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Relation between ureteral telocytes and the hydronephrosis development in children

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Abstract: Introduction: Hydronephrosis is an actual pediatric problem, affecting children in the ante- and neonatal periods. Intrinsic stenosis is due to external obstruction and creates a pathophysiological basis of this urological pathology. Co-localization of ureter with a renal vasculature also could not be omitted from this point of view. Mesenchymal cells, partially telocytes, are important for local fibrosis development and hydronephrosis formation as well. In the current study, we focused on identification of telocytes in the human ureters to hypothesize their role in hydronephrosis pathophysiology.
Material and Methods: The samples were taken from 18 surgically treated patients with hydronephrosis (due to ureteral obstruction and crossing renal vessel). The control group consisted of 10 patients suffered from a non-obstructive disease of the urinary tract — predominantly renal tumors. Tissue samples from a ureter were stained for c-kit, tryptase, CD34 and PDGFRα to identify telocytes. Routine histology was performed to analyze tissue morphology, collagen deposits and mast cell's profile.
Results: Telocytes were detected in the ureteral wall. In patients with hydronephrosis we revealed decreasing density of telocytes, the prevalence of collagen, rise in mast cells amount and the ureteral wall thickening. In ureters with crossing renal vessels as a primary etiologic factor more telocytes have been observed in comparison with the obstructive hydronephrosis.

C o n c l u s i o n s: A declined density of telocytes accompanied hydronephrosis development. Increased number of mast cells in the ureteral wall reflects a local inflammation, while detailed observation of collagen/muscle deposits and density of telocytes reveal a difference depended on etiologic factor (obstruction or crossing vessel) in patients with hydronephrosis.

Key words: hydronephrosis, telocytes, CD34, ureteropelvic junction obstruction, ureter.

Introduction

Hydronephrosis is a condition characterized by an excessive amount of urine inside the pelvocalyceal system leading to its dilation and distension [1–3]. The vast majority of the hydronephrosis among pediatric population is due to mechanical ureteral obstruction. Normally, physiological hydronephrosis is common only in pregnancy [4]. No doubt, one of the most frequent urological congenital pathology is antenatal hydronephrosis [5], affecting up to 4.5% of all pregnancies according to literature data [5, 6]. The prevalence is higher in boys with a peak in children younger than one-year-old [7]. Mostly the pathogenesis of neonatal hydronephrosis can be explained by ureteropelvic junction obstruction (UPJO), caused by gross changes in the ureteral wall [8, 9]. Grasso *et al.* mentioned that partial obstruction can result from an anomalous number or arrangement of smooth muscle cells within the upper ureteral wall causing peristaltic dysfunction [10]. Moreover, among structural changes that lead to hydronephrosis development, distinguish transient dilation of the collecting system, upper/lower urinary tract obstructive uropathy, and non-obstructive processes such as vesicoureteral reflux [11]. All of them can occur during fetal development. Important to note is that hydronephrosis can be also present in the absence of primary obstruction [7], when it is caused by secondary to extrinsic crossing vessels, kinks or adhesions over the UPJ area [12–14]. In some situations, the ureter is located near blood vessels or aberrant renal artery partly cross its wall, indirectly leading to hydronephrosis development [15]. Crossing vessels can be evaluated as a primary cause of UPJO and lead to hydronephrosis development [16].

In antenatal and early neonatal periods cellular components of tissue organization are extremely important for concerning in the context of disease development. Mesenchymal cells are conductors and effectors for local fibrosis. Newly described telocytes (TCs) or interstitial Cajal-like cells (ICLC) have a mesenchymal origin as well as communicate with surrounding cells by making contacts and indirect participation in angiogenesis, local fibrosis and inflammatory reactions [17–20]. Telocytes have a variable number of telopodes (Tps) (very long cellular extensions), which are probably the longest cellular prolongations in the human body. They demonstrate specific direct (homocellular and heterocellular junctions) and/or indirect (chemical, paracrine/

juxtacrine signaling, microvesicles and exosomes, sex hormone and microRNAs) contacts with various surrounding cells and have gene expression and immunohistochemical profiles [21, 22].

