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Sonographic assessment of renal length in the first year of life: the problem of "spurious nephromegaly"

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Abstract *Purpose.* Interest in the potential diagnostic or prognostic implications of nephromegaly as evidence for compensatory renal hypertrophy has recently been emphasized in a variety of clinical settings. This project was designed to compare the results of linear and nonlinear sonographic models in the interpretation of renal size and growth during the first year of life.
Materials and methods. We identified all renal and abdominal ultrasound examinations that were performed between March 1994 and October 1997 in full-term infants under age 1 year during which (1) both renal lengths were measured and (2) both kidneys appeared anatomically normal. Using three different computerized algorithms based on published standards for sonographic renal length in relation to age, we calculated z-scores for the renal lengths and compared the results of the three methods: in method A the standards at birth, 1 week, 4 months, 8 months, and 1 year were all used; in method B the 1-week standard was omitted; in method C the standards at 1 week, 4 months, and 8 months were omitted.
Results. We evaluated 1,234 renal measurements in 617 patients (293 boys, 324 girls; mean age 0.24 year). Compared with method A, z-scores were significantly increased when either method B or C was used ($P < 0.0001$). The mean increment in z-score was + 0.433 for method B and + 1.135 for method C. The prevalence of "nephromegaly" ($z > +2$) was significantly increased when subannual standards were omitted ($P < 0.0001$): using method A, 20 (1.6 %) kidneys were large for age compared with 74 (6.0 %) using method B, and 214 (17.3 %) using method C. All kidneys that were large for age based on method A were also large for age using both methods B and C. The rate of false-positive diagnosis of nephromegaly was 73 % (54/74 kidneys) with method B and 91 % (194/214 kidneys) with method C.
Conclusions. Although the use of multiple subannual standards for renal length in infants less than 1 year of age is time consuming and mathematically more complicated, omission of these standards results in a statistically significant increase in the frequency of "spurious" nephromegaly.
Learning objectives. Precise application of published standards is important in the interpretation of sonographic measurements of renal length. Omission of the subannual standards for renal length in children who are less than 1 year of age can result in an incorrect impression of nephromegaly.

Introduction

The importance of accurate and precise assessment of renal size and renal growth rate in children who undergo imaging studies because of suspected urinary tract disease has been repeatedly emphasized in the literature [1–8]. Over the years, renal size has been correlated with age as well as with a variety of morphometric parameters – including height, weight, body surface area, and lumbar vertebral height, among others. Although renal growth generally parallels both age and the rate of general somatic growth throughout childhood, this represents a tremendous oversimplification of what is actually a very dynamic relationship. At birth the renal weight and volume are only approximately 10% as much as in the adult [2, 7], and the maximum renal dimension is less than half of that at maturity [1, 2, 4, 7]. Renal growth is most rapid during the first weeks of life, with the renal length increasing by as much as 15–20% in full-term neonates during this brief period [1, 2, 4, 7]. Renal growth then gradually slows throughout the remainder of the first year of life, after which the rate of increase in renal length stabilizes at approximately 2–3 mm/year. After age 10 years, renal growth again declines until it ceases at maturity. This nonlinear pattern of renal growth is reflected in some published sonographic standards for renal length in relation to age in either of two fashions: (1) by the inclusion of multiple subannual standards – with separate means and standard deviations for renal length – during the first year of life [4] or (2) by the calculation of separate linear regression equations for renal size during the first year of life as compared with later in infancy and childhood [7]. While it has been previously noted that the use of different standards for renal growth during the first year of life makes the evaluation more complicated, it is very reasonable to assume that scrupulous application of the published standards is likely to enhance the accuracy of detection of renal lengths and rates of renal growth that fall outside of the normal range [1, 2, 8].

