DOES PRENATAL DIAGNOSIS AND EARLY POSTNATAL CARE OF POSTERIOR URETHRAL VALVES IMPROVE THE OUTCOME?

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Abstract

Introduction: Posterior urethral valves are severe congenital obstructive uropathies that could lead to renal failure and end stage renal disease despite the progresses in prenatal and postnatal diagnosis and management. Aim of the study: The aim of this paper is to study the relation between certain parameters and the long-term outcome of infants with and without a prenatal diagnosis of posterior urethral valves.

Material and methods: Records of all children with posterior urethral valves treated in our center from January 2000 to December 2014 were retrospectively reviewed and statistically analyzed. Results: 31 patients were analyzed; no significant relations between the existence of the prenatal diagnosis of posterior urethral valves and the long time impairment of the renal function were revealed ($\chi 2=3.02$, p=0.08, 95%CI); a multivariable statistic analysis showed that high postnatal age at diagnosis and treatment was a risk factor predictable for poor outcome through renal function impairment (HR=5.139 → 95%CI: 2.01-6.18). Conclusion: Our data shows no relations between the existence of prenatal diagnosis of posterior urethral valves and their outcome, but a smaller age at the moment of treatment was observed in the prenatal group, with lower rates of renal function impairment.

Key words: congenital obstructive uropathy, posterior urethral valves, prenatal diagnosis

Introduction

Posterior urethral valves (PUV) are one of the most severe forms of congenital obstructive uropathy, with a reported incidence of 1/ 3000-8000 male newborns (1). Despite the advances in prenatal detection of these malformations and in the possibilities of medical and surgical management, posterior urethral valves continue to be a common cause of renal failure, leading to dialysis and renal transplantation. The outcome of 13-64% of all of these patients is to end stage renal disease (ESRD) (2).

Currently the diagnosis of PUV is made during the fetal period, by routine prenatal ultrasound. This will allow parental counseling during pregnancy, early medical and surgical postnatal treatment, avoiding postnatal infectious complications. There are multiple controversies regarding the consequences of prenatal diagnosis on the postnatal outcome of these infants, and the relation between age at diagnosis and the risk of progress towards ESRD.

The aim of our study is to evaluate the characteristics, diagnostic tools, treatment options and long term outcome of children with or without prenatally detected PUV treated in our institution.

Materials and methods

Records of all children with PUV treated in our center between January 2000 and December 2014 were retrospectively reviewed. Data like annual incidence, demographic information, gestational age at diagnosis, birth weight, diagnosis circumstances, treatment and outcome were analyzed. All data were statistically processed and deemed relevant at a value of $p<0.05$.

Results

A total number of 31 patients with PUV were identified, including 12 cases (38.7%) with prenatal diagnosis. The annual incidence of the cases showed a relative homogenous distribution in time, but still with a slightly tendency of increasing starting from 2008. Also, from the 12 cases prenatally diagnosed, only two were identify before 2008, all other (10 cases) being diagnosed and treated between 2008 and 2014.

Regarding origin environment we found no differences between rural and urban area: 51.6% of all cases came from urban areas and 48.4% from rural areas.

Mean gestational age was 37.35 weeks +/- 1.4SD, and none of these boys were preterm baby. Mean birth weight was 3100g, with a minimum of 2000 grams and a maximum birth weight of 3950 grams. (Table 1)

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Mean GA lot	Mean -95%	Mean +95%	SD	SEM	Min	Max	Q25	Median	Q75
37.35	36.84	37.87	1.40	0.25	35.00	39.00	36	37	39

Table 1. Gestational age

	n	%
Evaluation of a prenatal hydronephrosis	8	25.8%
Urinary tract infections	12	38.7%
Urosepsis	5	16.1%
Acute urinary retention	4	12.9%
Neonatal occlusion	2	6.5%
Incidental	1	3.2%
Arterial hypertension	1	3.2%
Total	31	

