European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2012; 16: 213-219

Congenital ureteropelvic junction obstruction: physiopathology, decoupling of tout court pelvic dilatation-obstruction semantic connection, biomarkers to predict renal damage evolution

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Abstract. – The widespread use of fetal ultrasonography results in a frequent antenatally observation of hydronephrosis, ureteropelvic junction obstruction (UPJO) accounting for the greatest fraction of congenital obstructive nephropathy. UPJO may be considered, in most cases, as a functional obstructive condition, depending on defective fetal smooth muscle/nerve development at this level, with lack of peristaltic wave propagation – aperistaltic segment – and, therefore, poor urine ejection from the renal pelvis into the ureter. The UPJO-related physiopathologic events are, at first, the compliant dilatation of renal pelvis that, acting as hydraulic buffer, protects the renal parenchyma from the rising intrapelvic pressure-related potential damages, and, subsequently, beyond such phase of dynamic balance, the tubular cell stretch-stress induced by increased intratubular pressure and following parenchymal inflammatory lesions: inflammatory infiltrates, fibroblast proliferation, activation of myofibroblasts, tubulo-interstitial fibrosis. Reactive oxygen species (ROS), nitric oxide (NO), several chemo- and cytokines, growth factors, prostaglandins and eicosanoids, angiotensin-II are the main pathogenetic mediators of the obstructive nephropathy. Apoptosis of tubular cells is the major cause of the tubular atrophy, together with epithelial-mesenchymal transdifferentiation. Some criticisms on tout court semantic renal pelvis dilatation-obstruction connection have been raised considering that the renal pelvis expansion isn't, in any case, linked to an ostructive condition, as it may be verified by diuretic (furosemide) renogram together with scintiscan-based evaluation of differential renal function. In this regard, rather than repetitive invasive nuclear procedures that expose the children to ionizing radiations, an intriguing noninvasive strategy, based on the evaluation of urinary biomarkers and urinary proteome, can define the UPJO-related possible progress of parenchymal lesions, thus predicting which patients must require an obstruction correcting surgery and in which patients, instead, the hydronephrosis will spontaneously resolve.

Key Words:

Pyelo-ureteral junction, Kidney, Obstructive nephropathy, Urinary biomarkers, Diuretic renogram.

Introduction

Congenital uretero-pelvic junction obstruction (UPJO) is the most common cause of obstructive nephropathy, accounting for about 1:1,500 newborns. Since eighties, the widespread use of obstetric ultrasonography has resulted in earlier and more frequent observations of congenital hydronephrosis than in former times, thus implying intriguing changes in its post-natally proper management[1-4].

Etiology and Physiopathology

UPJO may be considered, in most cases, as a functional obstructive condition due to maturative abnormalities, during the gestation, in the smooth muscle and/or the innervation of the pyelo-ureteral transitional segment with following defective peristaltic waves – *aperistaltic segment* – to eject urine from the renal pelvis into the ureter. Smooth muscle discontinuity or disproportionate presence of longitudinal smooth muscle fibers, together with excessive collagen deposition, have been shown at this level, sometimes associated with an inappropriate innervation, it resulting in a defective propagation of the electrical activity produced by a pacemaker located in the pyelocaliceal region. Such *intrinsic functional obstruction* is "probe-patent", i.e. without any anatomic obstacle to uretero-pelvic catheter progression[2,3,5].

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Other, although much less common, either intrinsic or extrinsic obstructive factors may have a role in the UPJO (Table I).

In the last decades, both spontaneous congenital and surgically developed fetal animal models have been taken into consideration to deeply explore how uretero-pelvic junction obstruction can alter the kidney histology and affect renal function, thus allowing the identification of involved cellular and molecular mechanisms[3,5]. In this regard, the renin-angiotensin system appears to be implicated in the pyeloureteral embryonic development, so that the lack of angiotensinogen or ACE (angiotensin-converting enzyme) in genetically engineered transgenic mice may induce a pyelectasis quite similar to that of UPJO[6].

UPJO-dependent incremental intrapelvic hydrostatic pressure is the potential "prime mover" of lesions of the obstructive nephropathy. Nevertheless, at first, as compliant response to just increasing intrapelvic pressure, the expansion of the renal pelvis – acting as hydraulic buffer – can protect the renal parenchyma from the rising intrapelvic pressure-related potential damages (Table II). As soon as this phase of hydrodynamic balance has been overstepped, the intratubular pressure increases with following stretch of the tubular cells and then transmurally compression of peritubular afferent arterioles with subsequent renal hypoperfusion. However, decreasing in both plasmatic renal flow (PRF) and glomerular filtration rate (GFR), besides the urine drainage by the renal lymphatic vessels at the pyelocaliceal fornices (pyelo-lymphatic urine reflux), can still maintain the intrapelvic-tubular hydrostatic pressure within certains balance limits[5,7] (Table II).

