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REGULAR ARTICLE

Renal function and volume of infants born with a very low birth-weight: a preliminary cross-sectional study

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ABSTRACT

Aim: The aim of our study was to compare the function and volumes of kidneys of very low birth-weight (VLBW) and of extremely low birth-weight (ELBW) infants at pre-school ages.

Patients and methods: We did a revision of the neonatal records of infants born in our hospital that weighed ≤1500 g at birth. The children were divided into two groups according to their weight at birth: ELBW (<1000 g) and VLBW (1000–1500 g). At the age of 5.7 ± 1.4 years, the children underwent clinical, laboratory and ultrasound renal assessments.

Results: Sixty-nine children fulfilled the requirements for the study. The rate of neonatal treatment with aminoglycosides was higher in ELBW preterms. Renal function parameters, i.e. estimated glomerular filtration rate and albuminuria, did not differ between the two groups of children. Urinary α1-microglobulin excretion was significantly higher and kidneys were significantly smaller in the ELBW group than in the VLBW group.

Conclusion: No impairment or differences in renal parameters were found in pre-school children born ELBW compared with those born with VLBW, except for differences in kidney volume, renal cortical thickness and urinary α1-microglobulin excretion. Thus, patients born with ELBW would require a longer follow-up period.

INTRODUCTION

Low birth weight (LBW) has been associated with an increased risk of hypertension, cardiovascular events and impaired renal function in adulthood (1,2). However, the causal pathways of this association are poorly understood. Because nephrogenesis continues for up to 40 days after premature birth, pre-terms are at risk of kidney damage from postnatal nephrotoxic medication and malnourishment (3). Moreover, the remaining nephrons may undergo hyperfiltration and glomerulosclerosis (3,4).

Over the past two decades, extremely low birth weight (ELBW) infants have experienced a better survival rate because of the improved quality of neonatal care. Observational studies have shown that very premature babies have an increased risk of hypertension in adulthood (5). Moreover, children born pre-term seem to run higher overall risks of kidney problems than children born at-term (6). Therefore, recent investigations disagree on altered renal function and kidney size in school-aged children and young adults born prematurely and of LBW (7–9).

No studies have compared very low birth weight (VLBW) and ELBW categories of children born preterm. As differences between the two categories could reveal different renal prognoses, the aim of this report was to compare the function and volumes of kidneys of VLBW and ELBW babies at pre-school ages, using VLBW infants as the reference group.

Abbreviations
AGA, appropriate for gestational age; BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate; ELBW, extremely low birth weight; GA, gestational age; LBW, low birth weight; NSAID, non-steroidal anti-inflammatory drug; RI, resistive index; SGA, small for gestational age; VLBW, very low birth weight.

SUBJECTS AND METHODS

Recruitment of subjects

We reviewed 170 records of newborns born alive in our hospital between January 2000 and December 2004 that

weighed ≤1500 g at birth. Of the 170 potential initial patients, 73 patients could not be contacted because of incorrect addresses and phone numbers. The other 97 patients were invited to participate in the study. Of these, one had died and 27 declined to participate. In the end, the parents of 69 babies agreed to participate in the study and all the patients' parents gave written informed consent to perform analyses on their children. The Ethics Committee of our hospital approved the study protocol (Prot. N. 2430/CE of 02/10/2008).

The children were divided into two groups according to their weight at birth: extremely low birth-weight (ELBW < 1000 g at birth) and very low birth-weight (VLBW 1000–1500 g at birth). Small for gestational age (SGA) was defined as a birth weight under the -2 standard deviations, i.e. below the gender-specific 2.5th centile for gestational age, for normal foetal growth (10). We revised the at-birth charts of each preterm for creatinine levels and urinary output. According to the pRIFLE criteria, acute kidney injury (AKI) in the neonatal period is defined as a 50% decrease in creatinine clearance and reduced urinary output – 0.5 mL/kg/h over 16 h (11).

We compared kidney function parameters and volumes of ELBW and VLBW children. All the babies were born in the Verona city hospital (Neonatal Intensive Care Unit); they had no chromosomal anomalies, congenital infections or urogenital malformations. During pregnancy, the mothers had not taken any medication known to influence kidney development in the foetus. Gestational age, birth weight, laboratory data (serum creatinine), postnatal drug administration (ibuprofen/indomethacin and/or gentamicin/amikacin) and prenatal ultrasounds were reviewed from the medical records of each patient. The children participating in the study were not taking any medication at the time of enrolment in the study.

