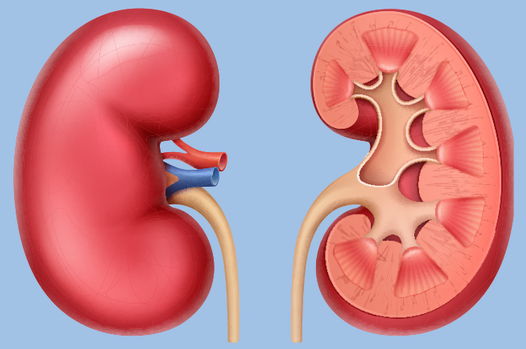
ChiKD Childhood Kidney Diseases

Vol. 27 No. 2, December 2023 pages 55-138

Childhood Kidney Diseases

Vol. 27 No. 2, December 2023

pISSN 2384-0242
eISSN 2384-0250



KOREAN SOCIETY OF PEDIATRIC NEPHROLOGY

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ChiKD CHILDHOOD KIDNEY DISEASES

https://www.chikd.org

pISSN 2384-0242
eISSN 2384-0250

Vol. 27 No. 2, December 2023

Published on 31 December 2023

Aims & Scope

Childhood Kidney Diseases (*Child Kidney Dis, ChiKD;* 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.

Readership

It is primarily for scientists and clinicians active or interested in the field of pediatric nephrology, but its readership can be expanded to other positions: researchers, clinicians, professors, medical health students, allied health professionals, and policy makers in the field of pediatrics, neonatology, nephrology, urology, pathology, endocrinology, cardiology, neurology, gastroenterology, gynecology/obstetrics, epidemiology, pharmacology, biochemistry, and molecular & cell biology.

Open Access

Publisher: Korean Society of Pediatric Nephrology
Editor-in-Chief:
Hyung Eun Yim Department of Pediatrics, Korea University, Republic of Korea

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Printing Office

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pISSN 2384-0242 eISSN 2384-0250

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https://www.chikd.org
pISSN 2384-0242 eISSN 2384-0250

Vol. 27, No. 2, December 2023

Review Articles

Original Articles

Case Reports

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https://www.chikd.org
pISSN 2384-0242 eISSN 2384-0250

Vol. 27, No. 2, December 2023

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Review Article

Child Kidney Dis 2023;27(2):55-63
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.009

Introducing the general management of glomerular disease from a pediatric perspective based on the updated KDIGO guidelines

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In 2021, a new chapter on the general management of glomerulonephritis (GN) was added to the Kidney Disease: Improving Global Outcomes (KDIGO). It emphasizes the importance of early general management of GN for improving long-term kidney outcomes and prognosis. The chapter introduces the management of glomerular diseases in 18 subchapters. Here, kidney biopsy for the diagnosis and evaluation of kidney function and the management of complications, such as hypertension, infection, and thrombosis, are presented. Moreover, the adverse effects of glucocorticoids and immunosuppressive therapy, which are commonly used drugs for glomerular disease, are mentioned, and a guideline for drug selection is presented. Each subtheme focused on items reflecting the interpretation of the "practice points" of the expert working group are introduced. In this review of the general treatment for GN in the KDIGO guidelines, excluding pregnancy and reproductive health, we focused on and compared various references pertaining to pediatric GN management.

Keywords: Adult; Child; Glomerulonephritis; Guideline

Introduction

The guidelines for Kidney Disease: Improving Global Outcomes (KDIGO) were updated in 2021, with detailed discussions on 10 diseases based on the general principles for managing glomerular disease [1]. The KDIGO presents high-quality treatment guidelines for adults and children by conducting a rigorous evidence-based review. However, pediatric recommendations are limited [1] due to lack of randomized controlled trials (RCTs) in children and the small number of patients studied. Nevertheless, these guidelines are crucial as they help minimize the discrepancies in treatment policies between adolescents and adults. Moreover, the KDIGO glomerular disease guidelines have an advantage over other recommendations because they are applicable to both children and adults, and specify the differences in treatment and the latest findings for children.

This review summarizes the general principles for managing glomerular diseases (first chapter of the KDIGO 2021 glomerular disease guidelines), focuses on practical points, and examines the contents of pediatric glomerular disease management. Additionally, we reviewed the guidelines for each disease and added comparisons from various references to highlight the differences in adult management. However, pregnancy and reproductive health in women with glomerular disease were

Received: June 1, 2023; Revised: September 12, 2023; Accepted: September 30, 2023

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excluded from subsection 1.15.

Kidney biopsy

Kidney biopsy remains the gold standard for diagnosing glomerular diseases. However, several methods have been developed for diagnosing glomerular diseases. For example, genetic testing can be used to diagnose Fabry disease and Alport syndrome, and familial focal and segmental glomerulosclerosis can be diagnosed in families with well-characterized mutations. Additionally, antineutrophil cytoplasmic antibody-associated vasculitis can be treated without diagnostic confirmation from biopsy [1]. A kidney biopsy is performed for diagnostic purposes for determining treatment options and predicting prognosis. Unlike adult nephrotic syndrome, pediatric steroid-sensitive nephrotic syndrome (SSNS) in patients aged <12 years or post-infectious glomerulonephritis is conventionally treated without biopsy because the clinical features are sufficient for diagnosis [1]. If nephrotic syndrome is accompanied by hematuria or decreased kidney function, if it occurs in patients aged <1 year or >12 years, or if there is no response to steroid treatment, idiopathic nephrotic syndrome should not be considered, and biopsy should be performed to determine the cause.

To ensure the adequacy of diagnosis, at least 8–10 glomeruli were obtained via kidney biopsy [1]. Kidney biopsy in children is an invasive procedure; therefore, appropriate specimens must be obtained using this minimally invasive procedure. Typically, two to three biopsy cores are obtained. Minimal trials are acceptable, as the number of glomeruli per core is reportedly higher at a younger age [2]. The most common complication of biopsy in children is perirenal hematoma, which occurs in approximately 37% [2], and the incidence of hemorrhage requiring transfusion is 0.6% to 2.0% [2,3]. Low estimated glomerular filtration rate (eGFR; <30 mL/min/1.73 m^2) was an independent risk factor for major complications [3]; thus, care must be taken during biopsy for such patients.

Repeat biopsies may be performed when evaluation of disease progression or a change in the treatment plan is required. Repeat biopsies were performed in the following cases [1]: (1) when the decrease in kidney function cannot be explained despite considering the natural course; (2) to consider whether treatment should be changed; (3) to evaluate whether a change in clinical or laboratory parameters occurs in the same diagnosis (e.g., class switching in lupus nephritis); (4) to evaluate the chronicity and activity, and to determine need for alteration of treatment (maintenance/strengthening/ tapering of treatment); or (5) to define a "point of no return/therapeutic futility."

Assessment of kidney function

Proteinuria and GFR

Evaluation of kidney function is important for diagnosis, prognostic evaluation, and determination of future treatment plans. Therefore, proteinuria and eGFR must be assessed [1]. Proteinuria is assessed using 24-hour urine collection, and evaluation of 24-hour urine collection is recommended whenever the medication dose is adjusted, a decision is made to administer or discontinue it, or if the clinical status changes. The definition for 24-hour proteinuria classifications in children is as follows [4]: normal ≤4 mg/m^2/hr, proteinuria 4–40 mg/m^2/hr, and nephrotic-range proteinuria >40 mg/m^2/hr.