Telocytes are present in the upper lamina propria of the human renal pelvis, ureter, and urethra, as well as in kidney (in sub-capsular space) and urinary bladder [23–26]. In the ureter and urinary bladder, they mainly exist in between smooth muscle bundles [25]. Telocytes have also been identified around renal tubules and vessels in the kidney cortex interstitium, with shed vesicles identified in close vicinity of TCs [26, 27]. In the upper lamina propria of renal pelvis, ureter, and urethra these cells have similar ultrastructural features which were different from those of bladder TCs:

1) thinner and longer cytoplasmic prolongations;
2) presence of dense core granules and microtubules;
3) no peripheral actin filaments.

Telocytes are responsible for Ca^{2+} waves generation and neuromuscular transmission, which brings them a specific value in the context of ureteral dysfunction [27–29]. They demonstrated a range of immunoreactivity to caveolin-1, estrogen and progesterone receptors in different parts of the urinary tract (renal pelvis, ureter, bladder, and urethra), that indirectly indicates that each region itself might contain subpopulations of telocytes [23]. Also, they could establish close contacts with macrophages in sub-capsular space of kidney, and with smooth muscle bundles, blood vessels and nerve endings in the ureter and urinary bladder [26].

Our study aimed to identify telocytes in the ureteral wall from patients with hydronephrosis compare their amount between study and control groups, and reveal a putative correlation with a macroscopic tissue organization of ureter, affected and unaffected.

Material and Methods

Subjects

The study retrospectively reviewed data of all children who underwent surgical treatment for hydronephrosis during the period 2011–2014 at Department of Pediatric Urology University Children's Hospital in Cracow Jagiellonian University Medical College, Cracow, Poland. The samples were taken from 18 surgically (mean age 22 months, male = 11) treated patients with ureteropelvic junction UPJ obstruction. The indication for surgery was based on the usual criteria (hydronephrosis detected with ultrasound and radionuclide renography). The control group consisted of 10 patients (mean age 18 months, male = 5), suffered from non-obstructive disease of

the urinary tract — predominantly renal tumors. Samples of tissue from the ureters were taken for further observation from the study group and control group.

Ethical approval

The study was conducted in accordance with the moral, ethical, regulatory and scientific principles governing clinical research. All surgical samples were retrieved with the approval of the Jagiellonian University Bioethical Committee using procedures that conformed to the Declaration of Helsinki guidelines (protocol number — KBET /78/B/2011).

Tissue processing

Tissue samples from fresh uretectomy specimens were collected and rinsed thoroughly with PBS (phosphate-buffered saline, 0.01 M, pH = 7.4), fixed in 4% phosphate-buffered paraformaldehyde, routinely processed and embedded in paraffin. Serial sections were cut and mounted on poly-L-lysine-coated glass slides.

Routine histology

The sections were deparaffinized, rehydrated and stained with either hematoxylin–eosin (H&E) to evaluate the gross tissue organization or Masson's trichrome staining to detect collagen deposits. Toluidine blue staining was performed for detection of mast cells.

Immunofluorescence

After deparaffinization and rehydration, the slides were incubated for 30 min in PBS with appropriate normal serum at room temperature, followed by overnight incubation at 4°C in a solution of PBS with appropriate normal serum containing a mixture of primary antibodies. After 5 washes (10 min each) in PBS, the specimens were then incubated for 1 h at room temperature with a mixture of secondary antibodies diluted in PBS. Finally, the slides were washed in two changes (10 min each) of PBS and cover-slipped with fluorescence mounting medium (Dako, Denmark) and covered glasses Menzel-Gläser. Labeled specimens were analyzed immediately. The primary antisera and secondary antibodies used are listed in Table 1.

Table 1. Type, sources and dilution of antibodies.