In our own practice, we manually plot the measurements of the renal lengths from all renal and abdominal ultrasound examinations on renal growth charts that are kept in the patients' permanent radiology film jackets. We created these growth charts based on data from widely used published standards for renal length from the radiology literature [4]. After instituting the use of these growth charts in 1994, however, we began to encounter unexplained "nephromegaly" – i.e., renal length more than two standard deviations longer than the mean for age – in a seemingly unreasonably large number of neonates and young infants whose kidneys otherwise appeared normal. Moreover, among patients who had follow-up studies, the nephromegaly frequently did not persist beyond the first year of life. When we re-evaluated the growth charts, we realized that in creating them we had omitted the subannual standards at 1 week, 4 months, and 8 months. This clinical experience led us to undertake the current project to evaluate the impact of inclusion or omission of these subannual standards for renal length during the first year of life on the detection of nephromegaly.

Materials and methods

We identified all renal and abdominal ultrasound examinations that were performed in our department between March 1994 and October 1997 in full-term neonates and infants under age 1 year during which (1) both renal lengths were reported and (2) both kidneys were reported at the time of the examination to appear anatomically normal – i.e., there was no evidence of hydronephrosis, renal cystic disease, renal ectopia, or visible cortical scarring or dysplasia. Patients who had previous surgical procedures involving the upper urinary tract were excluded. Sonographic evidence of uncomplicated duplex kidney was not considered to represent an abnormality and was not an exclusionary criterion. Similarly, patients with lower urinary-tract abnormalities or vesicoureteral reflux were included as long as they had no sonographically visible renal abnormalities. For the purposes of this project, the renal length itself was ignored in deciding whether or not a kidney was "anatomically normal," even when the length of the kidney was more than two standard deviations above or below the mean for age. No patient was included more than once. Only the first examination was included for patients who had more than one eligible examination during the study period.

For this project, we used the standards for maximum renal length in relation to age that were published by Rosenbaum et al. in 1983 [4] (1) because these are the standards that we routinely use in our clinical practice and (2) because these authors provide multiple subannual standards for renal length during the first year of life with mean values and standard deviations at birth, 1 week, 4 months, 8 months, and 1 year. We calculated z-scores – the units of standard deviation from the mean – for each measurement of renal length using three different methods: method A – the subannual standards at birth, 1 week, 4 months, 8 months, and 1 year were all applied; method B – the 1-week standard was omitted; method C – the standards at 1 week, 4 months, and 8 months were omitted. The z-scores that were generated using method A were taken as the "most accurate" values against which the results of the other two methods were compared. The z-scores were computer generated using algorithms that were specifically designed to correspond to the appearance created by manually plotting the renal-length measurements on printed growth charts that were based on the same standards. For the purposes of this project, "nephromegaly" was defined as a measurement of renal length with a corresponding z-score greater than + 2. Renal lengths with corresponding z-scores less than –2 were considered to be abnormally short for age.

Results

We evaluated 1,234 renal measurements in 617 patients (293 boys, 324 girls; mean age 0.24 year). Mean renal length was 5.20 cm (median 5.2 cm; range 3.0 to 8.3 cm) (Table 1). The mean z-score for renal length in relation to age using method A was –0.596 (median –0.595; range –3.882 to 4.903). That the kidneys tended to be slightly

Table 1 Ages and renal lengths in the 617 study patients

	Mean	Median	Min–Max
Patient age	0.24	0.11	0.00–0.99
Right renal length (cm)	5.14	5.1	3.2–8.1
Left renal length (cm)	5.24	5.2	3.0–8.3
Δ Renal length: right–left (cm)	0.09	0.1	–1.6–1.5

Table 2 z-scores for 1,234 renal lenghts in relation to age using methods A, B, and C

	Method A	Method B	Method C
Mean	–0.596	–0.163	0.539
Median	–0.595	–0.229	0.588
Standard deviation	1.032	1.329	1.660
Range	–3.882–4.903	–4.762–5.039	–4.867–6.073

shorter, in general, in relation to age, was probably related, at least in part, to the fact that patients who had multiple non urologic congenital anomalies and those who were small or underweight for age were not excluded. The left kidneys were slightly longer (mean length 5.24 cm) than the right kidneys (mean length 5.14 cm; $P < 0.001$). On average, the girls were slightly older (mean age 0.28 year) than the boys (mean age 0.19 year) and, as a result, had slightly longer kidneys (mean renal length for the girls 5.27 cm; mean renal length for the boys 5.10 cm). However, there was no significant difference in the z-scores for the renal lengths – which correct for age – between the girls and boys.