Since 24-hour urine collection in children can be inconvenient, especially in infants prior to toilet training, and can be overestimated in orthostatic proteinuria, the first morning urine protein-to-creatinine ratio (UPCR) was used. The 24-hour proteinuria and first morning UPCR show a high correlation [5]. The results of morning UPCR in children are interpreted as follows: UPCR >200 mg/g (>500 mg/g for children aged 6–24 months) is defined as proteinuria [6], and first morning UPCR performed at a urine specific gravity >1.015 of 200 mg/g or higher is defined as fixed proteinuria [4]. Persistent proteinuria is associated with poor prognosis. Regardless of the underlying disease, the target for first morning UPCR is to achieve a normal level of <200 mg/g or <8 mg/m^2/hr in 24-hour urine [1].

Evaluation using eGFR is easier than measuring GFR. The Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are eGFR formulas used for adults, whereas the Schwartz equation and its modifications are widely used for children. The equation for chronic kidney disease (CKD) in patients aged <25 years (CKiD U25 eGFR equation), applicable to both young adults and adolescents in the transitional state, was recently developed [7]. In addition to the Schwartz equation, the full age spectrum (FAS) equation can be applied as an eGFR formula in children [8,9]. The FAS equation is applicable to all ages over 2 years and has the advantage of less discrepancy in the transition state. The GFR value from the FAS equation was not inferior to that from the Schwartz-creatinine equation [8].

https://doi.org/10.3339/ckd.23.009

Evaluation of hematuria

Hematuria is an important sign of glomerular disease and is present in approximately 50% to 80% of patients [1]. Urine sediments for erythrocyte morphology, red blood cell (RBC) casts, and the presence of acanthocytes are characteristic markers of glomerular disease [10,11] and should therefore be examined. RBC casts in urine or acanthocytes with >5% urine RBCs indicate inflammatory glomerular disease [1]. The magnitude and persistence of hematuria can predict long-term outcomes in many glomerular diseases, particularly immunoglobulin A nephritis or vasculitis, and is thought to be a prognostic marker [1]; thus, regular follow-up is important for all glomerular diseases.

Management of complications of glomerular disease

Complications caused by glomerular disease may result from the clinical presentation rather than from a specific histological problem. Morbidity and mortality can be improved by addressing metabolic problems and thrombotic events while managing edema, proteinuria, and blood pressure (BP) [1].

Control of edema

Edema may be due to the development of proteinuria or a decrease in GFR. The mechanisms that explain the occurrence of nephrotic edema are as follows [12,13]: (1) Underfill theory: as the serum albumin level decreases with nephrotic-range proteinuria, the total extracellular fluid volume increases; however, the plasma volume decreases as oncotic pressure decreases. In these cases, BP is normal or decreased, and the renin-angiotensin-aldosterone system is activated [14]. (2) Overfill theory: primarily, sodium and fluid retention occur in the distal renal tubule and collecting duct; this mechanism increases the circulating volume, resulting in edema [12].

Salt restriction may be necessary to manage edema in nephrotic syndrome. A salt restriction of 2 g/day is recommended for adults [1]. For salt restriction in children, recommendations such as <2 mEq/kg/day to 1–2 g of salt per day, to a no added salt diet were suggested [15]. However, to date, no recommendations for sodium intake according to a child's age, weight, or sex have been put forth [15].

Loop diuretics should be considered as first-line therapy for edema [1]. It removes sodium and fluid by inhibiting the Na^+-K^+-$2Cl^-$ cotransporter on the apical surface of the thick ascending limb in the loop of Henle. Loop diuretics decrease the reabsorption of sodium in the renal tubule by 20% to 30% [13]. However, the effect of diuretics on nephrotic syndrome is limited, which is caused by an increase in the volume of distribution due to hypoalbuminemia and the urinary excretion of protein-binding drugs [1]. Because the urine output is dose-dependent on loop diuretics, if the initial dose is ineffective, the dose can be increased. Loop diuretics dose for infants and children is 1–4 mg/kg/day [12]. When high-dose loop diuretics are rapidly administered, caution should be exercised to avoid ototoxic complications such as hearing loss and tinnitus. If the response to oral administration is insufficient, the intravenous route may be changed. Gastrointestinal absorption of diuretics is not effective in severe nephrotic syndrome due to intestinal wall edema; therefore, intravenous diuretics may be necessary to provoke effectiveness [1].

Combination therapies, such as loop diuretics, thiazide, and aldosterone antagonists, are more effective for refractory edema than loop diuretic monotherapy alone is. Combination therapy with loop diuretics and thiazide increases urine output by more than 50% compared with loop diuretic monotherapy [12]. Thiazide removes sodium and chloride from the body by inhibiting the Na-Cl cotransporter in the distal renal tubule [12]. In nephrotic syndrome, sodium resorption increases in the distal renal tubule; therefore, thiazide is effective against loop diuretic-resistant nephrotic edema [12].

The addition of potassium-sparing diuretics such as amiloride and spironolactone can reduce potassium loss, and the addition of acetazolamide can improve metabolic alkalosis [1]. When diuretics are ineffective in treating edema accompanied by hypoalbuminemia, the addition of albumin improves intravascular volume depletion and blood osmolarity and increases the elimination of sodium and body fluid [1,12]; its clinical effect is greater in children [1]. If treatment-refractory edema persists, consider dialysis to avoid organ damage, such as pulmonary edema and heart failure.

Control of hypertension and proteinuria

Controlling BP and reducing proteinuria are important for the kidney prognosis [1]. Management of hypertension reduces the risk of cardiovascular disease and kidney function deterioration [1]. Implementing lifestyle modifications, such as appropriate salt intake, weight normalization, and regular exercise, is important for controlling hypertension. In glomerular disease patients, target BP should be lower than that of the general pop-

ulation, especially in children, which aim for ≤50th percentile of the BP distribution according to age, sex, and height.

Decreased proteinuria reduces glomerular hypertension and podocyte damage. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) inhibit angiotensin II, reducing intraglomerular pressure and hyperfiltration [16,17]. It results in reducing BP and proteinuria, slows the progression of kidney disease, and improves cardiovascular outcomes [16]. ACE inhibitors or ARBs can reduce proteinuria by 40% to 50% in a dose dependent manner [1]. An increase in creatinine levels may occur as an adverse effect of the drug owing to a decrease in intraglomerular pressure. Regular monitoring of the GFR and electrolyte levels is necessary because of ACE inhibitors or ARB-induced hemodynamic changes in the kidneys. ACE inhibitors or ARBs should be discontinued if the serum creatinine level increases by >30% from baseline [18]. In addition, ACE inhibitors or ARBs should be discontinued when there is a risk of kidney insult, such as dehydration, because adverse effects can be amplified. Evidence of differences in the therapeutic effects of ACE inhibitors and ARBs are limited. Additionally, it is unclear whether ACE inhibitor and ARB combination therapies are more efficacious. Combination therapy may be used in young adults without diabetes or cardiovascular diseases; however, its benefits and safety remain unclear [1]. In children, the anti-proteinuric effect and slowing of CKD progression with combination therapy are limited, and the results of related studies are inconsistent; therefore, a larger study is needed to obtain accurate results [19]. Mineralocorticoid receptor antagonists may be an alternative treatment option for patients with ACE inhibitor/ARB intolerance. When mineralocorticoid receptor antagonist was administered to patients with CKD who received ACE inhibitors or ARBs, proteinuria was reduced by 15% to 54% and BP was reduced by 40% [20]. However, a decrease in GFR was found in 25% of the RCTs, and one out of eight RCTs reported hyperkalemic events; therefore, the routine addition of mineralocorticoid receptor antagonist (spironolactone) to patients with CKD is not recommended [20].

