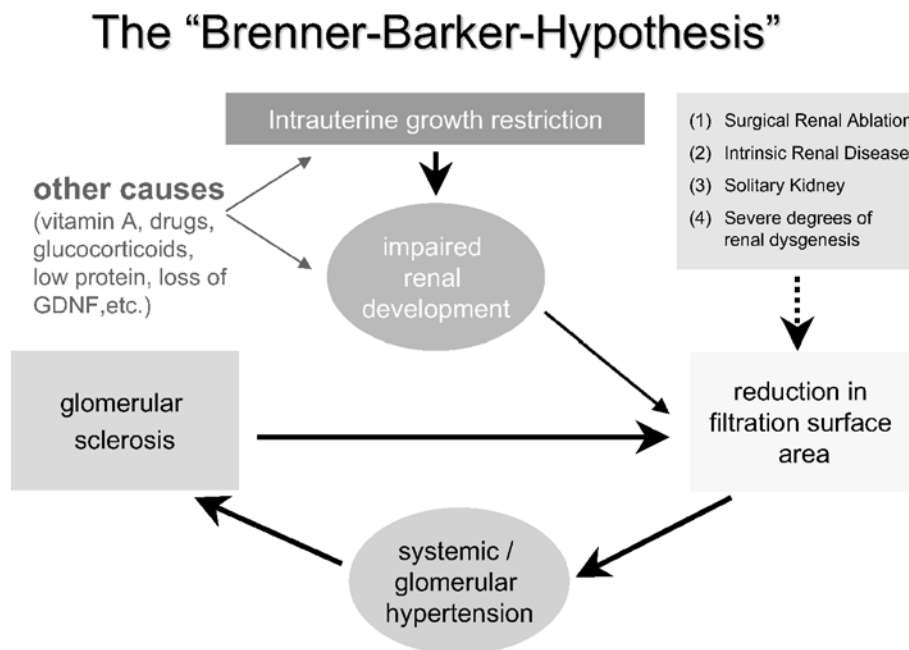
Major evidence for a potential pathophysiological role of the kidney in the genesis of essential hypertension came from studies following renal transplantation. Animal model cross-over studies using kidneys from hypertensive and normotensive rats suggest that hypertension “goes with the kidney”, i.e., if a normotensive animal received the kidney from a hypertensive animal it developed hypertension and vice versa [2]. In parallel, patients who received kidneys from donors with cerebral hemorrhage (as suggestive evidence of hypertension) tended to have higher blood pressure levels than patients with transplants from presumably normotensive donors [3]. Moreover, individuals who had end-stage renal failure as a result of hypertension despite no primary renal disease became normotensive when they received well-functioning allografts from a normotensive donor [4].

Recent experimental and clinical evidence points to the fact that not a global dysfunction of the kidney, but more specifically a structural abnormality, namely a reduction in kidney mass (nephron number), may cause the development of essential hypertension. Hypertension is commonly observed in certain inbred rats strains in which the filtration surface area is congenitally diminished (i.e., the Munich Frömter Wistar rat). In experimental animals as well as in patients, any reduction in filtration area (either acquired in the course of intrinsic renal disease or after surgical ablation) leads to the development of hypertension and progressive renal failure. In addition, it has been shown that in some individuals born with a solitary kidney or with more-severe degrees of dysgenesis (i.e., oligomeganephronia), hypertensive renal disease develops [5].

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Fig. 1 Linking two hypotheses—the Barker/Brenner hypotheses—how any reduction in renal filtration area could lead to glomerular and systemic hypertension and subsequent glomerulosclerosis (Brenner hypothesis) and how this could be influenced by intrauterine growth retardation and impaired renal development (Barker hypothesis)



The first to provide a pathophysiological concept of how any reduction in renal mass may lead to essential hypertension in more detail was the group of Brenner [6]. In 1988 they published their seminal paper “Glomeruli and blood pressure. Less of one, more the other” where they postulated that “a renal abnormality that contributes to essential hypertension in the general population is a reduced number of nephrons” [6]. From there on this concept was known as “The Brenner hypothesis” or “The nephron-underdosing hypothesis”. In recent years much experimental and clinical evidence has been accumulated and the hypothesis now presents a valid concept. In particular, studies of nephrectomy early in fetal or neonatal life (i.e., during the period of active nephrogenesis) documented the subsequent development of hypertension before microscopic glomerular damage developed in adult animals. This finding provides further evidence for a pathogenetic link between low nephron number and hypertension [7, 8]. Of particular note in view of a confirmation of the concept are recent data from an autopsy study of patients with essential hypertension [9]. Here, there was a significantly lower number of nephrons as well as a higher glomerular volume compared with age- and sex-matched normotensive patients, thus providing the first confirmation in humans for the hypothesis of Brenner et al. [6]. One important aspect of how a low nephron number would transfer into high blood pressure was glomerular hyperfiltration, which was postulated to derive from a reduction in nephron number (Fig. 1). This concept involves maladaptive structural and functional changes of hyperfiltrating glomeruli leading to increased glomerular pressure and glomerulosclerosis, which is then followed by systemic hypertension [10].

