Significance of MR Angiography in the Diagnosis of Aberrant Renal Arteries as the Cause of Ureteropelvic Junction Obstruction in Children

Stellenwert der MR-Angiografie in der Diagnostik aberrierender Nierenarterien als Ursache einer Ureterabgangsstenose bei Kindern

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Key words
- obstruction
- ureteropelvic junction
- children
- MRA
- MRI

Abstract

Purpose: To determine the importance of MRI with contrast-enhanced MRA for the detection or exclusion of aberrant or obstructing renal arteries in ureteropelvic junction obstruction in children.

Materials and Methods: Key word-based search in RIS database (ureteropelvic junction obstruction/ MRI) and retrospective comparison of arterial findings from preoperative contrast-enhanced MRA and intra-operative inspection. From 2007 to 2013, 19 children with ureteropelvic junction obstruction underwent contrast-enhanced MRA. Based on the results of the MRI scan and MAG3 scintigraphy, the children were referred to surgery (Anderson-Hynes-pyeloplasty).

Results: An aberrant renal artery was diagnosed with MRI in 14 of 19 children, and intra-operative inspection confirmed 13 of those 14. In the remaining 5 children, no aberrant vessel could be observed in MRI and this was confirmed intra-operatively in 3 of the 5 cases, while in the remaining 2, an aberrant vessel was found. Of the 14 children with aberrant vessels, 12 underwent surgery due to assumed ureteral obstruction, which was confirmed by surgery in 11 cases. In one case, an aberrant artery was found intra-operatively, but obstruction could not be confirmed. In one of the 14 children, the vessel was found in MRI, but its obstructing character was negated via MRA, which was confirmed intra-operatively. In the diagnosis of aberrant and obstructing renal arteries, contrast-enhanced MRA presents 85% sensitivity and 80% specificity, with a positive predictive value of 0.8.

Conclusion: MRI with contrast-enhanced MRA is suitable to detect aberrant and obstructing renal arteries. An obstructive effect of the aberrant vessel is to be assumed if the vessel has a close relationship to the ureteropelvic junction and if it is linearly stretched.

Key Points:
- MRI with contrast-enhanced MRA is a sure method for the detection of aberrant renal arteries in children with ureteropelvic junction obstruction
- the obstructive effect of the aberrant vessel can be derived from the close proximity of the vessel to the ureteropelvic junction and from the stretched course of the vessel

