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Isolated low initial differential renal function in patients with primary non-refluxing megaureter should not be considered an indication for early surgery: A multicentric study

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Summary

Introduction
Low initial differential renal function (DRF) in patients with primary non-refluxing megaureter (PNRM) is considered an indication for surgery as are an increase of dilatation and symptoms.

Objective
We hypothesized that low DRF is not necessarily a result of obstruction, but may be due to impaired development of the upper urinary tract. Thus, in the absence of symptoms, there is a low risk for further loss of renal function. This study aimed to assess whether initially low DRF is a reliable indicator of obstruction.

Study design
We reviewed data from four university centers between 1995 and 2010. Patients under 12 months of age with unilateral primary non-refluxing megaureter (PNMR) and a DRF between 10% and 40%, and followed minimally 24 months, were included. Patients were placed in two groups based on management: group A, surgical; group B, conservative. The dynamics of DRF in relation to age and type of treatment was studied. In each patient we recorded the earliest (initial) DRF, the last known (final) DRF, the age when MAG-3 scans were performed and the type of treatment.

Results
From 25 patients, 16 were treated surgically (group A) and 9 followed conservatively (group B). The initial mean DRF in group A was 33.1% and in group B 34.5%, at a mean age 3.0 and 3.6 months, respectively. The final mean DRF in group A was 40.1% and in group B 43%, at a mean age 59.9 and 46.3 months, respectively. Using two-way repeated ANOVA (age [initial DRF, final DRF] vs. group [group A, group B]), we found non-significant difference between the groups in the DRF, $F(1, 21) = 0.96$, $p = 0.338$, while we observed statistically significant and similar increase from the initial to final DRF in both groups, $F(1, 21) = 16.66$, $p = 0.001$ (Figure).

Discussion
This is the first study focusing on the evolution of renal function in patients with PNRM and low initial DRF. Results suggest that the diagnosis of obstruction is inaccurate in most infants with unilateral PNRM if it is based on low initial DRF only. Renal deterioration rarely occurs in asymptomatic patients, and even profoundly impaired kidneys have potential for improvement. Limitations of our study include retrospective design and lack of standardization of treatment among the four centers.

Conclusion
Low DRF in asymptomatic and anatomically stable patients with PNMR should not be considered an indication for early surgery. These findings challenge current practice and should be confirmed by a prospective study.

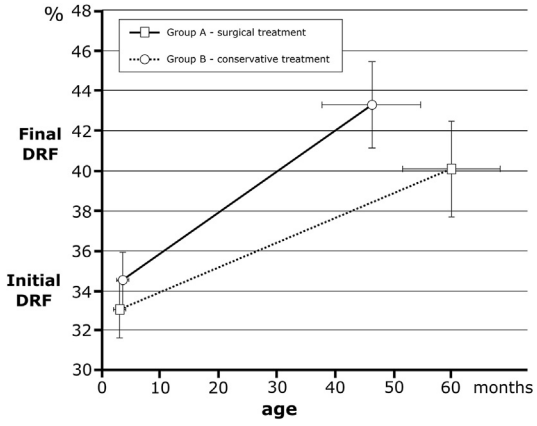

Figure Evolution of low initial DRF in patients with early diagnosed PNRM.

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Introduction

Initial non-operative management of primary non-refluxing megaureter (PNRM) is no longer a topic for debate. Multiple authors have confirmed the safety of this approach for asymptomatic cases with preserved initial differential renal function (DRF) [1–3].

Conversely, low initial DRF is currently considered an indication for surgical intervention even in the absence of symptoms [4]. However, relevant data supporting this approach are lacking. Based on the concept that primary megaureter is one of multiple clinical pictures forming the large family of congenital anomalies of kidney and urinary tract (CAKUT) [5], we hypothesized that low initial renal function is not necessarily a result of obstruction, but rather is due to the impaired development of the whole upper urinary tract, and, in the absence of symptoms, there is low risk of further loss of renal function. To test this hypothesis, we evaluated the dynamics of DRF evolution in conservatively treated patients with PNRMs with low initial DRF and compared them with surgically treated patients with low initial DRF.