The z-scores for renal length in relation to age increased significantly when the subannual standards were omitted (Table 2). Compared with method A, the mean increment in z-score for method B was + 0.433 ($P < 0.001$), and for method C the mean increment in z-score was + 1.135 ($P < 0.001$). The increment in z-score with method B was restricted to the first 4 months of life, after which it disappeared (Fig. 1). The increment in z-score with method C, on the other hand, persisted throughout the entire first year of life (Figs. 1, 2). The prevalence of nephromegaly was also significantly increased when the subannual standards were omitted: using method A, 20 (1.6 %) kidneys were large for age compared with 74 (6.0 %) using method B and 214 (17.3 %) using method C. All kidneys that appeared to be large for age using method A were also large for age using both methods B and C. The rate of false-positive diagnosis of nephromegaly was 73 % (54/74 kidneys) for method B and 91 % (194/214 kidneys) for method C.

The three methods produced somewhat less discordant results in regard to the detection of kidneys that were abnormally short for age: using method A, 85 (6.9 %) of the renal length measurements were small for age compared with 78 (6.3 %) using method B and

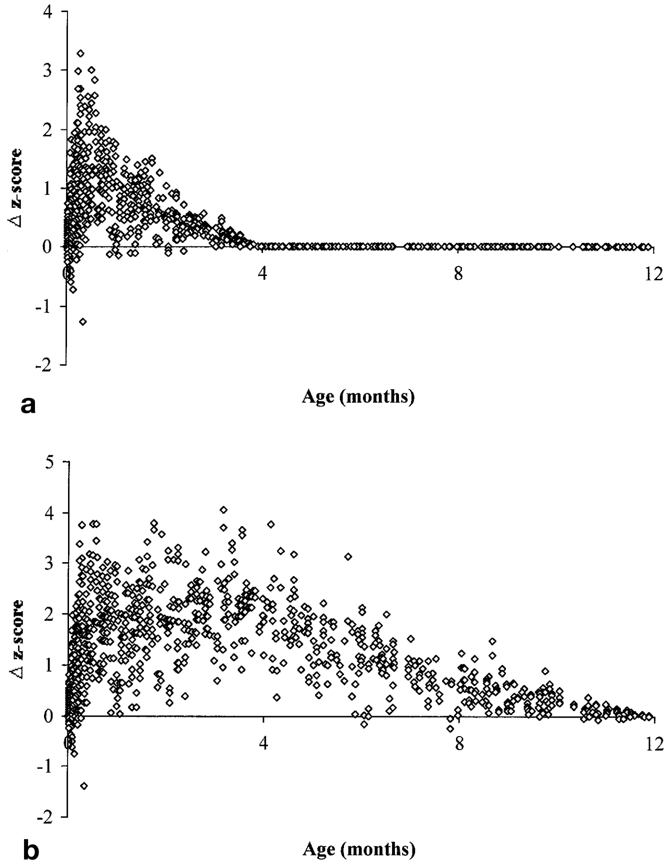

Fig. 1 **a** Increment in z-score for renal length in relation to age using method B as compared with method A (Δ z-score = z-score using method B – z-score using method A). **b** Increment in z-score for renal length in relation to age using method C as compared with method A (Δ z-score = z-score using method C – z-score using method A)

63 (5.1 %) using method C. All of the kidneys that appeared to be small for age using either method B or method C were also small for age using method A. Of the 85 kidneys that were small for age based on method A, 7 (8.2 %) were misidentified as being normal in length based on method B, and 22 (25.9 %) were misidentified as being normal in length based on method C.