Zusammenfassung


Ergebnisse: Eine aberrierende Nierenarterie wurde bei 14 von 19 Kindern in der MRT diagnosti-
is associated with a higher logistical effort compared to the function and urodynamics of the urinary system but Functional MR urography provides information regarding primary obstructive megaureter, vesicoureteral reflux). MRI of the kidneys with contrast-enhanced MRA is also disturbance (including stenosis of the orifice of the ureter, progression of kidney function. All urinary flow causes and urodynamic significance of the urinary flow disturbances in children are diagnosed via ultrasound. The diseases have a bilateral presentation in 30% of cases [1]. Ureteropelvic junction obstruction is one of the most common causes of urinary tract obstruction with an incidence of 3 in 1000 newborns. Boys are affected more often than girls. The disease has a bilateral presentation in 30% of cases [1]. Ureteropelvic junction obstruction is caused by a flow disturbance in the pyeloureteral junction. This is a complex system requiring the interplay of intrinsic and extrinsic factors. The arrangement of the smooth musculature and the innervation play an important role among the intrinsic factors. Secondarily, fibrosis and collagen deposits can occur due to chronic inflammation [2 – 4]. Thus, a differentiation is made between a primary (inherent) form and a secondary (due to chronic inflammation with secondary fibrosis and stenosis) form among cases of intrinsic stenosis. However, the transition to stenosis caused by adhesive bands, adhesions, kinks, or aberrant vessels is fluid [5] so that a differentiation should be made between primarily intrinsic and primarily extrinsic stenosis. Stenoses of a largely intrinsic nature manifest very early (newborns/toddlers) or even prenatally [6], while stenoses with a predominantly extrinsic genesis are first seen later in childhood [2, 3]. Left untreated, both causes can result in progressive impairment of kidney function. All urinary flow disturbances in children are diagnosed via ultrasound. The causes and urodynamic significance of the urinary flow disturbance are then evaluated. Ureteropelvic junction obstruction must be differentiated from other causes of urinary flow disturbance (including stenosis of the orifice of the ureter, primary obstructive megaureter, vesicoureteral reflux). MRI of the kidneys with contrast-enhanced MRA is also suitable for evaluating morphology and vascular supply. Functional MR urography provides information regarding the function and urodynamics of the urinary system but is associated with a higher logistical effort compared to conventional MRI and there is currently no evaluation software commercially available from an MRI manufacturer. This limits the application of the method in the daily routine [7 – 9]. The treatment of ureteropelvic junction obstruction is differentiated and the indication for surgery is clearly defined. It is typically made on the basis of a loss of renal function and/or a urodynamically determined obstruction in MAG3 scintigraphy. Exact information regarding the presence of lower pole vessels is important in multiple regards for the surgical procedure. For the indication: In the case of extrinsic ureteropelvic junction obstruction caused by an aberrant vessel, varying findings regarding the urinary flow disturbance and the renal excretory function are known. As a result, this finding often doesn't yield a clear indication for surgery. However, the detection of aberrant vessels supports indication determination. Early intervention prevents progressive damage to the renal parenchyma. Exact knowledge of the vessel course at the kidneys is useful for surgery since surgical correction of aberrant lower pole vessels is performed by transposition of the pyeloureteral junction while maintaining the pole vessels. Such knowledge therefore shortens the surgical time and minimizes the risk of bleeding complications. Color Doppler sonography is also suitable for evaluating vessel course in children and adults [2, 10 – 12]. The use of ultrasound contrast agents could result in significant improvement of the detectability of aberrant renal vessels compared to Doppler sonography alone [12]. However, the known limitations of sonography [13] are still present in this method. To date, ultrasound contrast agents have been used off label in children [14, 15]. In addition to Doppler sonography supplemented by contrast-enhanced sonography, CT angiography and MR angiography with and without contrast agent are available as noninvasive methods for vessel detection [2, 10, 12, 16, 17]. Improvements in CT technology have resulted in the spatial resolution of CTA being as good as or better than that of MRA [17]. However, radiation exposure continues to be a disadvantage of CTA compared to MRA and rules out use in children and adolescents. MRI with contrast-enhanced MRA can visualize vessels with a lumen of up to 1 mm [18]. However, to date there are only a few studies that have examined the usefulness of MRI with contrast-enhanced MRA in the detection of aberrant renal vessels in children [6, 19]. We took this as an opportunity to check whether preoperative MRI with contrast-enhanced MRA is sensitive enough to reliably diagnose aberrant renal vessels and whether this method is also suitable to provide information about the obstructive effect of an aberrant vessel. Materials and Methods A retrospective, key word-based (ureteropelvic junction obstruction, MRI) data analysis in the RIS from 2007 – 2013 was performed. The diagnostic report and image material of the MRI examination were then analyzed to determine whether an aberrant vessel is present and whether this vessel has an obstructive effect on the pyeloureteral junction. To answer this question, the relationship between the aber-
rant vessel and the pyeloureteral junction in the angiography series (source images) was analyzed. In addition, the source images of the angiography sequences were compared to the coronal T2-weighted STIR (or T2 FS) sequence and to the acquired maximum intensity projections (MIPs). Based on the literature [5, 20], a vessel was classified as obstructive if located in the immediate vicinity (<2 mm) of the signal-free renal pelvis in the angiograms. The OR reports for children having undergone surgery due to ureteropelvic junction obstruction including the histological finding of the OR specimen were then viewed and the preoperative MRI finding was compared to the intraoperative finding. The histological finding of the OR specimen (pyeloureteral junction) was viewed to determine whether the ureteropelvic junction obstruction had a largely intrinsic or largely extrinsic cause (in our case a vascular stenosis). To evaluate the success of the surgery, the postoperative renal pelvis width was then evaluated with ultrasound (criterion: reduction in the severity of the urinary flow disturbance by at least 1 degree) and the evaluation of the urodynamics (postoperative scintigraphy).