Table. 2. Postnatal diagnosis

Vesicoureteral reflux	Count	%
Absent	12	38.71%
Present	19	61.29%
gr IV left	3	9.68%
gr IV bilateral	2	6.45%
gr V left /right	7	22.58%
gr V right, IV left	2	6.45%
gr V bilateral	5	16.13%
Total	**31**	

Table. 3. Associated vesicoureteral reflux

MULTIVARIATE ANALYSIS	Beta	SE	Wald	Sig. p	Hazard Ratio Exp(β)	95% CI for Exp(B) Lower	Upper
Diagnosis age	0.094	.039	5.889	.015	**5.139**	2.018	6.184
Prenatal diagnosis	1.637	1.141	2.059	.151	**1.098**	0.549	48.071

χ2 statistic test = 1.577 df = 7; p = 0.0628; 95%CI.
CI – Confidence Interval, df-degree freedom, HR-Hazard rate SE-standard error

Table 4. Multivariable statistic analysis of evolution to end stage renal disease risk vs. diagnosis age

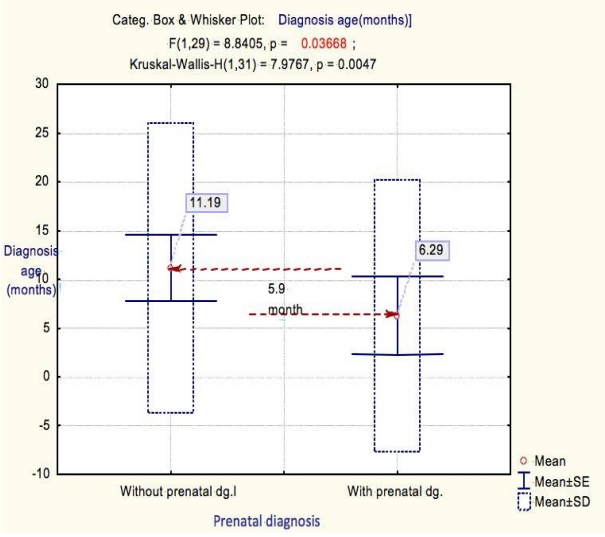

Fig. 1. Diagnosis age according to prenatal diagnosis

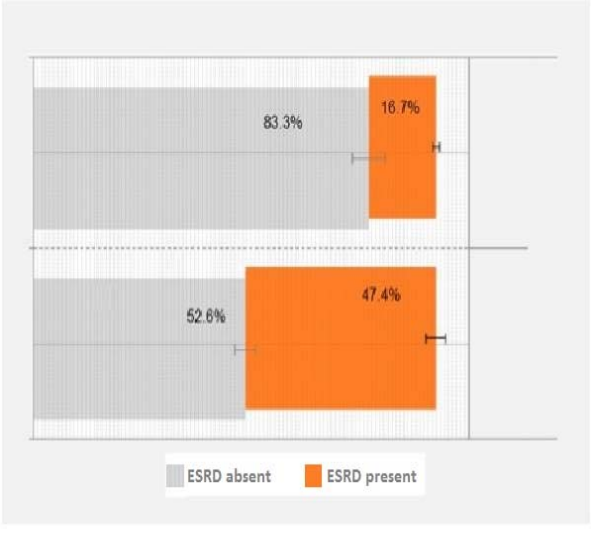

Fig. 2. Prenatal diagnosis vs. chronic renal

The mean gestational age at diagnosis, in the case of the 12 patients prenatally detected, was 31.42 weeks +/-3.03SD, with a minimal gestational age of 25 weeks, and a maximum of 36 weeks. The Q25 quartile indicates that 75% of the cases were late diagnosed during pregnancy, around 30 weeks of gestational age.

The prenatal diagnosis was suggested in all cases by dilatation of the fetal urinary pathways. In 10 cases (83.35%) the ultrasound identified bilateral ureterohydronephrosis, while in 2 cases (16.7%) a megacistys was also found. A direct sign of urethral obstruction ("key-hole sign") was not found in any of the 12 fetuses.