A significant persistent obstructive condition results in a progressive dangerous tubular dilatation with following spectrum of parenchymal lesions such as sequentially interstitial macrofage infiltration, fibroblast proliferation, tubular atrophy, tubular-interstitial fibrosis and glomerulosclerosis, nevertheless with high variability in the outcomes considering that a severe degree of unilateral obstructive nephropathy (differential renal function less than 35%) may result associated with an advanced parenchymal damage. A bilateral UPJO (10÷30% of cases) often coexists with multicystic renal dysplasia[5,8,9].

The inflammatory parenchymal lesions in UPJO are clearly identified events in response to intratubular hydrodynamic force alterations. Indeed, interstitial recruitment of inflammatory cells (monocyte-macrophages, granulocytes, T-cells, etc) are largely due to hyper-expression of *chemotactic agents* by stressed tubular cells. So, high parenchymal levels of interleukin-5 (IL-5) and eotaxin-2 suggest that such chemokines, produced by the damaged tubular cells, are chemoattractants for inflammatory circulating cells. Also urinary concentrations of MCP-1, *monocyte chemotactic peptide*, responsible for monocyte activation, are significantly higher in patients with UPJO than in healthy controls, however they decreasing after pyeloplasty in the normal range. Moreover, in children with UPJO, the urinary concentrations of cytokine TNF-α (*tumor necrosis factor-*α) are increased, whereas those of EGF (*epidermal growth factor*), a mediator of normal renal tubulogenesis and tubular regeneration, are decreased[5,10-12]. Also the endothelin-1 (ET-1), a potent vasoconstrictor, is involved in

Table I. Etiology of congenital uretero-pelvic obstruction.

• Intrinsic abnormalities:	– Inadequate fetal smooth muscle and/or nerve development at pyeloureteral level, with following defective peristaltic waves to eject urine from the pelvis – *aperistaltic junction* – with lack of "gulp action" on urinary bolus. The obstruction is functional, "probe patent"
	– Altered colinergic-, adrenergic-, nitrergic-, peptidergic neurotransmission
	– High ureter insertion to renal pelvis, but it's appears to be an epiphenomenon to pelvis dilatation. Moreover, the pattern of intrapelvic pressure seems to be extrinsic obstruction type-related (intrapelvic pressure volume-dependent) rather than that intrinsic (intrapelvic pressure linearly increasing because of a constant resistance)
	– Persistent fetal folds
• Extrinsic compressive abnormalities:	– Real aberrant crossing vessels, supplying the lower pole of the kidney, with "uretero-vascular tangle", that suggest particular carefulness in case of endopyelotomy
	– Rotational kidney
	– Retrocaval ureter; duplex collecting upper urinary tract

Table II. Physiopathology of ureteropelvic junction obstruction.

Aperistaltic condition of UPJ
(aperistaltic probe-patent segment)
↓
Lack of pyelic "gulp action"
with decreasing "urinary bolus" ejection into the ureter
↓
Increasing intrapelvic urine volume
↓
Compliant dilatation of renal pelvis
that, at first, acting as "hydraulic buffer",
can protect the renal parenchyma from the
potential damages due to increasing intrapelvic pressure
(phase of dynamic hydrostatic balance)
↓
==
↓
Beyond such phase,
raising intratubular pressure-related stress/stretch of
tubular cells can induce expression of
chemo- and cytokines
that act as chemoattractants for inflammatory
circulating cell. Moreover, transmurally
compression of peritubular afferent arterioles
causes hypoemoperfusion- and ischemia-related
structure/function renal damages

UPJO-dependent renal tissue damage, the urinary ET-1, in such condition, reaching levels forthfold higher than in healthy subjects, so that ET-1 urinary concentrations is a useful bio-marker as noninvasive tool for the diagnosis and follow-up of patients with UPJO[12]. Just the same goes for TGF-β1 (*transforming growth factor-β1*), whose up-regulation in inflammatory infiltrating cells closely correlates, in the obstructed kidney, with interstitial collagen deposition and fibrosis, while IGF-1 (*insulin growth factor-1*), instead, seems to be able to decrease the fibrosis in animal model obstructed fetal kidney[9,11-14].