**Examination preparation and implementation**

In children in whom anesthesia was not necessary for the MRI examination, no special preparation (additional fluid administration) was performed. If anesthesia was necessary, food and fluids were administered according to the protocol for anesthesia in children typically used at our hospital (fasting for 4–6 hours depending on age, clear liquid (tea) up to 4 hours prior to the administration of anesthesia). Intravenous administration of furosemide and additional fluid administration (infusion) were not performed. Under consideration of the typical contraindications, Dotarem (dose: 0.1 mmol/kg body weight) was administered intravenously in children under the age of 2 and Gadovist (dose: 0.1 ml/kg body weight) was administered in children over the age of 2. Injection was performed in all children manually via an indwelling venous cannula 22 GA (0.9 × 25 mm) over a period of approx. 10 s with subsequent injection of 10 ml NaCl 0.9%, total injection time approx. 15 s.

Angiography was started after prior acquisition of an unenhanced sequence immediately following injection and comprised 3 immediately consecutive measurements (arterial, venous, and parenchymal phase, total time 48 s) possibly supplemented by late acquisitions (Table 1).

All MRI examinations were performed using a 3-Tesla unit (Trio-Tim, Siemens, Erlangen, Germany). The initial evaluation of the MR examinations was performed in real time with the examination by a radiologist with a sub-specialization in pediatric radiology and multi-year experience. The retrospective image analysis was also performed by an experienced radiologist with a sub-specialization in pediatric radiology and corresponding expertise. There was only one different result between the two evaluators. The first and second interpretations in all other cases were in agreement.

Surgery was performed by 2 pediatric surgeons with multi-year pediatric urology experience. An Anderson-Hynes pyeloplasty is performed laparoscopically with resection of the pyeloureteral junction and anastomosis upstream from the vessel with retention of the same. This method is the method of choice in the case of ureteropelvic junction stenosis according to the guidelines of the German Society for Pediatric Surgery http://www.awmf.org/uploads/tx_szleitlinien/006–064.pdf.

The indication for surgery was determined on the basis of the obstruction detected on MAG3 scintigraphy, an increasing restriction of renal function by at least 5% and a restriction of renal function to less than 43%. Significant hydronephrosis, unilateral monstrous hydronephrosis (>5 cm), significant (>3 cm) bilateral hydronephrosis and a febrile urinary tract infection are also an indication for surgery [21]. All children underwent pre- and postoperative sonography of the urinary tract. The measurement/grading of the urinary flow disturbance was performed according to the specifications of the consensus group of the Pediatric Nephrology Workgroup in cooperation with the Pediatric Urology Workgroup of the German Society for Urology and the Pediatric Urology Workgroup of the German Society for Pediatric Surgery [22] as grade I-IV. The maximum longitudinal, transverse, and depth diameter (on the level of the hilum) of the kidneys and the width of the extrarenal and intrarenal renal pelvis including the calyx width in cross section were determined.

All examinations were performed using two Toshiba sonography units (ApioXG SSA–790A and Apio SSA–770A, Toshiba Medical Systems, Otawa, Japan).

The first postoperative control sonography scan was performed on the first or second day after surgery and then in the case of an uncomplicated further course prior to dis-
charge or after 3 weeks and during removal of the double-J catheter 6 weeks after surgery.
MAG3 scintigraphy was performed together with another sonography scan 3 months after surgery.

Results

In the indicated time period (2007 – 2013) MRI of the kidneys including MRA of the renal vessels was performed preoperatively in 19 children with ureteropelvic junction stenosis (13 boys, 6 girls, 0 – 15 years old, average age: 7.3 years). Preoperative ultrasound showed the morphological image of a grade III-IV urinary flow disturbance in all children with agreement between the ultrasound and MRI finding in 15 of 19 children. The urinary flow disturbance was estimated one degree higher with MRI than ultrasound in 4 children. The examinations were performed either on the same day or the following day.
The results of the preoperative MRA scan of these children are shown together with the intraoperative finding in Table 2.

Of the 14 preoperatively diagnosed aberrant vessels, all vessels except one (false-positive case) were confirmed intraoperatively, yielding a sensitivity and specificity for the detection of an aberrant and obstructing renal vessel of 85 % and 80 %, respectively. All visualized aberrant vessels were solitary arterial vessels originating from the aorta. Fig. 1 shows a sample image of an aberrant lower pole vessel originating from the abdominal aorta in the case of a right ureteropelvic junction stenosis.