Causes of low nephron number

The definite cause of low nephron number is currently unclear, i.e., genetic or environmental factors may play a role. Glomerular number is determined during nephrogenesis through a coordinate interplay of several factors [10]. Disturbance in any of these factors may lead to defects or deficiencies in nephrogenesis and thus to lower nephron number. This was recently demonstrated in mice that are heterozygous for GDNF (glial cell-derived nerve growth factor), a factor that is essential for nephrogenesis. These mice show about a 30% reduction in nephron number and subsequently develop hypertension in adult life [11]. Two other diseases, namely the branchio-oto-renal syndrome and the nail-patella syndrome, are known to be associated with reduced nephron mass leading to either renal hypoplasia or dysplasia. In both diseases the involved genes or products are known, i.e., EYA-1 and Lmx-1b. Like GDNF, both are involved in early nephrogenesis. This may further illustrate how disturbances of nephrogenesis lead to lower nephron number [11, 12]. Other factors that have been shown to interfere with nephron development and lead to a lower endowment of nephrons are vitamin A and glucocorticoid treatment during pregnancy [13], environmental toxins and some drugs (i.e., gentamicin), hyperglycemia [14], and also a low-protein diet or malnutrition during pregnancy as reflected by low birth weight [15, 16, 17]. Putative mechanisms of these effects are for example alterations in the components of the hippocampal/hypothalamic/pituitary/adrenal axis or in the expression of angiotensinogen (hypothalamus) and angiotensin II receptor type I [AT(1)] in the medulla oblongata. The surprising finding is that the period when the kidney and the brain are most vulnerable, is very early in development, when both organs are in an extremely primitive state of development [18].

Low birth weight and nephron number

In rats that were fed a low-protein diet, Vehaskari et al. [17] documented a correlation between reduced birth weight, decreased formation of nephrons, and adult hypertension. A relationship between weight at birth and the number and size of glomeruli has also been established in humans [19]. In an autopsy study using three-dimensional quantitative morphological techniques, Hughson et al. [20] confirmed a relationship between age, race, gender, total glomerular number, mean glomerular volume, body surface, and birth weight. According to their data the regression coefficient predicts a gain of 157,426 glomeruli per kilogram increase in birth weight [20].

Experimental data on blood pressure in models with low birth weight

Experimental data from animal models confirm the link between intrauterine growth restriction (IUGR) and the development of adult essential hypertension. Most experiments have been carried out in rats. Reduced sodium chloride administration to the mother induces failure to thrive in the fetus and postnatal hypertension as well as renal insufficiency [21]. A similar effect is achieved by the reduction of maternal protein intake in the second half of pregnancy [22, 23]. Likewise, IUGR and hypertension result from partial surgical ligation of placental perfusion in rabbits [24]. The mechanisms leading to hypertension in rats with IUGR are not entirely clear. One essential factor appears to be the reduction of intact nephron number by impaired nephrogenesis [13, 24, 25]. Another potentially important factor in the genesis of hypertension after IUGR might be an increase in the gene expression of various tubular sodium channels, possibly indicating a higher reabsorption ratio for sodium chloride in rats [26]. However, piglets with IUGR present with an increased renal loss of sodium chloride [27, 28].

Apart from these morphological data, functional data pointing to potential pathomechanisms have been collected. Initially, the focus of interest was on the role of the renin-angiotensin-aldosterone system (RAAS) [29]. However, an activation of the RAAS is not observed in all animal models [23]. In human stillborn fetuses that were growth retarded a persistent juxtamedullary expression of renin could be demonstrated [30].

Another important system in the regulation of mineralocorticoid activity is the renal cortisol/cortisone shuttle. The enzyme 11β -hydroxysteroid dehydrogenase type 2 (11β -HSD 2) regulates the inactivation of mineralocorticoid active cortisol to inactive cortisone (Fig. 2). Newborn and adult rats that suffered from IUGR have an increased renal expression of the mineralocorticoid receptor and a significant reduction of the 11β -HSD2 gene [23]. There is an increased cortisol/cortisone shuttle in about 20% of children with former IUGR, implying a decreased activity of the 11β -HSD 2 [31].