Material and methods

We reviewed charts of all patients with a diagnosis of primary megaureter referred to four university centers in Czech Republic (Prague, Brno, Olomouc, Hradec Králové) during a 15-year period between 1995 and 2010. Diagnosis of megaureter was based on ultrasound findings of a dilated ($\geq$7 mm) retrovesical ureter with or without detectable hydronephrosis. Only patients diagnosed before 12 months of age, with unilateral PNRM and a DRF between 10% and 40%, and followed minimally 24 months, were included. Patients with vesicoureteral reflux, ureteral ectopy, duplication anomalies, ureterocele, solitary kidney, and with a secondary megaureter (e.g., posterior urethral valves, prune belly syndrome, or neurogenic dysfunctional bladder) were excluded. All patients were put on antibiotic prophylaxis except for three in group A and two in group B. Patients were placed in two groups based on management: group A, surgical; group B, conservative.

The dynamics of DRF in relation to age and type of treatment was studied. DRF was assessed by a Tc-99m-MAG3 (mercaptoacetyltriglycine) diuretic renogram. In each patient we recorded the earliest (initial) DRF, the last known (final) DRF after a period of follow-up, the age when MAG-3 scans were performed, and the type of treatment. DRF was classified as stable if the final DRF deviated less than 2.5% from the initial DRF, as increased when the final DRF gained $\geq$2.5% and decreased when the final DRF dropped more than 2.5%. Drainage has not been considered, because most radiologists drew their area of interest from around the kidney and did not measure the activity on the megaureter.

To record the dynamics of dilatation and eliminate differences between different examiners in a retrospective study, we used the Pfister–Hendren classification of PNRM (type 1, dilatation is limited to the ureter; type 2, dilatation of the ureter and mild dilatation of the pelvis and calyces; type 3, large and tortuous ureter with huge intrarenal dilatation) [6].

Values of DRF are given as mean $\pm$ standard deviation (SD). Differences in DRF were assessed using two-way repeated ANOVA (age at initial DRF and final DRF in group A and group B). A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 25 patients fulfilled strict inclusion criteria. Sixteen patients were treated surgically (group A), and nine patients were followed conservatively (group B). The initial mean DRF in group A was 33.1 $\pm$ 5.9%, in group B 34.5 $\pm$ 4.4% at a mean age of 3.0 $\pm$ 2.2 and 3.6 $\pm$ 3.2 months, respectively. The final mean DRF in group A was 40.1 $\pm$ 9.5% and in group B 43.3 $\pm$ 6.5%, at a mean age of 59.9 $\pm$ 34.1 and 46.3 $\pm$ 24.9 months, respectively. The mean follow-up in group A was 42.8 $\pm$ 25.3 and 56.8 $\pm$ 34.5 months in group B. At the end of follow-up the DRF increased in 12 patient (75%), remained stable in two patients (12.5%), and decreased in two patients (12.5%) in group A; in group B, the DRF increased in seven patients (78%), remained stable in two patients (22%), and did not decrease in any of the patients.

Using two-way repeated ANOVA (age at initial DRF and final DRF in group A and group B) we found non-significant differences between the groups in the DRF, F (1, 21) = 0.96, p = 0.338, and we observed a statistically significant increase from the initial to final DRF in both groups, F (1, 21) = 16.66, p = 0.001. The interaction effect was not statistically significant, F (1, 21) = 0.19, p = 0.667, indicating that the increase in the DRF was similar in both groups (see Figure in the Summary).