Management of hyperlipidemia

Hyperlipidemia in glomerular diseases can result from diet, genetic predisposition, nephrotic syndrome, or medication-induced complications [1]. Common risk factors for hyperlipidemia include family history, obesity, diabetes, hypertension, prior cardiovascular disease, persistent proteinuria, and decreased kidney function [1]. The management of hyperlipidemia followed the guidelines for the general population. Lifestyle modifications, such as a heart-health diet, increased physical activity, weight reduction, and smoking cessation, are important and should be considered as first-line treatments, especially for children and adolescents [1]. Additional medications should be considered for hyperlipidemia caused by nephrotic syndrome or other glomerular diseases that cannot be controlled with lifestyle modifications alone. The most commonly used medication is statin [1]. Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have been shown to decrease the risk of atherosclerotic cardiovascular events in adult patients with CKD in several clinical trials. The kidney-protective effects of statins have not been established [1]; however, some data suggest that statins reduce microalbuminuria, proteinuria, and all-cause mortality in non-end stage kidney disease patients [1,21]. In children aged >8 years, statins can be initiated based on family history, extremely elevated low-density lipoprotein (LDL) cholesterol, or lipoprotein(a) [1]. According to the 2013 KDIGO clinical guidelines for lipid management in CKD, statin administration is not recommended for children aged <10 years because of limited data [22]. The lowest dose can be administered to prevent cardiovascular events in children aged ≥10 years with severely elevated LDL cholesterol levels. In addition, owing to safety and efficacy issues, multidrug regimens are not recommended [22]. If patients have intolerable dyslipidemia with statins or a high risk of atherosclerotic cardiovascular events, consider non-statin therapies such as bile acid sequestrants, fibrates, nicotinic acid, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and lipid apheresis. Bile acid sequestrants ezetimibe and PCSK9 inhibitors have been approved for the treatment of pediatric patients [23]. Bile acid sequestrants bind to bile acid, removing it from the enterohepatic circulation, upregulating the LDL receptor, and increased LDL cholesterol clearance [23]. Ezetimibe lowers LDL cholesterol levels by inhibiting intestinal and biliary cholesterol absorption [24], and PCSK9 inhibitors lower serum LDL cholesterol levels by inhibiting PCSK9, which degrades LDL receptors on the surface of live cells [25].

Hypercoagulability and thrombosis

Glomerulonephritis with severe proteinuria is associated with a high risk of thrombotic events. These mechanisms include hyperviscosity due to decreased intravascular volume after

https://doi.org/10.3339/ckd.23.009

hypoalbuminemia, urinary excretion of antithrombotic factors, and imbalance in the hepatic synthesis of pro-thrombotic factors [26]. Many thromboembolic events occur within 6 months of the first diagnosis [1]. The incidence of venous thrombosis is higher than that of arterial thrombosis, with deep vein and renal vein thrombosis being the most common. Pulmonary embolism can occur asymptomatically; therefore, caution should be exercised.

Thrombogenic risk factors include [1]: (1) the pathology of membranous nephropathy, the degree of proteinuria, and serum albumin levels (<2.5 g/dL); and (2) additional risk factors include a genetic predisposition to thrombosis, positive antiphospholipid antibodies, immobility, obesity, malignancy, pregnancy, and surgery. When thrombotic events such as venous thrombosis, pulmonary embolism, and nonvalvular atrial fibrillation occur in nephrotic syndrome, they are treated with a full-dose anticoagulant for 6 to 12 months or till the duration of nephrotic syndrome [1]. Intravenous heparin, followed by bridging with warfarin, is preferred, with a target international normalized ratio is 2–3 [1]. Because of fluctuations in serum albumin levels in nephrotic syndrome, the international normalized ratio should be monitored frequently. Direct oral anticoagulants have not been systematically studied in nephrotic patients for the prophylaxis or treatment of thrombosis [1]. When thromboembolism occurs in children, enoxaparin and heparin are administered for acute management and the treatment is changed to warfarin for long-term maintenance. The safety and effectiveness of direct oral anticoagulants in children has not yet been proven; therefore, traditional drugs have been maintained.

Patients at a high risk of thrombosis can be administered unfractionated heparin or low-molecular-weight heparin as a prophylactic anticoagulant [1]. Prophylactic anticoagulation therapy in children is limited and requires careful consideration. Non-pharmacological preventive measures, such as ambulation, compression stockings, and adequate hydration, should first be performed in high-risk patients (e.g., central venous catheter insertion, infection, and thrombophilia) [27]. Prophylactic anticoagulation therapy requires consultation with a hematologist. Relative or absolute contraindications to prophylactic anticoagulation are as follows [1]: (1) patient preference/ability to adhere; (2) bleeding diathesis; (3) central nervous system lesion prone to hemorrhage; (4) genetic mutations influencing warfarin metabolism/efficacy; (5) frailty; or (6) prior gastrointestinal bleeding.

Risk of infection

Patients with glomerular diseases are vulnerable to bacterial infections because of the reduced levels of immunological factors due to proteinuria, dilution of defense factors due to edema, and long-term immunosuppressant use [28,29]. In particular, they are vulnerable to encapsulated bacterial infections owing to the loss of circulating antibodies, and spontaneous bacterial peritonitis caused by *Streptococcus pneumoniae* may occur in the presence of generalized edema and ascites [28]. In cases of repeated infections, intravenous immunoglobulin was administered when the serum immunoglobulin G level was <600 mg/dL [1]. In cases of immunosuppressant treatment, a screening test for infection was performed before drug administration. Appropriate screening is dependent on exposure, which may be unique to particular geographic regions and/or occupations [1]. Serological tests for syphilis, human immunodeficiency virus, and hepatitis B and C are common indicators of underlying glomerular disease. The serological results are related to glomerular disease, and treatment should be considered either preceding or concomitant with immunosuppressants, which can aggravate infectious diseases. Latent tuberculosis, which is common in many populations, should be screened for and treated concomitantly with immunosuppression. Helminth *Strongyloides stercoralis* infections should be screened and treated in at risk individuals before the initiation of immunosuppression, especially with glucocorticoids.

