Arch Clin Biomed Res 2020; 4 (3): 184-194 *DOI: 10.26502/acbr.50170097*

Research Article

Early Detection of Renal Dysfunction in Adolescents Aged 10-13 Years Born with very Low Birth Weight

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Received: 11 May 2020; **Accepted:** 22 May 2020; **Published:** 29 May 2020

Citation: Borovitz Yael, Tschernichovsky Roi, Sokolover Nir, Davidovich Esti, Davidovits Miriam. Early detection of renal dysfunction in adolescents aged 10-13 years born with very low birth weight. Archives of Clinical and Biomedical Research 4 (2020): 184-194.

Abstract

Objective: Very low birth weight (VLBW), defined as less than 1500 gr, is an established risk factor for kidney disease in adulthood. To assess that, we examined whether VLBW manifests signs of renal dysfunction at as early as age 10 years, as reflected by elevated blood pressure, proteinuria and reduced glomerular filtration rate (GFR).

Methods: 103 children aged 10-13 years and born with VLBW underwent consecutive blood pressure measurements, spot urine analysis, and weight and height measurements. Prevalence rates of hypertension, pre-hypertension and proteinuria were calculated. Characteristics were compared between children with normal and abnormal renal function, to identify risk factors for renal dysfunction.

Results: The prevalence of systolic hypertension was 15.8% (95% CI 8.69% - 22.91%) of systolic pre-hypertension 6.9% (95% CI1.96% - 11.84%), and of proteinuria 15.7% (95% CI 8.64% - 22.76%) of the study population. Hypertension was associated with a significantly diminished mean birth weight compared to the remainder of the cohort (939.3gr vs 1111gr, P=0.024). Proteinuria and microalbuminuria were associated with lower mean current body weights: 27.2kg vs 36.7kg P=0.015 and 31.3 kg vs 36.8kg; P=0.023; and with increased mean estimated GFR (126.1 vs 108.3 mL/min per 1.73 m2; P = 0.0059).

Conclusions: In a cohort of children aged 10-13 years, who were born preterm with VLBW, disturbed kidney function presented in considerably higher proportions than in general populations of this age. The findings merit considering initiation of routine screening during early adolescence, for hypertension, proteinuria and GFR in this risk group.

Keywords: Prematurity; Hypertension; Pre-hypertension; Proteinuria; Albuminuria; Glomerular filtration rate

Abbreviations

birthweight (BW), birthweight standard deviation scores (BW-SDS); blood pressure (BP); estimated glomerular filtration rate (eGFR); extremely low birth weight (ELBW); glomerular filtration rate (GFR), hypertension (HTN); low birth weight (LBW); neonatal intensive care unit (NICU); normal birth weight (NBW); standard deviation (SD); very low birth weight (VLBW);

1. Introduction

Abundant evidence links low birth weight (LBW) with various measures of kidney dysfunction. Principally, epidemiological studies have associated LBW with elevated blood pressure (BP) in later life, which may reach overt hypertension (HTN) in adulthood [1]. Estimates of the magnitude of this effect have ranged from a 0.6 mmHg to a 5.2mmHg decrease in systolic BP for every additional kilogram of birth weight [2, 3]. LBW is also an established risk factor for proteinuria, as was first demonstrated in Australian aborigines, for whom LBW predisposes to overt albuminuria (OR 2.8; 95% CI 1.26-6.31); this finding was repeatedly replicated among LBW adults [4-7]. Finally, in addition to its role in the amplification of primary renal disease [7,9], LBW has been found to increase the risk of chronic kidney disease by 70%, according to a systematic review [10] and to increase the relative risk for the development of end-stage renal disease, according to a retrospective analysis of over 2 million children [11]. The hypothesized mechanism is congenital oligo-nephropathy, for which LBW and prematurity are known clinical surrogates [12]. In individuals with a low nephron number the filtration area is smaller, leading to sodium retention, hypertension and impaired reserve in the face of additional kidney injury [13].

