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Changes in Cajal cell density in ureteropelvic junction obstruction in children

Cem Senol [a], Metin Onaran [a], Serhat Gurocak [a], Ipek Isık Gonul [b], Mustafa Ozgur Tan [a]

[a]Department of Urology, Gazi University School of Medicine, Ankara, Turkey

[b]Department of Pathology, Gazi University School of Medicine, Ankara, Turkey

Correspondence to: Cem Senol, Department of Urology, Gazi University School of Medicine, Ankara, Turkey, Tel.: +90 532 205 5288

senolcem@gmail.com (C. Senol)

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Summary

Introduction
Congenital ureteropelvic junction obstruction is one the most common causes of neonatal hydronephrosis. The etiology of the ureteropelvic junction (UPJ) obstruction has not been clearly established. The presence of a hypoplastic, adynamic ureteral segment is thought to be the major cause of an UPJ obstruction.

Objective
We evaluated the distribution of Cajal cells using immunohistologic methods coupled with light microscopy of the UPJ tissues in obstructed and normal UPJs.

Study design
The study group consisted of 19 patients who underwent pyeloplasty for UPJ obstruction. Twelve patients who had been operated on for oncological indications constituted the control group. The sections were stained immunohistochemically using CD117 (c-kit) antibody; the numbers of CD117 (+) interstitial cells of Cajal were counted in 10 consecutive high-power fields under the light microscope and the cell density was determined for each case.

Results
The mean age of the cases who underwent dismembered pyeloplasty and the control group were 116 ± 116 months (14 male, 5 female; 6–420 months) and 279 ± 312 months (9 male, 3 female; 24–948 months) ($p = 0.1$), respectively. The mean interstitial Cajal cell number in the UPJ obstruction and the control groups were 2.37 ± 2.19 and 24.5 ± 9.73, respectively ($p < 0.0001$). Thirteen (68.4%) patients had very few, five (26.3%) patients had few, and one (5.3%) patient had many Cajal cells in the UPJ obstruction group. In the control group, all patients had more than seven cells per high-power field.

Discussion
We found that in cases of UPJ, obstruction the numbers of interstitial Cajal cells were decreased, being either absent or significantly reduced. Although data about the motility are currently not sufficient, the decrease in the number of Cajal cells in patients with UPJ highlights that they might be responsible for the initiation, coordination, and conduction of peristaltic activity along the pelvicalyceal system. Improvement and enhancement of contraction waves arising from the upper urinary system depend on interstitial cells of Cajal, which are the pacemaker cells in smooth muscles. We think that a decreased number of interstitial cells of Cajal have a close relationship with changing ureteral motility when we compare our UPJ obstruction cases with the limited data in the literature.

Conclusion
Further investigations on these cells will probably give detailed information about the neurophysiology of the urinary system and the diseases that cause congenital hydronephrosis.

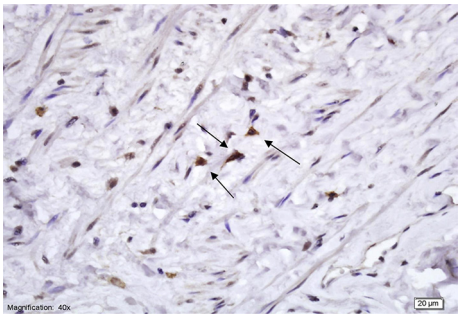

Figure CD117 (+) Cajal cells (arrows) in the material from patients who had ureteropelvic junction obstruction.

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Introduction

Congenital ureteropelvic junction (UPJ) obstruction is one the most common causes of neonatal hydronephrosis and its incidence is about one in 1500—2000 [1,2]. UPJ obstruction is more common in boys rather than in girls and is more often seen in the left ureter. Most infants are asymptomatic and diagnosis is given generally by antenatal ultrasonography. Flank or abdominal pain, nausea, vomiting, hematuria, palpable abdominal mass, renal stones, or severe hypertension may be seen in some of the patients [2,3]. The presence of hypoplastic adynamic segment is among the pathologies seen (e.g. crossing vessel, dysplastic segment, high insertion, etc.) [4].

Interstitial cells of Cajal (ICC) have been identified as one of the probable pacemaker cells for contractile activity of the ureter. They were first described by Santiago Ramon y Cajal in 1893 [5,6]. Histologically, ICC are usually the same size or a little smaller than the smooth muscle cells beside them. However, their shape may differ: the ones located in between smooth muscle cells are more fusiform, and the ones located around the neuronal plexuses are usually stellate shaped [7,8]. Their cytoplasm is rich in caveola, mitochondria, and thick intermediate filaments [9]. On their cytoplasmic membranes, they form tight gap junctions creating a network allowing cross-talking between them, which is enriched by the branching of fusiform or stellate-shaped cells forming ICC groups [9]. ICC express a tyrosine kinase receptor "c-kit (CD117)", a feature allowing them to be recognized easily by immunohistochemistry under a light microscope [10].

