**Aims & Scope**

Childhood Kidney Diseases (Child Kidney Dis; formerly Journal of the Korean Society of Pediatric Nephrology; ISSN 1226-5292, launched in 1997), the official journal of the Korean Society of Pediatric Nephrology, is a local peer-reviewed journal. It aims to improve kidney health in children and adolescent by covering clinical, and research works relevant to all aspects of pediatric nephrology. Its expected readers are clinicians and researchers around the world, although it has a particular focus on pediatric patients in Asia. Its publication types include reviews, original articles, case reports, editorials, and letters to the editor. The journal aims to serve pediatricians through the prompt publication of significant advances in pediatric nephrology and to rapidly disseminate recently updated knowledge to the public. Additionally, it will initiate dynamic, international, academic discussions concerning the major topics related to pediatric nephrology.

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Management strategies for congenital isolated hydronephrosis and the natural course of the disease

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Congenital isolated hydronephrosis encompasses a spectrum of physiologic states that spontaneously resolve and pathologic obstruction that necessitates surgical intervention. Distinguishing patients whose condition will resolve, those who will require stringent follow-up, and those who will eventually need surgical intervention present a challenge to clinicians, particularly because no unified guidelines for assessment and follow-up have been established. The recognition of the natural course and prognosis of hydronephrosis and a comprehensive understanding of the currently proposed consensus guidelines may aid in multidisciplinary treatment and in providing proper counseling to caregivers. In this review, we aimed to summarize the literature on the grading systems and management strategies for congenital isolated hydronephrosis.

Keywords: Congenital; Hydronephrosis; Ureteral obstruction

Introduction

Hydronephrosis refers to dilatation of the renal collecting system due to a build-up of urine resulting from drainage problems. Congenital hydronephrosis occurs in up to 1%–5% of all pregnancies [1,2]. More than half of the cases are transient and physiologic, whereas other cases are caused by disorders of the ureteropelvic junction (UPJ) including intrinsic stenosis (10%–30%), vesicoureteral reflux (VUR; 10%–30%), and congenital anomalies leading to secondary dilatation of the urinary tract [1,3,4]. To date, studies have shown that low-grade isolated hydronephrosis usually resolves during the first few years of life [5,6], whereas high-grade hydronephrosis requires intervention to prevent the progression of obstruction or deterioration of renal function [7].

Distinguishing children who require follow-up or intervention, determining the possibility of resolution and the time to resolution, deciding about performing pyeloplasty to relieve the obstruction and determining the timing of the procedure, and preserving the patient’s renal function are crucial issues for both clinicians and family members. To stratify the risk of early surgical intervention or the possibility of resolution, attempts have been made to create a unified grading system for urinary tract dilatation that can be used during the prenatal or postnatal period; however, no definitive consensus guidelines have been established to date [8].

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In this review, we aimed to summarize the literature (to date) on the proposed grading systems and management strategies for congenital isolated hydronephrosis, as well as to describe the natural history.

Detection and classification–grading systems

Currently, no standardized protocol exists for defining, classifying, and grading congenital hydronephrosis. Different terminologies with overlapping meanings are used to describe the status of dilatation (e.g., pelviectasia, pelviectasis, hydronephrosis, and urinary tract dilatation), and different clinicians from different subspecialties (e.g., pediatric urology, pediatric radiology, pediatric nephrology, and obstetrics) may use the terms to refer to similar conditions [9,10]. Consequently, several grading systems have been developed, leading to the use of various nomenclatures and causing a misunderstanding between the radiologist and the clinician [1]. In this context, we will review the most widely used and the recently proposed grading systems aimed at providing a unified classification during the perinatal period, including their validation in the literature.

Society for Fetal Urology classification

In 1993, the Society for Fetal Urology (SFU) proposed a 5-point numeric grading system (0–IV) based on the postnatal appearance of the renal pelvis, calyces, and renal parenchyma on ultrasonography (USG) images (Fig. 1) [6,2]. The SFU classification remains the most widely used grading system owing to its intuitiveness and ease of use, especially in cases of isolated hydronephrosis. However, interobserver and intraobserver variabilities exist owing to the nature of morphologic classification. Furthermore, since it was not originally developed for use in antenatal evaluation, it has not been widely adopted in subspecialties other than pediatric urology radiology (e.g., obstetrics and neonatology).

Grading based on the anteroposterior pelvic diameter

Anteroposterior pelvic diameter (APD) measurement, obtained from a transverse section of the renal hilum, is also widely used by itself or in conjunction with SFU grading. APD is an objective quantitative parameter widely used as a predictor of pathology and outcome, as well as of the resolution of the condition or the need for an intervention [1,8,13]. However, it also has limitations. Because APD measurement does not provide descriptive details of the renal parenchyma, calyces, ureter, and lower urinary tract, it does not accurately reflect the degree of hydronephrosis according to different renal pelvic configurations. Some studies argue that there is no threshold separating nonobstructive from obstructive dilatation of the kidney because renal dilatation is affected by many factors (e.g., hydration status, bladder filling, position, and respiration of the patient) giving its dynamic character [11,14]. Because of the advantages and disadvantages of both grading systems, SFU grading and APD measurement are commonly used together complementarily in clinical practice. As the authors have previously demonstrated, in cases showing a discrepancy between morphologic classification and APD measurement (i.e., higher grade in the SFU classification than that based on APD measurement), the resolution time should be predicted using the APD measurement rather than the SFU grade [15]. This is because normalisation of morphology occurs before improvement in the APD measurements.

<table>
<thead>
<tr>
<th>SFU grade 0</th>
<th>SFU grade I</th>
<th>SFU grade II</th>
<th>SFU grade III</th>
<th>SFU grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no splitting</td>
<td>Urine in the pelvis barely splits the sinus</td>
<td>Urine fills the pelvis, major calyces dilated</td>
<td>Uniformly dilated minor calyces, parenchyma preserved</td>
<td>Parenchymal compromise with thinning</td>
</tr>
</tbody>
</table>

Fig. 1. Society for Fetal Urology (SFU) hydronephrosis grading system. The SFU grading system is based on the degree of renal-pelvic and calyceal dilatation seen on renal ultrasonography images and the integrity of the renal parenchyma [12].

Urinary tract dilatation classification system

The urinary tract dilatation (UTD) classification system was developed in 2014 as a collaborative effort among eight different medical and surgical societies (American College of Radiology, American Institute of Ultrasound in Medicine, American Society of Pediatric Nephrology, SFU, Society for Maternal-Fetal Medicine, Society for Pediatric Urology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound) in an attempt to establish a standardized and simplified description of hydronephrosis that can be consistently applied across specialties for prenatal and postnatal evaluation and management [13]. This classification includes parameters such as the APD of the renal pelvis (normal, <10 mm), presence of central and peripheral calyceal dilatation, renal parenchymal abnormalities, ureteral abnormalities, and bladder abnormalities in two antenatal (UTD-A1 and UTD-A2) and three postnatal (UTD-P1, UTD-P2, and UTD-P3) categories (Fig. 2). This system is intended to stratify the risk of postnatal uropathies and the clinical outcomes and to conduct a cost-effective evaluation in high-risk patients rather than being a mere descriptive grading system [17]. However, the system may also cause confusion because the classification suggests the general term “urinary tract dilatation” to indicate all types of ureteral and kidney dilatation, including UPJ obstruction (UPJO), ureterovesical junction-type hydronephrosis, VUR, bladder pathologies, and posterior urethral valve formation. Its additional limitations include interrater discrepancy in the assessment of calyceal dilatation, the wide range encompassed by the UTD-P3 grade, and the complexity and time-consuming nature of its application in real clinical practice [11]. Nonetheless, some studies have validated the usefulness of the UTD grading system in predicting the need for surgical intervention or predicting urinary tract infection by showing a relationship between UTD grade and clinical outcomes [17–24].

Onen grading system

The Onen system was developed in 2007 for the assessment of prenatal and postnatal hydronephrosis with UPJ pathology, with emphasis on the quality of the renal parenchyma, and was updated in 2016 [12,25]. It is based on nonsubjective parameters (presence of dilatation of the pelvicalyceal system and quality of the renal parenchyma based on exact criteria [Fig. 3]) although the system is not widely used because of low recognition by practitioners, a few groups have recently reported its low subjectivity with a decreased interobserver agreement in Onen grades 2 to 3 [26,27].

Among the aforementioned grading systems, the SFU classification of congenital hydronephrosis seems to remain the
most widely used classification system by clinicians owing to familiarity and established practice patterns, followed by APD measurement and the UTD system [17,28,29].

Risk-based management and follow-up plan after birth

As previously mentioned, no universal guideline exists on the frequency and timing of USG examination and the required duration of follow-up. In addition, heterogeneity in clinical management exists among pediatric radiologists, pediatric urologists, and maternal-fetal obstetricians, partly because of the lack of prospective studies and different practices across different centers [10]. This section will cover the postnatal management of congenital hydronephrosis according to the current literature in the context of clinical decision-making (Fig. 4).

For unilateral hydronephrosis, postnatal evaluation should begin within the first week (after the second day, usually from the fifth to seventh days, to ensure adequate hydration) of life using renal USG. For bilateral hydronephrosis, early postnatal imaging is recommended. After the initial evaluation, follow-up and management are stratified according to severity, as assessed using the aforementioned grading systems.

In cases of known pretreatment hydronephrosis that show normalization on the first postnatal USG, the follow-up may be terminated. However, 15% to 45% of patients with normalized initial USG results show abnormal USG results on follow-up, suggesting the need for a second USG examination at 1 to 6 months of age (varying among studies) [31]. In the case of mild hydronephrosis (generally grade I and unilateral grade II in SFU grading and UTD-P1), observational studies anecdotally recommend less aggressive imaging follow-up [8,31], or no further follow-up [32], owing to the nature of spontaneous resolution during the first 2 to 3 years [8,29,31]. Irrespective of the suggestions, an APD of approximately 10 to 20 mm (cutoff value may vary among studies) can be managed conservatively [14,15,34]. Follow-up evaluations using USG after 3 to 6 months for the first year, every 6 months until 3 years, and every 1 to 2 years thereafter for (or according to the symptoms (flank pain, dysuria) artificated by the patient) are usually recommended [8,34,31]. Although extremely rare, late worsening after spontaneous resolution can occur in some patients (1%–5%) in a few months (up to 5–6 years) [35], even in patients with mild congenital hydronephrosis [12,36]. Clinicians should be aware of this possibility and educate the patients and caregivers about the possible need for follow-up imaging in intervals (varying from 1 to 6–12 months among studies) after resolution or when symptoms such as abdominal pain and urinary symptoms appear [18,34,36–38]. For moderate hydronephrosis with an intermediate risk of progression (bilateral SFU grade II, SFU grade III, and UTD-P2), a second USG examination is recommended in the first month and every 1 to 3 months thereafter, during the first year, depending on the stability of the patient’s condition. For the next 2 years, follow-up every 6 months is recommended. Annual follow-up or follow-up according to the symptoms (flank pain and dysuria) artificated by the toddler until 6 years is also recommended [8,34,31]. Diuretic renal scan (DRS), which can be performed from 6 to 8 weeks of age, is the most commonly used modality for assessing the presence of upper urinary tract obstruction in infants. It is usually recommended when two renal USG examinations, during at least 3 months, show no improvement or suggest the aggravation of moderate hydronephrosis. The indications for voiding cystourethrogram (VCUG) include bilateral hydronephrosis, ureteral dilation, abnormal renal echogenicity, and abnormal appearance of the bladder, which are suggestive of lower urinary tract disease (e.g., posterior urethral valve or VUR) [4]. However, the decision to recommend DRS or VCUG is dependent on the clinician’s discretion because less invasiveness and cost-effectiveness in evaluation are recently being emphasized, supported by the fact that most patients remain asymptomatic without severe pathology [8,31]. Duong et al. [39] suggested that DRS should only be performed in patients with APD <30 mm, major calyceal dilation (>10 mm), or renal parenchymal thinning and emphasized the need for more conservative management among patients with mild-to-moderate hydronephrosis. For severe, high-risk hydronephrosis (SFU grade IV, UTD-P3), USG examination should be repeated at 1 month, followed by DRS at age 6 to 8 weeks [8,31]. The possibility of a later follow-up using USG examination and DRS/VCUG depends on the results of second USG with DRS, and the plans for surgery. The index of obstructive uropathy (UIO) and the indications for surgical intervention will be addressed later.

Natural course of isolated hydronephrosis

According to existing studies, >50% to 70% of all cases of isolated hydronephrosis resolve regardless of the grade [5,6,15,40]. The resolution rate differs according to the baseline severity of hydronephrosis. Prior studies on low-grade hydronephrosis (SFU grades I–II and APD <10–20 mm) showed resolution or improvement in 56.0% to 97.4% of cases, implying a benign condition [6,41,42]. Elmaci and Donmez [11] evaluated the congenital hydronephrosis’ time to resolution in patients with APD <20 mm; those with APD >30 mm showed complete resolution in a median of 5 months, whereas those with an APD of 10 to 20 mm showed complete resolution in a median of 11 months. In addition, cumulative resolution rates were reported by several prospective and retrospective studies. In a prospective study, Braga et al. [19] reported the cumulative resolution rate at 3 years for each grade in the SFU and UTD systems (98% for SFU I, 87% for SFU II, 76% for SFU III, and 56% for SFU IV; 90% for UTD-P1, 81% for UTD-P2, and 71% for UTD-P3). In addition, the authors previously reported the cumulative resolution rates

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**Table:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>No dilatation, normal renal parenchyma</td>
</tr>
<tr>
<td>II</td>
<td>Mild dilatation, normal renal parenchyma</td>
</tr>
<tr>
<td>III</td>
<td>Moderate dilatation, normal renal parenchyma</td>
</tr>
<tr>
<td>IV</td>
<td>Severe dilatation, abnormal renal parenchyma</td>
</tr>
</tbody>
</table>

**Fig. 3.** Oten grading system. The diagram summarizes the Oten grading system, reflecting the 2016 update on grades 3 and 4 [34]. APD, anteroposterior pelvic diameter.

**Fig. 4.** Suggested follow-up and management strategies for congenital isolated hydronephrosis. The diagram summarizes the proposed guidelines from the literature: USG, ultrasonography; SFU, Society for Fetal Urology; UTD, upper tract dilatation; DRS, diuretic renal scan; VCUG, voiding cystourethrogram; prn, pro re nata.
of isolated hydronephrosis at 2 years in a retrospective study (81.7%, 65.6%, 37.6%, and 5.2% for SFU grades I, II, III, and IV, respectively [53]. Among cases of high-grade hydronephrosis associated with UPJ stenosis, approximately 27% show resolution, >50% remain stable, and the rest progress with possible renal function deterioration [5]. Surgical intervention has been required in approximately 25% of all cases, ranging from 5% to 50% depending on the study [15,43-46]. Therefore, after at least 2 to 3 years of watchful observation and evaluation, termination of follow-up may be possible since the outcome would be determined within these years.

### Prediction and decision of intervention

Disagreements about the definition of obstruction and the indications and timing of surgery in hydronephrosis due to UPJO remain. The appearance of symptoms of UPJO, such as pain and urinary tract infection, is indicative of the need for surgery. A differential renal function of >40% with impaired drainage (T½ >20 minutes) on DRS or a >10% deterioration of renal function on a serial renal scan is also generally considered a surgical indication [6,31,38,49].

Additional studies have presented the predictors of surgery and their corresponding cutoff values, including initial postnatal APD. cortical tissue transit time on DRS, renal pyramidal thickness, and renal parenchyma-to-hydronephrosis area ratio (PHAR) [34,47-51].

### Initial postnatal APD

Postnatal APD has been widely used as an index for evaluating and anticipating the presence of obstruction, with advantages of wide availability and absence of radiation exposure. In clinical practice, sequential changes in APD are mainly used to determine management plans. Although no absolute cutoff value of APD for performing pyeloplasty has been defined, several studies suggested different APD values, ranging from 15 to 30 mm, as significant predictors of surgical intervention [3,4,35,39,52]. Arora et al. [47] performed a prospective multi-variate analysis and showed that an APD of up to 24 mm in the first week after birth can predict the need for surgical intervention (sensitivity, 73.1%; specificity, 88.0%). The prospective cohort studies of Coelho et al. [39] and Dias et al. [34] suggested an APD of >15 and 18 mm as the cutoff value, respectively.

### Delayed tissue transit time in 99mTc-mercaptoacetyltriglycine DRS

Some recent studies have shown that delayed tissue transit time, which is defined as an absence of activity in the subcortical structures or in the pelvis on a 99mTc-mercaptoacetyltriglycine (MAG3) DRS within 3 or 8 minutes of tracer injection, can predict deterioration of UPJO in pediatric populations [5,53-55]. Song et al. [56] proposed that delayed tissue transit time on 99mTc-MAG3 DRS is a significant predictor of renal function improvement after pyeloplasty in patients with UPJO. Therefore, they suggested that delayed tissue transit time should be considered a candidate predictor of immediate pyeloplasty and decreased differential renal function.

### Renal pyramidal thickness

The renal pyramid is the first portion of renal parenchyma that becomes affected in high-grade hydronephrosis. The pyramidal thickness changes with age, making its clinical application difficult in a growing child. In contrast, the renal pyramid is a part of the parenchyma that grows slowly and shows only small changes in the first 9 years of life; thus, it is a feasible parameter for evaluation and comparison between serial USG images [57]. Pyramidal thickness measurement was not previously performed in patients with hydronephrosis until Hodhod et al. [58] measured pyramidal thickness in the supine position in the middle-third of the sagittal plane. In their study, multivariate analysis showed that a renal pyramidal thickness of ≥3 mm (sensitivity, 98.1%; specificity, 89.7%) predicted the need for surgical intervention.

