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Review Article

Arterial Hypertension in Children and Adolescents and Its Relation with Low Birth Weight as Expression of an Intermediate Stage between the Perinatal Period and Adult Hypertension - A New Piece in the Arterial Hypertension Puzzle?

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Abstract

Background: Currently, the perinatal period is considered to be related to primary adult arterial hypertension. In the intermediate period (which includes childhood and adolescence) between the perinatal and the adult hypertension stage, certain persons present with high blood pressure. In this paper, the relationship between this period and the low birth weight (LBW) found in the medical history of persons with primary adult arterial hypertension is studied. **Methods:** We carried out a systematic search in Medline for low birth weight, childhood and adolescence high blood pressure, and adult primary hypertension and low birth weight and picked up approximately 50 articles from the hundreds of titles and abstracts, reviewing them in order to find the missing piece of the puzzle: the intermediate stage of childhood and adolescence high blood pressure. **Results:** The present study points to the continuity of the mechanisms involved in primary/essential HTN, from the perinatal to the adult period. It draws the attention on the interval between the perinatal and the adult period that includes childhood and adolescence. **Conclusions:** Data in the literature seem to outline an evolution of HTN throughout the whole lifetime of the patient, from the perinatal period (in which intervene genetic, epigenetic, and environmental factors) to adult HTN. The time frame between these two periods appears as an intermediate stage which corresponds with childhood and adolescence.

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Keywords: Primary arterial hypertension; Low birth weight; Children; Adolescence; Intermediate stage

Introduction

Primary or essential arterial hypertension (HTN) represents 85-90% of the total HTN cases. Cutler et al. mention that 24% of the adults in the USA undergo treatment with antihypertensive medication [1]. In spite of all the notable progresses in the pathogenesis and treatment of primary HTN, its etiology still needs elucidation. Primary HTN has a strong family character and is characterized by a common onset in the adult. The question is about the period from birth until adulthood, why the familial factor becomes overt so late and if there is a continuum of the predisposition for HTN along this period.

A recent progress is represented by studies regarding the relation between the perinatal period and adult HTN. In the perinatal period, epigenetic and environmental factors can be involved, which can be reflected in adult HTN. The participation of genetic factors is also considered important. The first findings of Barker and Osmond, followed by other studies, pointed to the relation between the birth weight of the fetus and adult HTN. They observed that low birth weight (LBW) in the perinatal period is frequently associated with adult HTN [2]. In these studies, LBW was related to malnourishment in special circumstances, when nutrition was inadequate from the quantitative and qualitative point of view. Other external factors have been later on incriminated in the occurrence of LBW: low protein diet, corticosteroids, and placental insufficiency.

The perinatal stage stands out as an important period in the occurrence of primary HTN. Taking into consideration the existence in the evolution of primary HTN of a perinatal period and of a period represented by primary adult HTN, it is necessary to analyze the interval between these two periods. This intermediary period includes childhood and adolescence. Commonly, in this period HTN is absent. However, some persons have been found to present high blood pressure during this interval. This observation points to a continuum of the mechanism involved in the pathogenesis of primary HTN. A relation between LBW and adult primary arterial hypertension is well known. It has been also stated that there could be a possible relation between LBW and childhood and adolescent HTN. In this case one can discuss a continuity of perinatal HTN mechanisms. LBW could be considered like a marker of that evolution. We have also studied whether childhood and adolescent HTN progress towards adult HTN and thus, we have noticed continuity of HTN during this intermediate period.

The present paper analyzes blood pressure in children and adolescents in relation with birth weight, an important indicator, like a marker which permits assessment of the evolution to adult age of the factors involved in primary adult hypertension. The main objective of this paper is to address the intermediate stage in tracking blood pressure from the perspective of the new markers, in our case LBW. Knowing this intermediate stage opens perspectives to prophylactic measures for primary HTN. A relation between the perinatal period and primary adult hypertension through the intermediate period of childhood and adolescence lead us to analyze this so important disease.

Low birth weight and arterial hypertension – pathogenetic aspects

Pathogenesis of primary HTN involves genetic and environmental factors. Genetic studies analyzed the involved genes. An argument for the involvement of hereditary factors is represented by family history of hypertension in patients with primary HTN and in twins. Bloetzer et al. by screening hypertension in children, found a sensitivity of 41% for at least one parent history [3]. Fuentes et al. also found that children with family history of hypertension have a higher BP [4]. Similar results are reported by Himmelmann et al. who noted that offspring of mothers with HTN present higher incidence of HTN than controls [5]. One could not identify a single gene in primary HTN, since several genes are involved, which confers the disease a polygenic character. Genome Wide Association Studies (GWAS) found a limited number (a dozen) of loci associated with primary hypertension [6].

