UNIVERISTY OF MEDICINE AND PHARMACY
“CAROL DAVILA” BUCHAREST
GENERAL MEDICINE

PROGNOSTIC FACTORS IN POSTERIOR URETHRAL VALVES
THESIS SUMMARY

PhD Coordinator
Prof. Dr. Ionescu Sebastian

PhD Student
Bretan cas.Luchita Teodora

2023

Table of Contents

Introduction....2
GENERALITIES....2
1.1 Embryology of the urethral valves....2
1.2 Physiopathology of the posterior urethral valves....3
1.3 Diagnosis of PUV....5
II. PERSONAL CONTRIBUTIONS....5
2.1 Working hypothesis and general objectives....5
2.2 Research plan:....6
3. Results....8
3.1. Biological factors: nadir creatinine, initial serum creatinine, plasma renin activity.....8
3.2 Impact of the moment of diagnosis on renal function....9
3.3 Association of junctional stenosis/vesicoureteral reflux. Negative prognostic factors? 10
3.4 Pre- and perinatal parameters: oligohydramnios, prenatal ureterohydronephrosis and low birth weight....10
3.5 Imaging parameters....11
4. Conclusions....12
Bibliography....14
Published articles....15

Introduction

Posterior urethral valves represent the most common obstructive type of malformation placed at the lower urinary tract, in the male gender, having an occurrence of 1/5000-1/8000 live births. The study of this obstructive pathology has been attended for over 250 years when Morgagni described them over post-mortem dissections. The defining and classifying of the valves have been done only after 150 years later, by Young, who has also described the endoscopic treatment of the disease. The particularity of this disease is, because of the forming of the valves during intrauterine life, the bladder and kidneys will suffer structural and functional changes.

Prenatal ureterohydronephrosis is one of the most common prenatal anomalies, detected at 1-1.45% of the pregnancies. Even though the prevalence of the pregnancy is high, its post-mortem impact is uncertain. Considering the classification of the urinary tract dilations based on the quarters and the integration of the risk degrees, a reno-vesical ultrasound will take place at 48h postpartum, followed by micturating cystography in case of dilation persistence, ideally on the first week of birth. This has the purpose of diagnosing a certain vesicoureteral reflux but also an obstructive pathology, just like in the case of posterior urethral valves.

The surprise factor of the hasty diagnosis was that more and more studies show a weaker renal function and a worse prognosis for patients with antenatal diagnosis compared to the ones who got a diagnosis after clinical manifestations. Therefore, this confirms the hypothesis that antenatal screening identifies the more severe cases of posterior urethral valves. Considering that one of the major benefits of the prenatal diagnosis has been the possibility of treatment in utero for the removal of the subvesical obstacle, in the end it was observed that following the major risks from the fetal intervention, the long-term renal function will remain unchanged.

This thesis has set its goal the evaluation of the different factors that can be blamed in renal function alteration, classified in prenatal, biological and imagistic factors, including ultrasonography and cystography methods, analyzing the prognostic value of these in predicting long-term renal function development for patients with posterior urethral valves. The goal of this analysis is to help both medical personnel composed of neonatologist, nephrologist and pediatric surgeon/urologist, and the family in framing the patient in a risk category, followed by an adjusted management of each category.

GENERALITIES

1.1 Embryology of the urethral valves

To be able to understand the echo the urethral valves have over the whole urinary tract, there needs to be an understanding of the embryology of the disease. The embryologic origin of the valves has been long disputed.

In 1918, Watson has studied a new theory after the study of a 14-week newborn without a PUV diagnosis. During describing prostate development, verumontanum, seminal vesicles, ejaculatory ducts, he made an interesting discovery: during the 14th week of gestation, the epithelium on the surface of the seminal glands grows, having filled the space between verumontanum and the superior wall of the urethra. Watson assumed that posterior urethral

valves appear when this attachment of verumontanum to urethra persists after the period of proliferation, described as a " chemical change about which we know very little", referring to apoptosis, a concept that won the Nobel prize 80 years later.

In 1919 Young and contributors were those who synthesized the pre-existing theories, mainly supporting Watson's theory and were the first who realized a classification of PUV.

