ORIGINAL ARTICLE

Intrarenal reflux, an overlooked entity — retrospective analysis of 1,166 voiding cysturethrographies in children

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Abstract
Background The significance of intrarenal reflux as a risk factor for renal scarring and hypertension has been discussed. Fluoroscopic detection of intrarenal reflux depends on the equipment, the training of the radiologists and the timing of spot film acquisition.
Objective To evaluate the prevalence of intrarenal reflux and its association with age, gender, grade of vesico-uretero-renal reflux and the renal segments affected.
Materials and methods We retrospectively analysed 1,166 voiding cysturethrographies. Patients' ages ranged from 1 day old to 19 years old. Vesico-uretero-renal reflux was detected in 209 female and 164 male patients using a standardised technique with digital pulsed fluoroscopy. The point in time and grade of reflux were documented with spot films. All radiographs showing reflux were assessed for the occurrence of intrarenal reflux.
Results Intrarenal reflux was detected in 41 of 373 (11%) patients with vesico-uretero-renal reflux. Unilateral intrarenal reflux was found in 30 patients and bilateral in 11. The left kidney was more frequently affected than the right (31 versus 21). Only patients younger than 9 years of age were affected (mean age: 1.6 years, median: 0.8 years). Intrarenal reflux was independent of gender and was most frequently observed in grade IV reflux (59.6%) and less often in grade V (23.1%) and grade III (17.3%).
Conclusion Intrarenal reflux in this study was detected in 11% of patients with vesico-uretero-renal reflux, predominantly with reflux grade IV and in patients younger than 4 years old.

Introduction

Until today, all generally accepted radiologic grading systems of vesico-uretero-renal reflux [1, 2] have been classifying vesico-uretero-renal reflux according to the severity of reflux up the ureters and the degree of dilation of the ureter, the renal pelvis and the calices. However, they do not include intrarenal reflux. Important uroradiologists, such as Hodson [3, 4],

Ransley [5] have emphasized the crucial role of intrarenal reflux in the pathogenesis of scarred or shrunken kidneys. The phenomenon of intrarenal reflux may be the missing link explaining mechanisms of renal damage (a) by entry of bacteria into the tubular system of renal pyramids, (b) by reducing renal blood flow due to an increase of intratubular pressure or (c) by a combination of both [6]. The aim of this study was threefold: (1) To evaluate the prevalence of intrarenal reflux, (2) to investigate its association with age and gender, (3) to investigate its association with reflux grade, and (4) to determine affected kidney and renal segments.

Materials and methods

All voiding cysturethrographies were performed after informed consent by the parents and strictly followed the Guidelines of the European Commission of 1997 [7]. Ethical

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approval was not required for analysis of anonymised images, which were retrospectively evaluated. The image quality criteria of the European-wide survey of voiding cysturethrography were used when evaluating vesico-uretero-renal reflux [8]. In a retrospective study, all images of voiding cysturethrographies and referral criteria of patients examined from January 2000 to January 2004 were extracted from the radiology information systems. For further evaluation, data and images were anonymised.

Reflux grading was done using the criteria of the international system of radiographic grading of vesico-ureteric reflux published by the International Reflux Study in Children [2]. All voiding cysturethrographies were performed in a standardised four-phase technique. In the first phase, the position of the catheter is controlled. In the second phase, filling of the bladder by drip infusion with contrast media is monitored, followed by phase 3, which depicts voiding. In phases 2 and 3, radiographs collimated to the kidneys are acquired to document the maximal extent of vesico-uretero-renal reflux, preferably at the peak of voiding. In the succeeding post voiding phase, efflux of contrast media from the renal pelvic system and ureters into the bladder is observed. Voiding cysturethrography is always started with patients lying supine on the examination table. In cooperative children – normally older than 4 years – voiding is documented by radiographs collimated to the bladder and urethra while sitting, and accordingly in boys older than 6 years while standing. In newborns, infants and noncooperative older patients, the whole examination is performed while lying on the fluoroscopy table. The filling of the bladder is slowly accomplished by administering ionic iodine-containing contrast medium (Peritrast, Infuso 31%, sodium and meglumine amidotrizoate, iodine concentration 180 mg/ml; Köhler Chemie GmbH, Bensheim, Germany), at body temperature by drip infusion positioned 70 to 100 cm over table level. We used the simple formula of 30 ml times (age in years + 2) to calculate bladder capacity [9]. Under intermittent fluoroscopic monitoring ureterovesical junctions are scrutinised during the filling and voiding phases. In case of vesico-uretero-renal reflux, collimated oblique radiographs of ureterovesical junctions and kidneys are taken. During micturition, the bladder and urethra are imaged in a strict lateral view. In addition, steep oblique views are obtained in boys. After voiding, a last-image-hold image of the bladder is acquired to determine how well it has emptied; if reflux has occurred, delayed last-image-hold images are taken to assess the rate of drainage of refluxed contrast media back into the bladder. These images not only help to exclude coexisting obstruction, but also to predict the efficacy of multiple voiding. In 358 of 373 (96%) patients, a transurethral catheter was used for the bladder filling. Only in 15 patients (4%) was a suprapubic catheter used.