Inflammatory infiltrating cells, as well as resident stressed renal cells, are able to generate a large amount of ROS (*reactive oxygen species*, such as *superoxide anion*, *hydroxyl* and *hydrogen peroxide*) while a concurrent decrease in the expression of antioxidant factors, such as SOD (*superoxide dismutase*)[15,16]. As result of the progressive renal damage, the consumption of oxygen (O_2) rises in surviving nephrons, the oxidative stress and lipid-peroxidation-related products contributing to the development of tubulo-interstitial fibrosis by increasing fibrogenic cytokine production and the extracellular matrix interstitial deposition together with the expression of some transcription factors, such as NF-κB (*nuclear factor-κB*). Moreover ROS are able to promote tubular cell apoptosis by directly damaging their cytoskeleton and DNA and, in addition, by anoikis-related mechanisms because they affect the intercellular adhesion molecules[3,5,16].

Apoptosis of the tubular cells seems to be the main cause of the tubular atrophy together with epithelial-mesenchymal phenotipic transdifferentiation, what resulting in the formation of atubular – only glomerular nefrons[3,16,17].

Among the mechanisms underlying the pathogenesis of the unilateral obstructive nephropathy, the role of *nitric oxide* (NO), and, therefore, of the nitric oxide synthase (NOS) has been recently elucidated, particularly the endogenous inducible NOS (iNOS) rather than endothelial NOS (eNOS) and neuronal NOS (nNOS), resulting involved in increasing macrofage infiltration and fibroblast proliferation. Fibroblasts, expressing *fibroblast-specific-peptide 1* (FSP-1), besides induction of the interstitial fibrosis, undergo, under influence of some cytokines such as interleukin-1 (IL-1), the conversion to myofibroblasts, expressing α-*smooth muscle actin* (α-SMA), which, in turn, promote the expansion of extracellular matrix[3,5,18]. However, the role of NO in renal injury is still controversial, because it can induce opposite effects such as inflammatory-proapoptotic influences at its high concentrations whereas, at low concentrations, cytoprotective-antinflammatory advantages[16]. In this last regard, NO carries out compensating vasodilator effects against vasoconstriction of angiotensin-II and promotes natriuresis, thus showing a role in the paracrine control of renal hemodynamics and electrolyte balance. According to these data, it has been suggested that the liposome-mediated iNOS gene transfer might have a therapeutic utility in obstructed kidney[19,20].

The renal hypoperfusion-related and glomerular podocyte/proximal tubule cell stretch-induced activation of *renin-angiotensin system* (RAS) promotes, by increased production of angiotensin-II, progressive vasoconstriction in renal cortex and medulla that may be mitigated by non-peptide specific angiotensin-II receptor blockers such as losartan. Also enalapril, an ACE-inhibitor, can prevent, within certain limits, the increase in blood pressure in obstructive nephropathy and the progression of renal interstitial fibrosis. Indeed, angiotensin-II not only is an important mediator of hemodinamic changes but also plays an important role in inducing renal fibrogenesis and tubular epithelial-mesenchymal

transition both directly and by TGF-β1® Smad 2 and Smad3® Smad 4® nuclear transcription factors pathway[23]. Other powerful vasoactive substances (thromboxane A_2, bradykinin, prostacyclin, prostaglandin E_2, etc) are linked with morpho-functional changes in renal function during obstruction[3,5,9,16,21,23]. Kallikrein, a vasodilating kinin in itself, contributes to production of thromboxane$_2$, a potent vasoconstrictor, together with angiotensin-II, of afferent arterioles, with following rapid decline in PRF and GFR[16].

As far as renal function is concerned, dangerous implications of obstructive nephropathy, besides decline in PRF and GFR, are the loss of tubular capacity to both urine concentrate, because of down-regulation of major sodium tubular transporters and aquaporins, and acid eliminate because of the reduced proton (H^+)-*ATPase* tubular pump activity[16,19,24].

The controlateral non-obstructed kidney often develops a compensating hypertrophy, its adaptive growth-rate rising proportionally – as cross talk – with the progression of damage in the obstructed kidney[3,5,25].

Surgically corrected UPJO can lead to an improved renal function compared with preoperative functional findings. However, the loss of nephrons is definitive, the tubular deterioration may decrease but not entirely reverse, the interstitial fibrosis remains mean – while renin expression holding a pathological pattern[3,5,2].