We revisited the NICU charts for clinical data at birth of the children not contacted, of those who refused and of those who participated in the study. No statistical differences (chi-square test) were found between the enrolled (69 total) and missed patients (101) for the sex ratio (50.7% vs. 54.3% males), gestational age (29.2 ± 2.7 vs. 29.2 ± 2.9 weeks) and birth weight (1121 ± 289 vs. 1104 ± 299 g). Moreover, we found no differences for neonatal administration of NSAIDs (non-steroidal anti-inflammatory drugs; 17.4% vs. 18.1%) or aminogycosides (gestamicin/amikacin; 63.8% vs. 60.6%). Finally, we found no differences in the rate of AKI (10.3% vs. 8.8%), respiratory distress syndrome (63.8% vs. 67%), bronchopulmonary dysplasia (18.8% vs. 13.8%), sepsis (13% vs. 12.8%) or necrotizing enterocolitis (1.4% vs. 4.3%) after birth. No data concerning current therapies and unresolved physical complications were available for the missed children.

Clinical evaluation

The children underwent clinical assessments, measurement of growth parameters and blood pressure by the same medical investigators (MB, RM) when they were 5.7 ± 1.4 years old. Height was measured to the nearest 0.5 cm on a standardized, wall-mounted height board. Weight was determined to the nearest 0.1 kg on a standard physician's beam scale with the child dressed in light underwear and no shoes. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Body surface area (BSA, m^2) was calculated according to the Dubois formula (12). Systolic and diastolic BP were recorded as 'casual' sitting measurements using the automated Dinamap oscillometric technique according to the Fourth Task Force on Pediatric Hypertension (13). All clinical data were recorded (BF) on an electronic database (Microsoft Office Excel 2003).

Laboratory tests on renal function

Blood samples collected mid-morning (around 09:00–10:00 am) were stored in EDTA-coated tubes and immediately analysed in the laboratory of the Verona hospital (GG). In particular, creatinine was measured using a modified Jaffé reaction to improve assay accuracy by eliminating the non specific contribution of plasma proteins and bilirubin interference (14). Cystatin C was measured by immunonephelometry using a latex particle-coated method with specific antibodies to Cystatin C (15). We also measured blood electrolytes (calcium, magnesium, sodium and potassium), urea, uric acid and acid–base equilibrium (pH, bicarbonate and base excess). Samples of aldosterone and renin hormones were collected after a minimum of 2 h in a standing position and then again later after 10 min in a seated position (16).

Urine samples were collected during the morning by random spontaneous voiding. In urine, we assessed pH, gravity, α1-microglobulin (normal value for age <12 mg/L, <1.71 mg/mmol creatinine), electrolytes (sodium, potassium and calcium), uric acid and proteins, following standard laboratory methods.

The estimated glomerular filtration rate (eGFR) was calculated according to Schwartz's formulas (17). In particular, we used both the serum creatinine based equation and the serum creatinine/cystatin-C/BUN based equation to calculate the eGFR of our LBW children. These formulas are the most updated ones to calculate the eGFR, although they were not tested on children with GFR over 90, which is a limitation to this study.

Ultrasound assessment of renal parameters

Ultrasound assessment of kidney size and volume enables early recognition of either pathological growth or hypoplasia (18). Renal measurements were taken with the children in a supine position, scanning from the para-coronal angle with the transducer positioned to obtain the longest kidney length. The ultrasound probe was placed on the back of the child only when the presence of abdominal gases precluded adequate scanning from the standard position. For each child examined, kidney length, width and thickness were calculated as the average of three consecutive measurements by the same investigator (CB). The investigator (CB) was not aware of the birth weight category of each patient. Kidney volume was calculated using the echo machine software. Ultrasound was performed using a convex transducer

(frequent 4 MHz probe) on a digital last-generation scanner (Sequoia Systems; Acuson, Mountain View, CA, USA). Kidney volume was calculated using the ellipsoid formula (length × width × thickness × $\pi/6$). The parenchymal thickness was measured as the distance between the capsule and the margin of the sinus echo; the measurement was taken in the middle third of the kidney. Each child underwent Doppler ultrasound assessment of intrarenal arteries (CB). Resistive index (RI) was calculated as (peak systolic frequency shift – peak diastolic frequency shift)/peak systolic frequency shift (19).