It has been shown that ICC in the upper urinary tract may be responsible for the conduction of slow-wave electrical potentials between neurons and typical smooth muscle cells [11]. These slow waves activate the ion channels in smooth muscles and start the contraction cascade through which urine is carried from the renal pelvis to the ureter by peristaltism [12]. Therefore, it was thought that the absence of CD117 (+) ICC may result in the loss of peristaltic waves in the UPJ and, consequently, the transmission of urine to the ureter is impaired and a relative UPJ obstruction develops. An experimental study conducted by Ward et al. [13] revealed that slow waves have been lost in rats without ICC and, as a result, the coordination of peristaltism through the intestines has been disturbed. Therefore, these cells may play an important role in the initiation, propagation, coordination, and modulation of upper urinary tract peristalsis as well.

This study has been conducted to investigate the presence and determine the distribution of ICC in tissues resected from patients with UPJ obstruction and compare the results with the control group.

Materials and methods

Indications for pyeloplasty in our study group were acute symptoms of obstruction, unresponsiveness to a standard dose of furosemide in the dynamic renogram and/or increase in the anteroposterior diameter of the ipsilateral renal pelvis. Excisional biopsies with a resection margin of 2—3 mm above and below the UPJ in 19 patients who had undergone pyeloplasty due to UPJ obstruction were retrieved from the archives of the Department of Pathology. Three to six sections per case were re-evaluated under light microscopy and 4-μm-thick sections from the corresponding paraffin blocks were recut on one or two positive-charged slides for immunohistochemistry using the streptavidin—biotin—peroxidase method. Staining for CD117 have been described in elsewhere [14,15]. Briefly, following deparaffinization and dehydration, sections underwent heat-induced epitope retrieval in 0.01 M sodium citrate buffer at pH 6.0 for 20 min. Endogenous peroxidase was inactivated with 2% H_2O_2 for 10 min. As a primary antibody, CD117 (c-kit) antibody (Leica Biosystems, Novocastra, ready-to-use, RT4-CD117, mouse monoclonal antibody, clone T595, CE/UK) was used. Immunoreactivity was visualized by 3,3-diaminobenzidine (DAB) staining. Counterstaining was performed with hematoxylin. A known positive control section was included in each run to ensure proper staining. The number of CD117 (+) ICC was counted in 10 consecutive high-power fields under the light microscope and the cell density was determined for each case. The location and the morphology of CD117 (+) cells have been taken into consideration while counting, since CD117 (+) mast cells can mimic ICC. CD117 (+) cells with fusiform shape, oval nucleus, and dendritic extensions were counted as ICC; however, cells with round to oval, granular, basophilic cytoplasm with oval nuclei were evaluated as mast cells (Fig. 1).

The UPJ tissues of 12 patients with renal tumor constituted the control group. They did not have any radiographic findings suggestive of obstruction and underwent surgery for an indication other than obstruction.

SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) Version 15.0 was applied for statistical analysis. The distribution of Cajal cells in the UPJ obstruction and control groups were evaluated by the Mann—Whitney *U* test and the chi-square test.

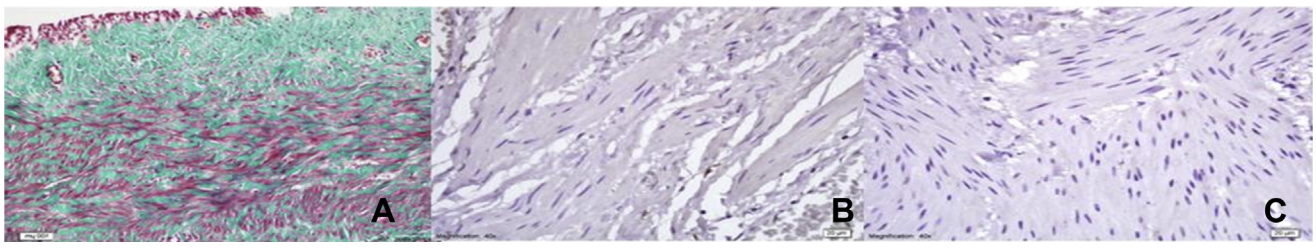

Figure 1 (A) Sclerotic fibrosis in the subepithelial connective tissue. (B) A few Cajal cells in the ureteropelvic junction material. (C) The ureteropelvic junction material that has no Cajal cells.