All voiding cysturethrographies were carried out on a Sireskop SX fluoroscopy unit (Siemens AG, Erlangen, Germany) with an additional filtration of 0.2 mm copper. Examinations were either performed with 3 or 7.5 pulses per s and without a grid. Four different sizes of image amplifier were available for electronic magnification with four different format sizes, 14 cm, 24 cm, 30 cm and 40 cm, respectively. They were chosen according to patient size and the image details that had to be depicted. Digital image acquisition was accomplished by FLUOROSPOT T.O.P. (Siemens AG, Erlangen, Germany). The aim was to document pathological findings not only by last-image-hold image, but also by collimated radiographs. Eventually, vesico-uretero-renal reflux was documented in 54 patients (14%) only by last-image-hold image, and in 319 patients (86%) by additional radiographs. Required dose rate was lower by factor 10 comparing last-image-hold image documentation to radiographs (17 nGy/s versus 200 nGy/s).

Film reading and reporting of all images were performed using the same workstation Impax DS 3,000 SPA SU4 (Agfa) with high-resolution 17-in. Barco CRT monitors (Agfa, Mortsel, Belgium). All images were analysed by two radiologists (KOS 26 years of experience; BK 11 years of experience) with respect to grade of vesico-uretero-renal reflux and presence of intrarenal reflux. In addition, the phase of appearance of reflux was recorded, i.e. the early filling phase, the late filling phase or the voiding phase. For further evaluation, vesico-uretero-renal reflux was consequently rated according to its maximum extent. If there was a grade I reflux in the early filling phase, a grade II reflux in the late filling phase and a grade IV reflux in the voiding phase, only grade IV reflux was rated. Default of digitised images and monitors was as follows: contrast agent black and air white. For image assessment, optimal contrast and brightness were adjusted by appropriate windowing. Figure 1 shows the two available image acquisitions last-image-hold image and radiograph, as well as achievable image quality. In addition, variability of intrarenal reflux in different phases during the voiding cysturethrography and the importance of high image quality for recognizing intrarenal reflux are demonstrated.

For statistical analysis, SYSTAT 11 (SPSS, Chicago, USA) was used.

Results

Patient age ranged from 1 day old to 18 years of age. Thirty-seven patients with reflux were excluded. Of these, 17 patients had either complex urogenital malformations or significant obstruction of the distal ureter or at the ureteropelvic junction. The latter anomalies were excluded because a significant pressure drop between the refluxing ureter and pelvic system prevents intrarenal reflux. These patients did not have urinary tract infections. In 20 patients, the conditions for optimal imaging were poor due to technical, exposure- or patient-related factors, i.e. severe constipation or meteorism.
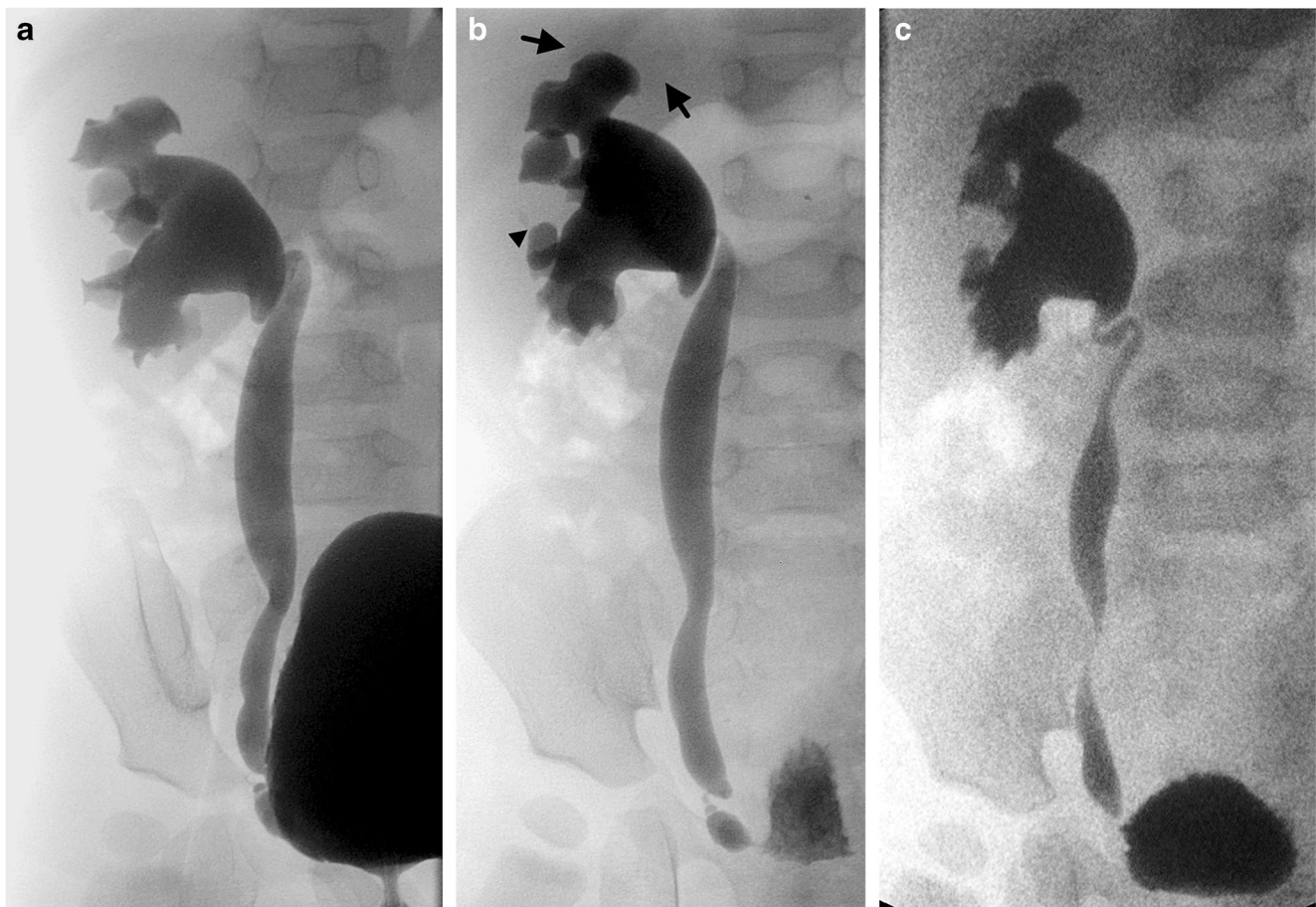
Fig. 1 Variability of intrarenal reflux of vesico-uretero-renal reflux grade IV in a 1-year-old girl. **a** No intrarenal reflux is seen at the beginning of voiding. **b** By the end of voiding, reflux increases to grade V with diffuse intrarenal reflux into the upper pole (*arrows*). Additionally, a tiny fornix rupture of a minor calyx can be seen (*arrowhead*). **c** The post-voiding last-image-hold image shows decrease of distension of calices. No intrarenal reflux is observable. Note the different image quality of the spot films obtained with a dose rate of 200 nGy/s (**a, b**) and the last-image-hold image with a dose rate of 17 nGy/s (**c**)