Antibody	Catalog number and company	Dilution
Primary antibodies		
Polyclonal rabbit anti-c-kit	A4502, Dako	1:100
Monoclonal mouse anti-CD34	M7165, Dako	1:100
Polyclonal goat anti-PDGFR alpha	AF-307-NA, R&D Systems	1:100
Monoclonal mouse anti-tryptase	M7052, Dako	1:100
Secondary antibodies		
Alexa Fluor 488 Goat Anti-Mouse	115-545-146, Jackson ImmunoResearch	1:400
Alexa Fluor 594 Goat Anti-Rabbit	111-585-144, Jackson ImmunoResearch	1:400
Alexa Fluor 594 Donkey Anti-Goat	705-585-003, Jackson ImmunoResearch	1:400
Alexa Fluor 488 Rabbit Anti-Mouse	315-545-045, Jackson ImmunoResearch	1:400

Microscopic examination of telocytes, mast cells, collagen deposits and the ureteral wall thickness Slides were examined using an MN800FL epifluorescence microscope (OptaTech, Warszawa, Poland) equipped with a Olympus DP74 digital camera. Digital images were collected at either 200× or 400× magnification. The qualitative analysis of cells was provided in 10 consecutive high-power fields of vision (400×) using the computer-based image analysis system Multiscan 18.03 software (CSS, Warszawa, Poland). All samples were assessed by two independent specialists (each blinded to the other) without any knowledge of the clinical parameters or other prognostic factors to avoid bias. The use of mast cell tryptase staining enabled c-kit-positive mast cells to be distinguished from c-kit-positive TCs. TCs were considered cells that were c-Kit positive and tryptase negative concurrently, with the characteristic morphology in tissue samples. Additionally, cells double positive for CD34 and PDGFRα with the characteristic morphology and localization were also recognized as TCs. In all sections the immunoreactive cells found were evaluated with respect to the relative frequency (arbitrarily graded as very few = (+), few = +, moderate density = + +, multiple density = + + +). The percentage of collagen deposits and muscle tissue have been analyzed in specimens, stained with Masson trichrome. The collagen and muscle fibers volume ration were performed in ten different fields of each sample. The ureteral wall thickness was also evaluated in ten different fields of each sample from both groups.

Mast cells were examined in samples stained with Toluidine blue and immunofluorescence. Double immunolabeling for c-kit/trypatse revealed double immunopositive cells, which were marked as mast cells. In both kinds of staining analysis of mast cells was performed in ten different fields of view and then converted and presented as the average number of cells per 1 mm^2 of ureteral surface.

Results

The histopathological changes in all ureter samples in this study were determined by hematoxylin–eosin and Masson's trichrome staining (Fig. 1). The study group was characterized by the prevalence of collagen deposits in compare with the control group. The amount of muscle fibers was lower in samples from patients with hydronephrosis compare with the healthy ureter. The gross structure of ureteral wall of patients affected by hydronephrosis was characterized by equivalent amount of collagen and muscle fibers deposits. In contrast, the ureteral wall from patients without hydronephrosis contains in one third higher muscle fibers than collagen (Table 2). The ureteral wall thickness was different in both groups. It was thicker in about 17 percentage among patients with hydronephrosis as compared with control (Table 3). The ration of the collagen/muscle fibers was equal in ureters, affected by obstruction, while tissue samples from vascular-etiologic hydronephrosis had a little bit less collagen and high muscle fibers amount.

