

Ureteropelvic junction obstruction in children by polar vessels: histological examination result

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Abstract

In children, ureteropelvic junction obstruction (UPJO) is mostly caused by intrinsic factors (IUPJO) such as abnormal amounts of muscle and collagen deposition; extrinsic UPJO are rare and often due to crossing vessels (CVs). What is not clear is whether there is also intrinsic UPJ pathology in patients with CV. The aim of our study was to compare the histology of the two types of obstruction and to determine whether these histologic features are distinguishable enough to enable to identify the cause of obstruction based on histologic appearance alone. We retrospectively reviewed pathology reports of 38 children with UPJO that underwent surgery in our hospital from 2008 to 2022. The intrinsic and extrinsic groups consisted of 18 and 20 patients, respectively. After hematoxylin-eosin and Gomori's trichrome staining the specimens were scored for fibrosis and muscular hypertrophy in histopathology, and CD117 antibody were used to detect interstitial Cajal-like cells. In our study, histological analyses revealed no differences between the CV and IUPJO specimens in terms of presence and degree of fibrosis and muscular hypertrophy; likewise, for presence of interstitial Cajal-like cells.

Introduction

In children, the obstruction of the pelviureteral junction (UPJO) is most commonly caused by intrinsic factors functionally linked to the presence of an aperistaltic junctional segment, site of structural wall alterations here. Less frequently the obstruction may be due to the presence of an external obstacle, which in most cases is identifiable with an abnormal vessel (CV).¹

At present, on the base of the clinical evaluation and the radiological imaging, it is possible to discriminate between intrinsic junctional obstruction and extrinsic obstruction. However, in the latter case it is not possible to discriminate, with equal certainty, if this is the only cause or if does not represent the triggering event of intrinsic structural wall alterations, such that, obviating only the presence of the external obstacle may not result in the resolution of the pathology that derives from it.²

This consideration arose from the growing consensus obtained by the technique of transposition of the anomalous vessel ("vascular hitch") (VH),³⁻⁵ described for the first time by Hellström *et al.* in 1949⁶ and modified a decade later by Chapman,⁷ and from the data emerged from the comparative evaluation of the histological samples related to cases of stenosis of the intrinsic and extrinsic joint.

These data focus on the analogies of the structural alterations found not only in the subjunctional area, as might be expected in cases of obstruction from an anomalous polar vessel, but also in the pelvis, joint and ureter immediately proximal as the intrinsic primitive.

Materials and Methods

In order to ascertain the accuracy of the therapeutic choice adopted, we performed a retrospective review with reassessment of the anatomopathological data of a cohort of 19 patients with obstruction of the pyeloureteral joint, of whose 10 with abnormal polar vessel and 9 with intrinsic obstruction, all underwent open Anderson-Hynes dismembered pyeloplasty (AHDP) in our surgery unit between 2008 and 2018.

The criteria for surgery were considered for all patients to be a progressive increase in the anteroposterior diameter (AP) of the renal pelvis on ultrasound evaluation (US), a differential renal function <40% or a decrease >10% between two scan examinations with diuretic renal scan (DRS), preferably using ^{99m}Tc -MAG3.

The chosen anatomopathological revision criteria were expected to evaluate the traits corresponding to the renal pelvis, the pelvoureteral junction and the proximal ureter. Blocks embedded in paraffin were prepared and after formalin fixation, 4-microns-thick sections were obtained and stained with hematoxylin-eosin, trichrome staining of Gomori, and in addition, immunohistochemical investigations related to the CD117 pattern (rabbit polyclonal antibody) were conducted. Specifically, the Gomori trichrome staining was used to establish the degree of fibrosis and muscle hypertrophy, identifying grade 0: non-alterations, grade 1: slight alterations, grade 2: moderate alterations, grade 3: severe alterations; with a 5 HMF (high magnification fields) optical microscope, CD117 was employed to identify the Cajal-like interstitial cells present in the samples analyzed.

The post-operative follow-up included the execution of US at 1, 3, 6 months and the repetition of the dynamic renal scan at 6 months.