A meta-analysis of twin studies in literature, including 3901 pairs of twins, performed by McNeil, shows that their relation with LBW does not bring conclusive evidence for genetic factors. The study included both monozygotic and dizygotic twins [7]. Bergwal et al. in their study on twins, show that LBW is associated with increased risk of hypertension independently of genetic factors, familial factors and risk factors [8].

Genetic factors are related to epigenetic factors. Ritz et al. consider that the transcription of the genetic code can be modified by epigenetic factors, a fact that could be related to plasticity during the development of the fetus [9]. Epigenetic modifications are associated, according to Dressler et al. with changes in gene expression [10]. The relation of the fetus with the environment influences intrauterine development. There is permanent interaction between environmental factors and its genes.

The influence on the intrauterine development of the fetus is reflected in intrauterine growth restriction (IUGR) in the nephrogenesis process, its consequence being a diminution of the number of nephrons. Thus, the fetus will present LBW and later HTN, which occurs mainly in adulthood, and less frequently in childhood or adolescence.

The fetus has to adapt to the intervention of such a complex of factors. During this process, in special circumstances, the fetus adapts its circulatory system so that to provide nutrition mainly to vital organs, to the detriment of other organs, for example the kidney. As a consequence, the process of nephrogenesis is clearly influenced by the diminution of the number of nephrons. The fetus will suffer IUGR and it will present LBW.

The fetus that has LBW associated with a low nephron number will develop later – mainly in adulthood- HTN.

Two hypotheses try to explain the relation between HTN and LBW- Barker's hypothesis and Brenner's hypothesis.

Barker's hypothesis-Low birth weight and arterial hypertension

Barker issued the hypothesis that, during the perinatal period, external factors can act to influence subsequent evolution, a process defined as "programming" [11]. Later, increased incidence of adult HTN was observed in children born during the famine, but no other causes of it were found.

Barker and Osmond found a reversed relation between LBW and HTN (Barker and Osmond) [2]. They showed that women with LBW at birth will have children who will present HTN in adulthood. Experimental and clinical studies provided data in support of this hypothesis, although there were also a few studies that did not confirm it. The correlation between LBW and HTN has become an important element in studies addressing HTN, the perinatal period appearing as an essential factor of primary HTN.

Placental insufficiency causes hypoxia of the fetus and it does not provide appropriate nutrition. Alexander et al note that placental insufficiency predisposes to LBW and HTN in growth-restricted offspring [12]. IUGR produced by placental insufficiency can determine a decrease in the expression of the genes involved in nephrogenesis. Fetal growth is disturbed by IUGR and LBW that affect the "programming" of fetus development.

This can also be altered by modifications of the maternal environment that can affect the methylation status of placental genes who affect fetal "programming" [13]. The relation between preeclampsia and primary HTN is mainly based on the fact that preeclampsia is accompanied by placental insufficiency. This can prevent the normal development of the fetus with IUGR and LBW. Furthermore, preeclampsia can influence fetal evolution by programming HTN, which can become manifest in infant, young, and adult offspring.

Davis et al, analyzing 18 studies on 45,249 individuals find that young adults born to preeclampsia women have increased BP and BMI [14]. Moreover, one has to take into account the fact that preeclampsia women present high incidence of paternal hypertensive history. It was found that premature babies, who also have LBW, present in adulthood high incidence of HTN.

In fact, LBW full-term babies and premature babies are associated with low nephron number [15]. Vasilyeva et al. found that in humans, 22% of pre-term born babies present LBW and develop HTN 15 years later [16]. Brenner's hypothesis is to be considered in the context of other factors: genetic, epigenetic and environmental, for example malnutrition, placental insufficiency, diabetes, mother's drug consumption, etc [17]. Barker's hypothesis about the intervention of environmental factors in the organogenesis, that results in LBW and adult HTN, points to a possible continuation of the activity of the involved factors in the intermediate period between the perinatal and the HTN period of the adult.

Similar remarks belong to Yliharsila who considers that effects of birth size on BP could perpetuate until adult age [18].

Brenner's hypothesis-Low nephron number and high blood pressure

Some studies noticed that patients with HTN have a lower nephron number, sometimes half of the nephron number of persons without HTN [19]. Genetic, epigenetic, and environmental factors are involved in the development of the kidney. In its intrauterine life, the kidney undergoes "programming" influenced by these factors which can alter the development of the nephrons, reducing their number. Concomitantly, there exists a relation between birth weight and the low number of nephrons, a fact confirmed by Manalich et al. [20].