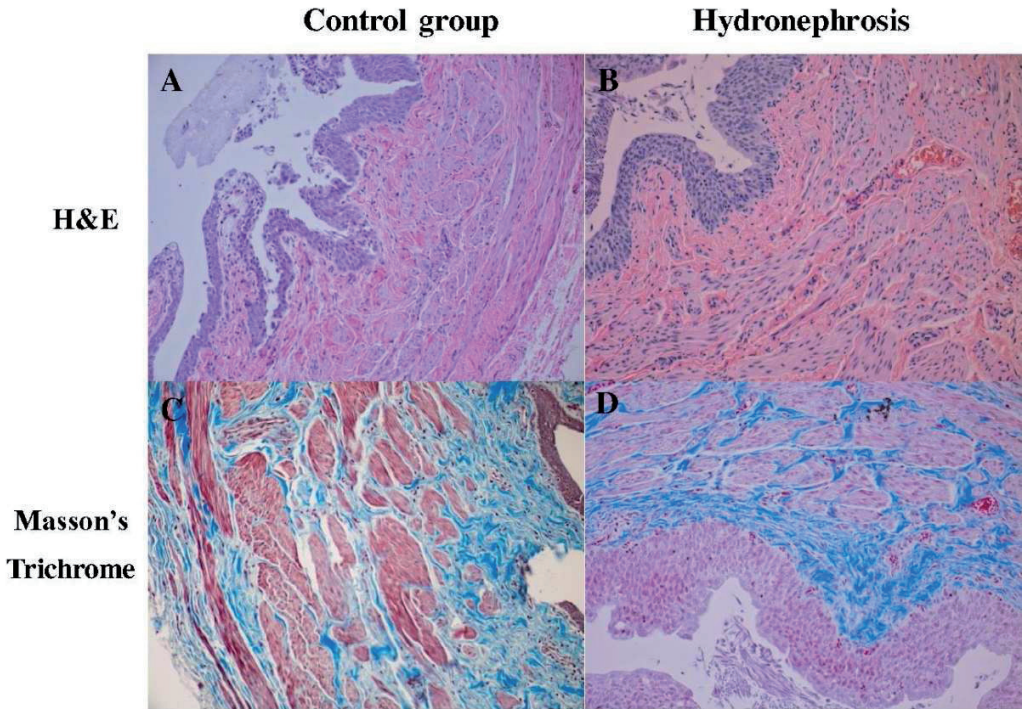

Fig. 1. Hematoxylin–eosin- and Masson's trichrome-stained sections of human ureter. The ureteral wall sections from the control group (**A**, **C**) compared with samples from patients with hydronephorosis (**B**, **D**). With Masson's trichrome staining, collagen deposits were blue in color; muscle fibers, red in color. Total magnification: 200×.

Table 2. The percentage of the collagen and muscle fibers in the normal ureter and samples from patients with hydronephrosis.

Ureter	Collagen (%)	Muscle fibers (%)
Control group	32 ± 10	54 ± 12
Hydronephrosis (obstruction)	40 ± 10	40 ± 10
Hydronephrosis (vas)	39 ± 14	42 ± 10

Table 3. Ureteral wall thickness in the control and study groups.

	Control group	Hydronephrosis
Ureteral wall thickness (μm)	685 ± 228	800 ± 212

An average amount of mast cells measured in ureteral wall from patients with and without hydronephrosis was different. Due to sensitivity of immunostaining, results were higher in samples labeled by c-kit/tryptase antibodies in compare with routine histology. Nevertheless, common trend was revealed in both types of staining: the number of mast cells in ureters from affected by hydronephrosis patients was about 1.5 times higher than in unaffected children. Consequently, this indirectly indicates the inflammation, that commonly accompanied the studied pathology (Table 4).

Table 4. Mast cells's profile in the control and study groups evaluated in two kinds of staining (Toluidine blue staining and c-Kit immunohistochemistry).

	Control group	Patients with hydronephrosis
Mast cells amount (toluidine blue staining)	25.1 ± 13	56.1 ± 20.9
Mast cells amount (IHC labeling)	38.7 ± 18.5	81.8 ± 26.9

Double immunopositive cells for CD34 and PDGFRα have been detected in the control group, within muscle layer of the ureteral wall (Fig. 2). Based on its morphology, immunoprofile and localization in the tissue, we considered that they represent ureteral telocytes. Some of these cells have been seen under uroepithelium. The control group has more double-positive cells in comparison with all samples from the study groups. In the ureter form patients with obstructive hydronephrosis, less telocytes have been revealed. The scanty architectonic of cellular pattern was mostly due to a prevalence of the collagen. Tissue samples from vascular etiology of hydronephrosis were characterized by relative intensive immunolabeling for mentioned markers than obstructive forms. The same results we had analyzed c-kit-positive/tryptase-negative cells (Table 5).