Results

Our non-blinding anatomopathological analysis and the epidemiological characteristics of a cohort considered allowed us to confirm the data present in the literature: the average age of patients with intrinsic joint obstruction (IUPJO) was 9.6 months (age ranged from 4 months to 45 months), that of the patients with extrinsic obstruction EUPJO was 6 years (age ranged from 3 years to 14 years) at surgery. 6 patients with intrinsic obstruction presented a constant and steady progressive increase of the AP diameter of the pelvis, this data was found only in 3 patients with extrinsic obstruction by CV (EUPJO-CVs); in 7 patients with extrinsic form, the AP diameter of the pelvis presented a fluctuating increase with long periods of stability on borderline values. Renal function in CVs is expected to be good as the obstruction is thought to be intermittent. However, we noted differential renal function on DRS below 40% in 7 (70%) patients with EUPJO by CVs, while this was below 40% in 4 (44.44%) patients with IUPJO.

The histological findings showed uniformly, at each level examined, grade 1 fibrosis in 2 (22%) cases of intrinsic stenosis and in 2 (20%) cases of CV stenosis; grade 2 fibrosis in 6 (67%) and 7 (70%) cases, respectively, and grade 3 fibrosis in 1 case for both groups. Grade 1 muscular hypertrophy was present only in 5 (50%) cases of CV stenosis, grade 2 in 8 (89%) cases of intrinsic obstruction and 5

(50%) of CV, while grade 3 hypertrophy in only one case of intrinsic stenosis (Figure 1, 2). There were no significant differences between the two groups in terms of detection and degree of fibrosis. For what concerns muscular hypertrophy, although it presents in both groups, it is expressed with greater severity in the patients with intrinsic obstruction. The immunohistochemical examinations performed to evaluate the density variations of the Cajal interstitial cells in the junctional area and in the above and below ones, using a CD117/c-kit, have highlighted findings dominated by the absence or reduction of the number of these in both groups with overlapping results. It is emphasized that, since the mast cells are CD117 positive, only the intramuscular positive cells with large nucleus, star-shaped or with two or more cytoplasmic extensions were counted.

The surgery was determining in all patients to the resolution of stenosis with reduction up to the normalization of pyelectasia to US. The renal functional uptake did not change significantly after the surgery in both groups but the percentage gain was greater in IUPJO patients compared to EUPJO-CV.

Discussion

Ureteropelvic junction obstruction (UPJO) is the functional or anatomic failure of urine transport from the renal pelvis to the ureter. It is the most common pathologic cause of antenatal hydronephrosis and occurs sporadically one in 750-1500 infants born alive,⁸ but familial inheritance has been reported. Irrespective of the underlying etiological factor, the renal pelvis can accommodate urine passage

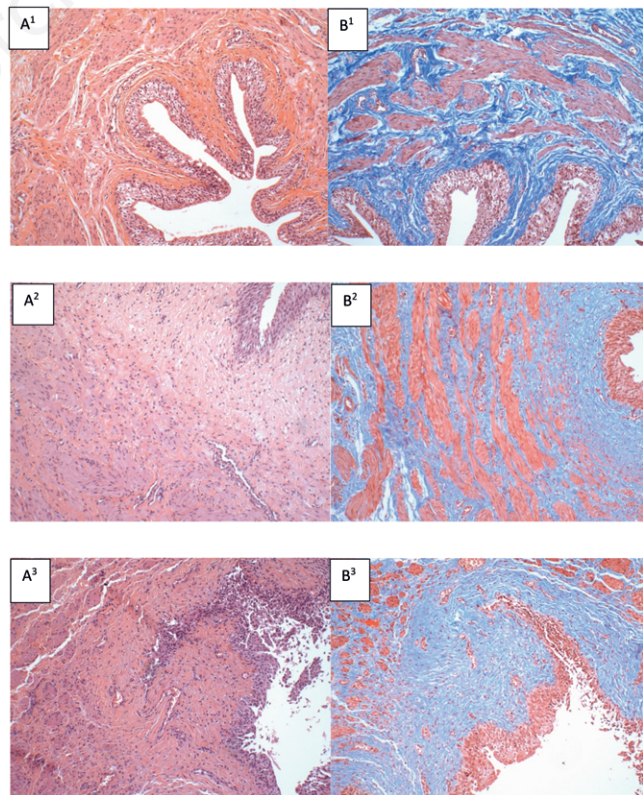


Figure 1. Histological appearance of IUPJO. (A¹ B¹) Grade 1 fibrosis - grade 2 muscular hypertrophy. (A² B²) Grade 2 fibrosis - grade 3 muscular hypertrophy. (A³ B³) Grade 3 fibrosis - grade 2 muscular hypertrophy.

