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Pathogenesis and prognosis of intrarenal reflux

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Abstract: Scar development in the children's renal cortex with vesicoureteral reflux (VUR) is one of the most important parameters of prognosis. It can develop regardless of the chosen treatment, even after the regression of VUR. The shape of the renal papillae, the ascending urinary tract infection, the greater than third-degree VUR, and finally the increased intra-calyceal pressure, induce the formation of renal scarring in the renal parenchyma. Renal scarring may complicate VUR independently of the therapeutic strategy (conservative or operative) and its regression. For restitution of this entity, many scientific terms have been used and the most common of them is intrarenal reflux (IRR). The effects of VUR on future renal function result from the limited ability of the affected kidney to grow (failure of renal growth) due to the existence of scars in the renal cortex, the worsening of these scars, or finally the creation of new scars. With the present study, we intend to clarify the etiology and the pathophysiology of IRR and the relation of VUR prognosis to newer biomarkers such as N-acetyl-beta-glycosaminidase, beta-2 microglobulin, Pentraxin- 3 and Liver-type fatty-acid-binding protein.

Keywords: intrarenal reflux, renal scar, renal papillae, vesicoureteral reflux, N-acetyl-beta-glycosaminidase, beta 2 microglobulin, Pentraxin 3, Liver-type fatty-acid-binding protein.

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Pathogenesis

Based on DMSA findings, a reflux nephropathy score (RNS) has been proposed using a 5-point scale from 0–4 [1, 2]:

- 0 = normal findings
- 1 = presence of a scar or scars in an area of one kidney (upper pole or lower pole or less often the middle of the kidney)
- 2 = presence of scars in 2 of the above areas

- 3 = presence of scars in 3 of the above areas
- 4 = generalized thinning of the cortex in both kidneys.

Most cases of vesicoureteral reflux (VUR) are detected pre-symptomatically either by investigating remaining congenital hydronephrosis or in the context of a preventive examination [1, 2]. Scar development as a consequence of VUR can be detected from the intrauterine period of life (fetal reflux nephropathy — FRN) [3].

It is not easy to distinguish congenital renal dysplasia from acquired damage of the renal cortex as both entities may coexist in the context of severe VUR. The pathogenesis of congenital renal dysplasia is interpreted based on the Stephens theory: the ectopic outlet of a ureter bud implies a corresponding extent of dysplasia of the ipsilateral renal unit, due to its abnormal differentiation of the metanephros [4, 5].

In addition, due to intrauterine VUR, increased intraluminal pressure develops in the urinary tract, with a consequent harmful effect on the developing metanephros [6–8]. During the initial diagnostic evaluation of children with VUR, scars are found in the renal cortex and especially in the poles in 30–50% of cases [3].

During the last decades, there has been a decrease in the cases of IRR and its effects [2, 4, 9]. This development is attributed to a) the prenatal diagnosis of congenital hydronephrosis, thus the early diagnosis of the underlying disease, before the development of complications. In 30% of cases, the remaining congenital hydronephrosis is due to VUR, b) in the early treatment of a febrile urinary tract infection with the appropriate antimicrobial treatment, and c) in a more effective therapeutic strategy of VUR [4].

The urothelium acts as an impermeable barrier to maintain the chemical composition of the urinary tract and prevent the invasion of microbes. The epithelial cells of the bladder fall off and epithelialize. The flow of urine acts as a mechanical barrier to the adhesion of microbes to the urothelium. The intrinsic relationship of the epithelial cells and the uroepithelial plate prevents the intra- and intercellular entry of microbes. This plaque, located at the top of the bladder, is a rigid protein structure composed of uroplakins [10, 11].

From an etiological point of view, the development of scars in the cortex of the kidneys has been associated with:

a) the form of the renal papilla [3]:

Normally the renal papilla has a conical shape. The orifices of the collecting ducts that exit on the surface of these conical papillae have a lateral direction so that their walls coincide, when exerting increased intra-calyceal pressure, in order to prevent IRR. On the contrary, if the renal papilla has a flat shape, IRR is favored, because the urinary tubules outfall vertically, without being able to prevent IRR even at low intracalyceal pressure. Flat renal papillae are most commonly seen at the poles, due to fusion of the renal lobes during embryogenesis. Based on this hypothesis, is explained the fact of the development of scars more often in the poles than in the middle of the kidneys.

b) urinary tract infection [2, 6]:

In the case of infection, the type of micro-organism matters: micro-organisms that have the ability to adhere to the urothelium with the fibrils they possess, have a harmful effect for a longer time as they are difficult to eradicate. However, if the urinary tract infection is treated on time, the harmful impact of the developing inflammation is reduced. During IRR ischemic damage is caused as a result of vasoconstriction of the afferent arteriole of the glomerulus. During IRR the Tamm-Horsfall protein acts harmfully in the interstitial space.