### Renal PHAR

Some studies have attempted to simultaneously measure the renal parenchymal volume and the grade of hydronephrosis using USG (without a renal scan) as a surrogate of renal function in patients with hydronephrosis [49,58]. In this regard, Rickard et al. [49] showed that the renal PHAR predicted the need for surgery (cutoff value, >0.5) in high-grade hydronephrosis (area under the receiver operating characteristic curve, 0.86; P <0.001) more efficiently than the APD measurement, SFU grade, and UTD classification.

### Risk of urinary tract infection

Observational studies have shown that patients with moderate or severe hydronephrosis show an increased incidence (13.8%–40.0% for moderate-to-severe hydronephrosis vs. 4.2%–14.0% for mild hydronephrosis) of urinary tract infection [25-61]. Patients with hydronephrosis with obstructive drainage patterns on renal scans, without VUR, have a higher risk than those without obstructive patterns [61-63]. Furthermore, in terms of benefits of antibiotic prophylaxis, different outcomes have been reported. Braga et al. [64,65] demonstrated a protective effect of antibiotic prophylaxis, especially in patients with high-grade hydronephrosis, in their systematic review and meta-analysis, whereas Estrada et al. [66] showed significant improvement in infection after prophylaxis even in patients with mild hydronephrosis. In clinical practice, the use of prophylactic antibiotics remains nonuniform owing to the absence of recommendations or guidelines from randomized control studies [67,68]. An ongoing randomized control trial on hydronephrosis with UPJO-like and non-refluxing megaureter by Braga et al. (Clinical Trials Registry no. NCT01410536) might aid in elucidating the effect of chemoprophylaxis. Therefore, clinicians are currently advised to decide whether they want to make use of antibiotics on a case-by-case basis while keeping in mind that high-grade hydronephrosis may confer an increased risk of urinary tract infection.

### Conclusions

Predicting the natural course of prenatally detected hydronephrosis has become possible with increasing knowledge and accumulated outcomes from cases treated with surgical intervention. Since no definite consensus exists about using a certain grading system in clinical practice, a practical, user-friendly system, combined with the use of an objective imaging modality that is generally accepted by multidisciplinary specialists, is needed. Furthermore, the establishment of the timing of the initial evaluation and follow-up intervals according to disease severity can aid in efficient management and help inform the caregivers and patients about the prognosis and follow-up plans.

### Conflicts of interest

Joo Hoon Lee is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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### Author contributions

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Project administration: YSP
Visualization: SHS, HMY, YAC, DHM
Writing—original draft: JHL
Writing—review & editing: JHL, YSP, KSK

All authors read and approved the final manuscript.

### References


BK polyomavirus (BKPyV) is a non-enveloped double-stranded DNA virus that was first isolated from a kidney allograft recipient and described in 1971 [1]. More than 90% of the general population is infected with this virus [2]. Primary infection of BKPyV usually occurs subclinically during childhood, and the virus remains in a latent state in the uroepithelium and renal tubular epithelial cells. Upon immunosuppression, BKPyV is reactivated, leading to tubular cell lysis and viruria. One-third to one-half of those who show viruria (>10^8 copies/mL) develop BKPyV-DNAemia after 2 to 6 weeks along with tubulointerstitial lesions; half of these patients develop BKPyV-associated nephropathy (BKVAN) after another 2 to 6 weeks, especially if plasma BKPyV loads are >10,000 copies/mL.

BKVAN occurs more commonly with more potent immunosuppression, and it is currently one of the most important causes of kidney allograft failure [3-5]. In addition, this virus is associated with ureteral stenosis and hemorrhagic cystitis [6]. Moreover, sporadic cases of pneumonitis, retinitis, colitis, capillary-leak syndrome, liver disease, meningoencephalitis, encephalitis, hemophagocytic syndrome, and urothelial cancer caused by BKPyV have been described [7]. BKVAN has a poor prognosis, and it has currently no treatment.

**Epidemiology**

BKVAN usually occurs within the first 2 years after kidney transplantation (KT). Viruria is first noted in 30% to 40% of KT recipients, with decoy cells positive in 20% to 30%, detectable BKPyV-DNAemia in 10% to 20%, BKVAN in approximately 10%, and graft loss from BKVAN in approximately 5% [8-11]. Interestingly, BKPyV viruria is identified in only 10% of immune-competent hosts; however, its prevalence is 30% to 60% in immuno-
compromised hosts. In addition, BKPyV-DNA clearly within 2 to 12 hours after allograft nephrectomy for BKVAN, implying the presence of replication foci in the kidney allograft. BKPyV-DNAemia is associated with worse outcomes after KT [7]. The 36-month graft survival rate if BKPyV is detected within 6 months post-KT is 79%, compared with 90% in controls [12]. Risk factors for BKVAN include tacrolimus use, potent immunosuppression, acute graft rejection, male gender, old age, younger age for children, delayed graft function, use of cadaveric graft, previous transplantation, human leukocyte antigen mismatch, ABO incompatibility, highly sensitized status, history of hemodialysis (vs. peritoneal dialysis), and a ureteral stent [13]. In other solid organ transplantations, BKPyV-related complications are not common, although cases have been reported following heart and lung transplantations [14,15].

In hematopoietic stem cell transplantation (HCT) recipients, hemorrhagic cystitis occurs in up to one-fourth of patients [16,17], 1-month post-HCT [16] and usually lasts more than a month. BKPyV-DNAemia or viruria, which was associated with acute kidney injury, long-term poor kidney function, and mortality, were noted in 18% and 45% of HCT recipients, respectively, in the first 3 months post-HCT [18].

Pathophysiology

The BKPyV DNA is enclosed in a viral capsid comprised of an outer layer of VP1 pentamer and an inner layer of VP2 and VP3 proteins [20]. Its genome is composed of circular dsDNA of approximately 5 kb that contains the early viral gene region, which codes the regulatory large and small tumor antigens promoting cell cycle entry/progression and viral replication, the late viral gene region which codes the viral capsid proteins VP1, VP2, VP3 for entry and assembly of progeny virions, and the non-coding control region [4]. Once infection occurs, BKPyV hijacks the host cell's DNA replication machinery for its own reproduction, hijacking the host cell's DNA replication machinery for its own reproduction, permitting early intervention and preventing progression to nephropathy or allograft loss. For screening, plasma DNA load is measured monthly for 9 months, and then every 3 months thereafter for 2 years after KT [5,22] or when allograft biopsy is performed for surveillance or as indicated and when unexplained allograft dysfunction develops (Fig. 3). BKPyV is suspected when the BKPyV viral load is >10,000 copies/mL with or without serum creatinine level elevation. Histological findings of tubular atrophy, fibrosis, and inflammatory lymphocytic infiltrates need to be differentiated from those of acute cellular rejection. Intraclear BKPyV inclusion bodies suggest BKVAN, which can be identified with special staining of large T antigen [22].

Diagnosis of BKVAN

Diagnosis of BKVAN is confirmed only by allograft kidney biopsy, with features of interstitial nephritis and large T antigen positivity with immunohistochemistry. If the plasma viral load either increases to >10,000 copies/mL in one of two measurements within 3 weeks or is sustained at >1,000 copies/mL in two measurements within 3 weeks, these are considered presumptive or probable BKVAN, respectively, which requires modification of immunosuppression and kidney biopsy if there is a risk of acute rejection and/or impaired kidney function (Fig. 2). Additionally, urine BKPyV viruria >10,000,000 copies/mL or presence of decoy cells indicates possible BKVAN, warranting plasma BKPyV viral load monitoring. If BKVAN is established, immunosuppression needs to be reduced, which can be accomplished even without biopsy confirmation. In 10% to 30% of cases, false-negative results were obtained as biopsy samples were taken early after BKPyV-DNAemia onset, and medullary tissue was not sampled [22].

The pathology of BKVAN is described using the histologic patterns of BKVAN proposed by the 2013 AST-IDCOP. In addition to viral cytopathic changes, acute tubular injury, interstitial nephritis, and severe interstitial fibrosis are denoted as patterns A, B, C, respectively, along with the degree of interstitial nephritis (Table 1) [23]. Meanwhile, the Banff 2017 Working Group Classification takes into account the intrarenal PyV load.

Screening of BKVAN

Since there is no effective treatment for BKVAN, screening for BKPyV is the most important strategy to prevent BKVAN. Recently, the American Society of Transplantation Infections Disease Community of Practice (AST-IDCOP) recommended a monitoring and management strategy for BKVAN (Fig. 3) [7]. Prospective screening of the plasma or urine can identify early viral replication, permitting early intervention and preventing progression to nephropathy or allograft loss. For screening, plasma DNA load is measured monthly for 9 months, and then every 3 months thereafter for 2 years after KT [5,22] or when allograft biopsy is performed for surveillance or as indicated and when unexplained allograft dysfunction develops (Fig. 3). BKPyV is suspected when the BKPyV viral load is >10,000 copies/mL with or without serum creatinine level elevation. Histological findings of tubular atrophy, fibrosis, and inflammatory lymphocytic infiltrates need to be differentiated from those of acute cellular rejection. Intraclear BKPyV inclusion bodies suggest BKVAN, which can be identified with special staining of large T antigen [22].
### Table 1. Histological patterns fo BKVAN according to American Society of Transplantation 2013

<table>
<thead>
<tr>
<th>Factors</th>
<th>Biopsy findings</th>
<th>Risk of graft loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral cytopathic changes</td>
<td>Mild (&lt;25%)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Intestinal inflammation</td>
<td>Minimal (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>Minimal (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>Minimal (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Viral cytopathic changes</td>
<td>Variable (11% to &gt;50%)</td>
<td></td>
</tr>
<tr>
<td>Intestinal inflammation</td>
<td>Significant (11% to &gt;50%)</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>Moderate (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>Moderate (&lt;50%)</td>
<td></td>
</tr>
<tr>
<td>R1: Intestinal inflammation</td>
<td>Moderate (11% to 25%)</td>
<td>25%</td>
</tr>
<tr>
<td>R2: Intestinal inflammation</td>
<td>Significant (26% to 50%)</td>
<td>50%</td>
</tr>
<tr>
<td>R3: Intestinal inflammation</td>
<td>Extensive (&gt;50%)</td>
<td>75%</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Viral cytopathic changes</td>
<td>Variable (sizable)</td>
<td></td>
</tr>
<tr>
<td>Intestinal inflammation</td>
<td>Variable (sizable)</td>
<td></td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>Extensive (&gt;50%)</td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>Extensive (&gt;50%)</td>
<td></td>
</tr>
</tbody>
</table>

**BKVAN, BK polyomavirus-associated nephropathy.** Adapted from Hirsch et al. Ann Transplant [23].

### Table 2. Banff histologic classification system of BKVAN

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCF ci score</td>
<td>BCF ci score</td>
<td>BCF ci score</td>
</tr>
<tr>
<td>pt1</td>
<td>pt2</td>
<td>pt3</td>
</tr>
<tr>
<td>1</td>
<td>0–1</td>
<td>1</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>2</td>
<td>2–3</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>0–1</td>
<td>3</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>2–3</td>
</tr>
</tbody>
</table>

**BKVAN, BK polyomavirus-associated nephropathy.** ci, interstitial fibrosis in cortex; NA, not available.

*The pt scoring is on the basis of the extent of virally induced tubular changes. The overall percentage of positive tubular cross-sections is estimated in the entire biopsy sample (all available cores, cortex, and medulla): pt 1, ≤10% of all tubules/ducts with viral replication, pt 2, >10% to ≤30% of all tubules/ducts with viral replication; and pt 3, >30% of all tubules/ducts with viral replication.*

The Banff ci score evaluates the extent of interstitial fibrosis in cortex: ci 0, ≤5% of cortical area; ci 1, 6%–25% of cortical area (mild); ci 2, 26%–50% of cortical area (moderate); and ci 3, >50% of cortical area (severe). Adapted from Nickelet et al. J Am Soc Nephrol [22].

(extend of virally induced tubular changes with intranuclear viral inclusion bodies and/or a positive immunohistochemistry reaction for SV40 T antigen) and Banff ci scores (Table 2) [22].

These histologic patterns/classes indicate the risks of allograft kidney loss, which range from <10% to >80%. In cases wherein there is evidence of rejection or intimal arteritis, or a positive C4d stain is observed, intensifying immunosuppression to treat rejection should first be considered before treating BKVAN.

### Treatment

#### Reduction in immunosuppression

The first-line management for BKVAN is the reduction in immunosuppressive agents (Fig. 1). Usually, a stepwise approach to reduce immunosuppression is adapted; calcineurin inhibitors (CNI) are initially reduced by 25% to 50%, followed by mycophenolate mofetil (MMF) by 50%, and finally MMF discontinuation if there is no improvement [24]. Another approach is initial MMF reduction by 50%, then CNI reduction by 25% to 50%, and finally MMF discontinuation. Steroids are often limited to prednisolone 10 mg or less, and targets of CNI trough levels are ≤6 ng/ml with tacrolimus and ≤150 ng/ml with cyclosporine. Additionally, mammalian target of rapamycin (mTOR) inhibitors were shown to decrease BKPyV-DNAemia and/or BKVAN [25].

Since cyclosporine and sirolimus, an mTOR inhibitor, inhibit BKPyV replication in vitro, switching immunosuppressants from tacrolimus to cyclosporine, CNI to sirolimus, MMF to sirolimus, or MMF to leflunomide can be considered, albeit with weak evidence [62]. However, reducing or modifying immunosuppression may be inadequate to prevent rejection, whereas excessive immunosuppression will worsen BKVAN and cause allograft dysfunction, tubulointerstitial nephritis, and fibrosis [7]. Therefore, prior to modifying immunosuppression, patient’s immunological risk, viral load, and kidney dysfunction must be considered [26].

#### Other management

No randomized clinical study has proven the efficacy of other adjunctive management aside from modification of immunosuppression.

**Intravenous immunoglobulins.** Intravenous immunoglobulins, which have indirect immuno-modulatory effects, contain high titers of potent BKPyV neutralizing antibodies that can directly neutralize BKPyV activity [5]. For BKVAN, 0.1–2.0 g/kg dose is used.

**Cidofovir.** Cidofovir is a nucleoside analog licensed by the U.S. Food and Drug Administration for the treatment of cytomegalovirus retinitis [23]. Its efficacy in BKVAN is controversial; however, cidofovir concentration in renal tissues and urine is high. Therefore, cidofovir can theoretically be effective against viral infection in the kidneys. Coincidentally, drug-induced anterior uveitis has been reported in 12% to 35% of cases. Cidofovir is given as a low-dose regimen at 0.25–10 mg/kg dose every 2 to 4 weeks, and serum creatinine, white blood cell count, ocular and visual symptoms should be monitored every 2 weeks [24].

**Fluoroquinolones.** Fluoroquinolones, including ciprofloxacin, inhibit BKPyV replication by affecting the helicase activity of the virus-encoded large T antigen [8]. However, in a randomized controlled trial to determine the effectiveness of a 3-month course of ciprofloxacin as BKPyV prophylaxis in KT, ciprofloxacin not only failed to improve the allograft outcome but also increased levels of BKPyV-DNA and incidence of fluoroquinolone-resistant Gram-negative infections [20].

#### Special consideration for children

Similar to other common infections, children often require immunosuppression before primary infection with BKPyV. Therefore, they are more likely to be BKPyV-seronegative, which increases both the risk, severity, and duration of viral replication [31–34]. Thus, children may benefit more from intravenous immunoglobulins administration [35]. If they are BKPyV-seropositive, this measure exposure to BKPyV was a recent event, which is why younger children harbor higher levels of immune effectors. Children with end-stage kidney disease often have urinary tract anomalies, which carry a viral risk reactivation similar to a ureteric stent [31]. In addition, there may be hyperfiltration due to donor–recipient size mismatch in pediatric KT, which may delay the diagnosis of BKVAN [7]. Therefore, screening in children must be extended to a longer period [7].

### Conclusions

BKVAN, although uncommon, threatens allograft survival in KT. Currently, there is no approved and effective treatment for BKVAN. To prevent BKVAN, meticulous screening up to the third year post-KT and appropriate modification of immunosuppression is necessary to improve outcomes.

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.
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Conceptualization: YHA, HGK
Project administration: YHA, HGK
Visualization: YHA, HGK
Writing—original draft: YHA, HGK
Writing—review & editing: YHA, HGK

All authors read and approved the final manuscript.

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Renal involvement in pediatric rheumatologic diseases

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Pediatric rheumatologic diseases are rare systemic diseases that can involve various organs, including the kidneys. Each rheumatologic disease can exhibit characteristic renal involvement, which requires proper treatment and diagnosis. In this review, we discuss renal involvement in classic rheumatologic diseases, including juvenile idiopathic arthritis, Sjogren’s syndrome, systemic sclerosis, and juvenile dermatomyositis. Reviews addressing lupus nephritis and antineutrophil cytoplasmic antibody-associated renal disease are complex and tend to cover a wide array of topics, and thus were excluded from this review.