In 1955 after macro and microscopic studies but also radiologic ones – using cystography, Stephens concluded that PUV appear as a result of abnormal implantation of Wolffian ducts in urethra, causing the appearance of an obstructive membrane, which can be found as a non-obstructive fine fold situated distal to verumontanum in healthy children.

1.2 Physiopathology of the posterior urethral valves

Considering their early development in the intrauterine period, PUV creates morpho functional changes upstream from the urinary tract, with consequences that affect the patient for their entire life.

Affected organ	Result	Natural evolution
Lung	Pulmonary hypoplasia	It can be fatal to newborn Survivors: respiratory sequela
Kidneys **Glomerular level** • **Obstructive uropathy**	RF reversible	Eases with treatment but recurrence with bladder dysfunction
• **Dysplasia**	RF irreversible	Permanent renal dysfunction which limits the growth and goes to progressive renal failure and HTA
Tubular level	Urinary loses of Na and H2O	Progression with age, nephrogenic diabetes insipidus
Bladder	Hypercontractility, low compliance, muscular hypotonia -> incontinence and incomplete evacuation	Bladder dysfunction is permanent and it changes over time
Ureters	Low contractility, reduced peristalsis	Initial improvement, but later the majority preset UHN

Table 1. The effects of urethral valves on the urinary system. . Campbell-Walsh urology. 10 ed. Philadelphia: Elsevier Saunders; 2012 [2]

During its normal development, the bladder fills and empties cyclically since the early intrauterine period. In the last trimester of pregnancy, the number of cycles reaches 30/24h. These cycles have the role of creating a normally compliant bladder, generating stretching forces that decrease the collagen content of the bladder wall.

The bladder, whose development is conditioned by the presence of obstruction, it hypertrophies. This hypertrophy leads to an increase in the evacuation pressure so that the complete emptying of the bladder can be achieved. This stage represents the compensated phase of bladder dysfunction. Over time, however, the increased bladder evacuation pressure leads to the remodeling of the bladder wall, with the additional increase of the intravesical pressure, which will ultimately lead to the presence of bladder residue, in progressively increased amounts, as the bladder evacuation capacity decreases.

The progressive distension of the bladder, due to the subvesical obstruction leads to the alteration of blood flow at the level of the detrusor, with ischemia at this level and decreased perfusion, which leads to the change to anaerobic type metabolism.

In 1982, Mitchell proposed the concept of a vicious circle of bladder dysfunction in which subvesical obstruction triggers a cascade of consequences, which ultimately lead to an uncompensated end-stage bladder - "valve bladder syndrome". The bladder, although it initially has a compensated stage by generating high evacuation pressures, begins to face the increase in urinary volume as the child grows. To this urinary volume is added polyuria, due to nephrogenic diabetes insipidus - through the evolution of renal dysfunction. Thus, as the volume of urine stored in the bladder progressively increases, it no longer succeeds in a complete evacuation, leading to an increase in the bladder residue. As the post-micturition residue increases, the bladder doesn't have any more periods of complete relaxation, and the muscle fibers are in a permanent state of partial or complete stretch. All these changes lead to the appearance of this valve bladder syndrome [2].

The constantly increased intravesical pressure is later transmitted to the ureter, renal pelvis and glomerular units, with functional and structural changes at each level. Ureterohydronephrosis is common in patients with urethral valves. The increase in renal echogenicity, the thinning of the renal parenchyma with the appearance of cortical cysts, the absence of cortico-medullary differentiation, are signs of renal dysplasia.

Renal dysfunction secondary to valve bladder syndrome has two etiologies: obstructive uropathy and renal dysphasia.

Obstructive uropathy is a well-known phenomenon, demonstrated in animal models. Although hydronephrosis occurs rapidly after the obstruction, irreversible dysplastic changes occur over time and remain constant even after the obstruction is removed [3].

Haecker et al, 2002, affirmed the existence of a primary renal dysplasia, which is added to the obstructive uropathy. The existence of a correlation between renal dysplasia in patients with PUV and the decrease in the renin-angiotensin system which modulates renal development has been demonstrated, as well as the decrease in the polymorphism of the angiotensin I receptor [4].