In light of the evidence presented above, the screening of LBW individuals for early signs of renal damage has been proposed, yet official guidelines have not been formulated [14]. Two important questions remain unanswered: at what age to commence screening, and for which birthweight categories. LBW - associated renal dysfunction has been demonstrated across all age groups [1], but the majority of studies

have focused on late adolescence and adulthood. As such, the timing of onset has not been sufficiently pinpointed. In addition, the bulk of available data relates to LBW as a whole (<2500 gr), with less emphasis on very low birth weight (VLBW; <1500 gr) and extremely low birth weight (ELBW; <1000 gr) individuals who might be better candidates for screening. Furthermore, the relevant literature often does not distinguish LBW due to prematurity from LBW due to growth retardation; the contribution of each etiology to renal outcomes remains inconclusive [13]. Recent publications shows that elevated blood pressure and altered renal function can be detected already at the age of 14 years in adolescents born premature [15]. Therefore, we sought to determine whether early signs of renal damage can be detected at as early as age 10-13 years in the specific population of preterm VLBW individuals.

2. Materials and Methods

2.1 Study population

Data on 299 VLBW infants born preterm (gestational age less than 36 weeks) between the years 2002-2004 at Schneider Children's Medical Center were obtained from the electronic archives of the hospital's neonatal intensive care unit (NICU). The following parameters regarding NICU hospitalization were collected: weight at birth and upon discharge, gestational age rounded down to the nearest week, whether the subject was a singleton or part of a multiple-gestation pregnancy, whether or not ventilation was administered and if so - the type of ventilation used and the duration in days, the presence of respiratory distress syndrome, congenital malformations of any kind, impaired renal function as reflected by elevated serum creatinine, intraventricular hemorrhage and any other diagnoses made during NICU hospitalization. We were able to establish contact with the families of 169 children and provided them with comprehensive information about the study. Parents of 103 children signed informed consent for their children's participation.

2.2 Data collection

The 103 participants of the study group were summoned to the nephrology clinic at the medical center, where they underwent history taking and a physical examination that included weight, height and BP measurements. VLBW was defined as < 1500 gr, and ELBW as < 1000 gr. Small for gestational age was defined as a birthweight (BW) that is < 10th percentile of the BW for the appropriate gestational age, based on growth charts specific to the Israeli neonate population [16].

Systolic and diastolic BP levels were measured according to the recommendations of the National High Blood Pressure Education Program, in three consecutive measurements, using a standard office electronic sphygmomanometer, with the cuff placed on the right arm and the child sitting quietly for 5 minutes prior to each measurement [17]. HTN was defined as systolic or diastolic BP values $\geq 95^{th}$ percentile for gender, age and height. Pre-HTN was defined as systolic or diastolic BP values that are $\geq 90^{th}$ percentile but $<95^{th}$ percentile.

Serum creatinine was analyzed by the enzymatic method. Estimated GFR (eGFR) values were calculated based on serum creatinine and height measurements using the Schwartz equation (eGFR=height [cm] X 0.413/serum creatinine [mg/dl]) [18]. Proteinuria was determined based on a spot urine sample using the immunonephelometric

assay, and defined as albumin / creatinine ratio > 30 mcg/mg or protein / creatinine ratio> 0.2 mg/mg. Children for whom abnormal results were detected in any of the parameters were informed and referred for further investigation in our nephrology institute.

2.3 Informed consent and ethics approval

The study was approved by the Ethical Board committee of the Rabin and Schneider Children's Medical Centers. Oral consent was given by the parents of each child during the initial recruitment phase. Written consent was given at the time of the study by one of the parents (as approved by the committee).

2.4 Statistical analysis

The data were analyzed using the BMDP statistical software package [19] and IBM SPSS© version 24. Continuous variables were compared, between groups, using one-way analysis of variance (ANOVA). A Chi Square goodness of fit test was used to compare observed with expected frequencies. Linear and logistic regression models were used to evaluate associations between NICU variables and later renal outcomes. A p-value of ≤0.05 was considered significant.