Keywords: Arthritis, juvenile; Kidney diseases; Rheumatic diseases; Sclerodermia, systemic; Sjogren’s syndrome

Introduction

The kidneys are important target organs involved with systemic disease, which includes rheumatologic disease. The field of pediatric rheumatology originated in the first half of the 20th century and has a relatively short history compared to other medical fields. It started principally with interest in juvenile chronic inflammatory arthritis, the most common childhood rheumatologic disease [1]. Currently, its scope is expanding to address rare disease groups that have recently been elucidated, including autoinflammatory syndrome. Pediatric rheumatologic disease mainly involves various acute and chronic diseases targeting the musculoskeletal system, blood vessels, and other tissues, and is still a significant cause of chronic illness in children worldwide; although it remains among one of the smallest pediatric subspecialties [2]. Pediatric rheumatologic diseases are frequently associated with renal disease as a part of systemic autoimmune disease, and in some diseases such as systemic lupus erythematosus and antineutrophil cytoplasmic antibody-associated vasculitis, the kidney is the main target organ that can indicate the long-term prognosis. Renal manifestations in childhood rheumatologic disease vary from asymptomatic to end-stage kidney disease (Fig. 1). It is important to recognize that renal abnormalities can be a symptom of rheumatologic disease because they can provide important signals towards establishing a personalized treatment plan. In addition, kidney abnormalities may be a presenting symptom of rheumatologic disease; in this case, clinicians should attempt to identify the underlying disease. In this paper, we review kidney problems that can be accompanied by representative pediatric rheumatologic diseases, including juvenile idiopathic arthritis (JIA), Sjogren’s syndrome (SS), systemic sclerosis/scleroderma, and juvenile dermatomyositis (JDM). Lupus nephritis and antineutrophil cytoplasmic antibody-associated renal disease tend to expand over a wide range of topics, and thus were excluded from this review.

Fig. 1. The spectrum of renal involvement in pediatric rheumatologic diseases.

Juvenile idiopathic arthritis

JIA is characterized by chronic, noninfectious inflammation of the joints and encompasses a complex group of diseases. It is the most famous and frequent rheumatoid disease in children and is classified into several groups, according to clinical and laboratory characteristics. In the early history of JIA, gold nephropathy was an interesting kidney disease associated with the use of intramuscular gold salts, although there is currently no gold treatment. The pathological picture of gold nephropathy is drug-induced membranous glomerulonephritis that usually resolves over time if gold treatment is stopped [3,4].

Although it is difficult to determine the cause of renal abnormalities in JIA, according to one prospective study in adults, proteinuria and decreased renal function were mainly due to drug side effects, while hematuria was associated with the disease itself [5]. The renal diseases associated with JIA have rarely been reported, yet include renal amyloidosis, glomerulonephritis, and drug-induced tubulointerstitial nephritis (TIN). Amyloidosis is the most characteristic lesion associated with chronic systemic inflammation in JIA [6].

Renal amyloidosis

Amyloidosis is characterized by the deposition of amyloid fibrils in organs and there are a number of subtypes. Amyloid A (AA) amyloidosis is caused by the overproduction of the precursor of AA protein, which is produced in response to systemic inflammation, while amyloid light-chain amyloidosis is caused by the overproduction of monoclonal immunoglobulin light chains. Only AA amyloidosis (secondary amyloidosis) can occur in children with JIA [7,8]. In the past, amyloidosis was the main cause of death in JIA; however, recently, the prognosis has improved [8-10]. Renal amyloidosis occurs most commonly in systemic onset JIA (sJIA), followed by polyarticular JIA (pJIA). Renal amyloidosis insidiously progresses, causing massive proteinuria from an asymptomatic state, and consequently leading to end-stage renal disease. Hematuria is rarely accompanied [8,11]. Regular urinalysis is required in patients with sJIA or polyarticular JIA as asymptomatic proteinuria is the most common initial symptom [7]. It can be confirmed by renal biopsy which demonstrates amyloid fibrils, although the correlation between the degree of amyloid deposition and clinical symptoms is not clear. Treatments that control the inflammatory cascade caused by the underlying diseases are critical. Several disease-modifying antirheumatic drugs and biologics have been used to control these diseases. Since renal amyloidosis occurs in a situation where JIA is not well controlled by standard drugs such as methotrexate, sulfasalazine, and hydroxychloroquine, it is usually treated by adding disulfiram-modifying antirheumatic drugs or biologics or switching biologics after the diagnosis of amyloidosis [12]. Interleukin-6 inhibitor, tocilizumab has become the standard treatment for sJIA, and it can play an important role in treating secondary amyloidosis by suppressing serum AA levels [13,14].

According to one large study conducted in 2008, of the 3,500 patients with JIA, 24 patients with biopsy-proven amyloidosis...
were detected. Ten patients died, but the cause of death was associated with JIA itself rather than with amyloidosis. Of the 14 survivors, three patients underwent kidney transplants, and 11 patients maintained normal renal function at last follow-up. Potassiumuria improved completely in four patients who initially had proteinuria [11]. Renal disease can be improved by early intensive treatment. Therefore, it is essential to monitor regularly the occurrence of amyloidosis in JIA patients.

Glomerulonephritis and drug-induced TIN

Several studies on adult rheumatoid arthritis (RA) suggest that there is an association between RA and different types of glomerulonephritis, although studies on glomerulonephritis in JIA are extremely rare. Mesangial proliferative glomerulonephritis is the most commonly reported type of glomerulonephritis in adults with RA [15]. In JIA, membranous nephropathy, mesangial glomerulonephritis, focal segmental glomerulosclerosis, and crescentic glomerulonephritis have also reported [16–23]. Nephrotic syndrome in JIA is extremely rare and is usually caused by amyloidosis rather than glomerulonephritis [20,22]. The pathogenesis of renal involvement in JIA remains unclear. Immunologic abnormalities related to the occurrence of JIA, including hypergammaglobulinemia, abnormal B and T cell milieu responsiveness, decreased T suppressor activity, and uncontrolled proliferation, are presumed to lead to renal involvement [23–24]. In JIA, the treatment for glomerulonephritis is generally conservative with antigen-convert- ing enzyme (ACE) inhibitors or angiotensin receptor blockers. However, severe cases with rapidly progressive glomerulonephritis or massive proteinuria require intensive treatments with immunosuppressors [16–22]. One should be aware that drugs used as treatments can also cause renal abnormalities. Drugs commonly used in JIA include nonsteroidal anti-inflammatory drugs, proton pump inhibitor, methotrexate, sulfasalazine, leflunomide, etc. Since these drugs can often cause renal abnormalities such as acute tubular necrosis and TIN. Clinicians should be careful to identify the cause of renal abnormalities in patients taking these drugs.

Sjögren’s syndrome

Primary SS is a chronic autoimmune disease characterized by inflammation of exocrine glands including salivary and lacrimal glands [25]. In addition, it can demonstrate various exocrinopathy involving respiratory, urogenital tract and skin. Furthermore, extraglandular and systemic symptoms can also be accompanied [26]. SS is typically classified as primary or secondary. Primary SS has no association with other autoimmune diseases, while secondary SS has another underlying or combined autoimmune disease such as systemic lupus erythematosus, RA, and mixed connective tissue disease [27]. The suggested pathogenesis is that genetically susceptible individuals are exposed to environmental factors such as infection, leading to inflammatory processes in target tissues [28]. Definite diagnosis of SS is difficult, because cardinal symptoms in SS can be common seen and SS is no diagnostic gold standard test. Clinicians generally use classification criteria for diagnosis, such as rheumatologic diseases. Antibodies to nuclear antigens Ro/SSA and La/SSB are the hallmarks of SS, but typically are not present in 30% to 50% of SS. Renal involvement is uncommon in patients with SS. 5% to 33% of adult SS patients and approximately 10% of pediatric SS patients have renal involvement [20,30]. TIN is most frequently reported. TIN usually results from activated lymphocytic infiltration (primarily CD4+ T lymphocytes) to tubular epithelium and interstitium around the renal tubules, and this pathophysiology is similar to the process that occurs in exocrine glands [31]. TIN presents tubular dysfunction including renal tubular acidosis (mostly distal type but, proximal or mixed type is also possible), renal Fanconi syndrome, Bartter and Gitelman syndromes and nephrogenic diabetes insipidus [30,32–36]. Hypocalcemia is a general symptom in SS-related renal disease, which is observed in about 40% of patients [32]. Actually, rheumatologic diseases are the second common cause of TIN accounting for 10% to 20% of all TIN cases [37]. Several rheumatologic diseases associated with TIN are described in Table 1.

Glomerular disease is less prevalent than tubular disease, and its pathophysiologic process is mediated by the immune complex, while TIN is mediated by direct lymphocytic infiltration. Membranoproliferative glomerulonephritis due to cryoglobulinemia is the most commonly reported condition. In a study of 22 children with SS, 13 children showed renal involvement, only three of whom had glomerulonephritis, including mesangial proliferative glomerulonephritis, immunoglobulin A (IgA) deposits, membranous glomerulonephritis, and pauci-immune crescentic glomerulonephritis [29,38–40]. Immunosuppressors are not universally required in patients with SS; however, immunosuppressors such as steroid may be helpful in cases of severe systemic symptoms, including arthritis, fatigue, and recurrent parotitis [28]. Patients with symtopmatic TIN also require treatment. Patients with TIN associated with SS generally respond well to treatment. In cases of steroid dependency, other immunosuppressors may be effective in reducing steroids. Steroid with rituximab and plasmapheresis are effective [28]. It is important to monitor for renal involvement in known SS patients, and it is also important to consider SS as the cause in patients with renal disease, primarily TIN, especially for nephrologists. However, it is challenging because symptoms such as sicca are insidious and commonly unclear [20]. In this case, high serum immunoglobulin G (IgG) level, positive rheumatoid factor, positive anti-Ro, anti-La, high erythrocyte sedimentation rate, and cryoglobulins are clues suggesting SS [28,41]. In a previous adult study, long-term renal prognosis appeared to be good, however, the risk of chronic kidney disease is significantly elevated relative to the general population [42].

IgG4-related disease

IgG4-related disease (IgG4-RD) is a new disease entity that has emerged in the last decade and shares several common symptoms with SS, such as glandular enlargement, sicca, arthralgia, and high levels of IgG [43]. It is characterized by highly increased levels of IgG4 (>140 mg/dL) and striking IgG4-producing plasma cell infiltration in the affected organ. The clinical manifestations varied widely. Diagnosis is usually made by histological examination demonstrating a classic fibrotic lesion with IgG4+ plasma cells. IgG4-RD is rare occurring mainly in middle-aged men. TIN is the most common renal disease in IgG4-RD. Obstructive acute kidney injury (AKI) caused by retroperitoneal fibrosis can occur [44]. The renal IgG4-RD in children has been reported very limitedly. In most cases, it occurs concurrently with other organ manifestations, except for one isolated renal IgG4 pseudotumor cases [45–46]. The use of steroid tends to be effective in most cases. IgG4-RD needs to be considered in cases with TIN accompanied by involvement of several organs, although it is rare.

Systemic sclerosis and localized scleroderma

Scleroderma disorders include both systemic sclerosis (SSc) and localized scleroderma (LS). LS is mainly restricted to the skin, whereas SSc affects the skin, vessels, and internal organs, including the gastrointestinal, pulmonary, and musculoskeletal organs [47]. It is an autoimmune disease characterized by vasculopathy and fibrosis. Renal involvement is uncommon in both SSc and LS, although mild renal dysfunction commonly

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**Table 1. Rheumatologic diseases associated with TIN**

<table>
<thead>
<tr>
<th>Rheumatologic diseases</th>
<th>Diagnostic clues</th>
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<tbody>
<tr>
<td>Sjögren’s syndrome</td>
<td>Anti-Ro, anti-La, RF, ANA, cryoglobulin (very) high ESR, high serum IgG</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Hypercalcaemia with/without hypercalcitremia Increased 25(OH)D, vitamin D High inflammatory markers Increased serum ACE level (not consistent, unclear in children) Autoantibodies usually (-)</td>
</tr>
<tr>
<td>IgG4-related disease</td>
<td>(Very) high serum IgG High serum IgG (140 mg/dL), IgG4 (+) plasma cell (pathology) Hypocomplementemia (hypocomplementemic TIN with extensive deposits) Autoantibodies usually (-)</td>
</tr>
<tr>
<td>Scleroderma (mostly systemic sclerosis)</td>
<td>Scl-70, ANA, centromere</td>
</tr>
<tr>
<td>TINU syndrome</td>
<td>Increased ESR, mild anemia</td>
</tr>
</tbody>
</table>

*Laboratory - Clinical*

*Recurrent parotitis, sicca syndrome, arthritis, neurological involvement (peripheral neuropathy and demyelinating disease), intestinal lung disease*

*Constitutional symptoms (weight loss, fatigue, fever), pulmonary symptoms (bilateral adenopathy, pulmonary infiltration), periarticular, subcutaneous nodules, polyclinchar arthritis, ocular diseases (iridocyclitis, uveitis) myositis, hepatosplenomegaly*

*Enlargement of the lacrimal and salivary gland (similar to Sjögren’s syndrome), submandibular lymphadenopathy, ocular inflammation pancreatitis, hepatitis disease, retroperitoneal fibrosis, arthritis, thyroiditis, periarticular ocular inflammation pancreatitis, hepatobiliary disease, interstitial lung disease*
occurs due to vasculopathy in SSc with a close frequency in children and adults with SSc. The most specific renal involve-
mment is scleroderma renal crisis (SRC), which is more common in SSc. It is characterized by progressive AKI with severe hyper-
tension, microangiopathic hemolytic anemia, and thrombo-
cytopenia and renal involvement may continue asymptomatic
until the late stages. In the past, it was a major cause of death,
but recently, with appropriate treatment, the mortality rate has
declining [22,46,49]. SRC has rarely been reported in children with SSc [47]. The pathogenesis of SRC still remains elusive, but
the essential process is suspected to be injury of endothelial

cells, leading to intimal thickening and proliferation of
branched renal arteries.

The common histologic finding is an onion skin lesion of
the renal interlobular artery. Additionally, episodic vasospasm in
cortical arteries contributes to renal ischemia or hyperperfusion
and activation of the renin-angiotensin system [48,50]. This
mechanism is often called the renal Raynaud phenomenon, in
connection with the fact that Raynaud phenomenon in fin-
gers and toes is a typical and essential symptom in SSc. Early
recognition of SRC is essential for its management. In adult
guidelines, ACE inhibitors are recommended as the first-line

treatment. If treatment is delayed, there is a possibility of irre-
versible kidney damage and death [51]. Special attention should
be drawn to the role of SRC in patients taking steroid since
studies have demonstrated an association between SRC and
steroid in adult. In severe cases, treatment with eculizum-
ab, a CS blocker, may be needed, similar to refractory systemic
thrombotic microangiopathy [48]. The effect of prophylactic
ACE inhibitor is not evident. Although, compared to other rheu-
matologic diseases, secondary amyloidosis is very rare in SSc, it
should be considered in cases of long-standing and progressive
SSc with proteinuria [52].

Juvenile dermatomyositis

JDM is a rare systemic autoimmune disease mainly affects skin,
or and muscles and accounts for 80% to 85% of all inflammatory
myopathies in children. It is characterized by proximal muscle
weakness and typical skin rashes, such as heliotrope rashes and
Gottron papules. Other organs can be involved including the
lungs, heart, gastrointestinal tract, and kidneys. Constitutional
symptoms such as fever, fatigue, anorexia, and weight loss are
common, and the onset is usually insidious. Histological find-
ings are characterized by vascular and periarterial inflamma-
tion, and vasculopathy is considered the key to the pathogen-

esis of myositis and cutaneous symptoms. It is also associated
with other manifestations including intestinal perforation,
ulcerations, pulmonary disease, and cutaneous calcinosis [53].
The spectrum of renal disease in inflammatory myopathies in
adults includes AKI, chronic kidney disease, glucosonephritis,
myoglobinuria, and hypertension, while data on children with
JDM are lacking [54]. Membranous nephropathy was the
most common chronic renal sequelae in adults with inflamma-
tory myopathy [55]. Few case reports in JDM demonstrated IgA
nephropathy and nephritic syndrome with AKI.

The children responded well to treatment with steroids and
methylprednisolone for the primary disease, JDM, and usually do
not require additional drugs for renal involvement except ACE in-
hibitors or angiotensin receptor blockers. However, in cases of
IgA nephropathy with nephritic–range proteinuria or progres-
sive AKI, additional immunosuppressants such as cyclosporin,
mycophenolate mofetil, azathioprine, and cyclophosphamide
should be considered [56,57].

Rhabdomyolysis with AKI is extremely rare in JDM, but can
occur especially in fulminant JDM with multorgan involvement
[58]. Macrophage activation syndrome may occur as a result of
excessive systemic inflammation in JDM such as sJIA, and one
case of thrombotic microangiopathy secondary to macrophage
activation syndrome in JDM has been reported [59].

Conclusions

Rheumatologic diseases in children can affect various organs,
including the musculoskeletal, cutaneous, pulmonary, heart, gastrointestinal, central nervous system, and kidneys. It is
necessary to understand the type of renal disease associated
with JDM to properly monitor and treat renal involvement
in patients with rheumatologic diseases. In certain cases
patients are initially expressing symptoms of renal disease
alone, we should try to find the underlying diseases,
and then renal disease can be a diagnostic clue for underlying
rheumatologic diseases.