1.3 Diagnosis of PUV

PUV are diagnosed in a proportion of 1:1250 prenatal ultrasounds, representing 10% of genitourinary disorders detected antenatally. The pathognomonic signs, with 95% sensitivity and specificity 80%, are: Thickened and increased in volume bladder, accompanied by ureterohydronephrosis uni- or bilateral. A bladder wall below 2 mm is considered normal, whereas a thickness greater than 3 mm is pathological. Poor bladder emptying may also be noted, during a 30-minute ultrasound monitoring. Progressive oligohydramnios is another sign of lower urinary tract obstruction, as is dilation of the posterior urethra, with the characteristic "keyhole" sign [5].

With much greater accuracy, fetal MRI can assess the degree of obstruction by measuring urethral dilation, distension of the bladder, its thickening and reduction of the amount of amniotic liquid.

Although the addressability to the doctor for dispensary of pregnancies has increased and at the same time the performance of ultrasound machines has increased, not all urethral valves are diagnosed in the prenatal period.

Postnatally, the urethral valves are detected by their clinical sound. From a clinical point of view, posterior urethral valves have nonspecific signs, varying according to the patient's age. The most common signs are those of a febrile urinary infection, often accompanied by a filiform, interrupted stream of urine or even acute urinary retention. In older children, urethral valves can be manifested by urinary incontinence. To establish the postnatal diagnosis, a series of imaging and biological investigations can be performed. Reno-bladder ultrasound shows ureterohydronephrosis, distended bladder with thickened wall and dilated posterior urethra. Rarely, the valve can be seen sonographically as an echogenic line (6) (7). Pathognomonic is the "keyhole" sign, in which the dilated urinary bladder and posterior urethra form a key hole.

Micturition cystography is the one that confirms the diagnosis by highlighting an obstacle at the level of the membranous urethra.

Laboratory tests and renal scintigraphy complete the diagnosis, by evaluating renal function.

II. PERSONAL CONTRIBUTIONS

2.1 Working hypothesis and general objectives

Posterior urethral valves represent the main obstructive pathology of the lower urinary tract in males, with an incidence of 1:5000-1:8000 in newborn boys. Despite primary treatment of posterior urethral valves, between 25 and 40% of patients progress to chronic renal failure. The question that is asked and that led to the conduct of the study is, are there any predictive factors of the evolution towards this chronic renal failure?

The project aims to demonstrate the relationship between biological and imaging factors as well as prenatal data, and the occurrence of chronic kidney disease in patients with posterior urethral valve. From the prenatal data, the following data was taken into the study: oligohydramnios, the presence of prenatal ureterohydronephrosis and birth weight below 3000g. Among the biological factors, according to data from the literature, initial serum

creatinine, nadir creatinine and plasma renin activity were chosen. Using imaging tests, the following were included: the parenchymal index, the echogenicity of the renal parenchyma - measured sonographically and the SWRD index (shape, wall, reflux, and diverticula), determined cystographically.

The study started from the hypothesis that there would be a series of factors that, once determined, could place the patient with a urethral valve in a risk group. Knowing this risk of developing chronic kidney disease would be of particular importance both for clinicians in order to establish an optimal monitoring plan, but also for parents, the latter being able to better understand the need for periodic follow-up and the fact that valve ablation will not represent, in all cases, the definitive treatment.

2.2 Research plan:

1. Analysis of the observation sheets of patients with urethral valve from the Surgery Clinic of Marie S. Curie Hospital Bucharest, in the period 2007-2021, noting the existence of prenatal diagnosis - ureterohydronephrosis, oligohydramnios.
2. Specifying the co-existence of other malformations or diseases that can influence the result of the study (multicystic renal dysplasia, severe prematurity).
3. Dosage of initial serum creatinine (mg/dL), plasma renin activity (μg/ml/24h)
4. Nadir creatinine values – the lowest value of creatinine in the first 12 months after treatment
5. Ultrasound measurement of the parenchymal index and assessment of renal echogenicity
6. Calculation of the cystographic SWRD index according to the table
7. Definition of chronic kidney disease GFR<90 mL/min/1.73m2
8. Analysis of the correlations between the markers mentioned above and the occurrence of chronic kidney disease.