Statistical analysis

The VLBW and ELBW subjects were analysed statistically by comparing categorical variables by means of the chi-square or Fisher exact test, while the Mann–Whitney test was used to compare continuous, not normally distributed variables. Data are reported as median and 95% confidence interval (CI). Bonferroni correction was applied for multiple comparisons. The Spearman correlation test was used to verify correlations between variables. Multivariate analysis was carried out by means of the logistic binary regression analysis model, using the birth weight categories (VLBW or ELBW) as the dependent variables and the VLBWs as the reference group. The variables inserted in this model were age, sex, height, total renal volume, urinary α1-microglobulin, eGFR Schwart's complex formula, administration of aminoglucosides and administration of NSIADs. For the selection of predictive variables, we used the backward stepping of variables and evaluation of the model using a goodness-of-fit chi-square statistics. Pressigned p-values > 0.05 controlled the stepping removal. The odd ratio (OR), 95% CI and p values are reported for variables with significance. Statistical analysis was performed using the SPSS 17.0 program for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Study population

The total number of children that fulfilled the requirements for the study was 69 (50.7% males), 22 of which were twins (31.9%). Gestational age (GA, as mean ± standard deviation) at birth was 29.2 ± 2.7 weeks and birth weight was 1122 ± 277 g. Forty-three children were born with a VLBW and 26 children were born with an ELBW; 27.9% and 30.8% were born SGA respectively (chi-square test $p = 0.993$). All the children were Caucasians (Italian).

During hospitalization in the Neonatal Intensive Care Unit, the children born of ELBW showed umbilical and inguinal hernias (one baby), C. *albicans* sepsis (one baby) and patent foramen ovale (two babies). Moreover, ELBW newborns required mechanical ventilation and had umbilical artery catheterization. Children born of VLBW showed umbilical and/or inguinal hernias (two infants), interventricular heart defect (one infant), patent foramen ovale (two infants) and *Listeria spp.* sepsis and convulsions (one baby). All the children were free of chromosomal anomalies and urogenital malformations.

A comparison between the characteristics of the VLBW and ELBW children at birth and at examination are summarized in Table 1. Body mass index (BMI) at examination was significantly lower in the ELBW group than in the VLBW group (20). Body surface area (BSA, Dubois formula) was comparable between the two categories of birthweight. Postnatal exposure to relevant medication included ibuprofen or indomethacin (NSAIDs, 17.4%) and gentamicin or amikacin (aminoglycosides, 65.2%). ELBW infants were more significantly treated with aminoglycosides and/or NSAIDs than the VLBWs. Systolic and diastolic blood pressures and did not differ between the two birthweight categories.

Renal function

In all infants, at examination, plasma creatinine concentration (as mean ± standard deviation) was 0.41 ± 0.08 mg/dL, plasma cystatin C was 0.36 ± 0.09 mg/L, estimated values of glomerular filtration rate (eGFR) using Schwartz's formula were 114.3 ± 18.4 mL/min/1.73 m^2 for the creatinine-based equation and 97.2 ± 10.9 mL/min/1.73 m^2 for the creatinine/cystatin-C/BUN based equation. In our population Pearson's correlation coefficient between Schwartz's two eGFR formulas was 0.848 ($p < 0.0001$).

Serum creatinine, cystatin C, eGFR and plasma renin activity did not differ between the two groups of children. Urinary α1-microglobulin was significantly higher in the ELBW group than in the VLBW group (Table 1). However, both serum biochemical (calcium, phosphorus, magnesium, BUN, uric acid, pH venous, bicarbonate, base excess, plasma renin activity, aldosterone to renin activity ratio) and urinary parameters (fractional excretion of sodium, potassium and uric acid, calcium/creatinine ratio and protein/creatinine ratio) were comparable between the two groups. However, a comparison of all the babies who received post-natal aminoglycosides (45 did) versus those who did not (24) showed statistically significantly higher α1-microglobulin excretion (Mann–Whitney test, $p = 0.013$). Applying Bonferroni's correction, α1-microglobulin was falsely statistically significantly different between the two groups. Moreover, VLBW infants who received post-natal aminoglycosides (20 did), compared with those who did not (23), showed statistically significantly higher α1-microglobulin excretion ($p = 0.032$). A comparison among ELBW infants was not performed because too few subjects did not receive neonatal aminoglycosides to make possible a statistical analysis (25 did versus 1).