In group A (surgical treatment) at the beginning of follow-up, we found the following megaureters according to the Pfister–Hendren classification: type 3, 13 patients; type 2, 3 patients; and type 1, 0 patients. Six patients were indicated to surgery for increased dilatation, two patients for increase in dilatation together with decrease in DRF, two patients for febrile urinary infection; in the other eight cases the only indication was the low initial DRF and persistent dilatation of the upper urinary tract. No patients had a history of pain or lithiasis. At the end of follow-up we found megaureter type 3 in two, type 2 in four, and type 1 in four cases. In five cases dilatation completely resolved. In one patient the data were lost. In summary, during follow-up of group A, dilatation disappeared in five, improved in seven, and remained stable in three patients.

In group B (conservative) we found megaureters of type 3 in one, type 2 in six, and type 1 in two patients at the beginning of follow-up. At the end of follow-up, no type 3 megaureters were found; we found type 2 in one case, and type 1 in five cases. In two cases dilatation completely resolved and in one patient data were lost. In summary, during follow-up of group B, dilatation disappeared in two, improved in four, and remained stable in two patients.

Discussion

The widespread use of ultrasound in recent decades has led to more frequent early diagnosis of asymptomatic patients with primary non-refluxing megaureter. It is known that only 17–27% of cases will eventually need surgery [3,7]. The key and most difficult question is to determine which infants need an aggressive approach and when it is best to operate to prevent renal damage resulting from obstruction and complications due to impaired urinary flow, especially infection and stone formation. In megaureters, assessment of obstruction is difficult. The drainage curve of the diuretic renogram is inaccurate in diagnosing obstruction and possibly predicting kidney function deterioration. It may be misleading because of high compliance of the dilated ureter. Its shape depends on hydration, timing of diuretics administration, bladder filling, on where the region of interest was drawn, and, finally, on obstruction [8].

The most recent British Association of Paediatric Urologists consensus considers the failure of conservative management (breakthrough febrile urinary tract infections, pain, increasing dilatation, DRF deterioration) and low initial DRF ($\leq$40%) the only key indicators for surgical treatment of PNRM [4]. Justification for early surgery if conservative management fails is obvious and is not a matter of debate. However, clear data supporting a surgical approach in asymptomatic patients with low initial DRF are lacking. The belief that patients with profound DRF impairment should be treated surgically originates from Koff's classic definition of obstruction: "any restriction to urinary outflow, which left untreated leads to loss of renal function" [9], and is in harmony with the standard anatomical concept of primary megaureter being caused by functional obstruction due to hypoplastic and/or adynamic distal ureteral segment.

Recent studies call this anatomical concept into question. Several genes, including mutations, especially of *PAX2*, *KAL*, *EYA1*, and *AGTR2*, transcription factors, and secreted proteins, contribute to normal ureteral development, which when deranged manifest various forms of CAKUT. The expression of the many regulatory molecules for kidney and urinary tract morphogenesis is not limited to the site and timing of initial ureteric budding, but instead continues throughout kidney development, so each minor mutation of multiple genes has multiple ontogenetic functions on the excretory system [5]. Therefore, if we admit that the primary cause of megaureter is a derangement of development of the whole upper urinary tract, then renal impairment may be one part of its clinical picture and not necessarily a result of obstruction. Therefore, the risk for developing an obstructive renal injury is low. In a classic study 20 years ago, Koff and Campbell [9] followed conservatively 16 patients with profound hydronephrosis caused by ureteropelvic junction (UPJ) obstruction and initial DRF of 40% or less for a mean period of 21 months. In 15 of them they observed a rapid improvement of DRF, concluding that asymptomatic unilateral hydronephrosis with low initial renal function carries low risk for loss of renal function [4]. If early profound impairment of renal function in patients with UPJ stenosis does not indicate obstruction in the majority of patients, why postulate that early low DRF in primary megaureter is caused by obstruction? Moreover, the spacious highly compliant megaureter in comparison with UPJ stenosis probably represents a protective factor to renal injury during a transient ureteric obstruction. Therefore, we hypothesized that the risk of obstructive renal injury in patients with primary megaureter is low too. To our knowledge, no similar study concerning PNRM has been published up till now.