The variables used in the study were the following:

1. Controlled variables: oligohydramnios, prenatal ureterohydronephrosis, birth weight, age at the time of the intervention
2. Independent variables: initial serum creatinine, nadir creatinine, plasma renin activity, renal parenchyma thickness, SWRD index
3. Dependent variables: glomerular filtration rate

Confounding factors, which could change the result of the study, are:

- High prematurity: it is associated with prolonged hospitalization, change in creatinine values, a small-caliber urethra, which does not allow valve resection per primam
- The association of complex cardio-respiratory malformations, which lead to the disturbance of the patient's homeostasis, with the impairment of renal function

Materials:

- Patients admitted to the surgery clinic of the Marie S. Curie Emergency Clinical Hospital for Children, Bucharest, with the diagnosis of posterior urethral valve, in the period 05.2007-05.2021

- Batch: 78 patients

The inclusion criteria consisted in the presence of the diagnosis of posterior urethral valve, conformed cystographically and later intraoperatively, and the consent of the parents, specified in the observation sheet, to participate in the studies and statistical process of the data.

Patients with insufficient creatinine values were excluded in order to be able to establish nadir creatinine, and also patients who did not show up for control more than 12 months after the surgical intervention were excluded.

The data analysis was carried out in the R programming language, version 3.6.2, and some tables and graphs in the Excel application of the Microsoft 365 for Enterprise package.

The significance threshold used was the standard one: 0.05 (below this value the results were considered statistically significant).

Regarding the comparison of proportions (when we want to see if there is a relationship between two categorical variables), the chi-squared test or its equivalent, the Fisher test, were used.

For the comparison of independent batches relative to numerical data, the following was used:

• 2-independent sample t-test when the data were normally* distributed
• Wilcoxon-Mann Whitney test when the data were not normally distributed.

* To evaluate the type of distribution i.e. if the data within a batch were normally distributed or not, the Shapiro-Wilk test was used, with a significance threshold of 0.05 (if the p-value was greater than 0.05, it was considered normally distributed and as such, parametric tests could be used).

Finally, regarding the prediction model used, given the type of output data (that we want to predict) – binary and categorical (kidney failure developed: yes/1 or no/0), we have opted for the logistic regression model or the logistic regression model. It concretely predicts the probability of kidney failure and has values from 0 to 1 (0% to 100%).

The patients included in the study are patients treated and monitored in the surgery clinic of the Marie S. Curie Emergency Clinical Hospital for Children in Bucharest, during the period 2007-2021. In order to carry out the study, both the agreement of the ethics committee of the hospital and the agreement of the patients' relatives were obtained, in the observation sheets there being a column regarding the agreement for statistical data processing. The study is both retrospective and prospective, as it was also based on the processing of data from the observation sheets regarding prenatal diagnosis, initial and nadir creatinine and imaging parameters for patients in the clinic before the start of the study, but also prospectively for patients diagnosed in during the course of the study, all being subsequently monitored periodically in order to establish the evolution towards chronic kidney disease.

3. Results

For a better structuring of the data, the factors analyzed for the prognosis of patients with urethral valve were divided into: biological markers, imaging, pre- and perinatal parameters and other associated malformations, so the vesico-ureteral reflux and vesico-ureteral junction stenosis.

3.1. Biological factors: nadir creatinine, initial serum creatinine, plasma renin activity.

In the specialized literature, there is an increased concern for the determination of early biological factors, which can guide the clinician and the parents from the beginning on the evolution of the patient with urethral valve. One of the most well-known and reference markers is nadir creatinine, which has already become a reference element. This is also the reason why we chose to present the biological factors from the very beginning, in order to later make correlations with prenatal and imaging data.

