

MORFOFUNCTIONAL AND THERAPEUTIC STUDY OF THE PRIMARY VESICoureTERAL REFLUX IN CHILDREN

PhD THESIS SUMMARY

Primary vesicoureteral reflux (VUR) is a common congenital urinary tract abnormality caused by a maturation defect of the vesicoureteral junction resulting in retrograde passage of the urine from the bladder towards the kidneys. Even if there is a tendency for spontaneous resolution of VUR, mostly in young patients with low-grade reflux, the main goal of this management is to preserve the kidneys function by minimizing the risk of acute pyelonephritis. It is possible to identify patients with risk of urinary tract infection and renal scarring by defining and analyzing the risk factors for each patient (age, sex, reflux grade, anatomic abnormalities and kidney status). Current management of VUR is ruled by “Guidelines of vesicoureteral reflux in children” elaborated by Tekgul S. et al. in 2012.

1. HISTOLOGICAL ASPECTS OF INTERSTITIAL CELLS OF CAJAL IN THE HUMAN UPPER URINARY TRACT

Introduction The mechanisms by which the ureter propels urine towards the bladder has myogenic origin, through peristaltic contractions. This pyeloureteral autorhythmicity is generated by specialized, electrically active cells, the interstitial cells of Cajal (ICC) located in the proximal regions of the upper urinary tract. The aim of the study is to describe the location of the ICC cells and their morphology, and quantitatively analyze their distribution along the human upper urinary tract.

Materials and methods 13 autopsy cases were included in the study, which were performed at the Pathology Department of the County Emergency Clinical Hospital. The selected cases aged between 7 months and 83 years who didn't have renal, urinary voiding system diseases. The tissue samples were collected from several levels of the upper urinary tract as follows: kidney, calyces, pyelon, pyeloureteral junction, proximal ureter, middle ureter, distal ureter-intramural part. The DAKO protocol was used for immunohistochemistry. Three distinct examiners analyzed randomized high power fields of each level. Three different fields per level were analyzed by each examiner. ICCs were morphologically studied and counted. The median and the range of the obtained data were calculated.

Results C-kit positive cells were indirectly highlighted by the presence of a finely granulated cytoplasm, which indicates a strong immunoreactivity to CD117. These cells were observed at the junction between the internal and external smooth muscle layers, and also between muscle bundles. Most often, the arrangement of the cells was parallel to the muscle fibers. Differentiation from other CD117 positive cells, such as mast cells or macrophages, was based on morphological features, as ICC are spindle-shaped or stellate, with cytoplasmic extensions at one or both cell poles and a large oval nucleus, whilst mast cells are round with round nucleus and no dendritic processes. Another differentiation criterion was the location of the cells, ICCs unlike mast cells and macrophages are not found in the lamina propria or submucosa. The ICCs were present at all upper urinary tract levels, being more numerous in the calyces and pyelon. Only scattered cells were present in the middle and distal ureter. The ICCs count showed a decrease from the proximal to distal part of the upper urinary tract. There was no correlation between the patients' age, sex and the number of ICC.

Conclusion The ultra-specialized behavior of these cells can be better understood through morphological functional studies in pathological conditions of the urinary tract. Understanding ICC abnormalities in the urinary tract can provide many explanations concerning congenital pathological conditions such as vesicoureteral reflux, pyeloureteral junction obstruction or primary obstructive megaureter.

2. CLINICAL ASPECTS OF THE PRIMARY VESICoureTERAL REFLUX IN CHILDREN. THE NECESSITY OF INDIVIDUALIZED THERAPY IN VESICoureTERAL REFLUX. ISSUES IN APPLYING THE EAU GUIDELINES

Introduction Compliance refers to the degree to which the patient follows doctors' recommendations correctly. This includes adherence to drug therapy, returning to control and follow-up. The aim of the present study is to quantify the compliance of the parents of VUR patients and to analyze its impact on treatment and the applicability of EAU guidelines in our patients.

Materials and methods This is a 4-year prospective study, between 1st of January 2012 and 31st of December 2015, which includes 202 patients aged between 1 and 174 months, diagnosed with primary VUR without LUTD in Pediatrics and Pediatric Surgery Departments in Targu Mures. To quantify the compliance with treatment, an algorithm was developed by taking into consideration the socio-economic, demographic status and the educational level of the parents. The analysis of the compliance lasted from the time of diagnosis of VUR, up to the first routine check, with an average of 6 months. If the score calculated with this algorithm was greater or equal to six points, the parents were considered to be compliant to treatment.

Results One hundred and twenty-three girls and 79 boys aged between 1 and 192 months were included in the study. A percentage of 34.7% of the children had less than 12 months at the time of diagnosis. Only 13 patients were prenatally diagnosed with hydronephrosis. In 92.6% of the cases the first presentation to the hospital was due to ITU. Urinalysis revealed proteinuria in 33.2% of cases. E.coli was the most commonly found bacteria in urine culture. Ultrasonography did not reveal changes in 32.2% of cases.. Anatomical abnormalities were highlighted in 47 patients, the most common being duplications, of which 15 were pelvicalyceal, 7 pelviureteral and 26 duplex kidneys. Renal scintigraphy discerned reflux nephropathy in 27 cases. A percentage of 54% patients were declared cured, 13.4% with unfavorable evolution and 32.7% unwatched patients. The average healing period was 13 months, with a minimum of 5 months and a maximum of 120. A total of 80 patients, representing 39.6%, were quantified as noncompliant by the algorithm developed by us. In terms of compliance, it is clear that noncompliant patients tend toward worsening ($p=0.0001$), most of them being unfollowed.

Conclusion Parents compliance is an important factor that must be considered in choosing the optimal treatment, avoiding lengthy and therapeutic options whose administration depends solely on them. The range of surgical options has increased lately in favor of the patient, so the surgical indication should be given without hesitation.

GENERAL CONCLUSIONS Our study provides information about the ubiquitous distribution of the ICC in the human upper urinary tract. There was no correlation between the patients' age, sex and the number of ICC. Parent's compliance must be considered in EAU guidelines application, being a negative predictive factor in VUR resolution. The need for individualization of therapy in patients with VUR makes EAU guidelines difficult to enforce, compels us to improve our algorithm to quantify the compliance of parents, and recognize the noncompliance as a negative predictive factor in the resolution of VUR.