3. Results

3.1 Perinatal characteristics (Table 1)

Of the 103 children in the study population, 56 were male. The mean and standard deviation (SD) BW for the cohort was 1085.7 (242.8) gr. Forty (39.6%) children qualified as ELBW. The mean (SD) weight at discharge was 2154 (204.1) gr. All children were born prematurely, with a median gestational age of 29.4 weeks (range 24-35). BW, BW standard deviation scores (BW-SDS) and gestational age did not vary significantly by gender. Six (5.8%) children were categorized as small for gestational age. Twenty-four (23.3%) were part of a multiple gestation pregnancy, of which 19 (18.4%) were one of twins and 5 (4.9%) were one of a set of triplets. Sixty-four (62%) children required some form of ventilation. The median (range) duration of ventilation was 2 days (0-75).

	Total sample (n=103)	**Male (n=56)**	**Female (n=56)**	**M vs F (p value)**
Birth weight (gr)*	1086 (243)	1048 (244)	1129 (237)	0.0944
Gestational age (weeks)+	29.4 (24-35)	29.2 (24-35)	29.6 (25-35)	0.4863
Birth weight SDS*	-0.634 (0.760)	-0.768 (0.782)	-0.480 (0.712)	0.0557
Weight at discharge (gr)*	2154 (204)	2165 (235)	2141 (162)	0.5882

+median (standard deviation)

***mean** (standard deviation)

Table 1: Perinatal characteristics.

3.2 Current characteristics of the study group (Tables 2, 3)

3.2.1 Anthropomorphic measures: Median (range) age was 11.6 (10-13.3) years. Mean (SD) weight was 36.4 kg (8.7) and mean (SD) height was 142.6 cm (8.6). Weight and height percentiles did not vary significantly by gender.

3.2.2 Blood pressure: The prevalence of systolic pre-HTN was 6.9% (95% CI 1.96% - 11.84%) and of systolic HTN 15.8% (95% CI 8.69% - 22.91%) (Table 3). Mean BW was lower in hypertensive children than in children with normal blood pressure (939.3 gr vs 1111 gr, P=0.024). However, in a Pearson's correlation analysis neither BW nor BW-SDS correlated negatively with systolic BP values at follow-up (R =-.021 and R = 0.54, respectively). The diastolic blood pressure measurements were within normal range for age.

Overall, mean (SD) systolic BP was 110.2 (10.6), and the mean (SD) systolic BP percentile was 68.1 (25.1). Mean (SD) diastolic BP was 56 (9.6), and the mean (SD) diastolic BP percentile was 36.16 (25.4). Mean systolic and diastolic BP values did not vary significantly by gender or BW category (VLBW vs ELBW). In addition, there were no demonstrable associations between systolic HTN and: BW values, BW categories, BW-SDS or gestational age.

3.2.3 Urinary protein excretion: The overall prevalence of abnormal urinary protein excretion was 15.7% (95% CI 8.64% - 22.76%). The prevalence of microalbuminuria was 14.3% (95% CI 7.37% - 21.23%), while the prevalence of proteinuria was 7.9% (95% CI 1.84% - 13.96%). There was no significant difference in BW between children with abnormal urinary protein excretion and those with normal protein excretion. Lower current weight percentile was found in children with proteinuria (27.2kg vs 36.7kg P=0.015) and microalbuminuria (31.3 kg vs 36.8 kg P=0.023) compared to children with normal protein excretion. Microalbuminuria was associated with a significantly elevated eGFR (126.1 versus 108.3; P = 0.0059).

Overall, the mean (SD) value of protein/creatinine ratio was 0.2 mg/mg (0.5), while the mean (SD) value of albumin/creatinine ratio was 64.3 mcg/mg (324.8). The mean protein/creatinine ratio and mean albumin/creatinine ratio did not vary by gender, age or BW category. Levels of proteinuria or microalbuminuria did not correlate negatively with BW values or BW-SDS. In a logistic regression model, there was a trend towards an association between extremely LBW (less than 1000 gr) and proteinuria, which did not reach statistical significance (p=0.052). No other associations were found between excessive urinary protein excretion and BW values, BW-SDS or gestational age.