A reference for risk factors in posterior urethral valves, but also for the division of patients into risk groups, remains a study by Coleman et al, published in 2015, regarding nadir creatinine values and the risk of developing renal failure of these patients. The importance of the study comes from the fact that it insists on lowering the nadir creatinine threshold, which until then in many studies was 1mg/dL (88.4μmol/ml). Thus, patients are divided into three classes, according to nadir creatinine values, as follows: low risk: patients with nadir creatinine below 0.4mg/dL, respectively 0.35 μmol/L; intermediate risk: patients with creatinine values between 0.4 mg/dL (0.35μmol/L) and 0.85 mg/dL (75μmol/L); high risk > 85 mg/dL (75 μmol/L). According to Coleman, all studied patients with nadir creatinine > 85 mg/d L developed renal failure (8, 9). The results also conformed to the current study, observing an incidence of 8.82% of renal failure in the group with nadir creatinine below 0.4, compared to 91.65 in the group with nadir creatinine values greater than 0.8mg/dl.

Taking this data into account, we studied the correlation between nadir creatinine, divided by intervals, according to Coleman's study. At the same time, keeping in mind that many patients do not respect the recommended monitoring periods thus making it difficult to calculate the nadir creatinine, we took into account the analysis of the correlation between the initial serum creatinine obtained at the time of the patient's presentation and the evolution towards chronic renal failure.

The initial creatinine was divided into 3 subgroups: lower (<) than 0.4, between 0.4 and 0.85 and respectively above (>) 0.85. We see that in the case of the first category, not even a case of kidney failure was registered. As we progressed regarding the numerical values of the initial creatinine (respectively to the other two subgroups of data), it is observed how the percentage of patients who developed renal failure increases, culminating in the third category (over 0.85). From a statistical point of view, these differences were also significant: X-squared = 29.242, df = 2, p-value = 0.0000004468.

The role of plasma renin activity (PRA) as an indicator of the evolution of patients with urethral valve was studied by Bajpai. In his prospective study published in 2013, he concluded that the mean of plasma renin activity was higher both before treatment and after treatment, in

patients who developed chronic kidney disease, compared to those with a favorable evolution (12.6±10.2µg/ml vs. 34.6±14.2 µg/ml, p=0.02) [10]. Plasma renin activity was correlated negatively with glomerular filtration rate, t=-2.816. Considering these aspects, we analyzed the correlation between plasma renin activity and the occurrence of renal failure in the patients included in the study. Taking into account that it is an analysis that is not performed in all laboratories in the country, is not compensated and is expensive, PRA could only be obtained in 35 of the patients.

Within the studied group, we observe from table 3.1 that there are very large differences from one group (those with renal failure versus those without), especially regarding the median (the criterion statistical parameter for statistical comparison). Moreover, from a statistical point of view, the differences are significant: W = 37.5, p-value = 0.0008303.

$`0`
Min. 1st Qu. Median Mean 3rd Qu. Max. NA's
10.00 12.78 14.35 16.80 21.27 29.30 24
$`1`
Min. 1st Qu. Median Mean 3rd Qu. Max. NA's
15.00 20.05 28.20 25.22 29.55 31.80 19

Table 3.1: Main statistic indicators of plasma renin activity based on renal failure.

3.2 Impact of the moment of diagnosis on renal function

Regarding the influence of the time of diagnosis of the posterior urethral valve on renal function, the opinions in the literature are divided. On the one hand, it is stated that an early prenatal or neonatal diagnosis leads to an earlier surgical treatment, which would lead to a decrease in intravesical pressure and a lower renal function. On the other hand, a late diagnosis would translate into some less obvious clinical and imaging signs until the time of diagnosis, which would suggest a lower degree of obstruction and a less impact on the kidneys and bladder.

The study aims to analyze the differences that exist between the groups of patients with early and late diagnosis regarding the development of chronic renal failure, as well as the analysis of the age at resection of the valve, respectively of urinary drainage through vesicostomy or urinary probe.

First of all, we must mention that those who had kidney failure represented 38%, respectively 30 patients. The 30 who had kidney failure were distributed according to late diagnosis between 8 without late diagnosis and 22 with it. It was observed that a higher percentage of those who did not have a late diagnosis developed renal failure than those with a late diagnosis. From a statistical point of view, however, the difference in percentages between those without a late diagnosis and those with, regarding the extent to which they developed renal failure is not significant: X-squared = 1.6333, df = 1, p-value = 0.2012.