Conflicts of interest

Seong Heon Kim is an editorial board member of the journal
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Mechanism, clinical consequences, and management of dyslipidemia in children with nephrotic syndrome

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Dyslipidemia in nephrotic syndrome (NS) is often characterized by marked increases in the levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and other lipoproteins, such as very low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein(a). It has been suggested that impaired catabolism of lipoproteins and cholesterol is mainly due to decreased lipoprotein lipase and hepatic lipase activity, and increased biosynthesis of lipoproteins in the liver. The management strategies for dyslipidemia in patients with NS consist of lifestyle modification, lipid-lowering agents represented by statins, second-line agents such as fibrates and bile acid sequestrants, and lipid apheresis. Compared with dyslipidemia in adult NS patients, whose risks of atherosclerotic disease and progressive renal injury are considered high, clinical data on dyslipidemia in pediatric NS patients are limited. Therefore, it is necessary to pay more attention to the evaluation and management of dyslipidemia in pediatric patients with NS in clinical practice.

Keywords: Child; Dyslipidemias; Nephrotic syndrome
Pathogenesis of lipid abnormality

Lipids, mainly triglycerides (TG) and cholesterol, circulate in the body in the form of lipoproteins. Lipoproteins are formed from lipids packaged in apolipoproteins and phospholipids. The main forms of lipoproteins are chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL), which differ in composition and function. It is known that there are three main pathways responsible for the synthesis and transport of lipids within the body. First, in the exogenous pathway, dietary lipids ingested as food are packaged into chylomicrons in the intestinal mucosal cells and enter blood circulation through the lymphatic system. In the blood, TG, the main component of dietary lipids, is released as free fatty acids by lipoprotein lipase (LPL) in the capillary endothelium and transported to muscle, adipose tissue, and other peripheral tissues for absorption, and the remaining chylomicrons are transported to the liver for clearance. Second, in the endogenous pathway, VLDL generated in the liver is converted into IDL by the liver, and then further into LDL and HDL. In patients with nephrotic syndrome (NS), the expression and activity of lipase activity, as well as the uptake of LDL into hepatocytes are reduced due to the reduction of cholesterol efflux through ATP-binding cassette subfamily B member 1, which is present in peripheral tissues. It has been suggested that impaired lipoprotein clearance is due to decreased hepatic lipase and LPL activity in the endothelium and peripheral tissues such as muscle and adipose tissues. In detail, as shown in Fig. 1, proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates the expression of hepatic LDLR. In patients with NS, LDLR degradation increases as the intracellular expression of PCSK9 increases. Therefore, the uptake of LDL into hepatocytes is reduced and the clearance of LDL is disturbed [3-5]. In addition, when the ratio of free fatty acids to albumin in the blood increases due to proteinuria, circulating angiotensin-like 4 levels increase, which leads to downregulation of hepatic lipase and a decrease in LDL clearance. Furthermore, as the permeability of the glomerular basement membrane increases and LPL activators decrease, LPL activity decreases and levels of IDL and VLDL increase [6,9]. Moreover, the protease cathepsin H in the blood increases due to the reduction of cholesterol efflux through ATP-binding cassette subfamily A member 1, which is present in peripheral organs [3]. In patients with NS, the expression and activity of acetyl-CoA acetyltransferase 2 (ACAT2) and 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor (PCSK9) increases, low-density lipoprotein receptor (LDLR) degradation increases, resulting in reduced uptake of low-density lipoproteins (LDL) clearance, and thus increasing plasma levels of intermediate-density lipoproteins (IDL), very-low-density lipoproteins (VLDL), triglycerides (TG).

Clinical consequences of dyslipidemia in NS

Atherosclerosis and cerebrovascular disease

In general, it is well known that dyslipidemia promotes atherosclerosis and is a risk factor for myocardial infarction and cerebrovascular disease (CVD). Dyslipidemia exacerbates platelet hyperreactivity, which increases the risk of thrombosis, and is often accompanied by atherosclerosis. Although clinical studies to confirm the increased risk of CVD in patients with NS are scarce, a case-control study reported that non-diabetic adults with NS have a 5.5-fold significantly higher risk of MI (95% confidence interval, 1.6-18.3) compared to those without NS [14]. Recently, a case-control study comprising 66 children with NS and 128 age- and sex-matched controls showed that carotid-intima media thickness as a surrogate marker of CVD is significantly higher in children with NS aged over 4 years [7]. Therefore, in patients with persistent NS and accompanying dyslipidemia, especially in the presence of other cardiovascular risk factors, lowering cholesterol levels is important for preventing the progression of atherosclerotic lesions [18].

Renal injury

It has been suggested in several experiments and observations that dyslipidemia, accompanied by proteinuria and hyperalbuminemia, may increase renal organ damage and cause glomerulosclerosis by directly affecting mesangial cells, podocytes, and tubular cells, which is referred to as “nephrotoxicity hypothesis” [19]. Under normal conditions, LDL is metabolized and used by mesangial cells; however, when excess LDL is stored in the extracellular matrix in dyslipidemia, it is oxidized and causes an increase in cytotoxic agents such as prostaglandin E2 and tumor necrosis factor. These cytotoxic agents have the potential to damage the glomerular epithelial and endothelial cells, resulting in sclerosis. In addition, it is hypothesized that increased free fatty acids bind to albumin and promote microcircopinyosis of podocytes through lipid-binding G-protein coupled receptors, resulting in podocyte injury and loss, leading to end-stage renal disease [20,21]. Furthermore, it was reported that albumin binding fatty acid may induce infiltration of macrophages and T lymphocytes to the tubulointerstitial space, leading to renal tubular cell injury and acute interstitial nephritis [22,23].

Several clinical studies, including prospective cohorts, reported that dyslipidemia could be a risk factor for renal injury represented as CKD progression. However, the findings were inconsistent among studies: some studies have reported that a high TC, TG, and LDL are associated with CKD progression, yet others did not [24].

Management of dyslipidemia in NS

The main approach for managing dyslipidemia is to treat the underlying renal disease that causes NS. Dyslipidemia usually improves when the underlying disease is treated with steroids, immunosuppressants, or angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Lifestyle modification

A heart-healthy diet, physical activity, and weight reduction are recommended as the first-line treatments for pediatric patients with NS. In early studies, 20 NS patients with persistent proteinuria were administered a low-fat, low-protein, vegetarian soy diet rich in unsaturated fatty acids and fiber for 8 weeks instead of their usual diet. It was reported that lipid profiles (TC, LDL, HDL, apolipoprotein A, and apolipoprotein B), except for...
Pharmacological treatment: statins

Patients with NS should decide whether to initiate lipid-lowering medication based on CVD risk and renal function. Currently, there are no agreed upon guidelines for initiating lipid-lowering medications in patients with NS. Studies that provide clear evidence for the use of lipid-lowering medications are lacking. Therefore, it is necessary to consider the potential benefits and risks of such medication for each patient with NS.

Statins are the most commonly used drugs for the treatment of dyslipidemia in patients with NS. Statins inhibit HMG-CoA reductase competitively, reduce hepatic cholesterol production, and promote LDL absorption in blood. However, studies on statin administration in patients with NS are scarce. It was reported that TC and LDL were effectively reduced by 20% to 45% in adult NS patients treated with statins, but there was a lesser reduction in TG and apolipoprotein levels [29,32].

Meanwhile, in a meta-analysis including four randomized controlled trials (RCTs) using statins as lipid-lowering agents, only one RCT in pediatric NS patients showed that the others did not show a clear blood lipid improvement [33]. It was reported that statins also reduce lipoprotein(a) levels in NS patients in cases with high baseline values [34].

Studies on the treatment of dyslipidemia in pediatric patients with NS using lipid-lowering agents are very limited. Because long-term safety data are lacking and the U.S. Food and Drug Administration has approved its limited use in pediatric patients with familial hypercholesterolemia, the use of lipid-lowering agents is relatively low in pediatric patients compared to adult NS patients. In cases with high baseline values, statins did not show a clear blood lipid improvement [34]. However, the gastrointestinal side effects of bile acid sequestrants have been reported to be high; therefore, their use was often limited [35].

Nicotinic acid and ezetimibe can also be used to treat dyslipidemia; however, there are no available clinical data on patients with NS until now.

Monoclonal antibodies against PCSK9 (e.g., evolocumab and alirocumab) and an LDL receptor inactivator, bococizumab, have been reported to reduce LDLR on hepatocyte surfaces to promote LDL uptake [3]. Recent studies reported that remission in NS patients was associated with a decrease in cholesterol and PCSK9 blood levels, and the LDL reduction effect in the group treated with a PCSK9 inhibitor was significant [42-44]. In addition, ACAT inhibitors were reported to improve proteinuria and dyslipidemia in NS animal models [2].

Lipid apheresis

Lipid apheresis has been used to treat patients with homozygous familial hypercholesterolemia and has recently been applied to the treatment of dyslipidemia in NS patients [3]. It has been reported that adult and pediatric patients with steroid-resistant NS treated with lipid apheresis with or without steroid showed reduced proteinuria and improved lipid profiles. This effect might be explained by the improvement in dyslipidemia, removal of autoantibodies, reduced potential vascular permeability factors and inflammatory cytokines, and improved responsiveness to immunosuppressants [20,45-47].

Pharmacological treatment: second-line agents

Fibrate, such as gemfibrozil, fenofibrate, and clofibrate, increase LPL activity, decrease triglyceride concentrations and decrease plasma concentrations of TG and LDL. There have been small-scale RCT studies in NS patients that reported that gemfibrozil treatment reduced plasma TG concentrations by approximately 50% and the LDL concentration by 13% to 30% compared to placebo [38,39]. However, it is known that myopathy risk increases when fibrates are used in combination with statins [40].

Bile acid sequestants such as cholestyramine and colestipol inhibit intestinal reabsorption of bile and block enterohepatic circulation of bile. Consequently, the expression of various liver enzymes involved in bile production increases, which in turn increases hepatic cholesterol breakdown and LDL absorption from the blood. In patients with NS, it has been reported that when cholestyramine was used, LDL was reduced by 19%, and when colestipol was used, it was reduced by approximately 30% [30,41]. However, the gastrointestinal side effects of bile acid sequestrants have been reported to be high; therefore, their use was often limited [34].

Acyl-CoA: cholesterol acyltransferase (ACAT) inhibitors are high-risk patients with NS who are at increased risk of atherosclerotic cardiovascular disease. There is evidence that ACAT inhibitors are effective in reducing plasma concentrations of TG and apoB. Furthermore, a recent trial showed that the use of ACAT inhibitors reduced the risk of myocardial infarction in patients with NS [33]. However, ACAT inhibitors have potential side effects, including renal impairment and hepatotoxicity. Therefore, it is necessary to consider the potential benefits and risks of such medication for each patient with NS.

Conclusions

In this article, the authors reviewed recently described mechanisms, clinical impacts, and several treatment methods for dyslipidemia in patients with NS. Compared with adult patients with NS whose risks of atherosclerotic cardiovascular disease, such as myocardial infarction or coronary arterial disease, are high, studies on dyslipidemia in pediatric patients with NS are still lacking. However, there are also possible risks of atherosclerotic cardiovascular disease and progressive renal injury due to high levels of plasma lipids, even in pediatric NS patients. In conclusion, more attention should be paid to the screening and treatment of dyslipidemia in pediatric patients with NS in clinical practice.

Conflicts of interest

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References

Dyslipidemia in nephrotic syndrome


Alport syndrome: new advances in the last decade

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Alport syndrome (AS) is a progressive hereditary nephritis that is often accompanied by sensorineural hearing loss and ocular abnormalities. It is inherited in three modes of X-linked AS (XLAS), autosomal recessive AS (ARAS), and autosomal dominant AS (ADAS). XLAS is caused by pathogenic variants in COL4A5, while ARAS and ADAS are caused by those in COL4A3 or COL4A4. There is currently no curative treatment for AS; however, angiotensin-converting enzyme inhibitors (ACEi) can improve the outcome of AS. In the past decade, multiple studies have shown that early intervention with ACEi upon isolated microscopic hematuria or microalbuminuria could delay disease progression, and early diagnosis is crucial for early treatment. Therefore, a new classification of AS based on molecular diagnoses has been proposed, including the paradigm shift of re-classifying female “carriers” to “patients” and “thin basement membrane nephropathy” to “ADAS.” In addition, with the detection of COL4A mutations in some patients with biopsy-confirmed IgA nephropathy, focal segmental glomerulosclerosis, and chronic kidney disease of unknown origin, it is suggested that the phenotype of AS should be expanded. In this review, we highlight the landmark studies and guidelines published over the past decade and introduce strategies for early diagnosis and treatment to improve the outcomes of AS.

Keywords: Angiotensin-converting enzyme inhibitor; Early diagnosis; Early medical intervention; Hematuria, benign familial; Nephritis, hereditary

Introduction

Alport syndrome (AS) is a progressive inherited kidney disease often accompanied by sensorineural hearing loss (SNHL) and ocular abnormalities such as lenticonus or retinal flecks [1]. Kidney symptoms of AS start with isolated microscopic hematuria, followed by the appearance of microalbuminuria (urine microalbumin-to-creatinine ratio, 30–300 mg/g), which progresses to overt proteinuria and a decline in kidney function [2]. AS, which affects one in approximately 5,000 people, is the second most common cause of inherited kidney failure after autosomal dominant polycystic kidney disease [3]. It accounts for 0.5% of new-onset chronic kidney disease (CKD) stage G5 (glomerular filtration rate [GFR] <15 mL/min/1.73 m² or treatment by dialysis [4]) cases in adults and 12.9% in children [5]. AS is caused by pathogenic variants in the COL4A3, COL4A4, and COL4A5 genes that encode type IV collagen α3, α4, and α5 chains, respectively. Type IV collagen has six different α chains, α1 to α6, which construct triple-helix structures, the major components of the basement membrane. In the embryonic glomerulus, classical chains of the α1-α1-α2 triple helix form the glomerular basement membrane (GBM), and with development, these are gradually replaced by novel chains α3-α4-α5 [6]. Basement membranes of the cochlea and ocular lens have similar type

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Electron microscopy findings: the glomerular basement membrane (GBM) abnormalities caused by COL4A4 mutations. The GBM in Alport syndrome (AS) patients demonstrates irregular thickening with abnormal splitting and lamination. In patients with a thin basement membrane lesion, which is currently proposed to be regarded as AS, the GBM shows abnormally diffuse thinning. Reused from Warady et al. [20]. Images were used with permission from J. Charles Jennette. www.unckidneycenter.org. Accessed March 9, 2022.

**Clinical suspicion of AS**

The most common symptom of AS is hematuria, which is persistent in 100% of XLAS male and ARAS patients, and may appear intermittently in approximately 95% of XLAS females and 50% of ADAS patients (GeneReviews). Recurrent gross hematuria (especially following upper respiratory infection) occurs in infancy or early childhood in 40% to 60% of cases, with an average age of 3.5 years in males and 9 years in females. Males without hematuria by the age of 20 years are unlikely to have AS [15]. Importantly, proteinuria does not appear without hematuria. Ocular abnormalities of AS are less sensitive than the associated HL; however, they are more specific, which means that they could be diagnostic. Lenticulosis and central fleck retinopathy occur only in AS and are associated with kidney failure before 30 years in male patients with XLAS [17].

**Histologic findings**

Conventionally, the diagnosis of AS was made pathologically; however, this can be challenging. There are no specific light microscopic findings in AS; mesangial proliferation, FSGS, and interstitial infiltration containing lipid-laden foam cells may be observed [18,19]. Electron microscopy findings typically show irregular thickening and thinning of the GBM, lamellation, and splitting in the lamina densa of a “basket-weave” appearance (Fig. 1) [20]. While these findings are very characteristic of AS, they appear later in the course of the condition; therefore, electron microscopy may show only diffuse GBM thinning in young male patients with XLAS or XLAS females, or ARAS/ADAS patients [15,22]. Immunofluorescence staining of type IV collagen α5 can be diagnostic, irrespective of the patient’s age. Typically, collagen type IV α5 chain expression is completely absent in XLAS male patients (both at GBM and Bowman capsule) and ARAS/ADAS patients; however, more than 20% of XLAS males and 20% of ARAS patients exhibit normal expression of α5 if their pathologic variants are non-truncating [13,22], as well as ADAS patients. XLAS female patients exhibit a mosaic pattern
of a5 staining (Fig. 2) [1]. The collagen type IV a5 stain in skin biopsy is valid only for XLAS since the epidermal basement membrane is mainly comprised of the triple helix of 15%–45% as the Bowman capsule [26]. Therefore, the normal expression of collagen type IV a5 in XLAS cannot exclude ADAS. Furthermore, non-specific focal GBM thinning may also be seen in IgAN [24]. Thus, kidney biopsy plays a supportive, not confirmatory role in the diagnosis of XLAS [25].

Advances in the last decade

Due to these limitations of histopathology and the remarkable development of molecular-based techniques in the past decade, genetic testing has become the first-line diagnostic technique for AS. Because COL4A genes are large, targeted next-generation sequencing, including all three novel chain genes, has become the primary genetic screening method instead of Sanger sequencing [12]. Although there is currently no curative therapy for AS, nephroprotective drugs such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers can delay the progression to kidney failure for years or even decades. In a large cohort study of XLAS males in Japan [27], kidney replacement therapy (KRT) was delayed by 17 years and 12 years in the non-truncating and truncating mutant groups, respectively, in the group of patients treated with either ACEi or angiotensin receptor blockers compared to those in the untreated group. In addition, multiple prospective and retrospective studies have reported the beneficial effects of early interventions with ACEi. The 2020 guideline emphasizes molecular diagnosis to enable early treatment and avoid immunosuppression [2].