Therefore, 1,166 voiding cysturethrographies were finally included for further detailed analysis of grading vesico-uretero-renal reflux and the presence of intrarenal reflux. Of these, vesico-uretero-renal reflux was observed in 373 patients (209 females and 164 males; 31.9%). The indication for the voiding cystourethrographies in these 373 patients was urinary tract infection in 351 patients (94.1%), prenatally diagnosed anomalies of the urinary tract in 17 patients (4.6%) and neurogenic bladder in five patients (1.3%). In 41 (11%) of these 373 patients, vesico-uretero-renal reflux was associated with intrarenal reflux (Fig. 2), corresponding to the 95% confidence interval of 8-15%. Unilateral intrarenal reflux was depicted in 30 patients and bilateral intrarenal reflux in 11. Unilateral intrarenal reflux occurred on the left side in 20, and on the right side in 10. Associated prenatally detected obstructive uropathies, mostly megacystis, were found in three boys and one female infant with intrarenal reflux. These four patients had grade IV or V reflux. The youngest patient with intrarenal reflux was 1 day old; the oldest patient was 9 years 7 months old (mean: 1.5 years, median: 0.8 years).

Female and male patients were equally affected (20 girls versus 21 boys). Figure 3 illustrates the distribution of intrarenal reflux with respect to age and gender. Intrarenal reflux occurs most frequently in the first year of life, decreases until the third year of life, and shows a small peak between the third and fifth years of life. During the first year of life, there is a slight
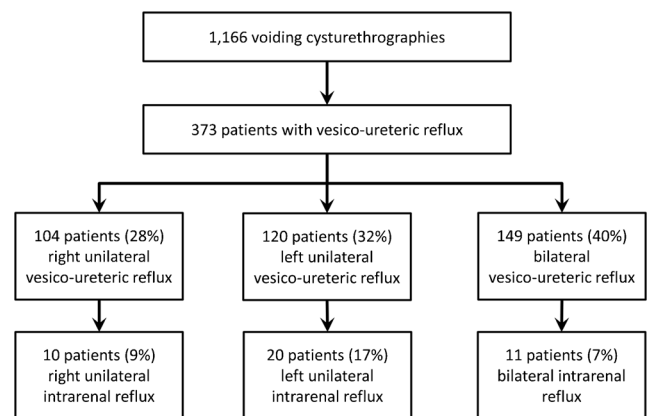
Fig. 2 Flow chart of the study cohort

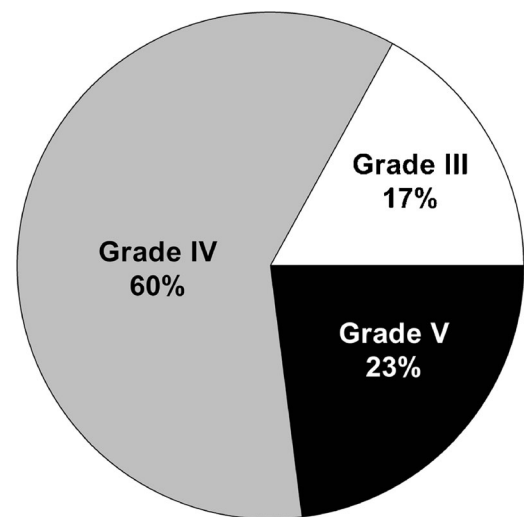Age and gender distribution of 41 patients with intrarenal reflux
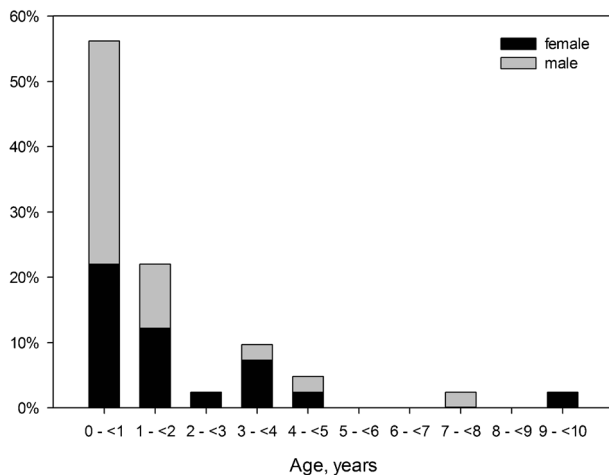
Fig. 3 Observation of intrarenal reflux by age. The graphic illustrates near equal frequency of intrarenal reflux in both genders, 21 males and 20 females. About 80% of intrarenal reflux occurred in the first 2 years of life. Moreover, intrarenal reflux was very rare beyond the age of 5 years