Discussion

In humans, nephrogenesis is initiated in the metanephros during the gestational weeks 4–5 and is completed by 32–36 weeks [2, 9, 10]. After this time, any further increase in renal size or functional reserve can be accomplished only through enlargement and maturation of existing nephrons, rather than through the formation of additional nephrons. The nephrons in the neonatal kidney are much smaller and functionally immature as

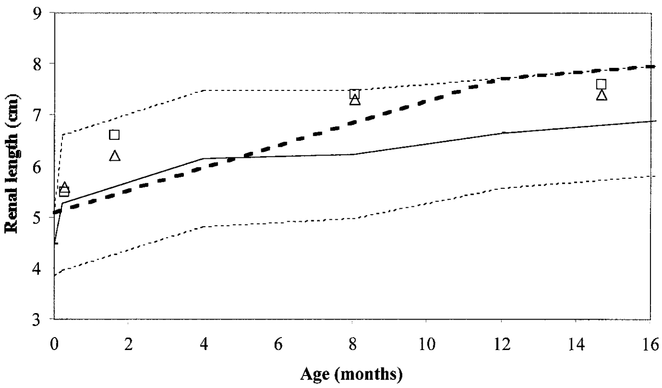

Fig. 2 Right and left renal length measurements from four serial US examinations in a male infant with transient, antenatal left hydronephrosis: The measurements are plotted on a renal growth chart that is designed according to method A. The *thin solid line* corresponds to the mean length for age, and the *upper and lower thin, dotted lines* correspond to two standard deviations longer and shorter than the mean for age, respectively. The *thick, dotted line* corresponds to two standard deviations longer than the mean for age based on method C. Note that all of the measurements are consistently within the normal range based on method A. However, the measurements for the three examinations under 1 year of age all appear very large for age based on method C, i.e., they all lie above the *thick dotted line* (Δ = right renal length; $\square$ = left renal length)

compared with those in the child or adult [9–14]. For example, the total glomerular surface area at birth is less than 10% of that observed in adults, the glomerular membrane is thicker and less permeable, and the convoluted tubules and loops of Henle are approximately one-tenth of their length at maturity, among other differences.

The physiologic demands of autonomous, extrauterine life compel rapid and profound adaptations in renal anatomy and physiology. The neonate must not only immediately assume metabolic and excretory functions previously performed by the mother via the placenta, but must also be able to continue to adapt in order to meet the demands of very rapid general somatic growth and development that continue throughout the first year of life. Remarkably, the neonate accomplishes all this simultaneously with accommodating to a dry extra uterine environment and wider fluctuations in the availability of fluid and nutrients than was the case in utero.

The cellular mechanisms and growth factors that are involved in the rapid enlargement and functional maturation of the kidney during the first weeks and months of life are incompletely understood [2, 9, 10, 12]. However, similar anatomic and physiologic adaptations have been observed in many species [15, 19]. Cellular proliferation and enlargement play an important role in the rapid expansion of mean nephron size and overall renal dimensions during the first weeks of life [2, 9, 12]. Proliferation of the proximal tubular epithelium is especially pronounced during this period and results in elongation of the convoluted tubules and a dramatic decrease in the glomerulotubular ratio. However, cellular growth and proliferation are only a part of the story. Cardiovascular accommodations that occur following interruption of the fetoplacental circulation are also important [10, 12, 13, 15–18]. Intrarenal blood flow is rapidly redistributed immediately following umbilical-placental interruption with a profound increase in the relative perfusion of the superficial cortical, as opposed to the deep cortical (juxtamedullary) glomerular beds. Increased renal vascular resistance secondary to enhanced activity of the renin-angiotensin system also likely plays a role in the renal hemodynamic alterations that occur in the neonate [20]. This results in an increase both in the total number of filtering cortical nephrons as well as in their glomerular filtering capacity and leads to a rapid increase in the glomerular filtration rate during the first weeks of life. The percentage of cardiac output that is delivered to the renal circulation rises, and overall renal tissue perfusion increases by as much as 18% in the first week and 58% by the end of the first month. Rapid expansion of the renal vascular volume leads to glomerular and renal tubular distention and thereby contributes to the increase in tubular length. The combined result of these proliferative and hemodynamic processes in the human neonate is that the renal length increases by 17% in the first week of life, and by 37% in the first 4 months [4].