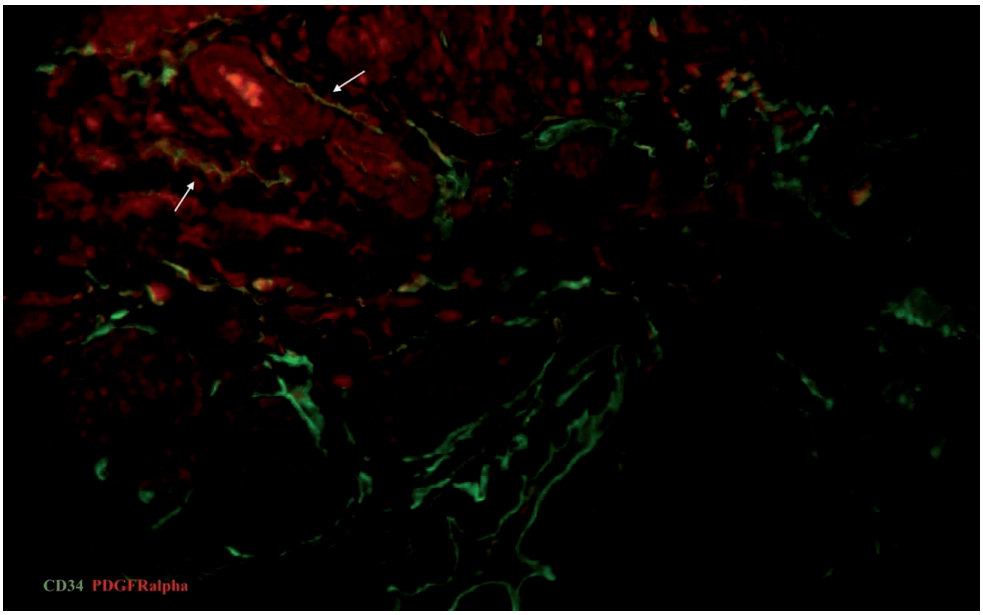

Fig. 2. Sample of ureter from patients with hydronephrosis stained for PDGFR alpha (red, Alexa Fluor 594) and CD 34 (green, Alexa Fluor 488). Double immunopositive cells with elongated bodies located between muscle fibers and close to blood vessels are identified as telocytes (some of them are marked by arrow on the image). Total magnification: 400×.

Table 5. Relative frequency of c-kit-positive/tryptase-negative, CD34-positive and PRGFRα-positive cells in ureteral wall of human unaffected and affected by hydronephrosis patients. 0 = absence of telocytes, (+) = very few, + = few, + + = moderate density, + + + = multiple density.

Patients	c-kit-positive / tryptase-negative cells	CD34-poisitve / PDGFRα-positive cells
Control group	+ +	+ +
Hydronephrosis (obstruction)	(+)	(+)
Hydronephrosis (vas)	+	+

Discussion

No one theory clearly explains the mechanisms of hydronephrosis development. We will consider several modern hypotheses in combination with focusing our attention on telocytes. Chuang *et al.* proposed that myocyte apoptosis leads to ureteral damage in the smooth muscle layer of obstructed ureters [30]. The congenital character of obstruction might also be connected with the co-existence of its apoptosis and local neuronal malformations in the ureteral wall [13]. Generally, cellular apoptosis is a result of the activation of the intrinsic and extrinsic pathways [31].

Oxidative stress and extracellular stress signaling play a crucial role in these physiological processes. Among the main inductors of the extrinsic pathway, we distinguish tumor necrosis factor-α (TNF-α), a major inflammatory cytokine in the human body, which also has a similar effect of telocytes population [32]. Decreasing of myocytes correlates with a fibrosis development and a grade of local inflammation. Also, diseases, accompanied by fibrotic transformation, are characterized by an increasing number of inflammatory cells and declining of telocytes (or even disappearance): hepatic fibrosis, gallstone disease, systemic sclerosis, primary Sjögren's syndrome, psoriasis, myocardial infarction uterine fibroid [33–41]. In ureteral tissue samples from hydronephrosis patients, we observed more mast cells in comparison with a control group. The opposite tendency has been revealed with TCs: in obstructive hydronephrosis were fewer cells, while in tissue samples with a crossed vessel more than in obstruction, but less than in the control group. Telocytes make stromal synapses with mast cells and indirectly involved in the production of nitric oxide (a component of the oxidative stress). Meanwhile, in a renal ischemia-inflammatory injury model, they activated the nuclear factor kappa B signaling pathway and upregulated the mRNA levels of pro-inflammatory cytokines such as IL-1 and tumor necrosis factor-α [42, 43]. Inflammation was common for both study groups (with obstruction and crossed vessels) and has not clarified a difference in both kinds of hydronephrosis. That is why we delved into the study of TCs in divided study groups. We can hypothesize that the involvement of telocytes in the inflammatory response could correlate with ureteral fibrosis and hydronephrosis development. Koleda *et al.* observed the link between age-related changes in the interstitial cell of Cajal-like cells density in congenital ureteropelvic junction. He concluded that the number of Interstitial cells of Cajal-like cells-dense fields decreasing with age may show the failure of compensation and regression of the compensatory changes [44]. We can extrapolate these data on our study and suspect that a low amount of TCs reflects a low adaptative feature of the ureteral wall and as a result — high risk of hydronephrosis development.