Fig. 4 Percentage of intrarenal reflux in 52 ureter-kidney units associated with reflux grades III to V

preponderance of the males; in older children, more females are affected. Table 1 shows the distribution of different grades of vesico-uretero-renal reflux of 522 ureter-kidney units of 373 patients. Fifty-two ureter-kidney units of 41 patients were affected by intrarenal reflux. Per definition of the international reflux study group, no intrarenal reflux is possible with reflux grade I. We found no intrarenal reflux in grade II reflux. However, intrarenal reflux was detected in grade III reflux in 9 of 118 ureter-kidney units, corresponding to 7.6%. Grade IV reflux was much more frequently associated with intrarenal reflux, 31 ureter-kidney units corresponding to 27.4% of 113 ureter-kidney units. The highest percentage (44%) of intrarenal reflux was found in grade V reflux (12 of 27 ureter-kidney units). With respect to absolute numbers, intrarenal reflux was most frequently observed in grade IV reflux (31 of 52 ureter-kidney units), i.e. 59.6% of all vesico-ureteral reflux of this severe type (Fig. 4).

Thirty-two of 373 patients (8.6%) with vesico-uretero-renal reflux had duplicated systems. In three patients, bilateral duplex systems were present. Fourteen patients had double

Table 1 Frequency of intrarenal reflux compared to all grades of vesico-uretero-renal reflux in absolute figures and percent

Grade of reflux	Uretero-renal units all cases with reflux	Uretero-renal units with intrarenal reflux	Percent
I	166	0	0%
II	98	0	0%
III	118	9	8%
IV	113	31	27%
V	27	12	44%
Total	522	52	10%

ureters connected with the right kidney, 15 with the left kidney. In 5 of 41 patients, intrarenal reflux was associated with unilateral bifid ureters. All five patients had intrarenal reflux into the upper pole, 1 patient also had it into the lower pole and another had it into the midzone as well as into the lower pole. Another known anomaly associated with vesico-uretero-renal reflux is paraureteral bladder diverticulum. Nine patients, five boys and four girls, had small paraureteral bladder diverticula, which were associated with low-grade reflux (grade I or II) in six cases. One boy with bladder diverticulum demonstrated grade IV reflux without intrarenal reflux. Two girls had intrarenal reflux, one unilateral grade III and the other grade IV reflux.

Table 2 gives an overview of grades of vesico-uretero-renal reflux in 41 patients with 52 ureter-kidney units affected by intrarenal reflux. Moreover, diverse combinations of affected kidneys can be discriminated. Intrarenal reflux most frequently occurs in grade IV reflux and was observed in 12 patients on the right side and in 19 patients on the left side. In grade V reflux, intrarenal reflux was found with the same frequency on both sides. A bilateral intrarenal reflux was identified in 11 patients, whereas unilateral intrarenal reflux was found in 20 patients in the left kidney, but only in 10 patients in the right kidney.

In girls, intrarenal reflux prevailed in grade IV reflux in 18 ureter-kidney units, followed by grade III reflux in 5 ureter-kidney units. In boys, intrarenal reflux could be depicted in grade IV reflux in 13 uretero-renal units and in grade V reflux in 8 uretero-renal units. In girls, intrarenal reflux appeared in two cases on the right side and in six cases on the left side in grade V reflux. Grade IV reflux, being more frequent on the left side (Fig. 5), is four times as often found in girls as in boys. In contrast, intrarenal reflux occurs in combination with grade V reflux on both sides twice as frequently in boys as in girls. Interestingly, grade V reflux is most often observed in boys in

Table 2 Overview of grade of vesico-uretero-renal reflux in 41 patients with 52 ureter-kidney units affected by intrarenal reflux

| Grade of reflux	Number of patients	Unilateral right intrarenal reflux	Unilateral left intrarenal reflux	Bilateral intrarenal reflux	Ureter-kidney units
III	8	1	5	1 x (III+III)	9
IV	25	5	12	1 x (III+IV)*	31
				1 x (III+IV)	
				5 x (IV+IV)	
				2 x (IV+V)*	
V	8	4	3	1 x (V+IV)*	12
				2 x (IV+V)*	
				1 x (V+IV)*	
				1 x (V+V)	
Total	41	10	20	11	52

*Patients with different grades of bilateral vesico-uretero-renal reflux and therefore are counted only once

the first year of life. However, in girls, grade V reflux is most frequently detected somewhat later in early childhood and is only half as frequent as in boys.

Furthermore, the appearances of intrarenal reflux during voiding cysturethrography were analysed. It is striking that intrarenal reflux was found more than twice as often in the voiding phase than in the late filling phase (Table 3, Fig. 6). Intrarenal reflux occurred during micturition in 73% of the cases, being more frequent on the left side (57.9%) than on the right side (42.1%). In the late filling phase, however, it was only in 27% of the cases that intrarenal reflux appeared, more often on the left side than on the right side. In both genders,