If the infection is confirmed, treatment is initiated, and depending on the severity of the disease, immunosuppressive therapy is initiated. Owing to the high risk of invasive pneumococcal infection in patients with glomerular disease, vaccination against pneumococcus and influenza viruses should be administered. Exposure to the varicella zoster virus can progress to a life-threatening course, especially in children. If a patient is exposed to the varicella zoster virus, zoster immunoglobulin should be administered, and antiviral medication should be added if symptoms occur [1]. Patients receiving regular complement antagonists (e.g., eculizumab) are vulnerable to meningococcal infections. Therefore, vaccination and administration of prophylactic antibiotics against meningococci are essential. A live vaccine is contraindicated in patients receiving immunosuppressive medication; live vaccine administration should be delayed until the dose of steroids (prednisone) is <20 mg/day or 1 to 3 months after the discontinuation of immunosuppressive medication [1]. In SSNS, vaccination, especially

varicella zoster vaccination, should be administered as soon as possible after the first remission. Vaccination of family members living together is important to reduce infections in immunocompromised children. Therefore, pneumococcal and annual influenza vaccinations should be administered. However, when family members are vaccinated with live vaccines, patients should avoid contact with gastrointestinal, urinary, and respiratory secretions for 3 to 6 weeks after vaccination. Prophylactic administration of trimethoprim/sulfamethoxazole can prevent *Pneumocystis* infection when immunosuppressants, such as high-dose prednisone or rituximab are administered.

Outcome measure

If glomerular disease is treated appropriately, the disease progression is halted or slowed down. Proteinuria and GFR are used to evaluate the kidney outcomes. A decrease of 30% or more in proteinuria or albuminuria is an indicator that progression to kidney failure has been prevented, and a decrease in renal function by 40% or more compared with the baseline GFR for 2 to 3 years can be a surrogate marker for progression to kidney failure [1]. Patients should also continue treatment to prevent non-kidney complications.

"Point of no return" means a situation in the natural history of a chronic glomerular disease where severe loss of kidney function (eGFR <20–30 mL/min/1.73 m^2), it is accompanied by extensive and irreversible kidney injury (primarily interstitial fibrosis and tubular atrophy, and/or bilateral renal atrophy) such that any therapeutic strategy being tested cannot reasonably be expected to alter the natural history of progressive deterioration in kidney function (therapeutic futility) [1]. Even patients who have reached the "point of no return" need persistent treatment to avoid non-kidney complications, such as cardiovascular diseases [1].

Administration of glucocorticoid and immunosuppressive therapy

Drugs that treat glomerular diseases should effectively prevent disease progression, while minimizing adverse effects. As the prescription and treatment effects of each drug are mentioned in the guidelines for each disease, this review explains the adverse effects of these drugs.

Glucocorticoid

Glucocorticoids are the main line of treatment for management of several glomerular diseases, particularly pediatric nephrotic syndrome. Nephrotic syndrome is classified according to the initial steroid response, better steroid response, and better prognosis. The well-known side effects of glucocorticoids include physical changes, such as weight gain, body shape changes, acne, growth retardation, and metabolic complications, such as hyperglycemia, diabetes mellitus, and hypertension. Intermittent treatment with high-dose glucocorticoids is unrelated to bone mineral content deficits in pediatric SSNS [30]; however, growth retardation and bone density loss may occur with long-term administration of glucocorticoids. Therefore, bisphosphonates and vitamin D should be administered to prevent these adverse effects. Hence, it is important to administer as few steroids as possible. Steroids are functional growth hormone antagonists that interfere with growth hormone excretion [31]. Growth can be improved by administering growth hormone [31].

Prophylactic antibiotics should be considered to prevent infections caused by long-term steroid administration. Additionally, H2 receptor antagonists and proton pump inhibitors can prevent gastrointestinal complications. However, proton pump inhibitors can cause hypersensitivity to immune reactions, leading to acute interstitial nephritis or acute kidney injury [32,33].

Calcineurin inhibitors

Calcineurin inhibitors reduce T-cell activation and stabilize the actin skeleton of podocyte [28]. It is the primary immunosuppressive treatment for steroid-resistant or dependent nephrotic syndrome. Nephrotoxicity is the best-known side effect of calcineurin inhibitors, although it is uncommon at low trough levels [1]. The risk factors for tubular interstitial lesions include the use of cyclosporine for >24 months and heavy proteinuria for >30 days during cyclosporine use [1]. Other metabolic side effects include as follows [1]: (1) hair growth and gingival hyperplasia (cyclosporine); (2) hypertension and hyperlipidemia (cyclosporine>tacrolimus); or (3) diabetes mellitus and tremor (tacrolimus>cyclosporine).

Cyclophosphamide

Cyclophosphamide depletes immune competent cells by adding an alkyl group to DNA. It also reduces the steroid requirement and risk of relapse in nephrotic syndrome [28,34]. Cyclo-

https://doi.org/10.3339/ckd.23.009

phosphamide can cause renal toxicity; thus, dose modification is required depending on kidney function. In addition, monitoring of marrow suppression is required, and the drug should not be used for more than 6 months. Oral hydration is sufficient to reduce bladder toxicity and sodium-2-mercaptoethane sulfonate should be considered when administering high-dose cyclophosphamide. Caution should be exercised when administering a high dose, as it increases the risk of cancer, including bladder cancer and infertility.

Rituximab

Rituximab is a monoclonal antibody against CD20 found in B cell [28]. Rituximab binding to CD20 causes rapid depletion of B cell populations and is effective in steroid-dependent or steroid-resistant nephrotic syndrome, recurrent focal segmental glomerulosclerosis and membranous nephropathy [35]. Rituximab can cause severe complications, such as anaphylaxis due to infusion reactions and hypogammaglobulinemia due to repeated administration. One study has reported a decrease in serum immunoglobulin G levels and an increase in the risk of infection after rituximab administration [36].

Dietary management in glomerular disease

For dietary control in patients with glomerular disease, a reduction in sodium intake helps to reduce BP and edema in patients with nephrotic syndrome. In adults, reducing protein intake based on kidney function is recommended [1]; however, restricting protein intake is inappropriate for growing children. A low-protein diet in children with CKD resulted in significantly low height and growth rates [37], and did not limit the progression of CKD [38]. For optimal growth in children, supplying protein up to the upper normal limit of the age/sex-suggested dietary intake is recommended in CKD stages 2–5. In end stage kidney disease, supplying protein rather than the suggested dietary intake by reflecting the amount of protein exiting from dialysis is recommended [39]. In patients with pediatric nephrotic syndrome, urine protein levels usually decrease within 2 weeks after the start of steroid therapy; therefore, the amount of protein intake is based on the nutrient requirement for healthy children of the same age, considering both the likelihood of progression to kidney failure and their growth [12].

In reduced GFR, calorie restriction with a body mass index higher than ideal is recommended to facilitate weight loss and prevent cardiovascular and kidney complications [1]. Patients with elevated serum cholesterol who are at risk of cardiovascular complications should follow a healthy diet, and fats should be restricted to < 30% of total calories, with saturated fats <10% [1]. In children with nephrotic syndrome, in whom dietary protein is not restricted, there is no need to consume a higher number of calories for their age [12]. Some patients receiving steroid therapy may gain weight, and adequate calorie intake is necessary to prevent obesity [12].

Goals of glomerular disease treatment, post-transplant glomerular disease

The overall goals of treatment of glomerular disease are lasting remission [1]. A complete remission is more desirable, but a partial remission may sufficient [1]. Treatment choice should take into account avoiding or minimizing the treatment-related adverse events [1]. Therapeutic drugs are selected on the basis of their risks and benefits. The treatment plan should consider the patients' convenience or quality of life. As most cases of glomerular diseases, except for minimal change disease, can recur after kidney transplantation [1], the risk of recurrence should be evaluated before and after transplantation, and donor selection and post-transplantation management should be determined. Despite the risk of recurrence after transplantation, transplantation is the best option for patients with kidney failure [1].