Assessment of renal size and rate of renal growth is a fundamental part of the imaging evaluation of the pediatric urinary tract [1–8]. To this end, numerous standards for interpreting both sonographic and urographic measurements of renal size – based on either the maximum length or calculated volume – have been published and are widely used clinically [4–7, 21–23]. The importance of precise application of these published standards in the identification and monitoring of renal lengths and rates of renal growth that fall outside of the normal range has been previously emphasized.

The clinical relevance of this evaluation is underscored in a variety of circumstances by the potential diagnostic or prognostic implications of sonographic demonstration of nephromegaly or an abnormal acceleration in the rate of renal growth, or both, as signs of compensatory renal hypertrophy. Renewed interest in the frequency and timing of compensatory hypertrophy in neonates who are born with solitary functioning kidneys, for example, has been stimulated by the window provided by prenatal sonography [24–26]. Sonographic evidence of compensatory renal hypertrophy has conventionally been assumed to be a desirable finding in patients who have solitary functioning kidneys – whether congenital or consequent to unilateral nephrectomy. Demonstration that the absence of nephromegaly in neonates who were born with multicystic dysplastic kidney is correlated with the presence of other urologic abnormalities, such as vesicoureteral reflux, offers some support for this concept [27]. Along related lines, Koff et al. [28, 29] have suggested that sonographic evidence of compensatory hypertrophy of the contralateral normal-appearing kidney in neonates who are born with unilateral pelvocaliectasis and have indeterminate findings at diuretic renography might have prognostic significance in predicting the future risk for worsening obstruction and functional deterioration in the dilated kidney. DeBaun et al. [30, 31] have presented evidence that the risk of Wilms' tumor in children with Beckwith-Wiedemann syndrome might be correlated with renal size. If their findings are confirmed, this might suggest that ongoing sonographic surveillance for tumor development might be unnecessary in some children who do not have nephromegaly.

The impact of the omission of the subannual standards on the interpretation of renal length disappears with time. As a result, in infants who have multiple examinations beginning early in life, omission of the subannual standards might produce the false impression of a retarded rate of renal growth in some patients. In our own clinical practice, it was our recognition of this phenomenon that alerted us to the error in the growth charts that we had previously been using. While it is true that few radiologists explicitly calculate z-scores for renal length in their clinical practices, sequential measurements in some patients would appear to be "dropping in percentile" when visually compared or manually plotted against the renal growth curves we were previously using, even when the absolute measurements are increasing over time. In infants with urinary-tract infection and vesicoureteral reflux detected early in life, for example, the impression that the rate of growth is unsatisfactory might be incorrectly attributed to renal injury secondary to the infection, [8, 32] potentially resulting in overly aggressive interventions.

Summary and recommendations

Precise application of published standards is important in the interpretation of sonographic measurements of renal length in children of all ages. Although the use of multiple subannual standards for renal length in infants less than 1 year of age is time consuming and mathematically more complicated, omission of these standards results in an increase in the frequency of "spurious" nephromegaly. The importance of avoiding over-diagnosis of nephromegaly is emphasized by the prognostic and diagnostic importance attributed to nephromegaly in a variety of clinical circumstances. Manually plotting sonographic measurements of renal length on properly designed, printed growth charts that are placed in the patients' film jackets is one practical method for overcoming this problem.

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