Brenner issued the hypothesis of the relation between the number of nephrons and HTN. According to him, people with low nephron number suffer phenomena of hypertrophy and hyper-filtration, by which the remaining nephrons maintain the functionality of the kidney, taking over the function of the missing nephrons.

At the same time, according to Brenner et al. the diminution of the nephron number could represent a cause of high blood pressure. The low nephron number is attributed an incapacity of eliminating sodium, which could represent a risk factor for HTN. Other factors could intervene as well: vascular reactivity and sympathetic nervous over-reactivity [17].

It is also to be mentioned that the association between low nephron number and higher adult BP was noticed in white adults and Australian Aborigines. It was not found in Afro-Americans probably by association of other factors. Barker's hypothesis and Brenner's hypothesis, with all the arguments that support the relation between the factors which intervene in the perinatal period and which could be in relation with primary HTN in adults cannot totally explain the pathogenetic mechanisms of HTN. An important part is played by the intervention of genetic, epigenetic, and environmental factors. (Figure 1).

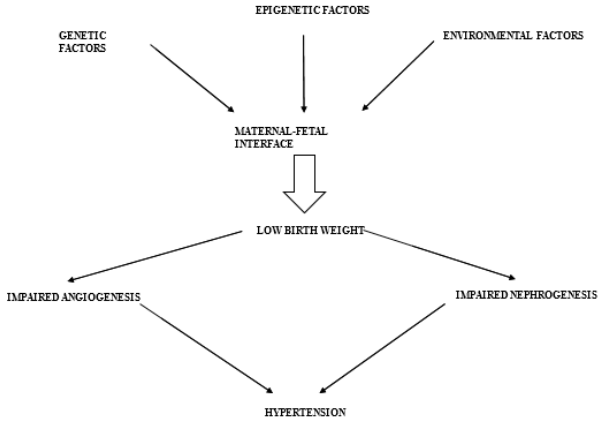

Figure 1: A synoptic view on the pathogenetic link between LBW and HTN.

Risk factors for arterial hypertension in the intermediate period

Obesity is considered the main risk factor for HTN in children and adolescents. Andrade considers that childhood obesity is one of the main factors predicting adult HTN. It is associated with other cardiovascular risk factors such as: dyslipidemia, abnormal glucose metabolism, insulin resistance, inflammation, and impaired vascular function [21]. Excessive salt consumption could also be a risk factor. Other risk factors (lack of physical exercise, exaggerated computer activity, smoking) are considered to act as epigenetic or environmental factors. The fact that these factors could act in combination with genetic factors in the intermediate stage supports the issue that the programming process of high blood pressure is not influenced only perinatally. Epigenetic and environmental factors can also be present and active in the intermediate stage.

For example, it was found that smoking can trigger the process of methylation at DNA level acting as an authentic epigenetic factor [22]. Another remark is that prophylactic measures for HTN are to be applied in this stage. Bucher et al classifies risk factors into preventable and non-preventable. Preventable risk factors for elevated blood pressure in children are: overweight, dietary habits, salt intake, sedentary lifestyle, poor sleep quality, and passive smoking. Non-preventable risk factors include: race, gender, genetic background, low birth weight, prematurity, and social-economic inequalities [23].

In order to analyze the relation between the intermediate period and the other two periods in the evolution of HTN, the perinatal and the adulthood period, respectively, we considered as a useful landmark the relation of these periods with LBW. If this landmark is present in the intermediate period, namely in childhood and adolescence, as well as in that one of adult HTN, one may consider that there is a continuum of the mechanisms involved in the pathogenesis of primary HTN.

Observations on the relation between the perinatal period, adult HTN, and the intermediate stage

Since the relation between the two periods of the evolution of BP, the perinatal period and adult HTN, includes an intermediate stage of BP, a presentation of the findings of specialized literature is necessary. We used as standard of reference the relation with LBW, the principal expression of the influence of the epigenetic and environmental factors.

Numerous studies support the hypotheses of Barker and Brenner. Some of them mention this relation without mentioning what happens between the perinatal period and adulthood. The perinatal period as a reference point usually addresses weight at birth, LBW being most often analyzed in relation to adult HTN as LBW is the most frequent expression of the epigenetic and environmental factors that act on the fetus.