The rationale for early ACEi treatment

In a study using the mouse model of ARAS, those treated with ramipril at 4 weeks survived twice as long as mice not treated with ramipril, whereas the group that started treatment at 7 weeks did not differ in survival compared to the untreated group [28]. A retrospective cohort study in Europe showed that amongst those who began treatment when they had only isolated hematuria or microalbuminuria, no one needed KRT until the age of at least 40 years [29]. Treatment initiation when patients had proteinuria (>0.3 g/day) with normal kidney function delayed KRT for 18 years (median age of KRT, 40 years). Later initiation at CKD stage G3 (GFR, 30–59 mL/min/1.73 m2) or G4 (GFR, 15–29 mL/min/1.73 m2) had the effect of postponing KRT by only 3 years (median age, 25 years) compared to the untreated group with a median KRT age of 22 years. Based on these studies, the Early Prospective Therapy European Community Trial in Alport syndrome (EARLY PRO-TECT Alport) was conducted in Germany to determine whether starting ramipril treatment on noticing isolated hematuria or microalbuminuria could delay the progression of the disease to its next phase (microalbuminuria or proteinuria, respectively). Early treated group (n=11, open-label [n=42]) developed disease progression in 27%, 41%, for each, whereas the placebo group (n=9) in 56%. Although not statistically significant, the authors concluded that the early initiation of ramipril might be beneficial in delaying progression by more than 40% [30].

Expanded phenotypes of AS

With the broad implementation of next-generation sequencing, several cases are re-diagnosed with AS even when their symptoms are not always compatible with AS. In a large-scale analysis of whole-exome sequencing in 3,315 patients with CKD of all causes, 10% were found to have genetic causes, of which 30% were diagnosed as AS with COL4A4 mutations. The majority of these patients (62%) had been misdiagnosed with hypertensive nephropathy, other kinds of glomerulonephropathy such as steroid-resistant nephrotic syndrome, or family history of progressive kidney disease [31,32]. So, is TBMN equal to ADAS? A guideline published in 2019 did not agree, as the likelihood of kidney failure is minimal [31]. However, the latest guidelines emphasize that all diseases caused by heterozygous mutations of COL4A3 or COL4A4 should be classified as “ADAS” for an earlier and more aggressive intervention since earlier ACEi treatment delays kidney failure for longer [2,33]. In a recent study, Yamamura et al. [34] reported that ADAS accounted for 17% of all AS cases, which is much higher than the 5% found in previous reports, suggesting the diagnosis of ADAS is underestimated [34]. Therefore, even when diagnosed with TBMN, especially if associated with COL4A3 or COL4A4 variants, regular follow-up is strongly recommended for the risk of kidney failure.

Early diagnostic tactics

Early genetic test necessity

The latest guideline proposed in 2020 by Ishash and Gross [2] recommends that genetic testing should be performed if AS is suspected in patients with persistent glomerular hematuria. Kidney biopsy is recommended if genetic testing has uncertain pathogenicity and AS is not suspected based on clinical data or family history. Kidney biopsy should include transmission electron microscopy, and if transmission electron microscopy is not available, immunofluorescence of the type-IV collagen stain is required.

Treatment guidelines

When should we start treatment and how do we monitor it?

The clinical practice recommendations from the Alport Syndrome Research Collaborative emphasize initiating early interventions. In XLAS male and ARAS patients, who progress to CKD stage G5 in 100% of cases, treatment should be started as soon as possible when the diagnosis is obtained in patients older than 1 year regardless of proteinuria (strong recommendation). For XLAS female and ADAS patients, treatment initiation is recommended if microalbuminuria develops during annual monitoring [2]. This differs significantly from their previous guideline in 2013 that did not recommend treatment with isolated hematuria and recommended optional treatment with microalbuminuria in XLAS males [33].

Which drugs should we use?

The drug recommended by the above-mentioned guideline is either ramipril or lisinopril. Ramipril is a well-established drug with evidence of efficacy and safety, which was adopted from protocols in the ESCAPE (Effect of Strict blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients) trials [39] and the EARLY PRO-TECT trial for children with AS [38]. Lisinopril is another ACEi with a comparable duration of action to that of ramipril, and it has obtained evidence from some pediatric studies [40,41]. In the ARAS mouse model study, ramipril prolonged the lifespan significantly more than candesartan did (11% vs. 38%, respectively) [42]. However, no AS studies in humans have compared ramipril with other drugs. One small study compared the antiproteinuric effects of enalapril to those of losartan in children with AS and found no significant difference between the two [43].

How to increase the dose of the ACEi?

It is emphasized that ACEi should be up titrated more rapidly and aggressively than previously recommended. The previous guideline in 2013 recommended increasing ramipril dose “every” 3 months until the target urine protein-to-creatinine ratio (UPCR, less than half of the baseline value) is reached [33]. However, the recent guideline in 2020 recommends increasing the dose “over” the first 3 to 4 months starting 1 mg/m2/day to a maximum of 6 mg/m2/day of ramipril irrespective of the degree of proteinuria if the patient can tolerate such an increase. The dosage needs to be increased as the child grows to maintain the maximum dose [2].
Dual renin-angiotensin-aldosterone system blockade

Data from the ESCAPE trial in pediatric CKD reported that a UPCR >0.1 mg/mg was associated with better kidney outcomes [44]. Therefore, the latest guideline suggested that considering the use of dual renin-angiotensin-aldosterone system (RAAS) blockade may be reasonable if the UPCR exceeds 1.0 mg/mg despite the maximum tolerated dose of ramipril or losartin. Losartin can be added in small amounts, at an initial dose of 0.8 mg/kg/day [2]. However, there is limited evidence of the efficacy and safety of dual RAAS blockade, and the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends not using dual blockade in another glomerulopathy. When using dual RAAS blockade, adverse effects such as hyperkalemia, kidney insufficiency, and hypertension should be periodically monitored [2,46].

Cyclosporine

Cyclosporine (CsA) is not recommended in patients with AS [2]. CsA diminishes proteinuria by directly stabilizing the podocyte cytoskeleton [46]. However, the long-term use of this drug may stimulate proinflammatory mediators such as transforming growth factor-β leading to interstitial fibrosis and tubular atrophy [47]. In small, uncontrolled studies conducted in Spain [48,49], France [50], and Italy [51], proteinuria significantly decreased throughout CsA treatment (5 mg/kg/day). However, the effect was temporary: proteinuria nearly returned to the baseline value after discontinuation in most patients, and kidney outcomes were conflicting with stable GFRs over 8 years [48,49] versus kidney function decline over 6 months, and some patients developed intimal fibrosis 20 to 27 months after CsA initiation [50].

Hearing and ophthalmologic evaluation and follow-up

HL in children, even in mild cases, affects speech-language, social-behavior, cognitive development, and academic performances [52]. Several papers have shown that HL in AS is sensorineural, progressive, and bilateral, often affecting the middle and particularly high frequencies [53]. Therefore, it can only be detected by formal hearing tests, especially during early childhood. Approximately 30% of XLSA males and 20% of ARAS patients exhibit detectable HL by age 10. In males with XLSA, HL increases to approximately 60% by age 20 and shows a genotype-phenotype correlation. ARAS patients show a high rate of HL when they have one or more truncating mutations [6,24,54]. Therefore, a hearing evaluation is recommended annually for XLSA males and ARAS, starting at the age of 5 to 6 years, and earlier if overt proteinuria occurs or symptoms suggestive of HL, such as speech delay, develop. For XLSA females, the probability of HL is less than 10% by age 40 years; however, HL eventually occurs in 30% of them [55]. It is recommended that females with XLSA perform a formal hearing test when overt proteinuria is present. All AS patients should avoid loud sounds. If HL develops, it usually responds well to hearing aids [2].

Ocular abnormalities in AS, lenticonus, and central foveal retinopathy have high diagnostic and prognostic values [27]. For XLSA males with truncating mutations and ARAS patients, it is strongly recommended that ophthalmologic investigations begin at age 15 (earlier if they have an abnormal vision) and annual check-ups should be performed. For females with XLSA and ADAS patients, ophthalmologic assessments are recommended if clinically indicated [2].

Other recommendations

Hypertension can accelerate the deterioration of kidney function. Therefore, it should be strictly controlled, and the target blood pressure should be in the 50th percentile [25]. As lifestyle modifications, maintaining a body mass index of <25 kg/m², moderating one’s dietary intake of meat protein and salt, and avoiding smoking are also recommended [2].

Research horizons

Future therapeutic options

In a clinical trial on AS-induced CKD [55], barloquinone, an activator of nuclear factor erythroid-related factor 2 (Nrf2), improved the GFR. However, another study of this drug in patients with type 2 diabetes mellitus and CKD stage 4 (BEACON trial) was prematurely terminated due to fatal cardiovascular complications (relative risk, 1.83; P=0.005) [56]. For safety and efficacy reasons, the Food and Drug Administration recently denied the approval of the drug in AS.

Other investigational approaches in AS include microRNA-21 antagonists as anti-fibrotic agents and exon-skipping gene antagons for treating muscular dystrophy [2]. Both are effective in animal studies and are now under clinical trials [2,57].

Conclusions

Advances in molecular genetics and clinical studies over the past decade have made early diagnosis and intervention possible in patients with AS. Also, histopathologic diagnoses other than AS cannot exclude AS, since some of such patients harbor disease-causing variants of AS. Therefore, even when the clinical and biological profiles are not compatible with AS, the COL4A3-COL4A4 mutations need to be considered, especially if there is a contributive family history. Female subjects affected by XLSA are no longer considered ‘carriers’ but ‘patients’, and individuals with heterozygous mutations in ‘COL4A3 and COL4A4 (even diagnosed with ‘TIMM’ should be monitored regularly due to the risk of kidney failure. XLSA males and ARAS patients older than 12 months need to undergo ACEI regardless of proteinuria, while other types can be monitored for microalbuminuria appearance, which indicates treatment.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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References

Kim. Recent updates of Alport syndrome

38

Kim. Recent updates of Alport syndrome

https://www.orpha.net


Genetic analysis using whole-exome sequencing in pediatric chronic kidney disease: a single center’s experience

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Purpose: Chronic kidney disease (CKD) has various underlying causes in children. Identification of the underlying causes of CKD is important. Genetic causes comprise a significant proportion of pediatric CKD cases.

Methods: In this study, we performed whole-exome sequencing (WES) to identify genetic causes of pediatric CKD. From January to June 2021, WES was performed using samples from pediatric patients with CKD of unclear etiology.

Results: Genetic causes were investigated using WES in 37 patients (17 males) with pediatric CKD stages 1 (n=5), 2 (n=7), 3 (n=2), 4 (n=2), and 5 (n=2). The underlying diseases were focal segmental glomerulosclerosis (n=9), congenital anomalies of the kidney and urinary tract including reflux nephropathy (n=8), other glomerulopathies (n=7), unknown etiology (n=6), and others (n=7). WES identified genetic causes of CKD in 12 of the 37 patients (32.4%). Genetic defects were discovered in the COL4A4 (n=2), WTI (n=2), ACTN4, CEP290, COLA43, CUBN, GATA3, LAMAS, NUP107, and PAI2 genes. WTI defects were found in patients whose pathologic diagnosis was membranoproliferative glomerulonephritis, and identification of CUBN defects led to discontinuation of immunosuppressive agents. Genetic diagnosis confirmed the clinical diagnosis of hypothyroidism, sensorineural deafness, and renal disease, Alport syndrome; and Joubert syndrome in three of the patients with CKD of unknown etiology (COLA44(n=2), CUBN(n=1)). Extrarenal symptoms were considered phenotypic presentations of WTI, PAI2, and CEP290 defects.

Conclusions: WES provided a genetic diagnosis that confirmed the clinical diagnosis in a significant proportion (32.4%) of patients with pediatric CKD.

Keywords: Genetics, Pediatrics, Renal insufficiency, chronic, Whole exome sequencing

Introduction

Chronic kidney disease (CKD) is a global health problem with increasing incidence and prevalence [1]. Children with CKD face mortality, lifelong morbidity, and a low quality of life [2-5]. Advances in medical care have substantially improved the survival rate of children with CKD [3]. Identifying the underlying cause of this disease is essential because the progression, treatment, and prognosis may differ according to etiology. However, traditional diagnostic approaches, such as kidney biopsy, can be unrevealing or contradicted when the kidneys are already failing [6]. Therefore, new diagnostic methods are required to identify the etiology of CKD.

CKD is a complex, genetically heterogeneous disease with both genomic and environmental causes. The heritability of CKD is relatively high (50%-75%) [7], and at least 15% to 20% of early onset CKD (before the age of 25 years) is caused by genetic variation. Nearly all children who progress to end-stage kidney disease (ESRD) have an inherited form of CKD [8,9]. In addition, approximately 17% of patients with ESRD do not have a primary renal disease diagnosis and are therefore labeled as patients with CKD of unknown etiology.

The diagnostic accuracy provided by genetic testing [8] can enable the establishment of treatment guidelines and aid in the accurate prediction of patient prognosis. Genetic diagnosis is crucial for identifying high-risk groups and for appropriate family planning. The prevalence of CKD caused by genetic defects is approximately 10% in unselected adults [9] and 20% to 30% in children with nephropathy [7,10]. These findings indicate that the clinical application of genetic testing could transform diagnostic pathways by providing a timely and accurate genetic diagnosis [11].

Sanger sequencing of the causative genes is typically performed to obtain a genetic diagnosis when CKD is suspected. However, the number of known causative genes for CKD is increasing, as is the number of CKD cases. Therefore, traditional Sanger sequencing is not cost-effective in most cases, making targeted exome sequencing or whole-exome sequencing (WES) the preferred approaches for genetic diagnosis [12-17]. WES can screen most genes associated with diseases and can therefore be applied across diverse categories of renal disorders. In addition, it can potentially identify novel etiologic genes associated with nephropathy. Therefore, WES is emerging as the preferred diagnostic tool for hereditary disorders [12-17]. It has provided a genetic diagnosis in up to 11.5%, 26%, and 32.7% of patients with congenital kidney anomalies, steroid-resistant nephrotic syndrome, and ESRD, respectively [12,18].

In this study, we present the preliminary results of utilizing WES to identify the genetic causes of pediatric CKD in Republic of Korea.

Methods

1. Study design and participants

We prospectively recruited 37 pediatric patients with CKD whose underlying etiology was uncertain or suspected to be monogenic. The male to female ratio of the patients was 20:17. All study participants were recruited from Seoul National University Children’s Hospital, Seoul, Republic of Korea. Buccal mucosal samples were collected and analyzed from January to June 2021. Details of DNA extraction and analysis of WES data have been previously described [20]. The identified variants were classified based on the American College of Medical Genetics and Genomics standards for the interpretation of sequence variants [21].

2. Statistical analysis

The diagnostic yield was calculated based on the variants classified as “pathogenic” or “likely pathogenic.” All statistical analyses were conducted using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and SPSS statistical software version 20 (IBM Corp, Armonk, NY, USA).

Results

1. Cohort characteristics

A total of 37 patients with CKD were recruited for this study. The underlying causes of CKD among the study participants were focal segmental glomerulosclerosis, congenital anomalies of the kidney and urinary tract (CARUT) including reflux nephropathy, ischemic disease, Fanconi syndrome, Barter syndrome, and CKD of unknown etiology (Table 1). One patient had a family history of CKD. The median ages at the time of CKD diagnosis and underlying causes were 6 and 13 years, respectively. The distributions of the CKD stages and clinical diagnoses are described in Tables 1 and 2.

2. Genetic findings and diagnostic yield

Diagnostic variants were detected in 12 of the 37 patients (32.4%), encompassing seven distinct monogenic disorders. The detected genes were COLA44 (n=2), WTI (n=2), ACTN4 (n=4), COLA43 (n=3), CUBN (n=1), GATA3 (n=1), LAMAS (n=1), NUP107 (n=1), and PAI2 (n=1). An additional three patients had variants of uncertain significance. The diagnostic yield (Table 1) was the highest among patients with CKD of unknown etiology (n=5, 30%). In contrast, diagnostic variants were not detected in some (n=7) of the clinically diagnosed CKD cases, including Alport syndrome, CARUT, and renal hypoplasia with diabetes mellitus.

3. Clinical implications of genetic diagnoses in the study

Table 3 summarizes the clinical characteristics and genetic results of the patients with diagnostic variants. In six cases including three patients with CKD of unknown etiology, WES...
Table 1. Clinical category characteristic and diagnostic yield of genetic diagnosis across clinical diagnostic categories

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>No. of patients (%)</th>
<th>Male sex</th>
<th>Sequencing performed</th>
<th>No of diagnostic variant present (%)</th>
<th>Singleton genetic diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>9 (24.3)</td>
<td>3</td>
<td>9</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>CARRT including reflux nephropathy</td>
<td>8 (21.6)</td>
<td>4</td>
<td>8</td>
<td>3 (37.5)</td>
<td>1</td>
</tr>
<tr>
<td>Other glomerulopathy</td>
<td>7 (18.9)</td>
<td>2</td>
<td>7</td>
<td>3 (42.9)</td>
<td>1</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>6 (16.2)</td>
<td>4</td>
<td>6</td>
<td>1 (16.7)</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>7 (18.9)</td>
<td>4</td>
<td>7</td>
<td>1 (14.3)</td>
<td>1</td>
</tr>
</tbody>
</table>

FSGS, focal segmental glomerulosclerosis; CARRT, congenital anomalies of kidney and urinary tract.