3.3 Association of junctional stenosis/vesicoureteral reflux. Negative prognostic factors?

Considered as separate entities, both ureterovesical junction stenosis and vesicouteral reflux through progressive ureterohydronephrosis and renal scarring produce a progressive degradation of renal function. For this reason, we considered it important to analyze the effect this association has on patients with urethral valves. From the total of 78 patients included in the study, 17 had in addition to the basic malformation posterior urethral valves and stenosis of the ureterovesical junction. Of the 61 without stenosis of the uretero-vesical junction, 25 had renal failure. Of the remaining 17 with stenosis, 5 had renal failure instead. However, from a statistical point of view, the association of uretero-vesical junction stenosis with the degree to which renal failure develops is not significant: X-squared = 0.34271, df = 1, p-value = 0.5583.

Regarding reflux (VUR) in the studied patients, of the 48 without VUR, 9 had renal failure. Of the remaining 30 patients with VUR, 21 developed renal failure. This difference in proportions is statistically very significant: X-squared = 18.379, df = 1, p-value = 0.0000181.

3.4 Pre- and perinatal parameters: oligohydramnios, prenatal ureterohydronephrosis and low birth weight

Since a significant number of patients did not have a prenatal diagnosis and, moreover, those with a late diagnosis do not have sufficient, documented data regarding the evolution of the pregnancy, the analysis of oligohydramnios was performed only in patients with a documented prenatal diagnosis. From the graph we see that the percentage of those with oligohydramnios (out of the 30 who are here in total), the percentage of those with renal failure is lower than those without oligohydramnios. However, statistically the difference in percentages is not significant: p-value = 0.3888.

Prenatal hydronephrosis is diagnosed in 1-5% of pregnancies. However, prenatal and postnatal management of hydronephrosis varies. Clinicians often use prenatal ultrasound findings such as calyceal dilatation, renal echogenicity and renal parenchymal thinning, ureterohydronephrosis, bladder dilatation, dilated posterior urethra, amniotic fluid volume, and gestational age to assess postnatal risk and determine subsequent management. Based on the hypothesis that ureterohydronephrosis contributes to the decrease of renal function over time, we also studied the impact it has on renal function in the short term, after the removal of the subvesical obstruction, objectified by the nadir creatinine value. Regarding patients with prenatal UHN values (30 – the rest were excluded), their distribution versus nadir creatinine intervals does not differ much from one interval to another. We also note that of the three intervals that can be seen graphically below, the extreme ones (below 0.4 and above 0.8) had no cases of UHN=1. Instead, in the median group/interval (between 0.4 and 0.8), we had 1 single patient. From a statistical point of view, these percentage differences were not significant: X-squared = 1.5517, p-value = 0.4533.

From the total of those with a birth weight below (<) 3000 g, a slightly smaller percentage had renal failure, namely 18 out of 43 patients - 41%, compared to 12 out of 25 in the control group, representing 48%. However, this difference is not significant: X-squared = 0.88339, df = 1, p-value = 0.3473. It should be mentioned that, although there are no statistical

differences in renal function impairment, these patients - especially those weighing less than 2500g required urinary drainage through vesicostomy or urethrovesical probe. Urinary drainage was maintained until the caliber of the urethra allowed the passage of the 8.5 Ch cystoscope. Thus, these patients had a longer hospital stay compared to the normotrophic term patients.

3.5 Imaging parameters

3.5.1 Ultrasound indices: parenchymal index, cortico-medullary differentiation, hyperechogenicity of the renal parenchyma

Odeh et al performed a retrospective study on ultrasonographic parameters, based on the fact that ultrasound can evaluate the kidney both quantitatively - by calculating the parenchymal area, and qualitatively - by measuring the echogenicity of the parenchyma and the parenchymal index. He thus demonstrated that the area of the renal parenchyma and the parenchymal index measured at the first ultrasound are statistically significant factors of progression to stage 5 chronic kidney disease [11].

One of the objectives of the thesis was to study to what extent a parenchymal index below (<) 10 an effect on the percentage in which patients has developed renal failure. At least graphically, the distribution difference is different from those with an index greater than or equal to 10, to those with an index below 10. And from a statistical point of view, it can be seen how this difference is significant: X-squared = 4.8618, df = 1, p-value = 0.02746.