Fig. 5 Typical intrarenal reflux in the upper pole and midzone of the left kidney in a 17-month-old girl. **a** Grade IV reflux appears during the late filling phase. **b** Intrarenal reflux can be depicted much better on the subsequently coned and magnified spot film
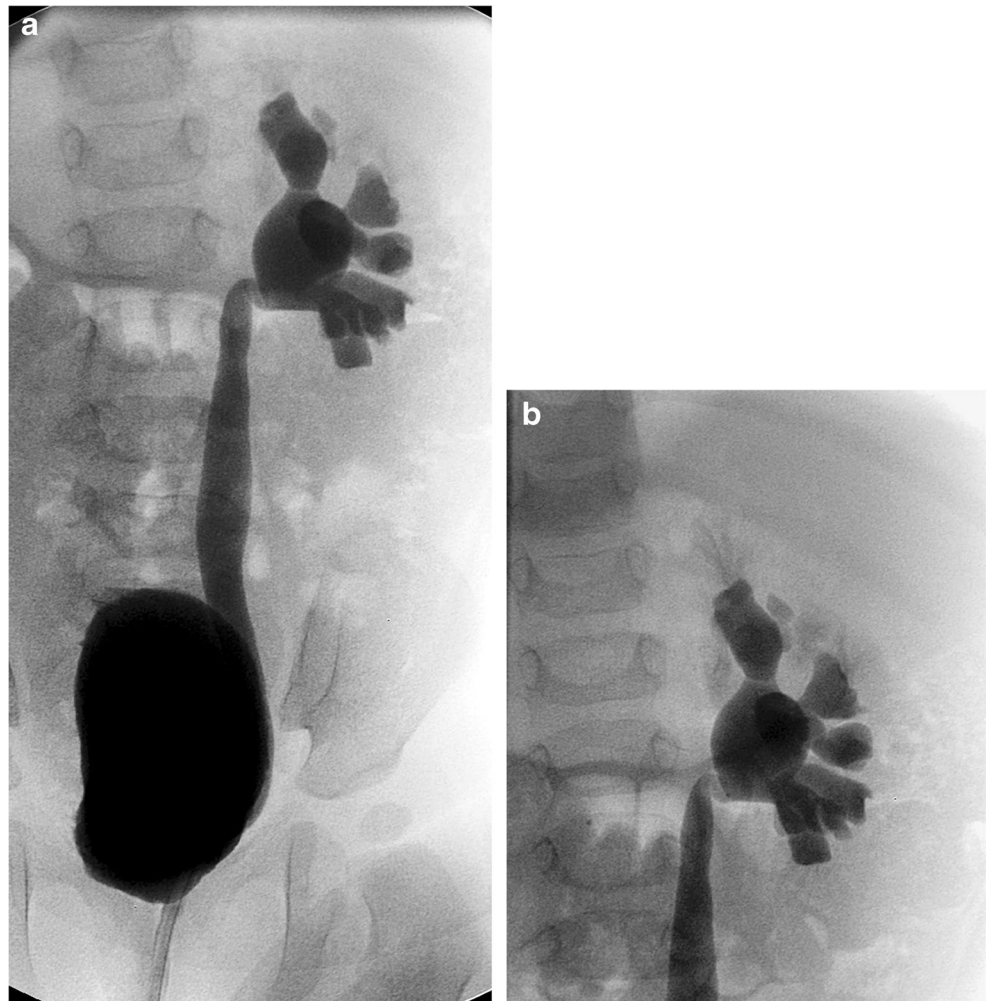
Table 3 Occurrence of intrarenal reflux during different phases of voiding cysturethrography

Phase of voiding cysturethrography	Intrarenal reflux of the right kidney	Intrarenal reflux of the left kidney	Total	Percent of intrarenal reflux
Early filling phase	0	0	0	0%
Late filling phase	5	9	14	27%
Voiding phase	16	22	38	73%
Total	21	31	52	100%

intrarenal reflux is most frequently depicted in the voiding phase, namely in 16 ureter-kidney units on the right side and in 22 ureter-kidney units on the left side. In the late filling phase, intrarenal reflux was observed less frequently: on the right side in five ureter-kidney units and in nine ureter-kidney units on the left. Intrarenal reflux was not found in any of the patients during the early filling phase.

Discussion

Voiding cysturethrography is definitely the only imaging study where bladder, urethra and – in case of vesico-uretero-renal reflux – the upper urinary tract can be imaged and evaluated at the same point in time [9, 10]. About 50 years ago, Hodson and Edwards [3] were the first to postulate a relationship between vesico-uretero-renal reflux and scarred or shrunken kidneys. Rolleston et al. [11] confirmed this hypothesis and showed later [12] that 29 of 49 kidneys with a high-grade reflux were already damaged when the first examination was conducted. They later developed renal scars. Jodal [13] described a distinct relationship between vesico-uretero-renal reflux, acute pyelonephritis and development of scarred kidneys. He found kidney scars in 66% of children with grade III or higher reflux, whereas kidney scars were found only in 5% of the children without vesico-uretero-renal reflux. In addition, the risk of developing scars was getting higher with increasing vesico-uretero-renal reflux. Hellström et al. [14] reported 12% of the children with reflux developed scarred kidneys. Furthermore, Jakobsson et al. [15] emphasized vesico-uretero-renal reflux being a risk factor for renal development in childhood, pointing out long-term consequences such as recurrent pyelonephritis, kidney scarring, progressive kidney insufficiency, hypertension, proteinuria, and elevated maternal and foetal risk during pregnancy. All these risk factors represent severe, albeit avoidable, consequences of undiagnosed vesico-uretero-renal reflux.