Table 2. Patient clinical characteristics of having whole-exome sequencing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n=97</th>
<th>Age at diagnosis of CKD (yr)</th>
<th>6.00 (3.00–10.25)</th>
<th>Sex, male/female</th>
<th>20:7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD stage</td>
<td></td>
<td>Stage 1</td>
<td>5 (13.5)</td>
<td>7 (13.5)</td>
<td>2:5 (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 2</td>
<td>7 (17.8)</td>
<td>2 (4.1)</td>
<td>2:4 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 3</td>
<td>2 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 4</td>
<td>2 (5.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 5</td>
<td>21 (56.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney transplantation state</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On dialysis (HD or PD)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).

Table 3. Diagnostic variants identified in whole-exome sequencing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>CKD stage</th>
<th>Clinical presentation</th>
<th>Gene symbol</th>
<th>Gene change</th>
<th>Clinical implications of genetic information</th>
<th>Family counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>CDH1</td>
<td>c.6883C&gt;T</td>
<td>2q36.3 deletion including CDH1</td>
<td>Family counseling</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>FAM20A</td>
<td>c.1259A&gt;G</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>M</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>GATA3</td>
<td>p.His420Arg</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>ACTN4</td>
<td>c.76dup</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>NUP107</td>
<td>c.6012-2T&gt;A</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>M</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>CUBN</td>
<td>c.718A&gt;G</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>WT1</td>
<td>c.4855+2C&gt;G</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>COL4A3</td>
<td>c.76dup</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>COL4A4</td>
<td>c.76dup</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>M</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>PAX2</td>
<td>c.6012-2T&gt;A</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>F</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>Joubert</td>
<td>c.6012-2T&gt;A</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>M</td>
<td>Stage 1</td>
<td>Forceps, F, UP-ESKD, 1</td>
<td>Joubert</td>
<td>c.6012-2T&gt;A</td>
<td>p.Arg406Ter</td>
<td>Family counseling</td>
</tr>
</tbody>
</table>

Discussion

In this study, we used WES to identify the genetic causes of pediatric CKD in Republic of Korea. The diagnostic yield of this approach was 32.4%, encompassing 10 genes, one copy number variation, and one microdeletion. This is similar to previous studies reporting detection rates of causal mutations. Mutations were detected in approximately 25% and 30% of patients with WES and from Sanger sequencing [15, 16], respectively. These causative mutations were detected in patients diagnosed before the age of 25 years. Furthermore, children with kidney failure had a detection rate of approximately 40% [6]. With rapid technological advances, we expect that regular real-time, re-interpretation, and reclassification of variants will increase these detection rates [22, 24].

The primary diagnosis in patients with ESKD is often inaccurate [25], resulting in its characterization as a CKD of unknown origin. In adults, WES provided a genetic diagnosis in 22 out of 92 patients (24%) with CKD of unknown etiology [26], whereas our study established a diagnostic yield of 50%. This shows that WES is effective in determining the genetic causes of CKD of unknown etiology. However, it is important to note that the number of patients in our study was small.

Establishing a precise genetic diagnosis can allow for the preemptive screening of extrarenal manifestations. Patients clinically diagnosed with isolated CARRT can have mutations in genes that cause syndromic diseases [27]. In other cases, extrarenal manifestations could be detected later in life. Moreover, subtle phenotypes may be initially overlooked and only identified through a genetic diagnosis. In these cases of reverse phenotyping, identifying a genetic mutation can lead to preemptive screening for extrarenal manifestations, leading to early provision of treatment where possible. In our study, extrarenal symptoms were identified to obtain a genetic diagnosis of WT1, PAX2, and CEP290 defects.

Recent KDIGO guidelines recommend discontinuing immunosuppressive agents if a monoclonal cause is diagnosed in a patient with focal segmental glomerulosclerosis. Furthermore, concerns regarding kidney donations by living donors may be
alleviated because of the reduced risk of recurrence [28]. In addition, genetic diagnosis aids in choosing potential donors among living relatives. For example, if Alport syndrome is diagnosed in a male patient, his mother needs to be tested for the presence of pathogenic variants before considering donating a kidney to her son. This is of clinical importance because we genetically identified Alport syndrome in patients with a clinical diagnosis of focal segmental glomerulosclerosis. This finding is an indication of variable phenotypic expressions caused by mutations in COL4A genes, such as hematuria or proteinuria, and is consistent with recent studies [19–21]. The limitations of our study include a relatively short study period and small sample size, in addition to its single-center design. Another limitation is that only one patient had a family history of CKD. In addition, some compound heterozygous variants were not investigated for phasing. The significance of variants of uncertain significance was not investigated further because it was beyond the scope of this study. The inherent shortcomings of WES include the possibility of missing mutations in introns, copy number variations, trinucleotide repeat expansions, methylation abnormalities, and mutations in exons with low coverage [22]. In conclusion, WES provided a genetic diagnosis in a considerable proportion of patients with pediatric CKD in Republic of Korea, which may confirm clinical diagnoses, provide guidelines for patient management, and aid in genetic counseling. Our study provides more evidence supporting WES as a new diagnostic method for identifying CKD etiology in children.

**Ethical statements**

This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 2011-0481-1175). All patients were enrolled after informed consent was obtained from them and their caregivers.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**Author contributions**

- Conceptualization: YHA, HGK
- Formal analysis: HL
- Funding acquisition: HGK
- Investigation: YHA
- Methodology: HGK
- Visualization: YHA
- Writing-original draft: HL
- Writing-review & editing: HGK

All authors read and approved the final manuscript.

**References**

Delta neutrophil index as a predictor of vesicoureteral reflux in children with febrile urinary tract infection

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Purpose: Delta neutrophil index (DNI) indicates immature granulocytes in peripheral blood and has been confirmed to be effective as a prognostic factor for neonatal sepsis. Also, it has been reported to have diagnostic value in acute pyelonephritis and in predicting vesicoureteral reflux (VUR) in the infant. We conducted the study to verify whether DNI is also helpful in the entire pediatric age group with febrile urinary tract infection (UTI).

Methods: Medical records of children hospitalized for febrile UTIs were analyzed retrospectively. All subjects underwent kidney ultrasound and voiding cystourethrography. In the group with and without VUR, we compared sex and age, and the following laboratory values: the white blood cell count, neutrophil, polymorphonuclear leucocyte, eosinophil, hemoglobin, platelet count, C-reactive protein, DNI value, and the finding of ultrasound.

Results: A total of 315 patients (163 males and 152 females; range, 0–127 months) were eligible, and 41 patients (13%) had VUR. As a result of univariate analysis, the white blood cell count, neutrophil, DNI, and ultrasonic abnormalities were high in the reflux group, and the hemoglobin and lymphocyte fraction values were low. The value of DNI and the abnormal ultrasound were significantly higher in the reflux group on the multivariate analysis. The area under the curve of the receiver operating curve was higher in DNI (0.640; 95% confidence interval, 0.536–0.744; P = 0.004), and the DNI cutoff value for VUR prediction was 1.85%.

Conclusions: We identified that ultrasound findings and DNI values were helpful predictors of VUR in pediatric febrile UTIs.

Keywords: Child; Urinary tract infections; Vesico-ureteral reflux

Introduction

Urinary tract infection (UTI) is a common bacterial disease in childhood. If appropriate diagnosis and treatment are not performed early, chronic renal failure or high blood pressure may occur due to renal scars [2]. In particular, in infants, about 30% to 50% of children with UTIs are known to have urinary tract abnormalities [1], and vesicoureteral reflux (VUR) is common. VUR is diagnosed in about 25% to 50% of children with febrile UTI and is well known to cause recurrent UTI and renal scar [4]. It can be diagnosed through voiding cystourethrography (VCUG), but discussions on the indication of the test have continued because it has a disadvantage in radiation exposure and invasiveness. Previously, VCUG was recommended in children between the ages of 2 months and 2 years with febrile UTI [5], but the revised American Academy of Pediatrics (AAP) guidelines in 2011 stated that VCUG should not be performed routinely after the first febrile UTI but performed in specific circumstances [6]. Therefore, young age, high C-reactive protein (CRP) concentration, family history of urinary tract diseases, and neurourological abnormalities have been suggested as risk factors for VUR to predict VCUG implementation [7,8], but the association is not clearly established.

Meanwhile, immature granulocytes appear in peripheral blood in the process of promoting granulocyte production in the bone marrow during infection or systemic inflammatory reactions, and recently, these immature granules have been steadily suggested as predictors of infection or sepsis [9–11]. However, it was difficult to apply clinical trials because manual calculation is required to identify immature granules, and accuracy depends on the examiner. Delta neutrophil index (DNI) was recently proposed as a new indicator to reflect the circulating fraction of immature granules [9]. DNI is an index calculated in leukocyte identification in ADIVA 2120 (Siemens Healthineers, Erlangen Germany), one of the types of automatic blood cell analyzer [12], which has the advantage of obtaining results quickly because it is automatically calculated during complete blood count. Because DNI reflects the number of immature granulocytes, it has been reported to help determine the severity of patients suspected of sepsis or systemic inflammation [9,13,14], and recent studies have also reported diagnostic value in young infants with febrile UTI [15]. Lee et al [15] identified that DNI showed a moderate specificity and low sensitivity for predicting the presence of VUR, especially in newborn infants. So, the authors conducted this study to confirm the clinical usefulness of DNI as a predictor of VUR in the entire pediatric age group with febrile UTI.

Methods

From December 2002 to April 2007, the medical records of children hospitalized for febrile UTI at Konyang University Hospital in Daejeon were analyzed retrospectively. Because VCUG was selectively implemented since 2011 after the changed AAP guideline, we selected patients with febrile UTI who were treated before 2011 who underwent both kidney ultrasound (USG) and VCUG to reduce selection bias.

Among them, 355 people (163 males and 192 females) who underwent both kidney USG and VCUG were included as the study subjects. Total white blood cell count, polymorphonuclear leukocyte, total neutrophil count, CRP, hemoglobin, platelet count, DNI value, and abnormalities of USG were compared in both groups with or without VUR. Those who did not perform either test or had congenital deformities such as single kidney, bladder diverticulum, or polycystic kidney disease were excluded.

We used the blood test results performed on the hospitalization date, and the total blood cell calculation value and DNI were automatically calculated by the automatic blood cell analyzer (ADIVA 2120; Siemens Healthineers). The DNI values calculated through the ADIVA 2120 automated blood cell analyzer are as follows: DNI=(the leukocyte subtraction assayed in the myeloperoxidase channel by cytochemical reaction)–(the leukocyte subtraction counted in the nucleolobularity channel by the reflected light beam).

USG-positive was defined as cases whose renal USG performed by radiologist confirmed one-sided or both-sided pelviectasia or hydronephrosis, and VUR was defined as cases reflux from VCUG was confirmed.

SPSS version 25.0 (IBM Corp, Armonk, NY, USA) and R package 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Through univariate and multivariate analysis and area under the curve value of the receiver operating characteristic (ROC) curve, we compared the effectiveness of the variables and obtained the cutoff value of DNI. The case of P<0.05 was judged to be statistically significant.

Results

Baseline characteristics

Of the 355 patients, 163 (51.7%) were boys and 192 (53.8%) were girls, and the average age was 14.0±22.9 months (median, 4.7 months; range, 0–127 months). There were 209 (66.3%) under the age of 1 year, 81 (25.7%) from 1 to 5 years of age, and 25 (7.0%) over 5 years of age, respectively (Fig. 1). There were 65 patients (20.6%) with USG-positive, and 41 patients (11.6%) diagnosed VUR on one or both sides by VCUG (Table 1).

Comparison of VUR positive and negative group

The mean age of reflux group was 14.2±20.1 months, which is not different from the group without VUR (14.0±23.2 months). Girls (n=24, 58.5%) were more common in the VUR group, and boys (n=46, 53.3%) were more common in the group without VUR, but there was no statistically significant difference between the two groups. Blood tests showed no difference in eosinophil fraction (P=0.293), polymorphonuclear leukocyte fraction (P=0.223), and platelet count (P=0.380), but the total white blood cell count (18.06±5.0×10⁹/L vs. 15.36±7.0×10⁹/L, P=0.033), neutrophil fraction (57.1%±19.3% vs. 50.7%±18.5%, P=0.039), and CRP (2.6±16 mg/dL vs. 4.20±20 mg/dL, P=0.003) showed higher

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values of the VUR group (Table 3).

The rate of abnormal findings on USG was 36.6% (15/41) in the reflux group and 18.2% (50/274) in the group without VUR (P = 0.007). Even in the group with VUR, as many as 63.5% (32/50) of patients showed normal findings on renal USG. In our study, the detection sensitivity of renal USG for VUR was only 34.5%. It is because VUR grades 1 and 2 do not have hydronephrosis, and grade 3 may not have hydronephrosis, depending on the status of the bladder. The DNI value was also statistically significantly higher in the reflux group (3.4%±10.0% vs. –0.2%±5.6%, P = 0.030) (Table 1).

Possible predictive factors for VUR

As a result of multivariate logistic regression analysis, the variables that differed significantly between the group with and without VUR were CRP, kidney USG, and DNI. It means that these indices can be used to predict the existence of VUR. The odds ratio (OR) of USG-positive, CRP, and DNI were 2.744 (95% confidence interval [CI], 1.249–6.026; P = 0.0012), 1.83 (95% CI, 1.93–1.604; P = 0.0001) and 1.079 (95% CI, 1.036–1.147; P = 0.004), respectively (Table 2).

We used ROC analysis to compare the predictive capabilities of these indices. The area under the curve of the ROC curve of the USG-positive was 0.408 (95% CI, 0.309–0.507; P = 0.005). CRP was 0.631 (95% CI, 0.540–0.721; P = 0.0005), and that of DNI was 0.640 (95% CI, 0.536–0.744; P = 0.004), the highest at DNI (Table 3, Fig. 2).

The cutoff value of DNI for the prediction of VUR

The cutoff of the DNI for VUR prediction was statistically significant when set to 1.85 (P = 0.050). The sensitivity was 68.2%, and the specificity was 66.7%. The positive predictive value was 23.5%, and the negative predictive value was 93.4%.

Discussion

UTI in children can lead to renal scars, chronic renal failure, and high blood pressure due to damage to the renal parenchyma if diagnosed early and not appropriately treated. VUR is diagnosed in about 25% to 50% of children with UTI, which can cause recurrence risk and renal scar [4], so continuous prophylactic antibiotic use or surgical correction through early detection of VUR has been considered necessary in all children with UTI. AAP recommended VCUG in all first febrile UTIs in guidelines of 1999 [5], but follow-up studies showed that the use of continuous prophylactic antibiotics or surgical correction did not reduce renal scars [6–10] in children with VUR. In addition, it was virtually impossible completely prevent renal scar in children with VUR [20–24] because most of the severe renal scars that cause hypertension and chronic renal failure, occurred prior to infection from the fetal period. Therefore, questions have been raised about the role of VCUG implemented after the first febrile UTI, and the changed guidelines recommend selective implementation. The 2007 British guidelines recommended VCUG only in atypical UTIs that did not respond well to treatment or recurrent UTIs in infants less than 6 months [25]. They suggested that VCUG was not required in children with uncomplicated UTIs over 6 months of age. The 2011 revised guidelines of AAP recommended VUCG only for children with abnormalities on USG, atypical clinical course, or children with recurrent UTI, and no longer for all children with first febrile UTI [6].

So, many researchers studies have been making efforts to find the predictor for VUR because of the invasiveness, and the risk of radiation exposure VCUG. Gostenhink et al. [7] suggested male, younger age, family history of urinary tract diseases, high level of CRP, and abnormal findings of USG findings as independent factors of VUR. The authors aimed to identify the value of DNI in predicting the presence of VUR in children with febrile UTIs. Recently Lee et al. [15] have identified the value of DNI with a comprehensive and more detailed study. In contrast, our study is a single institutional study and does not include di-mercaptosuccinic acid (DMSA) scan. However, we verified that DNI was still worth predicting the presence of VUR even when the child with UTI is older than 12 months of age.

Our study confirmed that DNI and ultrasonography were preferred predictors of VUR, which showed similar results to previous studies by Lee et al. [6]. Especially, the area under the curve value of DNI in the ROC curve was the highest, so it was found to be more useful as VUR predictor than the finding of USG-positive recommended by most guidelines.

The cutoff value, which can predict VUR, was set at 1.85, which is low in usefulness as a screening test due to its sensitivities.
Kim et al. Delta neutrophil index as the predictor for VUR


Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

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Author contributions

Conceptualization: JEK, JSO, JMY, KOK, EJC

Data curation: JEK, JSO, JMY, KOK, EJC

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Methodology: JEK, JSO, JMY, KOK, EJC

Project administration: JEK, EJC

Visualization: JEK, JSO, JMY, KOK, EJC

Writing—original draft: JEK, JSO, JMY, KOK, EJC

Writing—review and editing: JEK, JSO, JMY, KOK, EJC

All authors read and approved the final manuscript.

References


Purpose: To determine predictive factors for detecting renal parenchymal damages (RPDs) in infants with recurrent febrile urinary tract infection (fUTI).

Methods: From January 2015 to December 2021, 102 infants with recurrent fUTI and who underwent 99mTc-dimercaptosuccinic acid (DMSA) renal scan in our hospital were included in this study. Controls included infants with normal DMSA results performed 3 months apart from the 2nd episode of fUTI. DMSA-positive group included infants with positive DMSA results performed 3 months apart from the 2nd episode of fUTI or at the 3rd episode of fUTI. The recurrence rate, causative bacteria, renal size discrepancy of both kidneys, and laboratory findings including C-reactive protein (CRP) and spot urine sodium-to-potassium ratio (uNa/K) were compared between both groups.