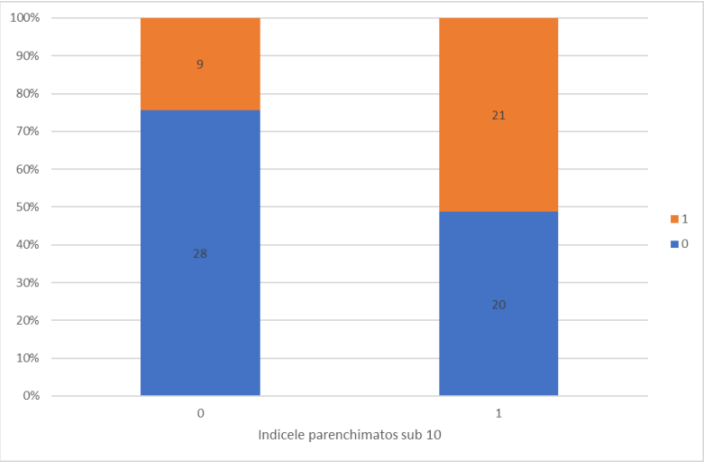

Figure 3.5.1. Distribution of renal insufficiency by parenchymal index

For the classification into risk groups and the conduct of the study, we put together the patients with the absence and those with the deletion, to contrast them with those with normal cortico-medullary differentiation. Of 44 patients with absent/obliterated cortico-medullary differentiation, 26 (59%) developed chronic renal failure. On the other hand, from the group of patients with normal cortico-medullary differentiation on the first ultrasound, only 4 out of 34

patients, respectively 11%, developed renal failure. It can be seen how from a graphic point of view, chronic kidney disease developed much more in those with absent or deleted cortico-medullary difference, compared to those in whom it was normal. Statistically, this analysis was significant: X-squared = 16.205, df = 1, p-value = 0.00005684.

To study the correlation between the hyperechogenicity of the renal parenchyma and the evolution towards chronic renal failure, we included in the same subgroup patients with slightly increased echogenicity and those with normal echogenicity, to compare them with those with renal hyperechogenicity. We see that on the one hand we had few with hyperechoic parenchyma, but all of them developed renal failure. Instead, in the others, approximately 32.3% (23 patients out of 71) developed renal failure. This percentage difference was identified as statistically significant: p-value = 0.0007706.

3.5.2. Cystographic parameters – SWRD index

Cystographic changes in patients with posterior urethral valves are well known. However, evaluating them is often subjective. The SWRD (Shape, wall, reflux, diverticula) index, proposed by Niyogi et al, proposed a simple and reproducible objective evaluation of the shape of the bladder, the trabeculations of its wall, the existence of reflux and diverticula. It can have values between 0 and 7 [12, 13].

The evaluation of the SWRD index is done at a bladder filling of two-thirds of the bladder capacity calculated for age. For the calculation of the contrast substance requirement, the ideal bladder capacity is taken into account, calculated according to the formula: Bladder capacity= (age + 1) x 30 mL. This formula applies to patients up to the age of 12, above this age a capacity of 400 mL is considered optimal.

In the study conducted, 42 patients had a SWRD index less than or equal to 3, while 36 of the patients had index values greater than 3. Patients with a SWRD index above (>) 3 had a higher percentage of renal failure than those <=3. Thus, from the group of patients with SWRD index <=3, only one developed renal failure - representing 2.43%, while, in the group of patients with SWRD index over 3, 29 of them developed renal failure during follow-up - respectively 80.5%. Also from a statistical point of view, this difference is significant: X-squared = 46.803, df = 1, p-value = 0.00000000000785.

4. Conclusions

Considering the reserved prognosis for a quarter of patients with urethral valves, with progressive deterioration of renal function and, according to the specialized literature, with evolution even to grade V renal failure, in 10% of cases, the correct diagnosis of this pathology is particularly important, but also advising the parents from the beginning regarding the need for lifelong monitoring. Both the parents and the patient - at the optimal age, must understand that only the removal of the subvesical obstruction, through resection of the valves, does not correct the bladder dysfunction also, for this there is drug therapy, intermittent bladder

catheterization or even urinary diversions. A correct initial information, but also an unified information from all the specialists involved in the care of these patients will lead to an increase in compliance, so that the follow-up of the patients is not abandoned after the valve resection.