The next interesting feature of TCs, especially in the urinary tract, is the existence of several layer-specific subpopulations of these cells. They differ from each other in some ultrastructural features and immunolabelling according to their location [28, 45]. The difference of immunopositivity of such markers as plated-derived growth factor receptor alpha (PDGFRα), α-smooth muscle actin (αSMA) and c-kit is typical for TCs in the urinary bladder. For instance, Vannucchi *et al.* published that in the submucosa of the human urinary bladder they are CD34/calret-positive, but PDGFRα/αSMA/c-kit negative. Cells located immediately under the urothelium were PDGFRα/ calret-positive and αSMA/CD34/c-Kit-negative, despite located deeper in the sub-urothelium — αSMA-positive. Dobra *et al.* described three different subsets of ureteral TCs which are neither endothelial nor epithelial in nature: (a) type I: the CD34-/CD105+ TCs of

the superficial layer of lamina propria; (b) type II: the CD34+/CD105± myoid TCs of the deep layer of lamina propria and (c) type III: the CD34+/CD105+ perivascular TCs [45]. Although different, all these subsets of TCs could belong to the stem/progenitor niche of the ureter. Our aim has not included the differentiation of TCs in the ureteral wall, but we observed TCs located close to blood vessels and also under uroepithelium. No significant difference in the location of TC in cases of obstructive hydronephrosis and resulted by crossed vessels has been observed.

Important to note is that telocytes have an significant role in pyeloureteric peristalsis [46]. Lang *et al.* described telocytes in UPJ and atypical smooth muscle cells as two populations of pacemaker cells [47]. Koleda *et al.* mentioned that telocytes express vanilloid receptor-like 1 protein (VRL-1/TRPV2) suggests the role they may have in the modulation of pyeloureteric peristalsis as sensors of physical and chemical stimuli [44]. His command also experimentally proved that the density of UPJ telocytes was different among normal ureters and obstructed. Increased expression of c-kit-positive telocytes in congenital UPJO may indicate the development of a compensatory mechanism for the failure of urine to be propelled from the renal pelvis through the ureter [44]. Li *et al.* showed that injection of renal TCs can attenuate renal dysfunction and ameliorate renal histological damage following renal ischemia-reperfusion injury [43].

Telocytes have gene expression profiles with up- and down-regulated genes on 1, 2, 3, 4, 17 and 18 chromosomes. Up-regulated genes functions common for these type of cells are related to cellular signaling, cell expansion and movement (migration, adhesion, migration, and division), embryogenesis, morphogenesis and tissue homeostasis (including immune homeostasis), tissue remodeling and repair, maintenance of oxidative microenvironment preventing tumorigenesis and anti-inflammatory responses. Until now, we do not know how TCs are involved in the pathogenesis of hydronephrosis, initiated by obstruction or vessel's co-location [48–54]. Due to their immunohistochemical profile we know that they are involved in contraction of excitable tissue, positive for sex steroid hormones and probably may be involved in obstruction of the ureter by ovarian vessel, physiologically occurs during pregnancy. Our preliminary results showed that both ureteral tissue samples (from obstructive and crossed vessels) hydronephrosis have more mast cells and an increased amount of collagen, correlated with a decreasing in TCs density. More detailed observation of macro- and microscopic tissue organization showed a slight difference in TCs between both study groups and collagen/muscle fibers ration as well. We intend to continue our research, which requires more specific analysis for stressing the role of telocytes in the pathomechanisms of hydronephrosis.

Conflict of interest

None declared.

Authors contribution

Michał Wolnicki and Veronika Aleksandrovych: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, study supervision, and final approval of the manuscript. Anna Gil: acquisition of data, analysis and interpretation of data. Artur Pasternak: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Krzysztof Gil: editing and revising of the manuscript, analysis and interpretation of data, and final acceptance of the manuscript.

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