3.2.4 eGFR: Notably, eGFR values were within the normal range for all participants. Mean (SD) eGFR was 110.8 mL/min per 1.73 m2 (21.6). Mean eGFR levels did not vary by gender or BW category; nor did they correlate negatively with BW values or BW-SDS.

	Total Sample (n=103)	**Male (n=56)**	**Female (n=47)**	***M vs F (p value)***
Age (years)	11.6 (10-13.3)	11.549 (10 - 13.4)	11.618 (10.2-13.3)	0.6682
Weight (kg) *	36.4 (8.7)	36.5 (9381.9)	36.1 (7794.1)	0.8243
Weight Percentile *	35.2 (29.8)	37.7 (30.8)	32.1 (28.5)	0.3506
Height (cm) *	142.6 (8.6)	142 (8.8)	143.2 (8.4)	0.4927
Height Percentile *	30.9 (26)	31.3 (25.9)	30.3 (26.3)	0.8421
Systolic BP (mmHg) *	110.2 (10.6)	109.3 (11.4)	111.3 (9.6)	0.3598
Systolic BP percentile *	68.1 (25.1)	67.2 (26.3)	70.2 (24.5)	0.5559
Diastolic BP (mmHg) *	56 (9.6)	55.1 (9.8)	57.2 (9.3)	0.2834
Diastolic BP percentile *	36.2 (25.4)	35.7 (24.7)	37.2 (26.4)	0.7701
Protein / creatinine ratio mg/mg *	0.2 (0.5)	0.23 (0.7)	0.17 (0.3)	0.6095
Albumin / creatinine ratio mcg/mg *	64.3 (324.8)	73.56 (397.1)	52.86 (208.4)	0.7556
eGFR ml/min/1.73m2*	110.8 (21.6)	111.2 (20.6)	110.2 (23)	0.8349

+median (standard deviation), *****mean (standard deviation)

Table 2: Present characteristics of the study group.

Systolic Pre-Hypertension	6.9% (95% CI 1.96% - 11.84%)
Systolic Hypertension	15.8% (95% CI 8.69% - 22.91%)
Systolic Pre - Hypertension or Hypertension	22.7% (95% CI 14.53% - 30.87%)
Overall excessive urinary protein excretion	15.7% (95% CI 8.64% - 22.76%)
Elevated urinary protein/ creatinine ratio	7.9% (95% CI 1.84% - 13.96%)
Elevated urinary albumin / creatinine ratio	14.3% (95% CI 7.37% - 21.23%)

Table 3: Prevalence of elevated blood pressure and urinary protein excretion.

3. Discussion

Due to significant improvements in neonatal care, the survival rates of infants weighing between 500-1500 gr have improved substantially. Consequently, increasing efforts have been directed to improving long-term outcomes [20]. The breadth of evidence linking prematurity and LBW with renal sequela, coupled with the profound impact of HTN and chronic kidney disease on the global public health burden [21], provide solid rationale for early detection of renal damage in this high-risk population.

We report prevalence rates of systolic HTN and systolic pre-HTN of 15.8% and 6.9% respectively among 10 to 13 year old children born preterm with VLBW. In contrast, the prevalence rates of HTN and pre-HTN in a general US pediatric population between 2011-2012 were 1.6% and 9.4%, based on data from the National Health and Nutrition Examination Survey (NHANES), of youth between the ages 8 – 17 year [22]. Those results followed a single round of 3 consecutive BP measurements, similar to our study. Similarly, a cross-sectional screening study of 6790 unselected adolescents aged 11-17, reported pre-HTN in 9.5% and HTN in 9.4% hypertensive, after a single screening round [23].

The association between LBW and later hypertension is believed to be mediated by a reduced endowment of nephrons. The correlation between small nephron number and enlargement of the remaining glomeruli suggests the occurrence of compensatory hypertrophy and hyper filtration. This process, although initially successful in sustaining adequate renal clearance in affected individuals, eventually accelerates the decline in renal function and the loss of existing glomeruli [12].