Kidney volume

Total kidney volume at examination (as mean ± standard deviation) was 84.5 ± 20.1 cm^3. Table 2 shows the results of the measurements of right, left and total kidney volumes for the VLBW and ELBW children. Kidney size (length, left cortical thickness and volume) was significantly lower in the ELBW children than in the VLBWs. Right cortical thickness was comparable between VLBWs and ELBWs. Similarly, the resistive index (RI) was comparable between VLBWs and ELBWs. Therefore, in VLBWs the right renal

Table 1 Comparison of the characteristics [showed as median and 95% confidence interval (CI)] of healthy children born of extremely low birth weight (ELBW) and of very low birth weight (VLBW)

	VLBW	ELBW	χ^2 test (p-value)
Number	43	26	–
Twins (n)	13	9	0.452
Gender (males/females)	25/18	10/16	0.091
NSAID (n, Yes/No)	3/40	9/17	**0.006**
Aminoglycoside (n, Yes/No)	20/23	25/1	**<0.001**
AKI (n, Yes/No)	4/38	3/23	0.546
	Median (95% CI)	Median (95% CI)	Mann–Whitney test (p-value)
Gestational age (weeks)	30.1 (29.9–31.3)	27.0 (26.3–27.7)	**<0.001**
Birth weight (g)	1,315 (1,248–1,352)	850 (775–883)	**<0.001**
Age at follow-up (years)	5.4 (5.2–6.1)	5.3 (5.2–6.3)	0.848
BSA (m^2)	0.77 (0.75–0.83)	0.73 (0.70–0.79)	0.181
BMI (kg/m^2)	16.0 (15.7–17.0)	14.2 (14.0–15.9	**<0.001**
Systolic BP (mmHg)	105 (103–110)	102 (97–111)	0.121
Diastolic BP (mmHg)	62 (59.9–65.1)	60 (56.4–65.4)	0.314
Creatinine (mg/dL)	0.41 (0.39–0.43)	0.42 (0.38–0.45)	0.860
Cystatin-C (mg/L)	0.62 (0.60–0.66)	0.67 (0.61–0.69)	0.262
Schwartz's eGFR (mL/min/1.73 m^2)*	114 (110–120)	109 (105–122)	0.603
Schwartz's eGFR (mL/min/1.73 m^2)†	96 (95–101)	94.5 (91–101)	0.298
α1-microglobulin (mg/L)	0.00 (0.53–2.31)	2.65 (1.96–5.03)	**0.017**
α 1-microglobulin/creatinine (mg/mmol)	0.00 (0.05–0.25)	0.16 (0.25–0.79)	**0.008**

Aminoglycoside = gentamicin or amikacin, AKI = acute kidney injury, BMI = body mass index, BP = blood pressure, BSA = body surface area (Dubois formula), NSAID = ibuprofen or indomethacin.

*eGFR by Schwartz creatinine based equation.

†eGFR by Schwartz creatinine/cystatin-C/BUN based equation.

Bold values highlight the statistically significant differences.

thickness was significantly less and the right RI significantly higher than in the left kidney. In ELBWs, renal thickness and RI were comparable between kidneys.

A comparison of all the babies who received post-natal aminoglycosides (45 did) versus those who did not (24) showed comparable total renal volume ($p = 0.209$). Moreover, VLBW infants who received post-natal aminoglycosides (20 did), compared with those who did not (22), showed comparable total renal volume ($p = 0.326$). A comparison among ELBW infants was not performed because too few subjects did not receive neonatal aminoglycosides to make possible a statistical analysis.

With the Spearman test, birth weight gave positive significant correlation with total renal volume, BMI, systolic BP and negative significant correlation with urinary α1-microglobulin excretion at follow-up (Table 3). Birth weight correlated positively, but with borderline significance ($p = 0.05$), with Schwartz's eGFR complex formula.