Conclusion

Studying glomerular diseases in children is difficult because of the low incidence, limited access, vulnerability, and difficulty in treatment as compared to those in adults. Nevertheless, the prognoses of glomerular diseases in children are a critical factor in determining their current quality of life and lifetime prognosis. Therefore, early detection, appropriate treatment initiation, and standardized treatment protocols are essential. Further focused research and developments are necessary for understanding and managing pediatric glomerular diseases.

Conflicts of interest

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

Funding

None.

Author contributions

All the work was done by SHL.

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ChiKD CHILDHOOD KIDNEY DISEASES

Review Article

Child Kidney Dis 2023;27(2):64-69
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.015

Comprehensive review of membranoproliferative glomerulonephritis: spotlighting the latest advances in revised classification and treatment

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Membranoproliferative glomerulonephritis (MPGN) is a complex group of renal diseases characterized by a specific pattern of glomerular injury that includes thickening of the capillary wall and mesangial expansion, leading to a heterogeneous group of conditions. This review article offers a comprehensive overview of MPGN, its new classification, pathophysiology, diagnostic evaluation, and management options.

Keywords: Complement system proteins; Glomerulonephritis, membranoproliferative; Immunoglobulins; Pediatrics

Introduction

Membranoproliferative glomerulonephritis (MPGN) is not a disease but a pattern of glomerular injuries characterized by thickening of the capillary wall (remodeling with formation of double contours) and mesangial expansion due to increased matrix deposition and hypercellularity observed on light microscopy [1-3]. MPGN most commonly presents in pediatric populations but can occur at any age [1]. There are no specific symptoms that uniquely represent MPGN; patients can present with various forms, including asymptomatic hematuria and proteinuria, acute nephritic syndrome, nephrotic syndrome, renal insufficiency, and even rapidly progressive glomerulonephritis. Hypertension and hypocomplementemia (complement components; C3 and/or C4) are often but not always present. These diverse clinical presentations result from differences in the underlying pathogenesis [1,2,4]. The condition can lead to progressive kidney damage and may ultimately result in renal failure if left untreated. The treatment depends on the etiology [5]. In this review, we explore the key aspects of MPGN to provide a comprehensive understanding of this complex renal disorder using a new classification.

Classically, MPGN was divided into three types based on the location of deposits found on examination by electron microscopy: primary (idiopathic) MPGN types I, II or III and secondary MPGN. The most common form, MPGN I, is characterized by subendothelial and mesangial electron deposits, while MPGN III exhibits both subepithelial and subendothelial electron deposits. MPGN II is also known as dense deposit disease (DDD) due to its electron-dense intramembranous deposits. However, this prior classification was not based on disease pathogenesis, resulting in pathogenetic heterogeneity.

Received: September 15, 2023; Revised: October 14, 2023; Accepted: October 19, 2023

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https://doi.org/10.3339/ckd.23.015

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New classification and pathophysiology

In most cases, MPGN results from deposition of immunoglobulins and/or complement in the glomerular mesangium and capillary wall when there are an increased level of circulating immune complexes and/or dysregulation of the alternative complement pathway. Advances in understanding the underlying disease have led to a new pathobiology-based classification of MPGN based on immunofluorescence findings. The MPGN pattern of injury is now classified into three groups (Fig. 1) [1,2,4].

Immunoglobulin/immune complex-mediated (immunoglobulin subgroup with or without a complement subgroup)

This can be present in two forms: immune complex-mediated glomerulonephritis (ICGN) with an MPGN pattern and glomerulonephritis with monoclonal immunoglobulin deposits.

ICGN with an MPGN pattern

This subtype arises from deposition of immune complexes within the glomeruli, leading to a distinctive MPGN pattern. It commonly occurs in association with various underlying conditions, including viral infections such as hepatitis C and hepatitis B; bacterial infections such as endocarditis and infected ventriculo-atrial shunts; and protozoa/other infections such as malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, and histoplasmosis. The subtype can also be linked to autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and mixed connective tissue disease. In some cases, it may manifest idiopathically when none of these specific conditions are evident. Diagnosis of this condition begins with a comprehensive evaluation aimed at uncovering the underlying disease trigger. However, when extensive assessment fails to reveal an underlying cause, it becomes necessary to explore the possibility of complement dysregulation [6,7]. This involves a systematic approach, encompassing the following steps: (1) Functional assay: tests for CH50, AP50 (complement alternate pathway activation 50%), and factor H function; (2) Quantification of complement component regulators: comprehensive assessment of C3, C4, factor I, factor H, factor B, and properdin levels; (3) Measurement of complement activation: evaluation of complement activation markers such as complement component 3d, activated factor B, and soluble membrane attack complex; (4) Autoantibody testing: screening for autoantibodies against factor H, factor B, and nephritic factors (C3, C4, C5); (5) Genetic testing: genetic analysis involving C3, complement factor H, complement factor I, complement factor B, and complement factor H-related proteins 1–5 through multiplex ligation-dependent probe amplification; (6) Plasma cell disorder assessment: examination of serum-free light chains, serum and urine electrophoresis, and immunofixation; (7) Immunofluorescence studies on kidney biopsy specimens: comprehensive immunofluorescence analysis of kidney biopsy specimens to detect the presence of immunoglobulin A, immunoglobulin G, and immunoglobulin M, C1q, C3, fibrinogen, kappa, lambda, and C4d. Notably, C4d typically exhibits a distinctive pattern characterized by bright staining, while immunoglobulin levels are often zero or minimal [8].

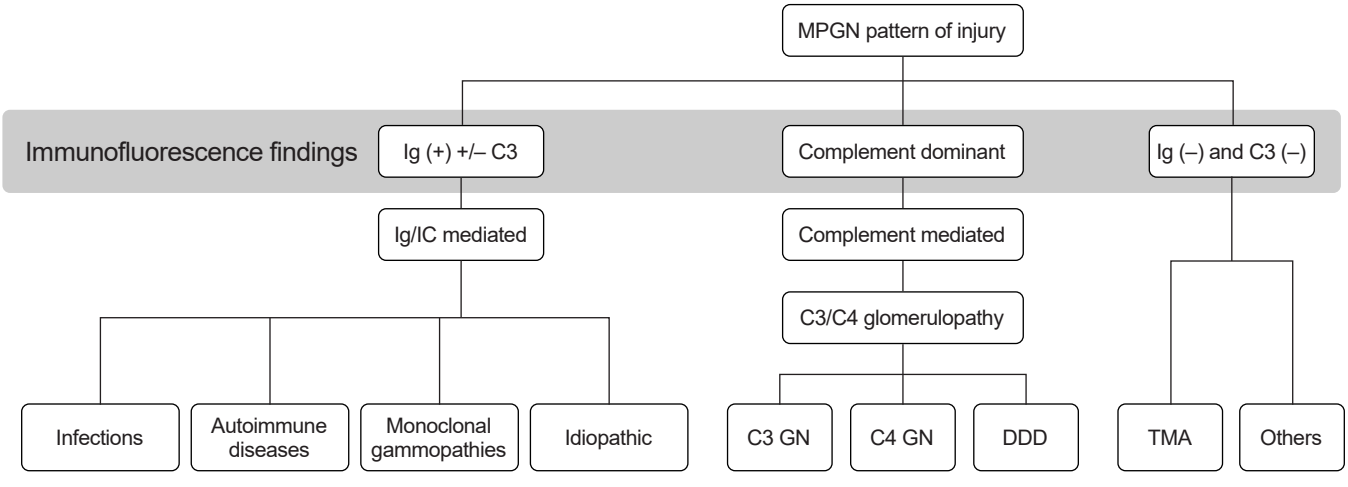

Fig. 1. Pathophysiology of membranoproliferative lesions [2-4]. MPGN, membranoproliferative glomerulonephritis; Ig, immunoglobulin; C3, complement component 3; C4, complement component 4; IC, immune complex; GN, glomerulonephritis; DDD, dense deposit disease; TMA, thrombotic microangiopathy.