with its compliance for a certain period of time but once it loses its viscoelasticity, progressive renal functional deterioration may ensue because of increased intrapelvic pressure.⁹ There exist two commonly proposed etiologies of UPJO: intrinsic and extrinsic obstruction. Among the many theories proposed to explain the forms of intrinsic obstruction, the most accredited is the one described in an animal study exposing the retrograde ascent of myogenesis from the uretero-vesical junction to the uretero-pelvic junction after ureteral recanalization; premature arrest of ureteral differentiation at the level of uretero-pelvic junction owing to an incompletely stenotic aperistaltic ureteral segment is the hallmark of intrinsic hypothesis.¹⁰ The extrinsic theory is mostly caused by a crossing lower pole renal vessel (aberrant, accessory, or early branching) causing an impingement on the ureter and obstructing flow; anterior crossing vessels are more common (41%) than posterior ones (7%).^{11,12} The incidence of an aberrant crossing vessel has been reported to be 6-11 %, but can be as high as 30 - 70 % in older symptomatic children; moreover, highly significant association of intrinsic obstruction with CV which in some cases reaches about 25%.¹³⁻¹⁵

However, to date, embryological, anatomical, and functional studies have failed to reveal the exact pathophysiological mechanism underlying UPJO. There is still an ongoing discussion whether CVs are even able to cause UPJO or whether they become trapped by an expanding renal pelvis in patients with intrinsic obstruction. IUPJO is often diagnosed very early in live or even prenatally due to the widespread use of prenatal ultrasound. EUPJO by CVs present at an older age. Based on the fact that a CV exists from the beginning, but starts to present varying symptoms sometimes later in life, it is an important consideration of how the development of the ureteral

wall is impaired by a pulsating and compressing CV. In theory, the alterations of the ureteropelvic segment caused by a CV are part of an individually ongoing process, depending on how long and how high the affecting pressure by the vessel is. Therefore, the moment in which the intrinsic component overcomes the polar vessel induced histological process is strictly patient-specific and it could explain the cases of failure after a vascular hitch procedure reported in the literature.^{16,17}

In our group of patients carrying CV stenosis 40% (4 patients) presented clinical symptoms, especially cyclic abdominal pain, in one of these kidney stones at US were found too, whereas in the group of intrinsic stenosis patients any clinical symptoms were registered. In our experience it is possible to have an initial diagnosis of intrinsic or extrinsic UPJO based solely on clinical and imaging findings but presumptive. Indeed, the carriers of abnormal polar vessel stenosis came later to the surgery due to the intermittence of pathological pyelic dilatation to the US and to the lengthening of the dismissal times of the tracer during renal scintigraphy. In these cases, the morphology of the scintigraphy curve, especially during the initial diagnostic assessment, presented a trend similar to the functional alteration curve, but more frequently associated with a differential renal function on DRS below 40%. These indicate the effect of the obstruction on the renal parenchyma and the importance of early detection.

Along the lines of other similar works, with this study we have intended to make our contribution to investigate the differences of the histopathological pattern between the EUPJO by CVs and IUPJO. In cases of intrinsic obstruction, different findings of histopathological changes have been described: increased intermuscular and intramuscular connective tissue, increased collagen that acts as an inelastic collar hampering ureteral peristalsis.^{2,18} Alterations of innervation, muscular hypotrophy or hypertrophy have also been reported as causative or resulting alterations of the ureteral wall¹⁹ and correlated to the AP pelvic diameter: greater the diameter, greater the degree of histological alterations identified. Foundation of this assessment could be found in our results: in 89% of IUPJO patients presented a Grade 2 of muscular hypertrophy and 1 patient had Grade 3. In our cohort of patients, the mean of the AP pyelic diameter, measured after complete voiding, was 28mm S.D. 10mm. In intrinsic stenosis patients, it has been observed that the AP diameter at US increased with the age of the patient, while in the cases in which the AP diameter value appeared stable or intermittent, at surgery the presence of a crossing vessel was assessed.