Although it was thought that an early diagnosis would improve the outcome of patients with urethral valves, it was demonstrated, both in the literature and in the current study, that prenatal screening would rather detect more severe cases of subvesical obstruction, implicitly with a better unpleasant prognosis. Neither oligohydramnios, nor low birth weight have been shown to be associated with a deterioration of renal function, neither in the first year of life – data objectived by nadir creatinine, nor over time.

Bibliography

1. Dewan PA. Congenital posterior urethral obstruction: the historical perspective. Pediatric Surgery Int. 1997;12:86-94.
2. Koff SA MK, Jayanthi VR. The valve bladder syndrome: Pathophysiology and treatment with nocturnal bladder emptying. Journal of Urology. 2002;167:291-7.
3. RL C. Prognostic factors and biomarkers of congenital obstructive nephropathy. Pediatric Nephrology. 2016;31:1411-20.
4. Haecker FM WM, Hacker HW, Stuhldreier D, Stuhldreier D. Renal dysplasia in children with posterior urethral valves: a primary or secondary malformation? Pediatric Surgery International. 2002;18:119-22.
5. Lissauer D MR, Kilby MD. Fetal lower urinary tract obstruction. Seminars in Fetal and Neonatal Medicine. 2007;12:464-70.
6. Bernardes LS AG, Saada J. Keyhole sign: How specific is it for the diagnosis of posterior urethral valves? Ultrasound in Obstetrics and Gynecology. 2009;34:419-23.
7. Berrocal T RS, Jaureguízar E, Gómez-León N, Lobato R, Martínez-Urrutia MJ, López-Pereira P. Contrast-enhanced sonourethrography versus conventional micturition cystourethrography in the assessment of the urethra: preliminary study. Cirugia Pediatrica. 2004;17:58-60.
8. Coleman R KT, Nicoara CD, Bader, McCarthy L, Chandran H. Nadir creatinine in posterior urethral valves: How high is low enough? Journal of Pediatric Urology. 2015;11:356.e1-5.
9. Coleman R KT, Nicoara CD, Bader, McCarthy L, Chandran H. Combined creatinine velocity and nadir creatinine: A reliable predictor of renal outcome in neonatally diagnosed posterior urethral valves. Journal of Pediatric Urology. 2015;11:214.e1-3.
10. Mandelia A BM, Agarwala S, Gupta AK, Kumar R, Ali A. The role of urinary TGF-β_1, TNF-α, IL-6 and microalbuminuria for monitoring therapy in posterior urethral valves. Pediatric Nephrology. 2013;28(10):1991-2001.
11. Odeh R ND, Bowlin PR, Braga LH, Lorenzo AJ. Predicting Risk of Chronic Kidney Disease in Infants and Young Children at Diagnosis of Posterior Urethral Valves: Initial Ultrasound Kidney Characteristics and Validation of Parenchymal Area as Forecasters of Renal Reserve. Journal of Urology. 2016;196(3):862-8.
12. Neyas A BR, AlThomali R, Alturkistani R, AlSawaf B, Alrefai W, Hefni L, Aldoobie L, Desoky S, Kari J, Safdar OY. Correlation between the estimated GFR and SWRD score in patients with posterior urethral valves at King Abdul-Aziz University Hospital. BMC Research Notes. 2019;12(1).
13. Niyogi A LK, Robb A, McCarthy L. Cystometrogram appearance in PUV is reliably quantified by the shape, wall, reflux and diverticuli (SWRD) score, and presages the need for intervention. Journal of Pediatric Urology. 2017;13(3):265.e1-e6.

Published articles

1. **Luchita T**, Serban A.M., Ionescu N.S. Prognostic factors and biomarkers in posterior urethral valves. Jurnalul Pediatrului. 2020; XXIII:31-4. http://jurnalulpediatrului.ro/magazines/91-92.pdf

2. **Luchita T**, Ionescu N.S. Initial serum creatinine and nadir creatinine - prognostic markers for renal outcome in patients with PUV. Jurnalul Pediatrului. 2020; XXIII:61-3. http://jurnalulpediatrului.ro/magazines/91-92.pdf