Regarding the postnatal diagnosis circumstances we found that the most frequent symptoms were those related to the urinary tract infection (38.7%) and urosepsis (16.1%). Only 8 cases from the 12 with prenatal diagnosis were transferred to our department immediately after birth for diagnostic confirmation of a suspected fetal urethral obstruction (25.8% of all cases). (Table 2)

Mean age at diagnosis was 9, 3 months+/-14,4SD, with a maximum of 48 months. 50% of all cases were diagnosed under the age of 2 months, while 25% of the patients were older than 14 months at diagnosis. For children with a history of fetal ureterohydronephrosis we found a mean diagnosis age of 2.3months+/-13.8 SD, smaller with 5.9 months comparing with the group without prenatal diagnosis (p=0.0047).(Fig.1)

At admission in our department blood and urinary test were performed in all cases. A renal ultrasound was also performed, and in case of a confirmed ureterohydronephrosis, a bladder catheter was placed to relieve bladder outlet obstruction. If necessary, antibiotic therapy was initiated for the treatment of the urinary tract infection (according to the antibiotic susceptibility of the identified germs), and after it, a diagnosis voiding voiding cystourethrography was performed. Beside the urethral obstruction, in 61,3% of the cases, the cystography also identified the presence of associated vesicoureteral reflux. (Table 3.)

After the imaging confirmation of the urethral obstacle, all children, except 4 cases, underwent surgical treatment. One of the cases was referred to us at the age of two years, with ESRD, which required dialysis. The outcome was unfavorable, with death due to multiple complications (including cardiac impairment). The other three cases were diagnosed in the infancy but in all three the urethral obstruction was associated with urosepsis and high degree vesicoureteral reflux. In one case the family didn't agree with the endoscopic procedure. In all the cases without surgical treatment the outcome was toward exitus; the pathological examination showing important degrees of renal and pulmonary hyperplasia. From the remained 27 cases, the treatment was represented only by endoscopic ablation of the urethral obstacle in 67.7% of the cases, endoscopic ablation associated with cystostomy in 6.5% of cases, with ureterostomy in 6.5% of cases, with pyelostomy in 3.2% cases, and endoscopic ablation with the need for a peritoneal dialysis catheter in one patient.

The outcome was unfavorable in eleven cases (35.5%) which developed a form of renal function impairment. Only two of the cases with prenatal diagnosis evolved through end stage renal disease, representing 16.7% from all cases with renal impairment. Our results revealed no statistical significant correlation between the presence of the prenatal diagnosis and the long time impairment of the renal function ($\chi 2$=3.02, p=0.08, 95%CI). (Fig.2)

On the other hand, a multivariable statistic analysis showed that high postnatal age at diagnosis and treatment was a risk factor predictable for poor outcome through renal function impairment (HR=5.139 → 95% CI: 2.01-6.18), while again, prenatal diagnosis didn't correlate with chronic renal disease (HR=1.09 → 95%CI: 0.54-48.07). (Table4.)

Discussion

PUV are one of the most frequent causes of congenital low urinary tract obstruction. They produce a wide range of urethral obstruction with variable severity, and thus, they represent a spectrum of diseases, ranging from mild obstruction with minor effect on renal function to severe diseases with premature renal insufficiency. Severe urethral obstruction can lead to devastating congenital anomaly that can be lethal in utero or during the perinatal period. They are usually associated with severe dilatation of the urinary pathways that will lead to a high rate of prenatal diagnosis of the malformation. Mild forms of the disease will be nearly subclinical, presented later in life with signs of urinary tract infection or micturation abnormalities (3). Recent progress in fetal ultrasonography lead to a progressively increase in the prenatal detection of congenital urethral obstructions.