Criticisms on Tout Court Semantic Connection Between Renal Pelvis Dilatation and Obstruction

The grading of renal pelvis dilatation on *in utero* ultrasound findings regarding its anteroposterior diameter (PAPD) includes: grade 0 = no hydronephrosis; grade 1 = mild pelvis dilatation (2÷5 mm) without calycectasis; grade 2 = moderate pelvis dilatation (6÷9 mm) with mild calycectasis; grade 3 = large pelvis dilatation (greater than 10 mm) and dilated calyces with normal renal parenchyma; grade 4 = very severe pyelocaliceal dilatation with thinning of renal parenchyma (according to SFU, *Society for Fetal Urology*)[27].

However, an expanded renal pelvis does not necessarily mean that kidney is obstructed and renal function is damaged. The distinction between bilated obstructed kidney and a dilated nonobstructed kidney remains a perplexing problem[12]. Therefore, the major challenge in the management of UPJO is to select the patients that must be subjected to early surgical measures, because of an effective obstruction with possible detriment of renal function, while planning, for non-obstructed patients, an appropriate watchful-waiting, considering that an improvement or even a complete resolution of neonatal hydronephrosis due to UPJO may be spontaneously occur[1,4,26,28-30].

The most common tests to assess wheter or not renal pelvis dilatation might be due to uretero-pelvic obstructive condition and, in such case, it might impact on the renal function, are, on the one end, the *diuretic* (furosemide) *dynamic renogram* using some radiopharmaceuticals (^{99m}Tc-DTPA, diethylenetriamine pentacetic acid; ^{99m}Tc-MAG_3, mercaptyl-acetyl-triglycine; ^{99m}Tc-glucophenate) with measurement of the rate of their pyelo-ureteral washout, and, on the other hand, the analysis of the functional renal reserve and *differential renal function* (split function) by ^{99m}Tc-DMSA (dimercaptosuccinic acid) scintigraphy. In addition, ^{99m}Tc-MAG_3 is an excellent radiopharmaceutical agent for evaluation of PRF, that correlates with differential renal function (28-32). Just according to such instrumental tests, the obstruction correcting surgery has been suggested when the diuretic renogram shows an obstruction pattern and the differential renal function (split function) is less than 40%[9,28-32].

Even diuretic-enhanced Doppler-US techniques can allow a functional evaluation of the obstruction by measuring the renal arteriolar *resistive index* (RI = peak systolic velocity – peak diastolic velocity/peak systolic velocity), RI increasing as blood flow decreases, proportionally to degree of the obstructive condition[33].

However, only single, all alone, measurements of both diuretic renogram and split renal function are often unreliable because of a common slow pyelo-ureteral washout of tracer and renal function inadequacy in newborn, so that these nuclear examinations only if closely retaken may suitably indicate an improvement or, instead, a deterioration of renal function, respectively in non-obstructed or in obstructed kidney. So, the worsement of hydronefrosis and the decrease in renal split function (together with compensatory growth acceleration of contralateral kidney because of active counterbalance between two kidneys) suggest the need for surgical measures[28,30,32,34-38].

According to these criteria, it appears to be clear that about 50% of children with neonatal hydronefrosis due to UPJO might receive a medical surveillance with eventually resort to surgery

in case of either subsequent decrease in differential renal function or persistent-recurrent urinary tract infections[9,28,35,38].

Considering that the medical surveillance implicates repetitive invasive nuclear procedures such as diuretic renogram and renal scintiscan, that, time after time, expose the child to ionizing radiations, some urinary biomarkers could be used as predictors for both structural and functional kidney damage, thus providing the clinicians with an intriguing *noninvasive strategy* hopefully replacing the invasive long-term follow-up in children with UPJO. The measurements of *urinary biomarkers* – TGF- β1, MCP-1, endothelin-1, TNF-α, EGF; tubular enzymes, such as lysosomal-derived N-acetyl-β-glucosaminidase, NAG, and brush border-derived both alkaline phosphatase, ALP, and γ-glutamyl transferase, γGT; microproteins, such as ß2-microglobulin and microalbumin compared with micrototal urinary protein; specific tubular cell death signals and epithelial-mesenchymal differentiation signaling molecules – integrating them with blood cystatin-C and creatinine levels, show an overall accuracy of about 81 to 95% in the diagnosis of congenital obstructive uropathy in children, moreover allowing to predict the clinical evolution of UPJO, so distinguishing the hydronephroses that require obstruction correcting surgery from those which will have a spontaneous resolution (Table III)[4,12-16,39-43].