In girls with VUR and asymptomatic bacteriuria, there is a small chance to develop scars in the future. It is pointed out that this possibility does not differ from whether the young patient receives continuous, intermittent, or no chemoprophylaxis. Finally, there is a correlation between the possibility of scar development and the degree of VUR. After a febrile urinary tract infection in a child younger than 5 years of age and unilateral reflux -I or II degree-, there is a 10% possibility of developing a scar in the pathological or even in the contralateral healthy kidney. On the contrary, if the degree of VUR is greater than grade III, then the possibility of developing a scar is tripled.

c) the development of increased intraluminal pressure in the drainage part of the urinary system:

IRR can develop as a consequence of increased intra-calyceal pressure, without the presence of upper urinary tract infection [6, 9, 12].

During VUR the increased intravesical pressure is transferred to the level of the renal papillae. The intra-calyceal pressure required in the newborn to cause IRR is 2 mm Hg. In the first year of life, it gradually increases up to 25 mm Hg and in the second year reaches 30 mm Hg. This explains the progressive reduction in the possibility of developing scars at the renal cortex as the child grows.

However, if the intra-calyceal pressure exceeds 35 mm Hg, then IRR can develop even in conical renal papillae.

Prognosis

The effects of VUR on future renal function result from the limited ability of the affected kidney to grow (failure of renal growth) due to the existence of scars in the renal cortex, the worsening of these scars, or finally the creation of new scars (development of IRR). The areas of the cortex, characterized by the development of scars, have no functional contribution to blood filtration.

In general, a kidney that does not have scars and does not develop episodes of pyelonephritis is expected to develop normally, regardless of the degree and duration of VUR.

The most serious complication of VUR is the development of scars in the renal cortex. 20% of those suffering from end-stage chronic renal failure are due to an

adverse progression of chronic atrophic pyelonephritis [7]. In 37% of adults with IRR, regardless of whether there is an underlying VUR, renal function deteriorates, while in 14% of this population, end-stage chronic renal failure is developed [8]. IRR is one of the most important etiological factors for the development of chronic renal failure (CRF) both in childhood and adulthood. This adverse development can happen even without the presence of a urinary tract infection or even if the UTI or renovascular hypertension are effectively treated [10].

In cases of UTIs lasting more than 48 hours, the rate of permanent renal damage formation was about 47% after 6 months, although in fevers lasting less than 48 hours, the rate was lower and about 21%. Those who received early chemoprophylaxis but did not undergo endoscopic treatment had lower possibilities of regression of the VUR. At the same time, obesity in VUR patients is another negative prognostic factor for the formation of renal scars. Therefore, children with obesity should be closely followed-up, and especially those with VUR should participate in specially designed weight loss programs, in order to reduce the risk of developing CRF in the future.

The abilities of compensation from the remaining functional parenchyma of both the pathological and the contralateral kidneys are essentially exhausted. Then, relatively slowly, the rate of glomerular filtration rate (GFR) begins to decrease.

This adverse development corresponds proportionally to the degree of glomerulosclerosis and proteinuria. The rate of deterioration of renal function can be slowed down by limiting the intake of protein and administering an inhibitor of the converting enzyme (ACE inhibitor) [11].

A key parameter for the prognosis of the functionality of a scarred kidney is the development of compensatory hypertrophy of the contralateral kidney. However, since it is a bilateral disease, the degree of blood infiltration is determined by the islets of normal renal parenchyma that are located between the scars.

An important prognostic parameter — after the diagnosis of VUR and its treatment either conservatively or surgically — is the development of new scars or the worsening of a pre-existing scar. Imprinting a permanent scar on DMSA can be done 8 months to 2 years after the episode of acute pyelonephritis. The cases in which the presence of a new scar was found — from 4–10 years of life and even at an older age — concerned exclusively children in whom the existence of scars had been demonstrated by imaging at the initial diagnosis of reflux [6, 13]. Indeed, in several of these children, the initiation of chemoprophylaxis was delayed or ineffective.

The development of a new scar after puberty has not been proven [14]. The frequency of the appearance of scars is inversely proportional to the age of the child: the younger the age, the more often. In 30% of children with new scars, VUR is no longer detected during their imaging: so, the development of a new scar is not excluded, but it also does not depend on the remission

of VUR. In 14–30% of children with IRR, renovascular hypertension develops which is attributed to the increased activity of the renin-angiotensin system [6].

Wennerstorm *et al.* studied the blood pressure of 57 children with renal scars and 1221 children with urinary tract infections. However, they found no significant difference in blood pressure values between the 2 populations [15].