Diplogenesis with dilation of the lower system was only seen once. In addition to the accessory lower pole artery causing the obstruction, two further accessory pole arteries were seen in the upper region originating from the aorta. Additional redundant renal arteries could be described in 3 children in addition to the obstructing vessel on the opposite side with only one urodynamically irrelevant grade I urinary flow disturbance being detected on this side both on MRI and ultrasound.
The detection or exclusion of an accessory renal artery via Doppler sonography was not performed.

<table>
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<tr>
<th>Table 2 Comparison of the preoperative detection of an aberrant renal vessel with the intraoperative finding of ureteropelvic junction stenosis, n = 19 children.</th>
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<td>preoperative MRI finding</td>
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<td>14 aberrant vessels including obstructive effect preoperatively assumed in 12 children</td>
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<td>1 × detection of a vessel but intraoperatively shown to be nonobstructive</td>
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<tr>
<td>1 × vessel preoperatively classified as nonobstructive, confirmed by surgery</td>
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<tr>
<td>1 × aberrant vessel not confirmed by surgery</td>
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<td>5 children without an aberrant vessel</td>
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<td>2 × not operatively confirmed, i.e., aberrant vessel not found intraoperatively</td>
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Fig. 1 A girl (3 months old) with right ureteropelvic junction obstruction caused by an aberrant lower renal artery. a grade 3 pyelectasis, T2-TSE fs cor, b MRA with maximum intensity projection, the aberrant lower pole vessel is leaving the aorta and has a stretched course (with arrow).

Fig. 2 A 2-year-old boy with grade 4 pyelectasis of the left side. In the MRI before operation, an aberrant lower pole vessel was found and an obstructive effect of the vessel was assumed. a Grade 4 pyelectasis; T2-TSE fs cor; b MRA with maximum intensity projection shows the aberrant lower pole vessel (arrow). The course of the vessel is not stretched but curved and at a distance from the uretero-pelvic junction.
Aberrant renal arteries are found in children with ureteropelvic junction stenosis in 18–28% or 49% [2, 3, 23]. The incidence of obstructive and aberrant vessels increases with age [2, 23]. Stenosis caused by an aberrant or obstructive vessel manifests later in childhood than stenosis caused by intrinsic factors [3, 23] with the obstructive effect of the vessel often being intermittently present [23].

The goal of our study was to evaluate whether MRI with contrast-enhanced MRA is capable of detecting aberrant renal arteries in children with ureteropelvic junction stenosis and whether it is ideally also possible to evaluate the obstructive effect of these vessels on the pyeloureteral junction via MRI/MRA without functional MR urography.

Of the 19 children who underwent surgery, an aberrant renal artery was able to be diagnosed preoperatively in 14 children via MR angiography. There was no aberrant renal artery in 5 of these 19 children. All preoperatively diagnosed vessels except for one were found intraoperatively and a negative MRA finding was confirmed by surgery in 3 cases. An aberrant pole artery that was not detected preoperatively was found in only 2 children. Therefore, it can be determined that with our examination protocol and at a field strength of 3.0 Tesla contrast-enhanced MRA can detect aberrant renal arteries in children with ureteropelvic junction stenosis with a high sensitivity (85%) and sufficient specificity (80%).

As initially described, the identification or exclusion of an aberrant vessel ensures the indication for surgery and reduces the risk of intraoperative bleeding. Accordingly, exact knowledge of the vascular supply of the child’s kidneys is extremely important for surgery. Therefore, it is desirable to obtain exact information about the vascular anatomy of the kidneys via imaging methods. Due to the lack of ionizing radiation, sonography and MRI with MRA are suitable for this purpose in children. Vessel visualization via CT angiography has a sensitivity of 97% and a specificity of 92% [20] for the detection of aberrant renal vessels in adults.

The advantages of CT angiography with modern equipment and corresponding examination protocols (narrow collimation) are the very high spatial resolution and very short examination time so that motion artifacts due to breathing and the proximity of the renal arteries to the aorta can be reduced [17]. In addition, corresponding post-processing programs with 2D and 3D reconstructions increase the value of CT [24]. However, despite the application of dose-optimized protocols, the main disadvantage of CT angiography is the exposure to ionizing radiation [25], so that this method should not be used in children to clarify questions regarding an accessory renal vessel. Moreover, the application of contrast agent containing iodine with known side effects is required [17, 24].