Gestational age for the newborns affected by the PUV is generally normal. Bilgutay et al. reveal in a study on 104 cases of urethral obstruction a prematurity rate (defined as gestational age less than 37 weeks) of 33% (4). In another series of 31 patients, in 2015, Roy and coworkers found a median for gestational age of 38 weeks (5). Our results are in concordance with these data, as in our group gestational age was 37 weeks ± 1.4 DS (minimum 35 weeks, maximum 39 weeks). The Q25 quadrille indicates that 75% of the pregnancies ended at a gestational age older than 36 weeks.

The widespread of fetal ultrasound has significantly increased in time the frequency of prenatal diagnosis in PUV, with reported incidence varying from 50% to 70% of the cases. Thakkar et al. reported in 2014 an incidence of 51% on a series of 71 cases (6). Our data revealed an incidence of 38.7% of prenatal suspicion of PUV; most of the cases prenatally suspected for urethral obstruction were children born after 2008 (10 of 12 cases), situation that can be justified by the increased use of obstetrical ultrasound in the last decade and also by the advances made in the medical technologies.

Medium gestational age at diagnosis in our group was 31.4 weeks (minimum 25 weeks, maximum 36 weeks) with 75% of the cases being identified at a gestational age older than 30 weeks. Prenatal diagnose in PUV can be suspected starting from 18th-19th week of gestation; most commonly the diagnosis is establish at 20th-38th week of pregnancy

(7). Different scientific reports proved that the earlier the prenatal diagnosis is suspected during fetal life (especially before 24 weeks of gestation), the bigger is the risk to an unfavorable outcome, to end stage renal disease (8).

The effect of prenatal diagnosis in posterior urethral valves is controversial. There are some authors who showed that patients with prenatal diagnosis have a higher risk to developed end stage renal disease (9), while others suggesting an improving of long term outcome for patients with fetal diagnosis (10). Reinberg et al. found in a series of 8 cases with prenatal diagnosis that 64% developed renal failure, showing that a poor prognosis was associated with prenatal diagnosis (11).

Our study didn't find a strong statistical correlation between the prenatal diagnosis and long time evolution to ESRD. Only 16.7% of all cases that developed ESRD had the urethral obstruction identified prenatally, fact that can lead to the idea that prenatal diagnosis will be associated with a low risk for developing renal function impairment. There are multiple reports in the literature that support the idea that the prenatal diagnosis didn't improve outcomes (12), (13), probably because more severe forms of the urethral obstruction are likely to show signs during the fetal period. Our results, which are in contradiction with these opinions, can be explained by a low rate of prenatal diagnosis in our series (38.7%), related to an inconsistent access to prenatal screening. On the other hand, we noted that only 8 neonates (66%) from the 12 with prenatal diagnosis were referred to our department for the postnatal investigation of a fetal renal abnormality. The other 4 cases were presented later in the infancy, as a result of acute urinary tract infection.

In our series, prenatal suspicion of a urethral obstruction was associated with a smaller age of postnatal treatment comparing with cases without fetal diagnosis. The mean age of definitive diagnosis, and beginning of treatment for prenatal group was 2.3 month, with 5.9 month smaller than the one in the group without postnatal diagnosis. Age at presentation and age at surgery are other subjects of controversy. A study in 2010 reported that posterior urethral valves diagnosed after one year of age are associated with a low risk of developing renal impairment, as chronic kidney disease developed in 48% of patients diagnosed before 1 year of age vs. 25% in patients diagnosed after 1 year of age (14). On the other hand, there are multiple reports that support the idea of a poor outcome associated with late presentation. Ansari et al. found that evolution to chronic kidney disease was more frequent (41% vs. 30%) in cases that underwent valve ablation after and before 2 years of age respectively.

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Conclusions

Our data shows no relations between the existence of the prenatal diagnosis of PUV and their outcome. However prenatal diagnosis was related to a lower age at the time of diagnose and postnatal treatment. Our study has some limitations as it is a retrospective study that includes a small number of patients from a single institution. Further studies will need to be conducted, with the analyses of other multiple risk factors implied in the long term outcome of these patients..

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