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Glomerulonephritis with monoclonal immunoglobulin deposits

This subtype is observed in patients with monoclonal gammopathies and infrequently in patients with overt hematologic diseases such as multiple myeloma, Waldenström macroglobulinemia, or B-cell lymphoma. Kidney injury results from direct glomerular deposition of monoclonal immunoglobulins. Diagnosis requires an evaluation of the presence of a hematologic malignancy. Tests such as serum and urine protein electrophoresis, immunofixation, and serum-free light chain levels are necessary, and consultation with hematologists should be carried out as needed [9].

Complement-mediated (complement-dominant subgroup)

This can be divided into C3/C4 glomerulopathy (C3G/C4G) and then further divided into DDD and C3/C4 glomerulonephritis (C3GN/C4GN). An evaluation of the etiology requires consideration of the alternative pathway of the complement [10,11].

C3/C4 DDD

C3/C4 DDD is defined by highly electron-dense osmophilic, predominantly intramembranous deposits.

C3 glomerulonephritis

C3GN shows C3 deposition at least two orders of magnitude greater than any other immune reactant. The alternative complement pathway is presumed to be the underlying mechanism. Other C3-dominant glomerular diseases, such as infection-related glomerulonephritis, must be excluded. Hypocomplementemia is present in only about 50% of cases [12,13].

C4 glomerulonephritis

C4GN is characterized by bright C4d staining with minimal or no deposition of C3 or immunoglobulin [14].

Membranoproliferative pattern without immune complexes or complement (immunofluorescence-negative subgroup)

An absence or traces of immunoglobulin or complement suggests thrombotic microangiopathy [2]. The change in classification from electron-microscopic to immunofluorescence-microscopic criteria has resulted in limited application of evidence from previous controlled trials to guide high-quality management decisions. Consequently, recommending appropriate management approaches for various diseases with MPGN injury patterns has become challenging [2,15,16].

Management

The reclassification of MPGN has created a significant knowledge gap in guiding the prescription of the most effective treatment modalities within the framework of the new MPGN classifications. Historically, the study by Tarshish et al. [17] underscored the positive impact of corticosteroid treatment on the prognosis of idiopathic MPGN in pediatric patients. In contrast, a recent study led by Kirpalani et al. [18] reclassified pediatric MPGN cases using an innovative taxonomy and demonstrated the effectiveness of corticosteroid treatment in improving estimated glomerular filtration rate (eGFR) in C3G, although such benefits were not observed in ICGN cases. Therefore, the previous treatment recommendations may not be directly applicable to the new classification, underscoring the necessity for further well-controlled studies to establish guidelines for the optimal management of pediatric MPGN. While the following management proposals are for clinical decision-making, knowing that they are based on low-quality evidence is crucial.

Immune complex-mediated glomerulonephritis

Assessing the underlying disease is the primary basis for treatment. Once the cause of ICGN is identified, treatment should focus on the underlying pathological process [19]. However, in cases where the cause remains unknown or is classified as idiopathic, it is advisable to consider the following steps. For those with nonnephrotic-range proteinuria and normal renal function, renin-angiotensin system inhibition may be a suitable option. In pediatric patients, the threshold for initiating immunosuppression may be lower than in adults, and mycophenolate mofetil could be considered as a glucocorticoid-sparing agent. Conversely, in cases of nephrotic syndrome with normal or near-normal renal function, glucocorticoid therapy should be considered (detailed management suggestions are provided in Fig. 2). Additionally, when abnormal kidney function is observed, particularly in the absence of crescentic involvement but with an active sediment, a comprehensive approach involving both glucocorticoids and immunosuppressive therapy coupled with supportive care is warranted. Detailed management recommendations for this scenario can be found in Fig. 3. Rapidly progressive crescentic ICGN may necessitate a more aggressive approach, involving high-dose glucocorticoids (typically 1–3 g of methylprednisolone) and cyclophosphamide. Finally, if renal function deteriorates to an eGFR of less than

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30 mL/min/1.73 m², a focus on supportive care is crucial, along with an evaluation of kidney transplant options. Each treatment approach should be carefully considered in the context of the patient's clinical status and response to therapy to achieve the best possible outcomes [2].

C3 glomerulopathy

At present, the optimal management strategy remains poorly defined. For cases of moderate-to-severe disease characterized by moderate-to-marked proliferation on biopsy and proteinuria exceeding 2 g/day, consideration of immunosuppression is warranted [20]. Additionally, in patients presenting with both proteinuria >1 g/day and hematuria or experiencing persistent kidney function decline over a minimum of 6 months, the initial treatment should involve a combination of mycophenolate mofetil and glucocorticoids. If this initial approach is ineffective, it may be prudent to explore the potential benefits of eculizumab. If a patient does not respond favorably to the aforementioned management strategies, participation in clinical trials, where available, should be considered [6,12,13,20-24].

Prognosis

The renal and patient outcomes in adult MPGN patients are known to be poor [12,13,25]. A similar result was found in Korean adults by Lee et al. [26]. They found the MPGN had the worst renal and patient outcomes among primary glomerulonephritis. The prognosis of MPGN in Korean children is yet

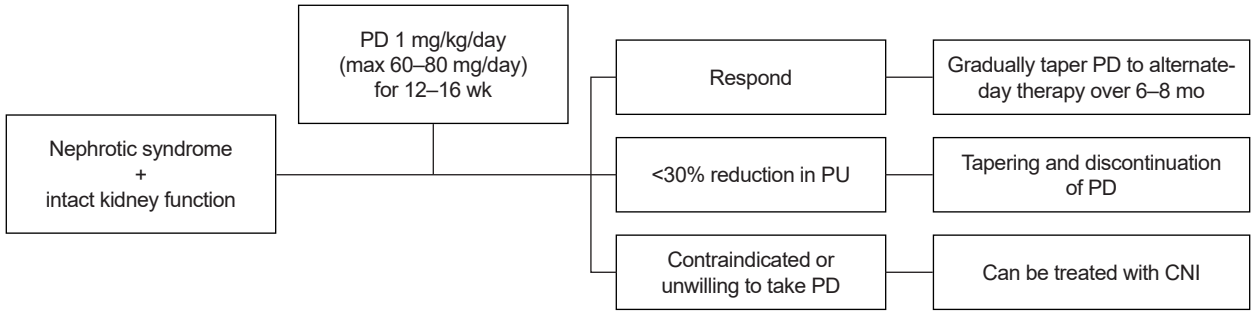

Fig. 2. Nephrotic syndrome with normal or near-normal renal function treatment suggestion [2]. PD, prednisolone; PU, proteinuria; CNI, calcineurin inhibitor.