Emerging Considerations and Perspectives

Since the Eighties, the widespread use of fetal echotomography has resulted in a frequent antenatally observation of hydronephrosis with following important changes in its postnatally management – diagnostic procedure, either proper medical surveillance or timing of corrective surgery –, thus, from them, any possible UPJO-related surgical issue resulting included in the field of pediatric surgery rather than mainly in the adolescent-adult one as in former times[1,5,27,28,30,44-49]. Historically, before the routine antenatal ultrasonography, the congenital obstructive uropathy became apparent, in the older child or even in the adult patient, through a variety of symptoms, such as flank pain, recurrent urinary tract infection, haematuria, nephrolithiasis, palpable hydronephrotic abdominal mass, sometimes together with so serious deterioration of renal function to entail a nephrectomy rather than a corrective pyeloplasty. Moreover, recurrent peripyelo-inflammatory complications may cause a fibrotic encasement of pyelo-ureteral junction (localized *secondary* retroperitoneal fibrosis)[6,9].

Table III. Most commonly used urinary biomarkers to replace invasive long-term follow-up.

- *Growth factors and peptides:* increased TGF-β1, MCP-1, endothelin-1, TNF-α; decreased EGF
- *Tubular enzymes:* NAG, ALP, γ-GT
- *Microproteins:* β-2 microglobulin and microalbumin
- *Tubular cell death molecular signals, epithelial-mesenchymal differentiation modulators*

Congenital pyelo-ureteral junction obstruction may be considered, in most cases, as a functional obstructive condition due to intramural defective fetal smooth muscle/nerve development with lack of peristaltic wave propagation at this level – aperistaltic probe-patent segment – and, therefore, poor urine ejection from the renal pelvis into the ureter. In fact, dysplastic changes in the smooth muscle layer and alterations in the interstitial cells of Cajal (ICC) distribution and density, together with low expression of EGF, may seriously influence the dynamics of pyeloureteral junction[50] (Table II).

Over the last three decades, the UPJO-related sequence of physiopathologic events has been elucidated such as, at first, the compliant expansion, of the renal pelvis that, acting as hydraulic buffer, can protect the renal parenchyma from the rising intrapelvic pressure-related potential damage, and, subsequently, beyond such phase of dynamic balance, the stress/stretch of tubular cells, induced by increased intratubular pressure, with following progressive development of parenchymal inflammatory lesions: interstitial recruitment of inflammatory circulating cells by the effect of chemotactic agents produced by stressed tubular cells, fibroblast proliferation, activation of myofibroblasts, up to tubular-interstitial fibrosis and glomerulosclerosis. The apoptosis of the tubular cells appears to be the major cause of tubular atrophy, often in association of the epithelial-mesenchymal phenotypic transdifferentiation. ROS, NO, some growth factors and transcription-factors, cytokines, vasoactive peptides – such as TGF-β1, VEGF, MCP-1, TNF-α, NF-κB, several interleukines, endothelin-1, angiotensin-2, eicosanoid tromboxane, prostaglandins – are the main pathogenetic mediators of the obstructive nephropathy[2,5-8,10-20].

As far as renal function is concerned, major alterations result to be the decline in the PRF and

GFR, together with altered expression of the sodium tubular transporters and aquaporins and decrease in proton (H^+)-ATPase tubule pump activity[21-26].

Some criticisms on *tout court* semantic renal pelvis dilatation/obstruction connection have been raised because that hydronephrosis isn't, in any case, synonymous with an obstructive condition and, therefore, it is reasonable to replace the old "morphological" paradigma, necessarily considering the pelvis dilatation tantamount to an obstruction, with more proper "functional" criteria founded on the evaluation of serial diuretic nephrograms and renal split function scintiscans, in order to distinguish the obstructed patients, that must be addressed to correcting surgery, from non-obstructed ones, that are subjected to a medical surveillance (watchful waiting)[12,28-31]. Rather than repetitive invasive nuclear procedures such as diuretic nephrograms, to monitor urodynamically relevant UPJO, and renal scintiscans, to watch the trend of split renal function, which expose the children to ionizing radiations, the novel intriguing strategy, based on measurements of *urinary biomarkers and urinary proteome*, has been proposed to identify the UPJO-related parenchymal lesions, thus allowing the prediction of which patients might require surgery – either open dismembered pyeloplasty or laparoscopic/endourologic options – and in which patients, instead, the hydronephrosis will spontaneously resolve[4,12-16,39-43,45-49].

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