Table 2 Comparison of renal ultrasound parameters [showed as median and 95% confidence interval (CI)] between healthy children born of very low birth weight (VLBW) and of extremely low birth weight (ELBW)

Ultrasound parameters	VLBW children, median (95% CI)	ELBW children, median (95% CI)	Mann–Whitney test (p-value)
Right kidney			
Length (cm)	7.28 (7.15–7.71)	7.00 (6.68–7.21)	**0.037**
Cortical thickness (cm)	1.00 (0.89–1.02)*	1.00 (0.89–1.02)§	0.934
Volume (cm^3)	43.0 (40.7–48.2)†	34.0 (32.9–40.4)¶	**0.008**
Resistive index	0.67 (0.65–0.68)‡	0.69 (0.65–0.71)**	0.376
Left kidney			
Length (cm)	7.52 (7.35–7.75)	7.18 (6.74–7.30)	**0.004**
Cortical thickness (cm)	1.20 (1.11–1.29)	1.00 (0.96–1.10)	**<0.001**
Volume (cm^3)	44.4 (42.7–49.6)	37.8 (34.1–42.2)	**0.008**
Resistive index	0.64 (0.62–0.67)	0.67 (0.64–0.69)	0.281
Right and left kidneys			
Total volume (cm^3)	86.3 (84.1–97.1)	73.8 (69.0–80.7)	**0.002**
Right volume (% contribution)	49.4 (47.1–50.6)	47.4 (45.5–52.7)	0.696

Right kidney versus left in VLBW: *$p < 0.001$, †$p = 0.433$, ‡$p = 0.043$

Right kidney versus left in ELBW: §$p = 0.073$, ¶$p = 0.438$, **$p = 0.191$.

Bold values highlight the statistically significant differences.

Table 3 Spearman correlation analysis of birth weight versus neonatal and at follow-up parameters

Variables	Spearman correlation coefficient	p-value
Birth weight (g)		
Correlated		
Total renal volume (cm^3)	0.346	**0.004**
BMI (kg/m^2)	0.248	**0.040**
α1-microglobulin (mg/L)	−0.252	**0.036**
Systolic BP (mmHg)	0.298	**0.020**
eGFR Schwartz's complex formula (mL/min/1.73 m^2)	0.237	0.050
Not correlated		
BSA (m^2), age at follow-up, diastolic BP (mmHg), U-Protein/U-Creatinine ratio (mg/mg), eGFR Schwartz's simplified formula (mL/min/1.73 m^2), PRA (ng/mL*h), ARR (ng/dL/ng/mL*h), U-calcium/creatinine ratio (mg/mg), FE-Na (%), FE-K (%), FE-uric acid (%)		

ARR = aldosterone to renin activity ratio, BP = blood pressure, BMI = body mass index, BSA = body surface area, eGFR = estimated glomerular filtration rate, FE = fractional excretion rate, PRA = plasma renin activity, RI = resistive index, U = urinary.

Schwartz's eGFR simplified, plasma renin activity (PRA), aldosterone to renin activity ratio (ARR), fractional excretion (FE, %) of sodium, potassium and urea and diastolic BP did not correlate with birth weight.

Binary logistic regression analysis of the ELBW and VLBW categories computed age, sex, height and urinary α1-microglobulin, Schwart's eGFR complex formula, total renal volume, and administration of aminoglycosides and/or NSAIDs. The analysis revealed that variables that predicted inclusion in the ELBW category were neonatal administration of aminoglycosides (OR = 30, 95% CI = 3.14–287; p = 0.003) and NSIADs (OR = 6.38, 95% CI = 1.02–39.9; p = 0.048) and the reduced renal dimensions at follow-up (OR = 0.918, 95% CI = 0.87–0.97; p = 0.002). Estimated renal function, microalbuminurias and α1-microglobulin excretion were excluded from the model.