Animal studies

A meta-analysis of animal experiments showed that general malnutrition or very low protein intake is associated with increased levels of systolic BP or mean BP. On the contrary, diastolic BP is influenced only by low protein intake [24]. As far as the involved mechanisms are concerned, studies performed on rats with regard to the relation between the perinatal period and HTN in adult animals (rats) find a deficit in the total nephron number and impairment of the renin – aldosterone system [25]. Woods demonstrates that protein malnutrition of the mother has "a suppressive effect on the renin-angiotensin system of the new-born and, at the same time, programs adult hypertension in adult mice" [26].

Human studies

As we have noted before, the first who mentioned an inverse relation between LBW and HTN were Barker and Osmond [2]. After conducting numerous studies they confirmed the existence of this relation. We mention some of these studies. Law and Shell analyzed specialized 1956-1996 literature making reference to 66,000 subjects aged 0-71 years and found that BP is in inverse relation to birth in children and adults (Law and Shell) [27].

Hardy et al reach a similar conclusion analyzing a British cohort of 3157 persons. They also find an inverse relation between birth weight and BP values [28]. The studies by Tamakoshi et al reveal an independent association of adult HTN with LBW. One cross-sectional study was conducted on a workplace population [29]. Analyzing a cohort of Swedish men aged 50, 60, and 70 years old, Koupilova et al. found an inverse correlation of birth weight with blood pressure at the age of 50. The relation does not increase after this age, respectively between 50-70 years, although it is considered that risk increases with age [30].

The inverse linear relation between LBW and adult HTN was suggestively named by Mu et al. "small baby hypothesis". In a meta-analysis including 78 studies and 28 articles (reporting 27 original studies) Mu et al. drew the attention on the existence of an inverse relation between birth weight and the risk for systolic HTN. Mu et al. found that this risk increases in those with low birth weight (<2500 g). They also noticed that those with <4000 g birth weight have higher risks of HTN than those born with a weight >4000 g [31].

It is worth mentioning that the "relation between birth weight and BP undergoes a process of amplification from childhood to adulthood" [32]. The evolution from the perinatal period to adult HTN is analyzed by numerous studies which fail to mention an evident intermediate stage. In fact, it is to be noted that the relation between LBW and adult HTN does not exclude the intervention of environmental and epigenetic factors in the fetus and it suggests an evolution of factors determining HTN in the period between the perinatal and the adult stage. This situation raises the issue of a latent intermediate stage.

Incidence of arterial hypertension in children and adolescents

The incidence of HTN in children is between 1-5%. It is to be noted that secondary HTN is more frequent in children, while primary/essential HTN is more frequent in adolescents. Studies conducted by Lo et al on a cohort of 199,513 children report an incidence of HTN in 3.8% and of pre-hypertension in 12.7% of cases, respectively [33].

It is to be noted that the incidence of hypertension during the period between the perinatal stage and adult HTN involves a significant number of persons. We note a similar HTN incidence in young persons. Secrii et al found HTN in 4% of a cohort of 795 students aged 23.47 +/- 3.23 years [34].

The relation between birth weight and arterial hypertension in childhood and adolescence

Primary HTN does not occur only in adults. It can also develop in childhood and adolescence. The relation with LBW is important since an inverse relation of LBW and HTN was found in adults with HTN. The question is whether this relation is present or not in childhood and adolescence.

Barker et al. were the first to show that the relation between in utero growth and blood pressure does not only concern adult but also childhood HTN [35]. Monitoring annually BP in children aged 5 through 21 years, Uiterwaal et al. find an inverse association between birth weight and systolic blood pressure [36]. Other authors, like Taylor et al. find, in a cross-sectional study on 8-11 years old children, a relation between LBW and BP, but only in girls [37].

The relation between LBW and HTN in adolescence was pointed to by Seidman et al. [38]. A significant number of children and adolescents present pre-hypertension and HTN. Variability of pre-hypertension and hypertension in adolescence was also noticed. Falkner et al observed in a group of 8500 adolescents (using serial determinations of BP), that 7% of the individuals with pre-hypertension detected in this period progress yearly at a 7% rate towards HTN. They also consider that pre-hypertension predicts HTN, but not only pre-hypertension represents a predictive factor of HTN [39].

However, not all authors agree on this hypothesis. Matthes et al. analyzing a cohort of 330 subjects, find that systolic blood pressure in LBW adolescents is not different from that of persons with normal birth weight [40].

The relation between LBW and HTN is difficult to assess as HTN in children and adolescents is under-diagnosed, requiring complex studies aimed at correctly appreciating its prevalence. These data suggest that HTN can have its onset before adulthood, in the intermediate period between the two poles of HTN: the perinatal period and adult HTN.