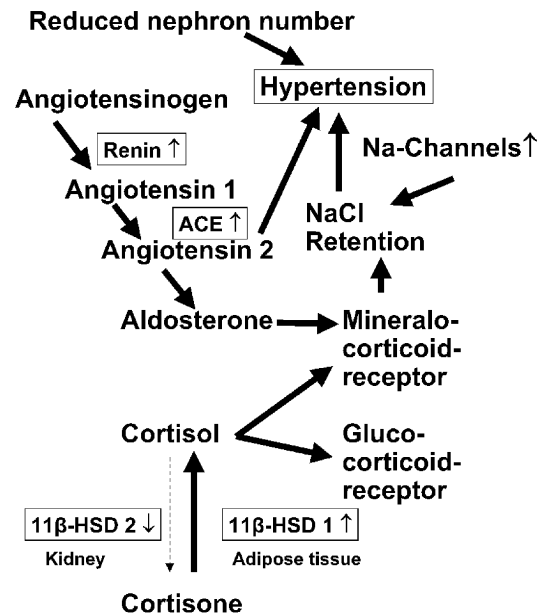


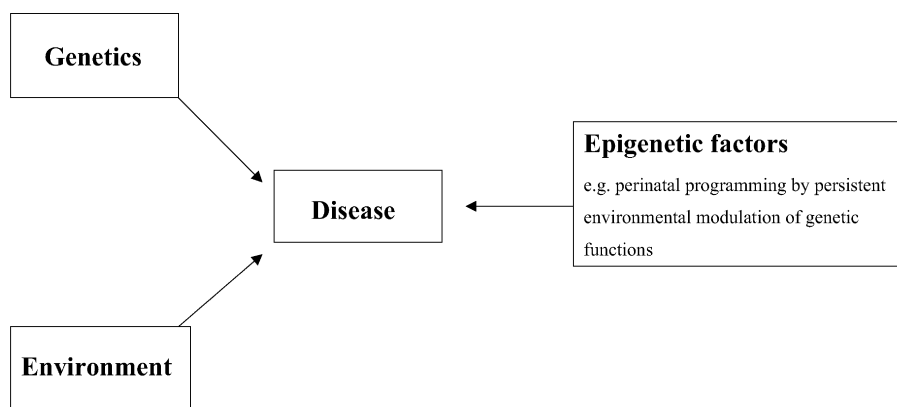
Fig. 2 Overview on potential pathomechanisms predisposing to the development of arterial hypertension after intrauterine growth restriction (11β -HSD 11β -hydroxysteroid dehydrogenase)

The genesis of hypertension after IUGR does not necessarily need to be exclusively of renal origin. Obesity, which is frequently encountered after IUGR, may contribute to the development of hypertension, e.g., by an increase in cortisol synthesis in the adipose tissue (11β -HSD 1) [32] or by an increase in sympathetic activity via elevated adipose tissue leptin synthesis [33].

Blood pressure in patients with low birth weight

The increased prevalence of hypertension in adults with former IUGR is well known [34, 35]. However, the genesis of hypertension in adulthood may be multifactorial. Therefore, it is of utmost interest to discover whether there are more children with hypertension after IUGR. The present data, however, are at best partially conflicting: Zhang et al. [36], for instance, did not find a relationship between blood pressure and birth weight in twin pairs. Likewise, in a large study of almost 900 children there was no evidence to suggest that children with a low birth weight who became overweight or obese had extra high blood pressure [37]. In contrast, 58 Israeli children with former IUGR aged 4–6 years had a significantly increased blood pressure compared with controls with normal birth weight [38]. Similarly, the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) based on nearly 2,000 children at the age of 3 years showed a slight but statistically significant increase in blood pressure in formerly growth-retarded compared with non-growth-retarded infants [39]. These results were also confirmed in Dutch children [40]. However, studies showing a positive association between increased blood pressure and low

Fig. 3 Schematic concept of perinatal programming



birth weight only show absolute differences in blood pressure ranging between 1 and 3 mm Hg.

Additional data are available on the role of IUGR in adolescence. At the age of 22 years formerly intrauterine growth-retarded young adults have slightly increased systolic blood pressure values. Accelerated weight gain in early childhood adds to this risk, which is partly mediated through the prediction of adult fatness [41]. Another study showed that early as well as late catch-up growth is associated with increased systolic blood pressure in adolescence, whereas only late catch-up growth is related to diastolic blood pressure. These findings suggest that catch-up growth, irrespective of age, is associated with increased blood pressure in adolescence [42, 43].

In summary, despite some studies documenting significantly elevated blood pressure values in children small for gestational age after IUGR, the effect is minor and appears to be influenced by the degree of catch-up growth and not by the low birth weight per se.

Concept of perinatal programming

Data on the inverse relationship between blood pressure and birth weight and the possible mechanisms underlying this phenomenon suggest an epigenetic effect of perinatal factors on the development of later diseases such as the metabolic syndrome. This effect is called “perinatal programming”. Perinatal programming describes the persistence of the environmental impact on genetic programs in an individual (Fig. 3); it is discussed not only for the metabolic syndrome, but also for hypertension and renal diseases [44, 45, 46]. Rather than being based on one another, IUGR and hypertension later in life appear to be two different endpoints of intrauterine programming. This notion is substantiated by findings in humans indicating that the phase of nutrient deprivation in pregnancy is more important for the programming of later diseases than the extent of calorie reduction [47]. Finally, programming is not only confined to entities of the metabolic syndrome but also involves a number of further endocrine and neuroendocrine functions such as appetite regulation [48, 49, 50].

Conclusion

It is far too early to definitely establish low nephron number as the one and only cause of essential hypertension. There is, however, substantial, steadily growing, and valid evidence that low nephron number, at the moment presumably best reflected by low birth weight, is a substantial risk factor for cardiovascular diseases in later life of some populations. Since at least several intrauterine risk factors for low birth weight and low nephron number are already known, it is certainly important to avoid these factors during pregnancy. In the near future it will be more important for pediatricians to identify children at higher risk for cardiovascular disease early in life in order to monitor and treat them adequately.

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