To test our hypothesis, we focused on the dynamics of DRF evolution in infants with unilateral PNRM and low initial DRF. As most patients with PNRM have preserved DRF [1–3,10] and cases with low initial DRF are generally indicated for surgery, it is difficult to obtain a number of patients complying with statistics in one center. We decided to conduct a multicentre study in cooperation with three other university centers in the Czech Republic (Olomouc, Hradec Králové, Brno) and retrospectively reviewed data collected from these four centers over 15 years (1995–2010). We compared groups of surgically and non-operatively treated infants statistically, regardless of the degree of dilatation and shape of the curve of diuretic renogram. Measurement of these variables was largely dependent on the method of examination and the examiner's experience and could not be statistically compared retrospectively.

However, we were interested in the evolution of dilatation in these two groups of patients. To eliminate differences between different examiners, we used the Pfister–Hendren classification of PNMR [6]. Despite no statistical difference between both groups in terms of age and initial DRF, we found less pronounced dilatation in group B patients than in group A. In group B, no cases of increased dilatation were observed; 2 (22%) patients remained stable, 6 (66%) improved, in one patient (22%) the data were lost.

The findings in this study confirmed our hypothesis regarding the low risk of renal deterioration in unilateral PNRM with initial low DRF. Group A (surgical) and group B (conservative) were statistically comparable at the beginning of the study and did not differ statistically at the end of follow-up. We proved a statistically significant increase in DRF in both groups at similar ages and did not confirm any difference of DRF evolution in these two groups of patients. The rate of DRF improvement was similar in both groups, regardless of type of treatment. We noted only two of 16 patients surgically treated (group A) and none of the conservatively followed children (group B) having a decrease in DRF. The two patients in group A who had progressive loss of function differed from other patients. The first patient had a rare combined obstruction at two levels (ureteropelvic and vesicoureteral junctions) and underwent pyeloplasty and ureteral reimplantation 2 months later. The second one showed a pronounced parenchymal hyperechogenicity of the affected kidney from the beginning of follow-up. These findings allow us to conclude that during the first 2–3 years of life, we may expect functional improvement in most kidneys with initial reduction of DRF in patients with a PNMR (Fig. 1).

It definitely does not suggest that the early surgery for obstructed primary megaureter is unnecessary or ineffective. Our findings just proved that in asymptomatic infants and toddlers with unilateral PNRM the presence of profound reduction of DRF is not an accurate or reliable indicator of

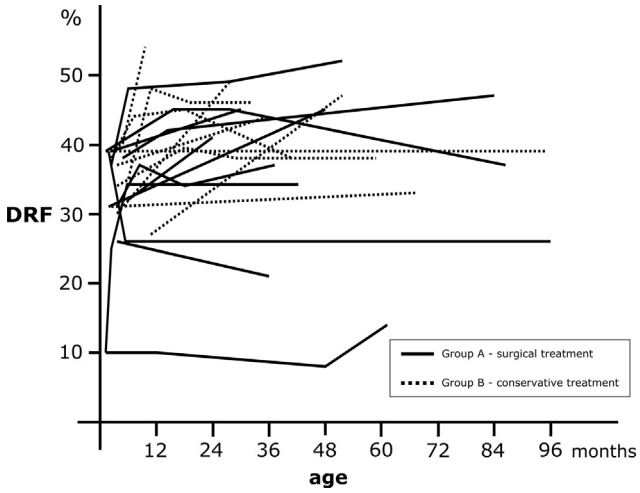

Figure 1 Differential renal function (DRF) (in %) contributed by affected kidney with primary non-refluxing megaureter is compared with patient age. Lines connect sequential measurements in the same patient.

obstruction, and, therefore, does not indicate that surgery is steadily required to protect the kidney from injury or to ensure improvement of renal function. We strongly believe that an increase in dilatation (especially intrarenal), and further decrease in DRF and a reduction of symptoms are the right indications to intervene.