Tracking arterial hypertension from childhood and adolescence to adulthood

One of the important remarks concerning the relation between perinatal and adult BP is represented by the continuity of HTN in the intermediate stage.

Chen and Wang conducted an important study entitled "Tracking blood pressure from childhood to adulthood - a systematic review and meta-regression analysis". Chen and Wang used 30 retrieved papers and 50 cohort studies and found strong

evidence for the fact that BP progresses from children to adults and for the existence of an association of childhood BP with BP in later life [41].

Bao et al. conducted in the USA a study (The Bogalusa Heart Study) which assessed BP in individuals aged 5-14 years. More than 16 years later they found that HTN persisted in time and had progressed to adult HTN [42]. It is important to note that pre-hypertension in adolescents is also a risk factor for the progression to persistent HTN and cardiovascular disease [43].

Genetic factors intervene in this evolution of HTN from childhood and adolescence. History of hypertension plays its part. Thus, Munger et al. report "persistent elevation of blood pressure among children with family history of HTN" [44]. Birth weight is found to influence both BP values and their variability [45]. Lauer et al. in the Muscatine study conducted on 2445 subjects whose initial HTN was determined at ages of 7 to 18 years, then 20-30 years later, found that adult BP correlated with childhood blood pressure [46].

The Kangwa study is most significant for blood pressure tracking from childhood to adulthood. This study consisted in measuring BP about 14 times in 24 years in 286 persons and found stability of blood pressure tracking from childhood to adult [47]. The progress to HTN in this phase seems to involve genetic factors and situations that depend on epigenetic factors, but also on the influence of other factors, such as environmental factors. Thus, obesity, frequently associated with HTN in children and adolescents is influenced both by genetic and by environmental factors, such as high consumption of sweets and high general caloric intake, or unhealthy nutrition.

An early onset of HTN in childhood and adolescence, respectively in the intermediate period between the perinatal and the adult period, underlines a more precocious expression of genetic factors, spontaneous or more probably related to epigenetic, or environmental factors. The present study points to the continuity of the mechanisms involved in primary/essential HTN, from the perinatal to the adult period. It draws the attention on the interval between the perinatal and the adult period that includes childhood and adolescence. This period can be defined as an intermediate period. Other authors, like Law et al, also drew attention to the fact that "essential hypertension is initiated in fetal life and amplified from infancy to adult age" [48].

The evolution of primary HTN can be discussed in three periods or stages: the perinatal period, an intermediate period or stage, including childhood and adolescence, and the stage of adult primary/essential HTN. If we compare primary/essential HTN with an unsolved puzzle, the remark about the intermediate period between the perinatal and the adult stage -assimilated to a real stage in the evolution of HTN- can be considered as a new missing piece that completes the puzzle.

Conclusions

* Data in the literature seem to outline an evolution of HTN throughout the whole lifetime of the patient, from the periuterine period (in which intervene genetic, epigenetic, and environmental factors) to adult HTN.

*The time frame between these two periods appears as an intermediate stage which corresponds with childhood and adolescence. In this stage HTN may be absent or clinically overt.

*LBW is present in certain adult patients with primary HTN, a fact which is highly indicative of a relation between HTN and the perinatal period.

*LBW is signaled in certain children and adolescents who present HTN, data which could plead in favor of a relation between HTN and the perinatal period. HTN in children and adolescents evolves frequently into adult HTN. It seems that there is a continuum in the evolution of HTN.

* LBW could be utilized as marker of primary arterial hypertension

*The possible intervention during this period of some environmental or epigenetic factors defined as risk factors requires prophylactic measures.

* Primary HTN needs to be approached as a unitary entity.

Perspectives

The intermediate stage between the perinatal period and adult HTN, although less studied, requires a special attention due to a potential involvement of epigenetic and environmental factors, which may later influence the occurrence and evolution of HTN. One has to identify the pathogenetic mechanisms in the intermediate stage, as well as the risk factors involved. Biomarkers of this evolution need also to be identified.

Genetics and epigenetics will probably provide new data about HTN. We foresee the future genetic perspective of gene therapy of primary HTN. Identifying environmental factors and their intervention in the evolution of pathogenetic mechanisms involved in primary HTN, will allow a better control of this disease.

The control and even interruption of the pathogenetic chain of primary HTN which spans over the perinatal period to the adult period through the intermediate stage could represent future objectives, even though they seem difficult to achieve at this stage of our knowledge in the field of HTN.

Declaration of interest

The authors report no conflicts of interest.

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