Intrarenal reflux may have far-reaching consequences – for example, pressure-related damage of papillae with growth disturbances of kidneys. In addition, there is a risk of bacterial invasion deep into the kidney tissue ensuing irreversible consequences such as loss of nephrons and extensive scarring [16]. Persisting high intrapelvic pressure can lead to focal scarring, intrarenal reflux and a shrunken kidney. An Ask-Upmark Kidney is a segmental hypoplasia of the kidney considered to be a consequence of an almost always coexisting

Fig. 6 Bilateral grade IV reflux in a 14-month-old girl. **a** At the end of filling, reflux is seen but not intrarenal reflux. **b** At the end of voiding, severe intrarenal reflux is visible into all segments of the kidneys with further dilatation of all calices
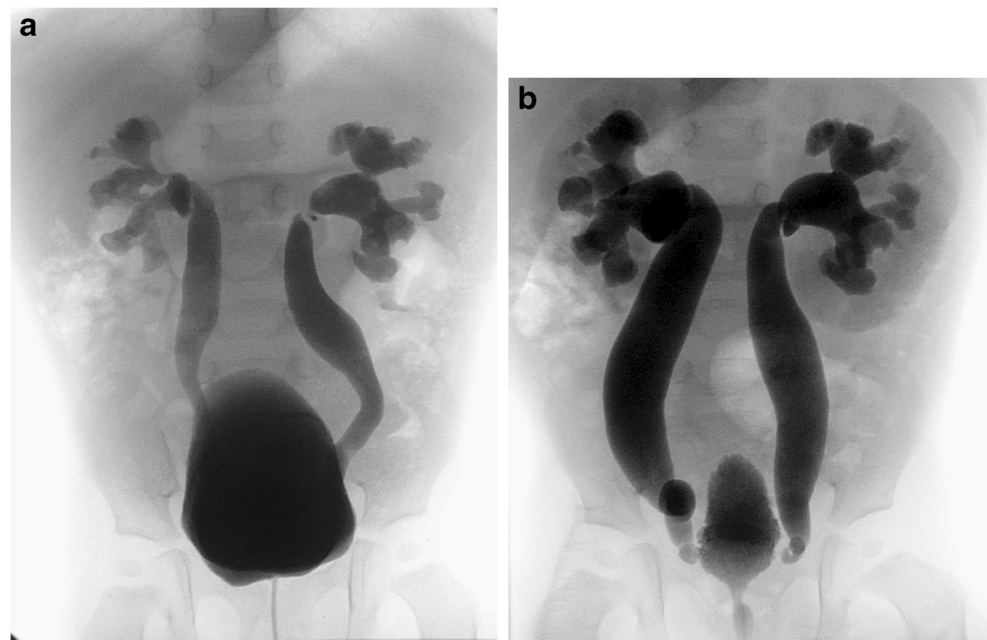
vesico-uretero-renal reflux. This segmental hypoplasia leads to scarred distortion, frequently preparing ground for intrarenal reflux. As early as in 1981, Hodson [4] reported about the relation between this segmental renal hypoplasia and the occurrence of vesico-uretero-renal reflux, pointing out that the latter one does not necessarily coincide with infection. He emphasized the decisive role of the enormous individual variation of both the number of papillae (lobes) and the patterns and degree of their fusion, and concluded that some papillae are so constructed that they allow free reflux into the kidney (pyelo-calico-tubular backflow) under certain conditions. Another theory states that intrarenal reflux always leads to ischemia of affected parts of the kidney: Rolleston et al. [11] documented kidney damage in 13 of 20 kidneys with intrarenal reflux (65%). In 12 of the 13 kidneys, damage was found exactly where intrarenal reflux had been documented before. As 65% of children had focal renal damage, a definite relationship of cause and effect can be assumed between intrarenal reflux and renal scarring. Rolleston et al. [11] and Ransley and Risdon [17] also corroborated the intimate relationship between morphology of papillae and the occurrence of intrarenal reflux. Furthermore, Ransley and Risdon [18] also reported about the development of focal renal scarring in the exact same regions where intrarenal reflux had been found in a high percentage (65%) of patients. Lebowitz and Mandell [19] found a strong correlation between infected urine and focal parenchymal scarring of renal lobes, in which intrarenal reflux was verifiable. In 1986, Smellie [20] reported about the occurrence of scarred kidneys within so far seemingly normal kidneys in a cohort of some 200 children (ages 3 months to 10 years) that she studied over 20 years. Of these children, 98% had urinary tract infections and 87% had voiding cysturethrography. Scars predominantly occurred in the same region where intrarenal reflux had been detected. The term "reflux nephropathy" and the association between renal damage and vesico-uretero-renal reflux were established for the first time by Bailey in 1973 [21]. Rolleston et al. [11] detected vesico-uretero-renal reflux in 42% of the patients ages 3 days to 12 months (mean age: 3 months). Twenty-nine of 49 kidneys (59.2%) with high-grade vesico-uretero-renal reflux were already damaged at the time of the first presentation. This emphasizes the importance of early detection, especially in regard to long-term consequences.

Lebowitz [9] continued to stress the significance of screening children with vesico-uretero-renal reflux on a regular basis, as intrarenal reflux can be a rather fleeting phenomenon. Intrarenal reflux is sometimes detected at one single moment only during voiding, or on only one examination and not on others. Therefore, intrarenal reflux cannot be discovered at any point in time and reports of its incidence are probably grossly underestimated. A reason for the fleeting nature of intrarenal reflux is almost certainly related to the infant's papillary duct openings. This is one reason why intrarenal reflux

appears often in the very young and is seldom found in children older than 5 years. This was clearly confirmed in our retrospective study. Nonetheless, vesico-uretero-renal reflux may persist longer without intrarenal reflux in follow-up examinations. In our study, we made similar observations. Most severe intrarenal reflux could only be detected at the height of micturition. In our work, more than 70% of intrarenal refluxes were detected during this phase of voiding cysturethrography. This important finding has not been mentioned in prior publications. This may be one explanation for the extreme variation of intrarenal reflux, between 1% cited by Fukui et al. [22] and 10% reported by Cremin [23]. Insufficient techniques during voiding cysturethrography, e.g., inadequate bladder filling, too narrow collimation of the X-ray field and focusing only at the lower urinary tract during voiding, are significant factors that intrarenal reflux is missed, even in high-grade reflux. Another cause is image quality: If only last-image-hold or frame grabber images are stored, using low- or ultralow-dose voiding cysturethrography technique [24], the full potential of voiding cystourethrography is not exploited.