In children, Doppler sonography achieves a sensitivity of 92.8% and a specificity of 76.5% [2]. Another study found that children with decompensated ureteropelvic junction stenosis have a significantly higher resistance index (RI) on the obstructed side than on the healthy side and these parameters normalize after surgery. These asymmetrical RI values with a pathologically increased RI on the obstructive side compared to the healthy side also developed in the case of worsening of the flow situation. However, the RI can also be influenced by heart rate, anemia, and inflammatory hyperemia [10]. As a rule, sonography depends on the experience of the examiner and the method is not readily accepted by people who are not familiar with the method [13]. In contrast, MRI with MRA is examiner-independent and provides clear and highly reproducible image material so that it makes sense to use this method for detecting aberrant renal vessels. The method provides the surgeon with images that are more familiar and more closely resemble the anatomy than those provided by sonography.

In principle, MR techniques with and without contrast agent can be used for vessel visualization. The unenhanced MR angiography techniques (arterial spin labeling with steady-state-free precession technique) that can be used for renal vessel visualization are sensitive to magnetic field inhomogeneities and a high background signal and typically require longer examination times than contrast-enhanced MR angiography [16]. However, contrast-enhanced MRA has a shorter examination time, is less susceptible to flow and motion artifacts, and can better suppress the background signal (subtraction sequence before and after contrast enhancement). In addition, the renal pelvicalyceal system and ureter can be better visualized after contrast enhancement. However, the coordination between the start of the sequence and the administration of the contrast agent can be problematic with the bolus arriving either too early or too late [17]. The need to administer gadolinium-containing contrast agents with the risk of nephrogenic systemic fibrosis is also a problem in corresponding high-risk patients that does not exist in the case of unenhanced MRI techniques.

A study [26] including 30 patients aged 14–73 years achieved a sensitivity and specificity of 100% for the detection of aberrant obstructing renal vessels via MRI and contrast-enhanced MRA. These results could not be reproduced by other investigators. Zamparelli [19] et al. examined 14 children with hydronephrosis with highly T2-weighted HASTE sequences in coronal angulation with a slice thickness of 5 mm and fat suppression but without contrast agent on a unit with a field strength of 1 Tesla and were able to detect an aberrant vessel in 4 children. The sensitivity was 80%. Without contrast-enhanced MRA, this study may not be sufficiently sensitive for vessel visualization.
In a study comparable with the present study, Calder [6] et al. examined 14 children aged 6–15 years on a 1.5 Tesla unit and used highly T2-weighted coronal TSE sequences in 3D technique and for angiography they used T1-weighted, fat-suppressed 3D gradient sequences (VIBE). In addition, MIPs were created from these sequences. The analysis was performed on a 3D workstation [6]. An aberrant vessel could be detected preoperatively by MRA in 9 children, while no vessel could be detected prior to surgery in 5 children. All findings were confirmed by surgery. Even if comparison of the results of the two studies does not yield complete agreement, there is satisfactory congruence between the results.

In patients with ureteropelvic junction stenosis, histopathological changes (fibrosis, anomalies of the arrangement of the muscle fibers, hypertrophy of the smooth musculature, collagen deposits, inflammatory processes) could be detected in the pyeloureteral junction [27]. The penetration of urine via an epithelium defect with consecutive migration of mastocysts into the mucosa with resulting tissue reaction leading to fibrosis is assumed as the cause of these changes [28]. According to another hypothesis, changes in the neuuropeptides or neurotransmitters with an increase in the muscle-stimulating neurotransmitter endothelium E1 play a role in ureteropelvic junction stenosis. Therefore, it could be shown that this transmitter is elevated in rats with ureteropelvic junction stenosis [28].

These histological changes are apparently the result of a not yet clarified complex process and are less common in patients with aberrant vessels crossing the pyeloureteral junction than in patients with a ureteropelvic junction stenosis without a crossing vessel so that it is assumed that the obstructing effect of the vessel varies [27].

In addition to the detection of an aberrant vessel, preoperative information regarding the obstructing effect of the vessel is important. This effect can be derived from the proximity of the vessel to the pyeloureteral junction. A vessel was viewed as obstructive in the present study if located in the immediate vicinity (distance of <2 mm) of the pyeloureteral junction. In particular, the coronal T2-weighted images and the MRA images (original images and MIPs) were used for this observation.