Results: Only 3.8% of 79 infants with a 2nd episode of fUTI showed positive DMSA results. fUTI occurred more frequently within 12 months of follow-up in the DMSA-positive group than in the control group (69% vs. 13%, P<0.001). CRP values were significantly higher in the DMSA-positive group than in the control group (7.3 mg/dl vs. 3.7 mg/dl, P=0.001). Spot uNa/K were significantly lower in the DMSA-positive group than in the control group (0.6 vs. 1.1, P<0.001).

Conclusions: Congenital renal scar and RPDs on the DMSA scan were more frequently found in infants with recurrent fUTI than those in the control group. High CRP values and low spot uNa/K in acute infections were helpful in predicting the presence of RPD in infants with recurrent fUTI. High-grade VUR, a common abnormality of CAKUT causing high-grade vesicoureteral reflux (VUR) (7).

High-grade VUR, a common abnormality of CAKUT causing recurrent fUTI, is a main target of the bottom-up approach in the fUTI imaging strategy mainly because it is an anomaly that needs early surgical management in children with fUTI who have renal scars (8). Nonetheless, if further fUTI does not recur, an acquired renal scar (ARS) is less likely to develop in the future. Among children with fUTI, pyelitis that does not cause renal scarring is more common than pyelonephritis that causes renal scarring (9). If renal scarring does not occur in children with fUTI, immediate surgical treatment is not needed, and if eventually needed, it could be postponed for a later time. Hence, we prefer performing a DMSA scan before a VCUG during the 2nd episode of fUTI.

Renal scarring can lead to renal complications like proteinuria or hypertension, and progression into CRI through recurrent pyelonephritis and so on (6-8).

There have been many reports studying the factors predicting renal scarring in fUTI children. Procalcitonin, high-grade VUR, previous renal scarring, urine pentraxin-3, plasma neutrophil gelatinase-associated lipocalin, and urinary interleukin-6 or interleukin-8 positively correlated with the presence of renal scarring in fUTI children (10-15). Although procalcitonin was a better predictor of renal scarring, it was more expensive than C-reactive protein (CRP). The other predicting factors were clinically impractical methods in the general clinical field and correlated with the presence of VUR.

Some authors have published a few reports pertaining to spot urine sodium-to-potassium ratio (uNa/K) as a useful predictor of acute pyelonephritis in fUTI children excluding pyelitis or lower UTI with other fever focus (16-18). In these studies, authors paid attention whether spot uNa/K could be useful for predicting renal parenchymal damages (RPDs) leading into renal scar.

The aim of this study was to retrospectively analyze the laboratory and radiological findings in children with fUTI who had undergone a DMSA scan in our hospital according to our urinary tract imaging strategy and to determine the factors that predict the presence of RPDs including spot uNa/K.
Han et al. Challenging urinary tract infection imaging strategy

Fig. 1. Schematic view of our hospital's diagnostic approach for febrile urinary tract infection (fUTI). KB, kidney and bladder; DMSA, 99mTc-dimercaptosuccinic acid; VCUG, voiding cystourethrography.

Table 1. Comparison of data between the DMSA-positive group and controls according to urinal tract imaging strategy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=26)</th>
<th>DMSA-positive (n=28)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>42±21</td>
<td>35±18</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>24/2</td>
<td>55/21</td>
<td>0.03</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>10±76</td>
<td>12±102</td>
<td>0.01</td>
</tr>
<tr>
<td>Recurrent APN after DMSA scan</td>
<td>9 (33)</td>
<td>10 (36)</td>
<td></td>
</tr>
<tr>
<td>Interval between the 1st and 2nd episode (mo)</td>
<td>2.3±12.7</td>
<td>3.3±13</td>
<td>0.13</td>
</tr>
<tr>
<td>Urine culture-negative fUTI</td>
<td>2 (8)</td>
<td>3 (4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Same bacteria as that in the 1st episode on urine culture</td>
<td>14 (56)</td>
<td>52 (68)</td>
<td>0.16</td>
</tr>
<tr>
<td>Non-ESBL etiology cause</td>
<td>5 (20)</td>
<td>8 (30)</td>
<td>0.29</td>
</tr>
<tr>
<td>ESBL-positive</td>
<td>9 (35)</td>
<td>20 (70)</td>
<td>0.18</td>
</tr>
<tr>
<td>Congenital scar</td>
<td>9 (35)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blood tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>7.3±7.7</td>
<td>3±1±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cell (μL)</td>
<td>18,309±7,744</td>
<td>16,043±5,526</td>
<td>0.12</td>
</tr>
<tr>
<td>Procalcitonin (μg/mL)</td>
<td>6.1±90</td>
<td>1±92</td>
<td>0.09</td>
</tr>
<tr>
<td>Urine tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein/creatinine ratio</td>
<td>14±19</td>
<td>16±19</td>
<td>0.03</td>
</tr>
<tr>
<td>Urine Na (mEq/L)</td>
<td>22.3±16.0</td>
<td>28.1±24.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Urine K (mEq/L)</td>
<td>346±140</td>
<td>190±160</td>
<td>0.07</td>
</tr>
<tr>
<td>Urine Na/K ratio</td>
<td>0.6±0.4</td>
<td>1.1±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both kidney size discrepancy on US (cm)</td>
<td>0.7±0.8</td>
<td>0.4±0.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). DMSA, 99mTc-dimercaptosuccinic acid; APN, acute pyelonephritis; fUTI, febrile urinary tract infection; ESBL, extended-spectrum beta-lactamase; Na, sodium; K, potassium; US, ultrasonography.

*Student t-test

Table 2. Results of 13 infants who received voiding cystourethrography

<table>
<thead>
<tr>
<th>VUR grade</th>
<th>Overall</th>
<th>cRS</th>
<th>Focal defect</th>
<th>Multifocal defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VUR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>
| VUR, vesicoureteral reflux; cRS, congenital renal scar.

Results

Among 79 infants with the 2nd episode of fUTI, only three (3.8%) showed positive DMSA results on the scan performed 3 months after the last episode, including an infant who had cRS. Among 27 infants with a 3rd episode of fUTI, four (14.8%) had normal renal cortices, eight (29.6%) had mild cortical defects, eight (29.6%) had cRS, and seven (25.9%) had moderate to severe cortical defects (photopenia) with normal renal contour line. Moderate to severe cortical defects were defined as the presence of one or two cortical defects (photopenia) with normal renal contour line. Moderate to severe cortical defects were defined as the presence of multiple focal cortical defects (photopenia) on the DMSA scan. Patients with normal DMSA findings were included in the control group.

We compared clinical characteristics; CRP, WBC, uNa/K, urine culture, and renal US between the DMSA-positive and control groups. Mean values of blood and urine samples from the 1st and 2nd episodes in each patient were calculated. All data were retrospectively analyzed.

All variables are presented as mean±standard deviation, and Student t-test was used when factors were compared between two independent groups. Continuous variables were analyzed using Wilcoxon-Mann-Whitney test. Statistical significance was defined as P<0.05.

Discussion

The recurrence of fUTI has already been known as a strong predisposing factor of cRS regardless of age of occurrence [9]. This study also showed that infants with positive DMSA results had more frequent episodes of fUTI than controls, however, the follow-up period was short. In this study, only 3.8% of infants with a 2nd episode of fUTI had positive result on the DMSA scan performed 3 months after the acute infection. In this study, the detection rate of cRS at the 2nd episode of fUTI was 2.5%, but it increased to 29.6% at the 3rd episode. Similar to high-grade VUR, cRS seems to be a strong independent predictive factor of recurrent fUTI. Previous renal scarring has already been known as a predictive factor for new renal scar formation [12]. Although a study reported that non-E. coli UTI was associated with the development of renal scars, this study contradicted that result [20]. This study supported the result of a report that CRP could predict renal scarring in children with fUTI [21]. Some studies also reported on the association between serum procalcitonin

This study supported the result of a report that CRP could predict renal scarring in children with fUTI [21]. Some studies also reported on the association between serum procalcitonin
treatment at a tertiary hospital. In conclusion, RPFs on the DMSA scan were found more frequently in infants with recurrent UTI than in the control group. High CRP values and low uNa/K sampled at the acute phase of infection were helpful in predicting the presence of RPFs in infants with recurrent UTI.

Ethical statements

The CHA University Institutional Review Board approved this study and the consent procedure (No. CHA 2021-09-041). The informed consent was waived because of the retrospective nature of this study.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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None.

Author contributions

Conceptualization: JHL, JHH, SR
Data curation: JHH
Formal analysis: JHL, JHH
Methodology: JHL
Visualization: JHH
Writing-original draft: JHL, JHH, SR
Writing-review & editing: JHL, JHH, SR
All authors read and approved the final manuscript.

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Recurrent hemolytic uremic syndrome caused by DGKE gene mutation: a case report

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Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury without any association with preceding diarrhea. Dysregulation of the complement system is the most common cause of aHUS, and monoclonal humanized anti-C5 antibodies are now recommended as the first-line treatment for aHUS. However, if the complement pathway is not the cause of aHUS, C5 inhibitors are ineffective. In this study, we report the second reported case of aHUS caused by DGKE mutations in Republic of Korea. The patient was an 11-month-old infant who presented with prodromal diarrhea similar to typical HUS, self-remitted with conservative management unlike complement-mediated aHUS but recurred with fever. While infantile aHUS often implies genetic dysregulation of the complement system, other rare genetic causes, such as DGKE mutation, need to be considered before deciding long-term treatment with C5 inhibitors.

Keywords: Atypical hemolytic uremic syndrome; Complement factor H; DGKE epsilon; Eculizumab; Thrombotic microangiopathies

Introduction

Hemolytic uremic syndrome (HUS) is a form of thrombotic microangiopathy (TMA), characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury [1]. In children, enterohemorrhagic Escherichia coli (EHEC) producing Shiga toxin is the most common cause of HUS (typical HUS), accounting for 90% of pediatric cases. However, some past, plasma therapy (plasma exchange or plasma infusion) was applied to ameliorate the dysregulation of complement activation, which is often insufficient to prevent permanent damage to the kidneys. Currently, monoclonal humanized anti-C5 antibodies, such as eculizumab, which block activation of the complement pathway, are the first-line treatment for aHUS with excellent renal outcomes [3]. However, C5 blockade is not always safe because the complement system plays a crucial role in the immune system, as indicated by the fatal outcome of meningococcal infection in patients who were treated with eculizumab, the first monoclonal humanized anti-C5 antibody approved for the treatment of aHUS [4]. Therefore, C5 blockade is only indicated when dysregulated complement activation is involved in the pathophysiology of aHUS.

While C4H mutations are the most common cause of aHUS, especially in children [4,5], gene other than those involved in the complement system have also been implicated in aHUS DGKE, encoding diacylglycerol (DAG) kinase epsilon (DGKE), is one such gene. Lemaire et al. [5] identified this gene using whole-exome sequencing of a patient with infantile aHUS. DGKE is found in the endothelium, platelets, and podocytes in endothelial cells, anadecylase acid-containing DAG activate protein kinase C, promoting thrombosis, and DGKE normally inactivates DAG signaling [5]. Therefore, DGKE mutations result in a thrombogenic status, which is not related to complement pathway activation. DGKE mutations are known to cause steroid-resistant nephrotic syndrome or membranoproliferative glomerulonephritis [6]. In Republic of Korea, an aHUS case caused by a DGKE mutation has been reported previously [6], but the details of the clinical course are not well documented.

Here, we report the second case of aHUS caused by DGKE mutations in Republic of Korea.

Case report

An 11-month-old male patient presented to a local pediatric clinic with a fever. Antibiotics were prescribed for the pre-clinical episode. At the age of 40 months, 29 months after the first episode, he experienced a third episode of aHUS along with a fever of up to 39°C and melena. The fever subsided after 2 days, but he looked pale after 4 days, so he visited a local pediatric clinic. He was found to have anemia (Hb, 9.8 mg/dL) and 4 level (18 mg/dL) were within normal limits. He had oliguria (80 mL/day, 7.8 mL/kg/day); thus, hemodialysis was administered. He did not recur despite discontinuation of medications.

At the age of 57 months, he was transferred to our institution. In laboratory workup, mild anemia (Hb, 9.4 mg/dL) and mild creatinine elevation (0.42 mg/dL, baseline 0.35 mg/dL) were noted along with elevated plasma Hb (14.6 mg/dL) and lactate dehydrogenase (585 IU/L), suggesting hemolysis. Hematuria (100 RBC/HFP) and proteinuria (UPCR, 5.60 g/day creatinine) were evaluated by urinalysis. Both stool polymorph chain reaction and culture were negative for EHEC. After admission, the patient’s general condition and laboratory abnormalities improved without treatment for several days. Suspecting an aHUS relapse, a kidney biopsy was performed. The glomeruli were mildly increased in size and had focal mild hypercellular endothelial cells and tram-track appearance. Two global sclerotic glomeruli were noted among the 57 glomeruli. Slight focal infiltration of mononuclear cells was observed in the tubules. Diffuse thickened glomerular basement membrane, slight effacement of the foot process, subendothelial widening and mesangial interposition were observed by electron microscopy. In immunofluorescence staining, C3 and Lambda were reported as +/–, and IgM and C4d were reported as positive in the glomerular capillary loops and peritubular capillaries (Fig. 1). Therefore, the pathological findings were consistent with chronic TMA. The TMA gene panel revealed a homozygous nonsense mutation (c.3498C>T in exon1 [p.Arg500*]) in DGKE. This gene covers 25 genes associated with TMA and HUS (ADAMTS13, C1S, C2, C3, C4A, C4B, C5, C5B, C5L2, C6, C9, CFI, CFIIR, C3, MASP1, MASP2, MBL2, MCP1, MHC2, MOCOS, MPERT, RTC), and aHUS caused by DGKE mutations. Protonuria was monitored during follow-up. When he was 31-month-old, his protonuria increased to 1.7, therefore, erapril was prescribed. After 2 weeks, protonuria disappeared and he did not recur despite discontinuation of medications. At the age of 40 months, 29 months after the first episode, he experienced a third episode of aHUS along with a fever of up to

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ChKD CHILDHOOD KIDNEY DISEASES

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Shin et al. A case of recurrent HUS caused by DGKE mutation

In general, HUS in young children is typically followed by bloody diarrhea due to EHEC infection. Typically, they have a history of ingesting raw or undercooked food. Otherwise, aHUS should be suspected, especially in very young infants. Unlike typical HUS, aHUS does not spontaneously remit and often relapses. Since it can be fatal, aggressive management is necessary, previously with plasma and now with C5 inhibitors, if aHUS is associated with complement dysregulation. The CHF mutation was first suspected in a case of very young aHUS. For aHUS with a CHF mutation, C3 levels often decrease, and approximately 60% to 70% of patients lose renal function if not properly managed [11]. However, our patient had normal C3 levels and a self-remitting course, which was not consistent with aHUS associated with complement dysregulation. In such cases, a DGKE defect must be suspected. Currently, correct genetic diagnosis is more important because of the availability of C5 inhibitors, the treatment of choice for complement-related aHUS.

Eculizumab, the currently available C5 inhibitor, is an antibody targeting the complement pathway, it is unrelated to the DGKE mutation, which is related to the coagulation pathway. There have been some case reports of DGKE mutation-associated aHUS in which eculizumab was effective [12]. However, these cases might have recovered even without eculizumab, since DGKE-associated aHUS is usually self remitting. Eculizumab has been proven to be relatively safe and very effective for aHUS, but it is regularly administered to prevent relapse of aHUS once indicated. Therefore, even when aHUS is suspected, causes other than complement system dysregulation must be considered before deciding to administer C5 inhibitors. Other than DGKE mutations, secondary causes of aHUS include medication, malignancy, infection, autoimmune diseases, and genetic causes, such as cobalamin C defect or G6PD deficiency.

Despite the self-remitting course of aHUS caused by DGKE defects, the long-term outcome of DGKE defects is not favorable. Chronic kidney disease stages 4 and 5 are common in patients with DGKE mutation [7]. Until the last follow-up, our patient showed third relapse. Chronic relapse of aHUS or development of membranoproliferative glomerulonephritis and/or steroid-resistant nephrotic syndrome might occur in this patient in the future. Therefore, careful long-term follow-up was indicated in this case.

HUS in infants is not common, mandating the suspicion of aHUS. While CHF or other complement-related aHUS is more prevalent, DGKE mutations need to be suspected in cases with normal complement levels and spontaneously recovering courses. Although aHUS related to DGKE may recur, a C5 inhibitor is not indicated. However, close follow-up is necessary, because other glomerulopathies may have occurred in this case.

Ethical statements

This study was approved by the Institutional Review Board of Seoul National University Hospital (No. H-2011-048-1171). Informed consent from patient was obtained.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: BSS, YHA, HGK
Data curation: BSS
Formal analysis: BSS
Funding acquisition: YHA, HGK
Investigation: BSS
Methodology: BSS
Project administration: HGK
Visualization: BSS
Writing-original draft: BSS
Writing-review & editing: HGK

All authors read and approved the final manuscript.