Another reason for the elusive nature of intrarenal reflux may be the morphology of papillae. Concerning this point, Ransley and Risdon [17] and Ransley [25] undertook experimental investigations with pigs and were able to show that either flat or concave papillae enable occurrence of intrarenal reflux because orifices of the papillary ducts are widely open and lose complete closure with increasing pressure. Tamminen and Kaprio [26] investigated exactly this pathogenesis in children in 1977, showing that depicting intrarenal reflux while voiding at maximal intrapelvic pressure is crucial.

Certainly, an apparently sufficient filling volume of the bladder does not allow a conclusion concerning intravesical pressure. On the other hand, there may be technical reasons why vesico-uretero-renal reflux cannot always be detected or is often insufficiently imaged. This may be the case if bladder filling with contrast medium was insufficient or the full extension of vesico-ureteral reflux was not documented. Therefore, Jequier et al. [27] recommended multiple bladder filling in voiding cysturethrography to increase the reliability of this procedure. In most publications, the volume of adequate bladder filling is not mentioned. In addition, images obtained by conventional radiography (film cassettes) have possibly been over- or underexposed in the past. Employing digital radiography, optimal windowing of the images plays a decisive role and a subtle intrarenal reflux may be easily missed because of improper window settings. During post-processing, the advantage of digital radiography is that optimal windowing is possible and soft-tissue contrast can be adjusted individually, thus enabling detection of even subtle/elusive intrarenal reflux. Currently, the aforementioned international grading system, defining five grades of vesico-uretero-renal reflux, is widely used [2]. In our opinion, this grading system is incomplete because of the

high prevalence of 20% or more of intrarenal reflux, which is not represented by this grading system.

In our patients with high-grade reflux, the prevalence of intrarenal reflux was 27.4% in grade IV reflux and not less than 44.4% in grade V. Similar figures of intrarenal reflux were reported concerning grade III to V reflux by Kim et al. [28]. In contrast to our survey, intrarenal reflux occurred predominantly in male infants (98%). We found a nearly equal distribution between males and females, 21 versus 20 cases, respectively. In addition, the proportion of intrarenal reflux of high-grade IV and V reflux in the Korean study were far beyond 50%. The reason is that patient selection is not comparable in both surveys. Furthermore, 30% of patients with grade II reflux had intrarenal reflux. However, this high incidence of intrarenal reflux in grade II reflux contrasts all prior publications.

Finally, a new radiologic classification of vesico-ureterorenal reflux should definitely include supplementary information on whether intrarenal reflux is present and, if so, to what extent and which renal segments are affected (i.e. intrarenal reflux in upper/lower pole, midzone or entire kidney). Our analysis clearly reveals that due to poor or not standardised technique or insufficient image acquisition, intrarenal reflux is often overlooked.

Considering the far-reaching consequences of undetected and, therefore, untreated vesico-uretero-renal reflux, it is astonishing that in almost 50 years, no standardised concept for diagnosing intrarenal reflux has been established. Therefore, we demand the acquisition of collimated radiographs of the kidneys in all patients with grade II reflux or higher to ensure adequate detection of intrarenal reflux while voiding, as undiagnosed intrarenal reflux represents a high risk factor for irreversible renal damage and long-term consequences. Even though intrarenal reflux can be detected by contrast-enhanced voiding urosonography [29, 30], voiding cysturethrography remains the gold standard for one simple reason: The anatomical orientation of the 14 renculi of the human kidney does not allow simultaneous sonographic examination, neither in axial nor in coronal orientation from the back. In addition, the left upper pole of the kidney is especially difficult to examine even by an experienced sonographer. Sometimes this part of the kidney is not visible to its full extent, neither in supine nor in prone position. And it is right there where intrarenal reflux is most commonly found. Finally, even for an experienced examiner, it is impossible to detect a bilateral intrarenal reflux with ultrasound because intrarenal reflux is a fleeting phenomenon. Furthermore, contrast-enhanced sonography, a cross-sectional method, cannot detect intrarenal reflux in all cases for anatomical reasons. In addition, small paraureteral diverticula can also easily be overlooked in patients with associated vesico-uretero-renal reflux by voiding urosonography. Our study demonstrated that these paraureteral diverticula can occur with high-grade reflux and intrarenal reflux in some cases. A recent publication argued

that the detection of intrarenal reflux has no therapeutic consequence as there is no difference in renal scarring in patients with grade IV reflux with and without associated intrarenal reflux [31]. In this study, the follow-up periods of 18 and 36 months were relatively short as compared to other studies [20]. Boubnova et al.'s article [31] defines the entry criteria for age, gender and reflux grade. However, the most important criterion is whether the voiding phase was included in the control group because intrarenal reflux is much more frequent during voiding. This criterion was not mentioned in the paper.

This is an important drawback because development of renal scarring takes at least 2 years. However, a more recent and much larger study [22] clearly demonstrated that patients with grade IV reflux and intrarenal reflux are more prone to breakthrough infections. Consequently, this group of patients has a very high risk of developing renal scarring, as in earlier studies mentioned above. Finally, the more recent study [22] emphasized that ureter reimplantation in this risk group must be considered and not reinfection prophylaxis with antibiotics.