Other authors proceeded in the same manner [2, 5, 6, 20]. In CTA a distance of 2 mm from the pyeloureteral junction was viewed as significant with regard to an obstruction [5, 20].

Calder et al. [6] interpret the immediate proximity of the vessel and ectatic renal pelvis as an indication of an obstruction and also state that detection of a vessel does not necessarily mean that this is the only cause of the obstruction. Zamparelli et al. [19] do not provide any measurements for classifying a vessel as obstructive.

Veyrac et al. [2] evaluate a vessel as significant in the case of a urinary flow disturbance if it is detectable on Doppler sonography in the immediate vicinity of the dilated renal pelvis.

All aberrant vessels that we preoperatively classified as obstructive were located in the immediate vicinity of the renal pelvis, i.e., there was practically no measurable distance between the renal pelvis and vessel (lumen). If a distance between the vessel and the renal pelvis can be determined, we would set the limit at <2 mm based on the literature.

An obstructive effect that could not be confirmed intraoperatively was assumed preoperatively in only one child. This may be the result of varying states of hydration with good filling of the renal pelvicalyceal system at the time of MRI examination and less good filling at the time of surgery. For this reason it seems advisable to use the recommendation of Stenzel et al. [9] in the future (i.v. application of a neutral crystalloid solution with a dose of 20 ml/kg body weight beginning 60 minutes before the examination and continuing with a similar rate during the examination). Other investigators [29] also recommend i.v. fluid administration beginning approx. 30 minutes before the examination.

Other authors assume that there is no imaging method with which the obstructive effect of a vessel on the pyeloureteral junction can be detected because despite detaching and lifting of the vessel (no cutting) with subsequent fixation above the pyeloureteral junction (so-called vascular hitch [30]), the obstruction can remain [31], or because there are cases in which an aberrant vessel is obstructive in the sense of an extrinsic stenosis but there are also histological changes in the pyeloureteral junction that indicate an intrinsic stenosis [32]. These authors therefore recommend performing an intraoperative water load test following immobilization and clamping of the vessel before and after lifting of the vessel to differentiate an extrinsic stenosis caused by the vessel from a stenosis caused by intrinsic factors [32, 33]. At present, MAG3 scintigraphy is the gold standard for functional preoperative evaluation of an obstruction and was therefore used in our patient group. This method entails radiation exposure and should be perspective replaced by an adequate functional MRI examination via which the urodynamics of the urinary system can also be evaluated [29].

The results of the present study show that the immediate proximity of the vessel to the pyeloureteral junction in combination with a scintigraphically detected flow disturbance is already sufficient to postulate an obstructive effect of the vessel. This result is also confirmed by the histological findings of the surgical specimens which showed only mild to moderate changes in the pyeloureteral junction in 11 cases, i.e., stenosis largely caused by the vessel was present. On the other hand it cannot be ruled out that the obstructive effect of the vessel can cause histological changes even in the pyeloureteral junction. As a result it could be proven that in the case of the presence of an obstructing vessel histological changes can be additionally seen in the pyeloureteral junction that are less pronounced than in the case of a stenosis caused by intrinsic factors [27]. This suggests that the aberrant vessel either triggers or increases an intrinsic stenosis [2, 3, 6].

A larger number of patients would have resulted in a more valid statement regarding vessel detection. Therefore, the relatively small number of examined children together with the retrospective character of the study are the limitations of the present study.

**Conclusion**

MRI is capable of visualizing aberrant renal vessels with high sensitivity and sufficient specificity without the ioniz-
ing radiation of contrast-enhanced MRA in an examiner-independent manner and with reproducible image material. The results of this study also show that MRI with contrast-enhanced MRA is capable of verifying the obstructive effect of an aberrant pole vessel in ureteropelvic junction stenosis on the basis of a close spatial relationship in connection with a suitable functional method (MAG3).

Clinical Relevance of the Study
As a result of contrast-enhanced MRA, the close proximity of the vessel to the pyeloureteral junction can be visualized in a reproducible manner and with high sensitivity so that an obstructive effect of the vessel can be determined.

Detection of an aberrant and obstructive renal vessel in children contributes to the determination of indication for surgery in children with ureteropelvic junction stenosis, primarily in cases with varying findings of urinary flow disturbance. Knowledge of the vessel anatomy is important for the surgical procedure, particularly in the case of minimally invasive interventions. It helps to avoid complications.

References

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