We believe these findings are especially important for children younger than 1 year when reimplantation of a grossly dilated ureter into a small infantile bladder may be a challenging operation and when a number of temporary or alternative options such as JJ stenting, refluxing ureteral reimplantation, or endoscopic balloon dilatation carry a significant risk of complications [11—13]. In the first year of life it appears relatively safe to follow the asymptomatic unilateral PNRM with low initial DRF non-operatively, provided there is a close follow-up.

The strength of this study is a relatively large number of conservatively followed patients with low initial DRF who are rarely reported because they are currently indicated for early surgery [10]. Our study brings an important argument for a prospective and now ethically acceptable study in patients with PNRM and initially low DRF.

A weakness of our study is its retrospective nature. Indications for surgery and ultrasound studies varied between the four institutions and, therefore, were not controlled.

Conclusions

Our results suggest that the diagnosis of obstruction is inaccurate in most infants with unilateral PNRM if it is based on low initial DRF only. Our experience indicates that renal deterioration rarely occurs in this population and that even the functionally impaired kidneys have good potential for improvement. Therefore, an initially low DRF in asymptomatic and anatomically stable patients with PNMR should not be considered an indication for early surgery. These findings challenge current practice and should be confirmed by a prospective study.

Conflicts of interest

None.

Funding

None.

References

[1] Keating MA, Escala J, Snyder III HM, Heyman S, Duckett JW. Changing concepts in management of primary obstructive megaureter. J Urol 1989;142:636.
[2] Baskin LS, Zderic SA, Snyder HM, Duckett JW. Primary dilated megaureter: long-term followup. J Urol 1994;152:618.
[3] Liu HYA, Dhillon HK, Yeung CK, Diamon DA, Duffy PG, Ransley PG. Clinical outcome and management of prenatally diagnosed primary megaureters. J Urol 1994;152:614.
[4] Farrugia MK, Hitchcock R, Radford A, Burkit, Robb A, Murphy F. British Association of Paediatric Urologists consensus statement on the management of the primary obstructive megaureter. J Pediatr Urol 2014;10:26—33.
[5] Ichikawa I, Kuwayama F, Pope JC, Stephens 4th FD, Miyazaki Y. Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT. Kidney Int 2002; 61:889—98.
[6] Pfister RC, Hendren WH. Primary megaureter in children and adults. Clinical and pathophysiologic features of 150 ureters. Urology 1978;12:160—76.
[7] Di Renzo D, Aguiar L, Cascini V, Di Nicola M, McCarten KM, Ellsworth PI, et al. Long-term followup of primary non-refluxing megaureter. J Urol 2013;190:1021—6.
[8] Arena F, Baldari S, Proietto F, Centorrino A, Scalfari G, Romeo G. Conservative treatment in primary neonatal megaureter. Eur J Pediatr Surg 1998;8:347—51.
[9] Koff SA, Campbell KD. The nonoperative management of unilateral neonatal hydronephrosis: natural history of poorly functioning kidneys. J Urol 1994;152:593—5.
[10] Shukla AR, Cooper J, Patel RP, Carr MC, Canning DA, Zderic SA, et al. Prenatally detected primary megaureter: a role for extended followup. J Urol 2005;173:1353—6.
[11] Farrugia MK, Steinbrecher HA, Malone PS. The utilization of stents in the management of primary obstructive megaureters requiring intervention before 1 year of age. J Pediatr Urol 2011;7:198—202.
[12] Kaefer M, Misseri R, Frank E, Rhee A, Lee SD. Refluxing ureteral reimplantation: a logical method for managing neonatal UVJ obstruction. J Pediatr Urol 2014;10:824—30.
[13] Angerri O, Caffaratti J, Garat JM, Villavicencio H. Primary obstructive megaureter: initial experience with endoscopic dilatation. J Endourol 2007;21:999—1004.