Conclusion

Using a standardized 4-phase voiding cysturethrography with pulsed fluoroscopy and obtaining spot films enabled detection of intrarenal reflux in 11% of 373 patients with vesico-ureterorenal reflux. The majority of patients with intrarenal reflux, nearly 90%, were younger than 5 years of age and more than 80% had high-grade reflux. Last-image-hold images are not sufficient to detect subtle intrarenal reflux. Optimal imaging during voiding is important because the majority of intrarenal reflux exclusively occurs in this phase.

Compliance with ethical standards

References

1. Heikel PE, Parkkulainen KV (1966) Vesico-ureteric reflux in children: a classification and results of conservative treatment. Ann Radiol 9:37–40

2. Lebowitz RL, Olbing H, Parkkulainen KV et al (1985) International system of radiographic grading of vesicoureteric reflux. International reflux study in children. Pediatr Radiol 15:105–109

3. Hodson CJ, Edwards D (1960) Chronic pyelonephritis and vesico-ureteric reflux. Clin Radiol 11:219–231

4. Hodson CJ (1981) Neuhauser lecture. Reflux nephropathy: a personal historical review. AJR Am J Roentgenol 137:451–462

5. Ransley PG (1976) Opacification of the renal parenchyma in obstruction and reflux. Pediatr Radiol 4:226–232

6. Hodson CJ (1969) The effects of disturbance of flow of the kidney. J Infect Dis 120:54–57

7. European Commission (1996) European guidelines on quality criteria for diagnostic radiographic images in paediatrics: Report 16261. Office for Official Publications of the European Communities. Luxembourg, pp 31–33

8. Schneider K, Perlmutter N, Arthur R et al (2000) Micturition cystourethrography in paediatric patients in selected children's hospitals in Europe: evaluation of fluoroscopy technique, image quality criteria and dose. Radiat Prot Dosim 90:197–201

9. Lebowitz RL (1986) The detection of vesicoureteral reflux in the child. Investig Radiol 21:519–531

10. Hellström M, Jacobsson B (1999) Diagnosis of vesico-ureteric reflux. Acta Paediatr Suppl 88:3–12

11. Rolleston GL, Maling TM, Hodson CJ (1974) Intrarenal reflux and the scarred kidney. Arch Dis Child 49:531–539

12. Rolleston GL, Shannon FT, Utley WL (1975) Follow-up of vesicoureteric reflux in the newborn. Kidney Int Suppl 4:59–64

13. Jodal U (1987) The natural history of bacteriuria in childhood. Infect Dis Clin N Am 1:713–729

14. Hellström M, Jacobsson B, Mårild S, Jodal U (1989) Voiding cystourethrography as a predictor of reflux nephropathy in children with urinary tract infection. AJR Am J Roentgenol 152:801–804

15. Jakobsson B, Jacobson SH, Hjälmås K (1999) Vesico-ureteric reflux and other risk factors for renal damage: identification of high- and low-risk children. Acta Paediatr Suppl 88:31–39

16. Ransley PG, Risdon RA (1979) The pathogenesis of reflux nephropathy. Contrib Nephrol 16:90–97

17. Ransley PG, Risdon RA (1975) Renal papillary morphology and intrarenal reflux in the young pig. Urol Res 3:105–109

18. Ransley PG, Risdon RA (1979) The renal papilla, intrarenal reflux, and chronic pyelonephritis. In: Hodson J, Kincaid-Smith P (eds) Reflux nephropathy. Masson, New York, pp 126–133

19. Lebowitz RL, Mandell J (1987) Urinary tract infection in children: putting radiology in its place. Radiology 165:1–9

20. Smellie JM (1986) Urinary tract infection, vesicoureteric reflux, and renal scarring. Semin Urol 4:82–85

21. Bailey RR (1973) The relationship of vesico-ureteric reflux to urinary tract infections and chronic pyelonephritis-reflux nephropathy. Clin Nephrol 1:132–141

22. Fukui S, Watanabe M, Yoshino K (2013) Intrarenal reflux in primary vesicoureteral reflux. Int J Urol 20:631–636

23. Cremin BJ (1979) Observations on vesico-ureteric reflux and intrarenal reflux: a review and survey of material. Clin Radiol 30:607–621

24. Linke SY, Tsiflikas I, Herz K et al (2016) Ultra low-dose VCUG in children using a modern flat detector unit. Eur Radiol 26:1678–1685

25. Ransley PG (1977) Intrarenal reflux: anatomical, dynamic and radiological studies- part I. Urol Res 5:61–69

26. Tamminen TE, Kaprio EA (1977) The relation of the shape of renal papillae and of collecting duct openings to intrarenal reflux. Br J Urol 49:345–354

27. Jequier S, Jequier JC (1989) Reliability of voiding cystourethrography to detect reflux. AJR Am J Roentgenol 153:807–810

28. Kim SW, Im YJ, Hong CH, Han SW (2010) The clinical significance of reflux in voiding cystourethrography (VCUG). Korean J Urol 51:60–63

29. Darge K, Trusen A, Gordjani N, Riedmiller H (2003) Intrarenal reflux: diagnosis with contrast-enhanced harmonic US. Pediatr Radiol 33:729–731

30. Colleran GC, Barnewolt CE, Chow JS, Paltiel HJ (2016) Intrarenal reflux diagnosis at contrast-enhanced voiding urosonography. J Ultrasound Med 35:1811–1819

31. Boubnova J, Sergent-Alaoui A, Deschenes G, Audry G (2011) Evolution and prognosis value of intrarenal reflux. J Pediatr Urol 7:638–643