In the current study the prevalence of excessive urinary protein excretion based on a single urine specimen was 15.7%, whereas reported prevalence in studies conducted on general pediatric populations range from 5-15% [24]. For example, in a study of 8,594 school-aged children by Vehaskari et al, proteinuria was detected in at least one of four dipstick measurements in 10.7% of subjects [25]. In slightly older children, a cross-sectional analysis of 2515 adolescents aged 12-19 years, reported a 8.9% prevalence of microalbuminuria, as detected by random morning spot urine testing [26]. The study also showed that the median albumin/creatinine ratio decreased with increasing BMI z -scores, which corresponds with our finding of a significantly lower current weight in the children with proteinuria and microalbuminuria in our cohort.

Chi - square goodness of fit tests were conducted to compare the frequencies observed in our study population with the above observations on normal BW population. In all tests the differences between observed and expected frequencies showed high statistical significance ($p<0.03$).

Our finding of significantly elevated eGFR among children who presented with albuminuria might be attributed to glomerular hyper filtration [27]. Reduced renal mass may initially be adequate for normal kidney function, relying on hyper filtration of the existing nephrons, which manifests clinically as proteinuria [28]. However, in the long term, hyper filtration injury may result in increased intra-glomerular pressure and secondary glomerulosclerosis [29].

Our findings are supported by a recent analysis of 5325 children aged 12-15 years from the NHANES, of whom 9% had a history of LBW, and 1.3% had a history of VLBW [30]. The authors demonstrated that elevated BP occurred more frequently in VLBW children than in NBW controls (VLBW 11.2%, NBW 2.4%). Contrary to our study, however, the frequency of albuminuria did not vary by BW category, and no association was found between VLBW status and albuminuria in either univariate or multivariate logistic regression models. In a retrospective cohort study, systolic BP was significantly higher among 172 singleton VLBW survivors (mean difference of 3.2 mmHg, $p<0.05$) than among sex-matched NBW controls at the same age of 15 years [31]. Diastolic BP was also higher among the VLBW cases, but this did not reach statistical significance. Proteinuria was not evaluated.

Our study has several limitations. First, is the lack of a NBW control group. Second, although we determined BP values based on the lowest of 3 consecutive measurements, all measurements were performed during a single visit and Ambulatory Blood Pressure Monitoring (ABPM) was not utilized. In addition, our measurements of protein excretion were based on a single specimen and not on 24-hour urine collection, and the single specimen was not taken during first-morning void. In studies with multiple screening cycles, repeat visits tend to show a reduction in the frequencies of hypertension and proteinuria. However, it is notable that a single measurement of elevated BP is in and of itself a risk factor for being diagnosed with HTN in later life [32]. A third weakness is participation bias: enrollment in the study required significant compliance on behalf of the participating families, indicating that the children who comprised our cohort come from homes where awareness of preventive care is emphasized; this may have attenuated any VLBW-associated morbidity. Finally, although our medical center is a tertiary center serving a heterogeneous population, the study is a single-center study.

Based on our findings, we recommend routine evaluation of renal function in all VLBW, children at least from the age of 10 years. Abnormal results should be verified and repeated, and a strict nephrological follow-up regimen should be tailored to any individual for whom renal dysfunction has been diagnosed.

4. Conclusion

Children born with VLBW are at an increased risk for kidney damage. First signs might be detected as early as age 10 years, and therefore close nephrological follow up should be mandatory for this age group. Early detection of kidney damage and appropriate treatment may improve the long term outcome of children born with reduced renal mass. Further studies are warranted to help better guide the nephrological management of VLBW children.

4.1 What is already known on this topic

Children born with VLBW are at an increased risk for kidney damage in later life due to reduced renal mass. First signs can be albuminuria/proteinuria and elevated blood pressure. Early treatment can prevent or delay chronic renal failure in this population.

4.2 What this study adds

Our findings show that first signs of renal damage can be detected as early as the age of 10 years. This finding may help implement policies for early

screening and treatment of children and adolescents born with VLBW.

Source of Funding

None.

Conflicts of Interest

We declare that there are no conflicts of interest.

Contribution

Borovitz Yael and Tschernichovsky Roi equally contributed to this work.

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