Like to what is reported in the literature about the histopathological changes, in our reviewed CV specimens, we did not find variations statistically significant both in terms of presence and in terms of entity, expressed in degrees, for the so-called intrinsic alterations, such as muscular hypertrophy and fibrosis, compared with histomorphological aspect of IUPJO specimens.

In the literature it has been identified a relevant status of edema and of chronic inflammation, which result in an increased fibrosis in CV -EUPJO segments, this suggests that an early surgery could affect the extent of fibrous component.²⁰

A similar consideration emerged from the assessment of the density interstitial of Cajal cells in both groups. It is well known that Cajal cells are required to generate smooth muscle electrical slow waves. As in gastrointestinal motility, Cajal cells may play an important role in the propagation, coordination and modulation of ureteropelvic peristalsis.²¹ Cajal cells, which express CD117 on their surface, were determined using monoclonal antibodies as markers, which however have the limit of binding also to mast cells.²² In our study, this was remedied by counting only positive intramuscular cells, star-shaped or with two or more cytoplasmic extensions. Studies in the literature report that the number of Cajal cells in

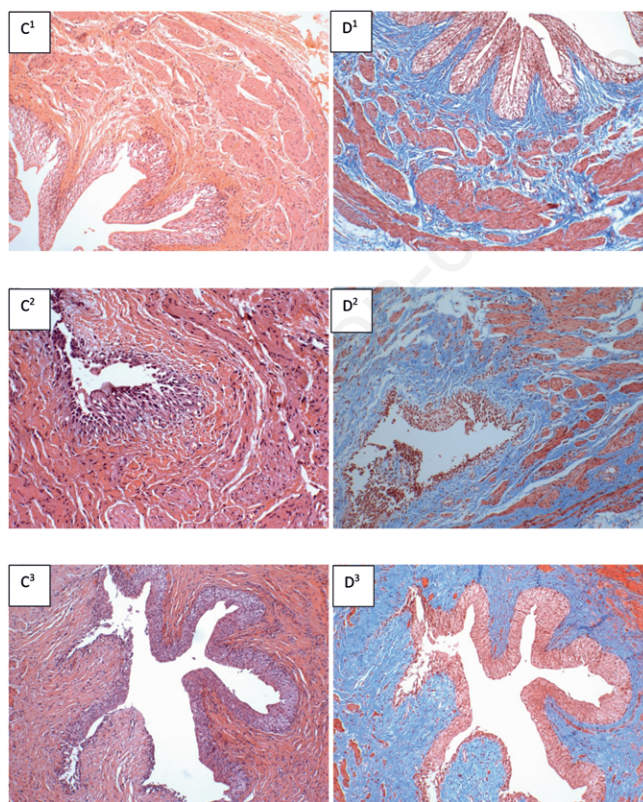


Figure 2. Histological appearance of EUPJO-CVs. (C¹ D¹) Grade 1 fibrosis - grade 1 muscular hypertrophy. (C² D²) Grade 2 fibrosis - grade 2 muscular hypertrophy. (C³ D³) Grade 3 fibrosis - grade 1 muscular hypertrophy.

obstructed UPJ segments is higher than in normal UPJ segments to compensate for the effects of the obstruction, but which then decreases during the late period of obstruction and with them the peristaltic activity.²³ The comparison between IUPJO and EUPJO by CVs showed superimposable reduction of interstitial Cajal cells.

Conclusions

Our data revealed no significant differences between EUPJO-CVs and IUPJO patients concerning the pathologic features of fibrosis, muscular hypertrophy and reduction in Cajal cells. Although this means that it is possible to have an initial diagnosis of intrinsic or extrinsic ureteropelvic junction obstruction, however it may not be possible to strictly discriminate an intrinsic case with an additional extrinsic component from a primarily intrinsic stenosis because of lower pole aberrant vessels. These two disorders may coexist or trigger each other.

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