One of the main manifestations of IRR is proteinuria. Zang and Bailey found that proteinuria progressively worsened from 8.5% at the child's initial evaluation to 31% after approximately 14 years [16]. The presence of proteinuria, but mainly its progressive deterioration, is both an essential and unfavorable prognostic factor for future renal function. The mechanisms involved in the progressive development of focal glomerulosclerosis are: a) autoimmunity b) the escape of macromolecular substances from the vascular glomerulus and the urinary tubule into the interstitial space — such as the Tamm-Horsfall protein c) the development of hypertension and d) hyperfiltration [2, 3, 9]. This develops at the level of the renal glomerulus, i.e. the hyperperfusion and the hyperfiltration of the remaining healthy nephrons, in order to meet the metabolic needs of the organism: it is the most recent point of view for the pathophysiological interpretation of the effects of IRR. Several studies have attempted to estimate the prognosis — in the long term — using objective parameters such as creatinine value at 18 years, presence of proteinuria, measurement of NAG (N-acetyl-beta-glucosaminidase), and beta-2 microglobulin [17].

Matsuoka *et al.* studied patients who underwent surgery 10 years ago to correct VUR, measuring serum creatinine, urine protein, and blood pressure. GFR was calculated postoperatively and correlated with preoperative factors such as age, gender, number of UTI episodes, degree of VUR, degree of renal parenchymal damage, proteinuria, and hypertension. Factors associated with long-term prognosis were analyzed. It is important to study those, which are associated with the progressive deteriorating functionality of the kidneys. In their study, they proved that severe VUR with renal parenchymal destruction is associated with a long-term drop in GFR. 56% of patients with VUR and creatinine clearance <75 ml/min/1.73 m2 aged <20 years ended up with end-stage RF. Proteinuria is associated with a gradual decline in renal function, and patients with a measured daily proteinuria >0.2–0.3 g are considered high risk. Values >1 g progressively result in end-stage CRF. An equally important, independent prognostic factor is the age of the patient at the time of surgery. The older the age, the more proportionally increased the possibility of kidney scar formation. Therefore, if the reflux is classified as moderate or minor and the degree of renal parenchymal damage was moderate or minor, the patient is expected to maintain normal renal function until adolescence. The long-term prognosis after surgery is important in patients with VUR >80% grade IV, who can potentially develop into second-grade CRF 240 months later [18].

The ratio of the value of the distal diameter of the ureter-measured at its widest part in the lower pelvis divided by the value of the distance between O1–O3 lumbar vertebrae is a reliable and predictive indicator for the clinical implications regarding the degree of VUR. With measurements in these patients, is calculated the possibility that the VUR will spontaneously resolve, and thus long-term repeated episodes of pyelonephritis, renal scarring, and loss of renal function will be prevented. In cases where the aforementioned index was >0.43, the reflux was automatically regressed and therefore the corresponding conclusions regarding the development of long-term pathology could be drawn (rarely regresses to values <0.35). An increase in the ratio >0.1 (depending on the patient's baseline), is a statistically significant factor for long-term remaining VUR, in which case there is a greater possibility of renal scar formation. If the ultrasonographic measured width of the ureter is greater than 7 mm, then it constitutes an unfavorable prognostic factor for VUR resolution [19].

Newer data on the use of specific biomarkers recently studied, that can potentially predict the development of renal scar, are analyzed below.

Such are procalcitonin, which is not a specific indicator as it also increases in cases of systemic inflammation and sepsis, angiotensinogen, and endothelin-1, which have greater sensitivity and specificity [20].

Pentraxin 3 (PTX3) is a mediator of inflammation. While it belongs to the category of long pentraxins, CRP and serum amyloid belong to short pentraxins. Pentraxin 3 is synthesized in peripheral tissues (dendritic cells, macrophages, fibroblasts, activated endothelial cells, monocytes, neutrophils), while the other two are synthesized in the liver. Pro-inflammatory cytokines activate these factors. Urinary PTX3 value and urinary PTX3/urinary creatinine ratio were observed to be elevated in patients with renal scar formation. Overproduction of PTX3 is observed in renal tubular epithelial cells under inflammatory and fibrotic conditions. Therefore, in patients with renal scars, a high urinary PTX3 value is a prognostic indicator for the long-term presence of inflammation in the renal parenchyma [21]. Due to the inflammatory response, local ischemia, interstitial renal parenchymal damage, and fibrosis, permanent renal scarring may develop [22].

Neutrophil gelatinase-associated lipocalin (NGAL) belongs to the lipocalin family, is excreted in the urine from the ascending limb of the loop of Henle and from the collecting tubules, and accumulates in cases of renal tubular damage. It is proved to be a reliable indicator of long-term follow-up of renal scar formation in the renal parenchyma, in patients with VUR [23].

Kidney injury molecule-1 (KIM-1) is a transmembrane protein, expressed in the proximal convoluted tubule, produced after ischemic, toxic, acute kidney injury and used as a sensitive biomarker for chronic interstitial injury, but not for renal scarring, in which we are interested [23].

Liver-type fatty-acid-binding protein (L-FABP) appears at high levels in states of tissue damage and hypoxia. It is therefore secreted in the urine by structurally damaged tubular cells.

The measurement of the aforementioned indicators is used prognostically for the manifestation of reflux nephropathy, with greater sensitivity, NGAL [23].

Conflict of interest

None declared.

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