References


Discussion

This is a case of recurrent HUS that showed spontaneous remission with supportive care. Because of the infantile-onset and relapse history, aHUS was suspected, and a DGKE mutation was identified by a genetic test. The homozygous nonsense mutation of this patient (c.1498C>T in exon11 (p.Arg500*)) has not been reported before. However, as it is a truncating mutation, the mutation is considered as pathogenic in this patient. Similar to previous reports on DGKE mutations, our case presented at a very early onset (median age < 1 year) with aHUS with a self-limiting disease course [9,10]. His initial presentation was accompanied by diarrhea; therefore, typical HUS was suspected at first. However, aHUS is often triggered by infection, and the first episode in our case was triggered by gastrointestinal infection.

Fever

Hb, UPCR, urine protein/creatinine ratio

Fig. 2. Laboratory data. Fever events are annotated with red arrows. Hb, hemoglobin; UPCR, urine protein/creatinine ratio.

40°C and hematuria. Spontaneous remission was achieved within 1 month without medication. At the last follow-up at the age of 46 months, his blood pressure and laboratory findings were unremarkable, without proteinuria. Hb and UPCR levels during follow-up are displayed in Fig. 2.

Fig. 1. Pathologic findings. (A) Electron microscopy image. Diffuse thickened glomerular basement membrane and focal slight effacement of foot process were marked with red arrows. (B) Electron microscopy image. Subendothelial widening and mesangial interposition were marked with blue circle. (C) Periodic acid–Schiff staining image (×400). Endothelial cells were mildly circ器ular in the glomerulus and glomerular size was mildly increased (marked with black arrow). Some glomerulus showed tram-track appearance (marked with green arrowheads).

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Shin et al. A case of recurrent HUS caused by DGKE mutation


Idiopathic infantile hypercalcemia with severe nephrocalcinosis, associated with CYP24A1 mutations: a case report

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Nephrocalcinosis often occurs in infants and is caused by excessive calcium or vitamin D supplementation, neonatal primary hyperparathyroidism, and genetic disorders. Idiopathic infantile hypercalcaemia (IIH), a rare cause of nephrocalcinosis, results from genetic defects in CYP24A1 or SLC34A1. Mutations in CYP24A1, which encodes 25-hydroxyvitamin D 24-hydroxylase, disrupt active vitamin D degradation. IIH clinically manifests as failure to thrive and hypercalcemia within the first year of life and usually remits spontaneously. Herein, we present a case of IIH with CYP24A1 mutations. An 11-month-old girl visited our hospital with incidental hypercalcemia. She showed failure to thrive, and her oral intake had decreased over time since the age of 6 months. Her initial serum parathyroid hormone level was low, 25-OH vitamin D and 1,25(OH)2 vitamin D levels were normal, and renal ultrasonography showed bilateral nephrocalcinosis. Whole-exome sequencing revealed compound heterozygous variants in CYP24A1 (NM_000782.4:c.376C>T [p.Pro126Ser] and c.1310C>A [p.Pro437His]). Although her hypercalcemia and poor oral intake spontaneously resolved in approximately 8 months, we suggested that her nephrocalcinosis and renal function be regularly checked in consideration of potential asymptomatic renal damage. Hypercalcemia caused by IIH should be suspected in infants with severe nephrocalcinosis, especially when presenting with failure to thrive.

Keywords: Case reports; Failure to thrive; Hypercalcemia; Nephrocalcinosis; Vitamin D3 24-hydroxylase

Introduction

Nephrocalcinosis, a possible cause of chronic kidney disease (CKD), is rarely identified during infancy. Because it may lead to kidney damage [1,2], the underlying causes need to be identified and managed, if possible. Nephrocalcinosis is commonly caused by primary hyperparathyroidism, long-term use of loop diuretics or vitamin D, distal renal tubular acidosis, and hereditary disorders, such as Bartter syndrome [1,3]. Therefore, evaluation of childhood nephrocalcinosis includes urine analysis of hematuria, protein excretion, pH, calcium excretion, and other minerals such as uric acid, oxalic acid, phosphate, and citrate. Analyses of serum calcium, phosphorus, magnesium, uric acid, alkaline phosphatase, pH, bicarbonate, and creatinine levels are also required. Additional studies including parathyroid hormone (PTH), vitamin D metabolites, and molecular genetic

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idiopathic infantile hypercalcemia (IIH) is a rare disorder caused by a genetic defect in the key enzymes involved in calcium and vitamin D metabolism. The incidence of IIH is approximately 1 in 30,000 live births, and until now, two causative genes have been identified for IIH: CYP24A1 (IIH type 1) and SLC34A1 (IIH type 2) [1,2]. CYP24A1 encodes 25-hydroxyvitamin D-24- hydroxylase (CYP24A1), a component of the mitochondrial inner membrane P450. When vitamin D, cholecalciferol, is administered to the human body through the skin and diet, it is metabolized through 25-hydroxylation in the liver and then via 1α-hydroxylation in the kidney to produce biologically active 1,25-dihydroxyvitamin D$_{25-OH}$D$_3$. This active 1,25-(OH)$_2$D$_3$ is catabolized by CYP24A1, making it a water-soluble metabolite of calcitriol [3]. CYP24A1 also catalyzes 25-hydroxyvitamin D$_{25-OH}$D$_3$, the precursor of active vitamin D. Thus, CYP24A1 plays a critical role in regulating active vitamin D levels, and defective CYP24A1 increases the concentration of 1,25-(OH)$_2$D$_3$, in the blood. SLC34A1 encodes the Na+/phosphate (Pi) cotransporter NaPi-IIa, a transmembrane cotransporter in the proximal renal tubule, which plays an essential role in absorbing Pi from primary urine [4]. Defective absorption of Pi due to dysfunctional NaPi-IIa in IIH type 2 stimulates inappropriate synthesis of 1,25-(OH)$_2$D$_3$. Therefore, both IIH types 1 and 2 present with an inappropriately high concentration of 1,25-(OH)$_2$D$_3$, calcitriol. Calcitriol regulates serum ionized calcium levels by stimulating intestinal calcium reabsorption and renal calcium reabsorption at the distal tubule (along with PTH) or activating PTH when serum calcium levels are low. PTH stimulates osteoclast formation and differentiation, which in turn induces calcium mobilization from bones [5]. Therefore, in IIH, abnormally elevated active calcitriol levels eventually cause hypercalcemia via its action on the intestine, kidneys, and bones.

In patients with IIH, the classic manifestations include vomiting, anorexia, polyuria, polydipsia, hypotonia, and failure to thrive within 1 year of life, most commonly within 3 to 7 months of age. Unexplained fever, constipation, and hypertension can also occur. Laboratory evaluations usually reveal suppressed serum PTH levels, mildly elevated 25-(OH)D$_3$, and 1,25-(OH)$_2$D$_3$ levels, and hypercalcemia, often accompanied by nephrocalcinosis [7,8]. The management of IIH is mainly conservative, with a recommendation of low-calcium diet and avoiding excessive vitamin D. When necessary, intravenous fluid hydration can be used to alleviate hypercalcemia and dehydration. If symptomatic hypercalcemia persists, glucocorticoids to prevent renal calcium reabsorption and inhibition of 1,25-(OH)$_2$D$_3$ activity, bisphosphonates for inhibition of osteoclast activity, or azole agents (e.g., ketoconazole) for inhibition of P450 enzymes can be considered. Pi supplementation is necessary in case of defective NaPi-IIa in IIH type 2 [8]. In rare cases, rapid hemodialysis management is required to treat life-threatening hypercalcemia [6,9].

Herein, we present a case of severe nephrocalcinosis, where in genetic analysis revealed IIH type 1 with pathogenic compound heterozygous variants of CYP24A1. This report has its significance in that this case is the first report of IIH type 1 patient from South Korea, among whom genetic analysis had been done.

**Case report**

An 11-month-old girl was transferred to our hospital for a second opinion on incidentally discovered hypercalcemia. Hypercalcemia was found at a primary hospital during laboratory workup for fever. Initially, her calcium level was 13.4 mg/dL (reference: 8.6–10.2 mg/dL), ionized calcium level was 1.55 mmol/L (reference: 1.15–1.33 mmol/L), and spot urine calcium/creatinine was 2.19 mg/mg (reference: ≤0.6 mg/mg creatinine), respectively. Serum phosphate level was 5.0 mg/dL, and blood urea nitrogen and creatinine were 23.8 mg/dL and 0.44 mg/dL, respectively. The albumin level was normal and intact PTH level was low, less than 0.7 pg/mL. The urine analysis at the primary hospital showed hypercalcemia, but there was no nephromia or proteinuria. Urine electrolytes (sodium, potassium, uric acid, phosphorus, and magnesium) were not abnormally elevated. When she was initially brought to our hospital, physical examination results were nonspecific and unremarkable. The fever had subsided, but poor oral intake, which was noticed at the age of 6 months, persisted. At that time, her serum calcium and phosphorous levels were 2.2 mg/dL (reference: 8.8–10.5 mg/dL) and 4.7 mg/dL (reference: 4.1–6.2 mg/dL), respectively, ionized calcium level was 1.62 mmol/L (reference: 1.05–1.35 mmol/L), and creatinine level was 0.54 mg/dL. Serum albumin level was 4.7 g/dL (reference: 3.3–5.2 g/dL). Urine analysis revealed no hematuria or proteinuria, and urine calcium to creatinine ratio also improved so there was no hypercalciuria. Her spot urine calcium to creatinine ratio was 0.36 mg/mg.

She was born after 37 weeks and 4 days of gestation, with a birth weight of 3.2 kg (62nd percentile). She had no developmental delays. She had been fed approximately 600 mL/day of powdered milk and 200 mL/day of weaning food. She was receiving 5 mL/day of multivitamin supplementation containing cholecalciferol (4000 IU/100 mL).

Further evaluations for hypercalcemia revealed low PTH levels (0.7 pg/mL, reference: 8–76 pg/mL) excluding hyperparathyroidism, normal PTH-related peptide (less than 11 pmol/L), 25(OH) vitamin D (46.7 ng/mL, reference: 30–100 ng/mL), and 1,25(OH)$_2$ vitamin D levels (23.4 pg/mL, reference: 19.6–54.3 pg/mL). Kidney ultrasonography revealed decreased echogenicity of the medullary pyramids, indicating nephrocalcinosis (Fig. 1A).

Echocardiography was performed to rule out Williams syndrome, Jansen’s metaphyseal chondrodysplasia, or blue diaper syndrome [10].

**Fig. 1.** Renal ultrasonography of the index patient, showing diffuse echogenicity filled in both renal medullary pyramids. (A) Initial examination. (B) Follow-up examination (after 9 months).
were 10·2 mg/dL, with ionized calcium levels at 1·39 mmol/L. At the last visit, which was after 8 months from the first visit to our hospital, serum calcium levels and ionized calcium levels were 10·3 mg/dL and 1·39 mmol/L, respectively. Her body weight at the initial visit to our hospital was 71 kg, which was less than the 3rd percentile for her age. After 2 months, her body weight was 93 kg, which was in the 25th to 50th percentile for her age, and her height was 73 cm, which was in the 5th to 10th percentile. During the last follow-up at the age of 21 months, the patient’s body weight and height were 12 kg (75th–90th percentile) respectively. Follow-up kidney ultrasonography was performed 9 months after the visit, and bilateral kidney nephrocalcinosis was found to be still present (Fig. 18).

Discussion

Herein, we have discussed a typical case of IIH type 1, presenting with severe nephrocalcinosis associated with hypercalcemia and normophosphatemia. Other case reports of IIH in South Korea were those of IIH type 2 (SLC34A1 mutation) (22,13). In one report, nephrocalcinosis was prenatally detected at 28 weeks of gestation. The patient was treated with intravenous hydration, furosemide, and corticosteroids for hypercalcemia (22.6 mg/dL with 14.9.7 mmol/L) for 7 days. Follow-up kidney ultrasonography was performed 9 months after the visit, and bilateral kidney nephrocalcinosis was found to be still present.

In the contractility of smooth muscles, this may contribute to delay of gastric emptying and subsequent reduced appetite [14]. Furthermore, hypercalcemia promotes gastrin secretion, which may contribute to nausea and poor oral intake [15]. Thus, if infants with nephrocalcinosis exhibit poor oral intake, hypercalcemia should be considered, of which IIH is a rare cause. Other more common causes of infantile hypercalcemia include vitamin D overdose and Williams syndrome. Therefore, workup of serum vitamin D metabolites and echocardiography screening are necessary to clinically exclude these etiologies and suspect IIH. Since IIH remits spontaneous in many cases, radical management might not be necessary, and close follow-up is indicated, as shown herein. Nonetheless, long-term follow-up, including kidney function, is necessary because there is a chance of ongoing subclinical metabolic abnormalities in these patients.

The natural history and long-term outcomes of IIH are not well known. Clinical symptoms seem to disappear spontaneously with the normalization of serum calcium levels. However, one study involving long-term follow-up of 18 patients with IIH showed that the renal prognosis of survivors of IIH tended to be poorer than that of the general population, demonstrating a high prevalence of CKD, with CKD II in 77% and two cases of end-stage kidney failure despite avoidance of vitamin D supplementation and sun exposure [16].

A limitation of this report is that phasing of the variants was not possible in this case. Thus, we are not sure whether the two variants exist as cis or trans isoforms. In addition, these mutations are variants of unknown significance and have not been classified to be pathogenic or likely pathogenic according to ACMG (American College of Medical Genetics and Genomics) guidelines. Although, the whole-exome and whole-genome sequencing indicated that the patient met 1 criterion of “moderate evidence of pathogenicity,” and 2 criteria of “supporting evidence of pathogenicity.” Furthermore, these variants have been reported with extremely low frequency from gnomAD database. Secondly, in silico prediction tools and conservational analysis supported deleterious effects on the gene product. Thirdly, the patient’s phenotype is highly specific for IIH. The patient’s clinical presentation and course are compatible with those of IIH type 1, suggesting that this rare disease needs to be considered.

We reported a case of IIH caused by CYP24A1 mutations that presented with fever, failure to thrive, and severe nephrocalcinosis. When idiopathic hypercalcemia and poor oral intake or nephrocalcinosis are present, consideration of IIH as a causative disease is necessary. A proper and timely diagnosis of this disease can help in the correct management. Although the patient’s hypercalcemia resolved, her nephrocalcinosis persisted, implying that careful regular check-ups for her kidney status are needed as subclinical renal injury may still progress.

Ethical statements

The Institutional Review Board of Seoul National University Hospital approved this study (IRB No. 2021-048-172). The study received informed consent for the report from the parents of the patient.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: JY, HGK, YHA
Data curation: JY, HGK
Formal analysis: JY, HGK
Funding acquisition: HGK, YHA
Investigation: JY, HGK, YHA
Methodology: HGK, YHA
Project administration: HGK, YHA
Writing–original draft: JY, HGK
Writing–review & editing: JY, HGK
All authors read and approved the final manuscript.

References

GENERAL INFORMATION

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Shared data should be cited.


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- Minor revision: The author should address the comments from the reviewers, which will be confirmed by the reviewers.
- Major revision: The author should address the comments from the reviewers and make the appropriate corrections for review by the reviewers.
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1) **Reviews:** This type of article offers concise reviews of important topics in pediatric nephrology. Review articles are accepted after peer review. They should have the following structure: title page, unstructured abstract of no more than 200 words and keywords, main text (introduction, body text, conclusion), references, tables, figures, and figure legends. The length of the text excluding references, tables, and figures should not exceed 5,000 words. The number of references is limited to 100.

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Table 1. Recommended maximums for manuscripts according to publication type

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2. **General guidelines**

- Manuscripts must be written in English. Authors (particularly non-native English speakers) who submit a manuscript should have it checked by a professional editing service prior to submission and must submit proof of English editing.
- The manuscript must be submitted in MS Word format (doc or docx).
- The text of the manuscript, including tables and their footnotes and figures, must be double-spaced and in standard 12-point font on an A4 size page. All pages should be numbered consecutively starting with the title page.
- Drug and chemical names should be stated in standard chemical or generic nomenclature. For medicine, use generic names. If a brand name should be used, insert it in parentheses after the generic name.
- Units of measure should be presented according to the International System (SI) of units. All units must be preceded by one space except percentage (%) and temperature (°C).
- Descriptions of genes or related structures in a manuscript should include the names and official symbols provided by the US National Center for Biotechnology Information (NCBI) or the HUGO Gene Nomenclature Committee.
- The terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors) should be correctly used. The sex and/or gender of study participants and the sexes of animals or cells should be reported, and the methods used to determine sex and gender should be described. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer).
- Statistical expression: mean and standard deviation should be described as mean±SD, and mean and standard error as mean±SE. P-values should be described as P<0.05 or P=0.003.

3. **Reporting guidelines for specific study designs**

For specific study designs, such as randomized controlled studies, studies of diagnostic accuracy, meta-analyses, observational studies, and randomized controlled studies, authors are encouraged to also consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and the National Library of Medicine (https://www.nlm.nih.gov/services/research_report_guide.html).

**FORMAT OF MANUSCRIPTS**

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1. **Title page**

The title page should include: (1) the concise and informative title of the article; (2) the full name(s) of the author(s); (3) the in
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2. Aier A, Pais P, Ramam V. Psychosocial aspects of chil-
dren with chronic kidney disease and their families. Clin

Book or book chapter:
3. Volpe JJ. Neurology of the newborn. 5th ed. Philadelphia:
Saunders/Elsevier; 2008.
4. Hong CE. Textbook of pediatrics. 9th ed. Seoul: Korea Text-

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6. International Committee of Medical Journal Editors. Read
the Recommendations for the Conduct, Reporting, Ed-
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