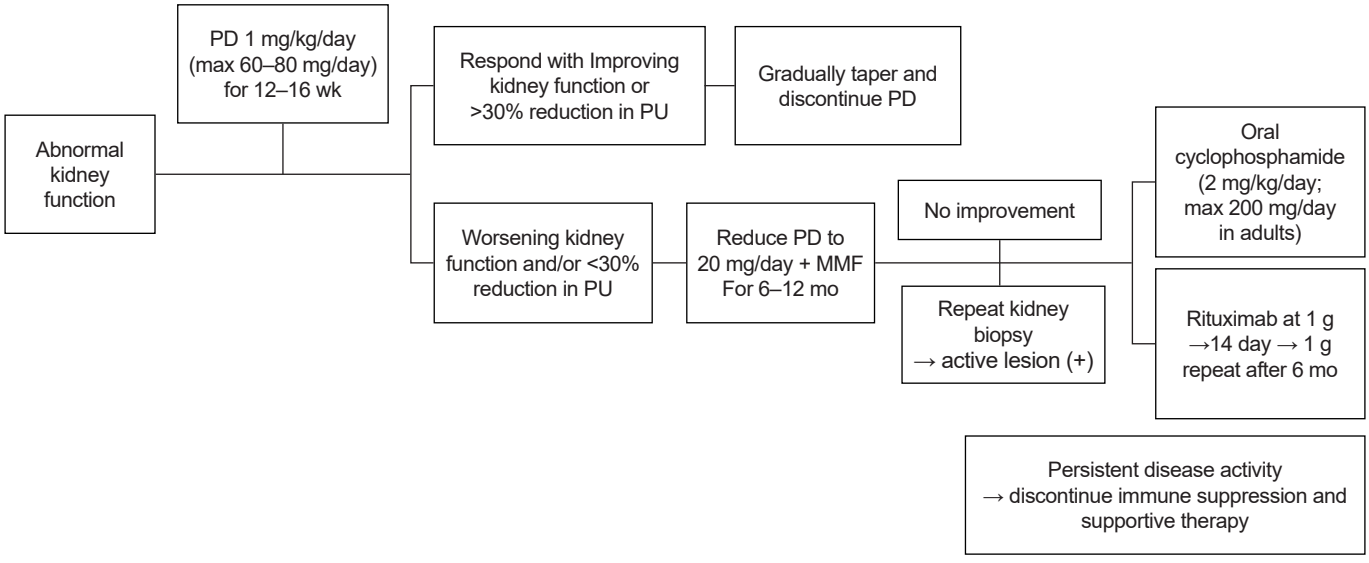

Fig. 3. Abnormal kidney function (without crescentic involvement) and active urine sediment with or without nephrotic-range proteinuria treatment suggestion [2]. PD, prednisolone; PU, proteinuria; MMF, mycophenolate mofetil.

to be known. Pediatric patients diagnosed with ICGN and C3G often experience a more favorable clinical course compared with adult patients, marked by well-preserved renal function [18]. Progression to advanced chronic kidney disease is rare in children. However, C3G tends to carry a more unfavorable renal prognosis when contrasted with ICGN. In cases of C3G, early steroid intervention may be beneficial [18]. Additionally, hypertension is an independent risk factor for poor renal outcomes in adult MPGN [25]. Like adults, pediatric patients with hypertension showed lower eGFR compared to normotensive [18]. Therefore, hypertension control may be beneficial for pediatric MPGN patients. However, current pathologic criteria alone may prove insufficient for accurate prognosis in children presenting with ICGN and C3G, and further research is warranted [18].

Conclusion

MPGN is a pattern of glomerular injury, not a disease, and is a complex renal condition that requires a thorough evaluation to reveal the underlying causes and indicate effective management options. Early diagnosis and appropriate treatments are crucial for improving the prognosis and quality of life of individuals living with MPGN. As our understanding of the disease continues to evolve with the changed classification based on pathophysiology, new treatment options and approaches offer hope for better outcomes for affected individuals.

Conflicts of interest

Jeong Yeon Kim 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.

Funding

None.

Author contributions

All the work was done by JYK.

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Review Article

Child Kidney Dis 2023;27(2):70-75
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.019

An overview of Dent disease

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Dent disease is a rare inherited kidney tubulopathy caused by mutations in either the *CLCN5* (Dent disease 1) or *OCRL1* (Dent disease 2) genes, and which is often underdiagnosed in practice. A diagnosis is clinically suspected in patients with low-molecular-weight proteinuria, hypercalciuria, and one of the following: hematuria, nephrolithiasis, nephrocalcinosis, hypophosphatemia, or chronic kidney disease. Inheritance is X-linked recessive, meaning, these symptoms are generally only found in males; female carriers may have mild phenotypes. Genetic testing is only a method to confirm the diagnosis, approximately 25% to 35% of patients have neither the *CLCN5* nor *OCRL1* pathogenic variants (Dent disease 3), making diagnosis more challenging. The genotype-phenotype correlations are not evident with the limited clinical data available. As with many other genetic diseases, the management of patients with Dent disease concentrates on symptom relief rather than any causative process. The current treatments are mainly supportive to reduce hypercalciuria and prevent nephrolithiasis. Chronic kidney disease progresses to end-stage between the ages of the third to fifth decades in 30% to 80% of affected males. In this review, we aimed to summarize the literature on Dent disease and reveal the clinical characteristics and molecular basis of Korean patients with Dent disease.

Keywords: Dent disease; Genetic diseases, X-Linked; Proteinuria

Introduction

Dent disease is a rare X-linked inherited kidney disorder whose most manifestations result from proximal tubule dysfunction [1]. It classically presents as low-molecular-weight (LMW) proteinuria, hypercalciuria, nephrolithiasis or nephrocalcinosis, and progressive kidney insufficiency [1-3]. The condition was first recognized in 1964 by Dent and Friedman in two unrelated young males with renal rickets stemming from injury of the kidney tubule [2]. About 30 years later, Wrong et al. [1] studied 25 patients from five different families and reported the disorder as a familial form of renal Fanconi syndrome. They termed the condition "Dent disease" and suggested that it was inherited in an X-linked pattern. Shortly, the disease-associated gene was identified and fully characterized [4] and is now described as an X-linked recessive kidney disease caused by pathogenic gene variants.

The accurate incidence of Dent disease is unknown [5] and the wide variability of clinical symptoms, along with the absence of family history, makes diagnosis difficult. In addition, its rarity means that clinicians have a relatively restricted understanding of Dent disease, which can lead to misdiagnosis and inappropriate intervention. LMW proteinuria is one of the major features of disease presentation, essentially universally present in all affected males, and is also present in carrier females to a lesser degree. By contrast, other phenotypic symptoms of Dent disease can vary according to the ethnicity of the patient. Typical symptoms of Dent disease tend to manifest in

Received: October 11, 2023; Revised: December 9, 2023; Accepted: December 13, 2023

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early youth and can proceed to end-stage kidney disease between the ages of the third and fifth decades [5,6]. Despite the limited clinical data, there are differences in the clinical features and molecular basis of Dent disease patients in different ethnicities [7-10]. In this review, we aimed to summarize the literature on Dent disease and to reveal the clinical features and molecular basis of Dent disease in Korean patients.