DISCUSSION

Several investigations seem to disagree with renal dysfunction in individuals born with a VLBW. In particular, eGFR, albumin excretion and kidney size measured using ultrasound in VLBW infants were all normal at 8 years of age (21). However, mean percentiles for kidney length and volume, determined using ultrasound, and eGFR were comparable with controls in children aged 6–12 years who were born extremely premature (7). Other studies reported that renal dimensions correlated significantly with birth-weight (9), but the finding of loss of kidney mass was not a prognostic indicator of deteriorating renal function in individuals born ELBW (22). Moreover, very prematurely born individuals and SGA showed minimal differences in kidney size and function than controls at the age of 20 years (8,23). Thus, these findings in human studies did not support the hypothesis that prematurity contributes to the alteration of renal function in childhood or even in young adulthood (8,9).

Other studies have reported that LBW may be associated with abnormal kidney development and malfunction in adulthood (24,25). Circumstantial evidence obtained from animal and human studies supported that low nephron quantity in adult born IUGR increased the risk of kidney damage and renal pathology (26). In particular, kidneys of LBW rats showed glomerular hypertrophy and an increased risk of developing renal sclerosis (24). Accordingly, autoptic studies in newborns and children have reported a marked association between LBW and a reduced number of nephrons (27). Moreover, VLBW infants with postnatal acute renal failure showed low glomerular supply and clear evidence of active glomerulosclerosis (28). When the number of nephrons is reduced, the compensatory hypertrophy causes the glomeruli to function under increased intracapillary hydraulic pressure, which, over time, causes damage to the capillary walls. Recently, five adult patients born under 1500 g and at less than 30 weeks of gestational age showed glomerulomegaly, segmental glomerular sclerosis and proteinuria (29). Thus, in humans, VLBW and prematurity have been linked to low glomerular numbers, high glomerular size and progressive susceptibility to renal disease in adulthood (6,29) because of the pathological development of secondary glomerulosclerosis (29).

We compared VLBW and ELBW infants (using VLBW infants as the reference subjects) to detect differences in renal function and dimensions among them, increasing the evidence reported in the previous literature (5,7–9,17,22,23,30). Our study did not reveal significant differences in eGFR, using the new Schwartz formulas (17), between children born with ELBW and VLBW, in agreement with the previous findings (21). Moreover, in our study, VLBW and ELBW infants had a comparable protein excretion rate. In agreement, the previous investigations reported no differences for microalbuminuria between AGA and SGA, and between VLBW and LBW infants (5,30). Instead, in young adults the prevalence of microalbuminuria in SGA was 3.8%, 2.4 times higher than that of AGA subjects (23). Thus, longer follow-up is required for our patients to detect signs of glomerular dysfunction with age.

In our study, total renal volume and left cortical thickness were smaller in our 5- to 6-year-old children born with ELBW than with VLBW, contrary to the findings reported elsewhere that were normal or minimal (7,8,23). However, we found higher values of urinary α1-microglobulin in babies born with ELBW than with VLBW; the former were more frequently treated with aminoglycosides, although none had values over the limits of normal range. However, ELBW infants showed smaller kidneys at follow-up. In short, reduced renal volume may be associated with low birth weight, and the increased urinary α1-microglobulin may be associated with neonatal administration of aminoglycosides. Such findings may not be good prognostic signs in infants born with ELBW. As the nephrotoxic action of aminoglycosides on renal tubular function is greater in patients born prematurely (30), follow-up of infants born

with ELBW is recommended to determine whether they will show overt signs of tubular damage with age.

We report some limitations to the present preliminary study. In particular, one bias could be the high number of missed patients, the low number of patients enrolled, the lack of comparison with normal controls and the inclusion of babies that were SGA and AGA in the same LBW category. Moreover, another bias could be the BP measurement that was taken during a single visit.

In conclusion, no impairment or differences in renal parameters were found in pre-school children born with ELBW compared with VLBWs, except for differences in kidney volume, left renal cortical thickness and urinary α1-microglobulin excretion. These may not be good prognostic signs. Thus, patients born with ELBW would require a longer follow-up period.

CONTRIBUTOR'S LIST

Dr MZ had primary responsibility for protocol development, patient screening, enrolment, outcome assessment, preliminary data analysis and writing the manuscript. Drs MB, BF, CB and RM participated in the development of the protocol and analytical framework for the study and contributed to the writing of the manuscript. Dr GT performed the final data analyses. Drs LC, GG, PB, VF supervised the design and execution of the study and contributed to the writing of the manuscript.

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