Genetics

Two gene variants have been identified up to now [11]. Dent disease 1 is named for patients with mutations in the chloride channel-gated 5 (*CLCN5*) gene and comprises approximately 50% to 60% of patients with clinical diagnosis [4,11]. A further 15% to 20% of cases are resulted in mutations in inositol polyphosphate-5-phosphatase (*OCRL1*) and are recognized as Dent disease 2 [12]. Genetic heterogeneity caused by yet-to-be-identified genetic variants is supposed to be liable for the residual cases, which are classified as Dent disease 3 [13].

Dent disease 1 and *CLCN5* mutations

The first disease-associated gene found to be linked to Dent disease was *CLCN5* on the X chromosome (Xp11.22) (Fig. 1). *CLCN5* encodes chloride channel-5 (CLC-5) antiporter, which is mainly located in the renal and intestinal epithelia. It is primarily presented in the proximal tubule and intercalated cells [14] and is essential for the uptake of LMW proteins through receptor-mediated endocytosis in the proximal tubule [15]. With the loss of CLC-5 function, the endocytosis of the kidney proximal tubule epithelial cells is suppressed, and the carbohydrates, amino acids, and hormones cannot be reabsorbed, causing LMW proteinuria [16]. More than 250 different pathologic variants of *CLCN5* have been identified [17,18]. The reported mutations are missense (35%) or frameshift (31%), nonsense (16%), splice site (10%), and large deletions (4%) [17]. The spectrum of pathogenic variants in patients with Dent disease 1 is very diverse, while the type of pathogenic variants does not look like reliably predicts long-term prognosis or disease outcome [17].

Dent disease 2 and *OCRL1* mutations

The second disease-associated gene to be linked as responsible for Dent disease was the *OCRL1* gene [12], which maps on the long arm of the X chromosome (Xq25) and is also known to cause Lowe syndrome (Fig. 1) [19]. Interestingly, some *OCRL1* mutations cause the Lowe syndrome, and others cause the isolated renal phenotype of Dent disease. *OCRL1* encodes a lipid phosphatase that hydrolyzes phosphatidylinositol 4,5-bisphosphate [20], which acts as an intracellular messenger for membrane trafficking and cytoskeleton shapes and functions [21]. A study of zebrafish showed that the absence of *OCRL1* leads to impaired endocytosis [22], similar to what is seen in cases of CLC-5 depletion. All *OCRL1* genetic variants revealed in Dent disease are distributed in the 5' half of the gene, in exons 1–15, while pathogenic variants for Lowe syndrome are mainly distributed in exons 8–23 [5,20,23]. Thus far, more than 140 pathogenic variants in the *OCRL* gene that cause Dent disease 2 have been reported [7].

Clinical phenotype

The clinical phenotype of Dent disease reflects a dysfunction in proximal tubular solute reabsorption. LMW proteinuria is the

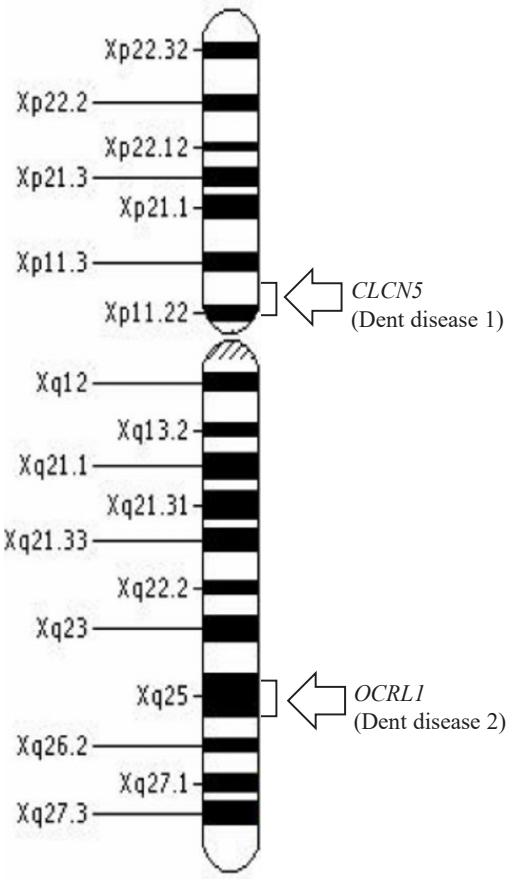

Fig. 1. Genes and loci for Dent disease.

most consistent symptom of Dent disease and is essentially universally present in all affected males and carrier females to a lesser degree. It occurs in infancy before any other evidence of kidney dysfunction [1]; it can also be an isolated finding in adults [24]. Protein excretion typically occurs at a rate of 1–2 g/day, with LMW proteins accounting for 50% to 70% of the total urine protein [20]. Proteinuria in Dent disease reflects a defect in the reabsorption of filtered urine proteins rather than the damage of the glomerulus or tubule [1]. It begins in early childhood and worsens with age [10]. Approximately 50% of patients have proteinuria in the nephrotic range. However, serum albumin levels tend to be normal, so these patients do not typically develop nephrotic syndrome [25].

Along with LMW proteinuria, hypercalciuria is highly prevalent and is reported in more than 80% of patients with Dent disease [9-11]. However, symptoms are often intermittent and some patients may be asymptomatic [26]. The degree of hypercalciuria is higher in children compared with adults [6], but it also tends to decrease along with the decrease of the glomerular filtration rate (GFR) [10]. Although the hypercalciuria mechanism is undetermined in Dent disease, it has been ascribed to the vitamin D_3 synthesis stimulation by inappropriately high parathyroid hormone levels in the proximal tubule, with consecutive stimulation of calcium absorption in the intestine [6,18,27].

Nephrocalcinosis may come from hypercalciuria, as the degree of hypercalciuria in Dent disease is in approximately 75% of male patients with Dent disease 1 and 40% with Dent disease 2 [28]. Nephrocalcinosis manifests frequently during adolescence and sometimes during early childhood, although the existence and severity of nephrocalcinosis do not always agree with the risk of developing chronic kidney disease (CKD) [6]. Approximately 30% to 50% of male patients ultimately develop kidney stones despite the considerable interfamilial and intrafamilial variability [6,10]. Nephrolithiasis seems to result from the association of hypercalciuria and a defect in the handling of calcium oxalate phosphate crystals in the medullary collecting duct [10,29]. An estimated 50% of female carriers have hypercalciuria, although nephrolithiasis is rare [5].

Kidney function declines progressively, and the GFR generally declines at a rate of 1.0–1.6 mL/min/1.73 m^2 per year [10]. This will lead to end-stage kidney disease, which will occur in two-thirds of patients. However, this can vary, and some patients can reach an advanced age with only modest or even minor renal impairment [1]. In the most aggressive cases, GFR declines measurably in late childhood and may reach end-stage in a patient's early twenties; however, more typically, progression to end-stage kidney failure occurs when a patient is in their 40s or 50s [6,30]. The mechanism of kidney failure is not well understood.

In addition to the main clinical features, other symptoms of proximal tubular dysfunction such as, aminoaciduria, phosphaturia/hypophosphatemia, kaliuresis/hypokalemia, and glycosuria may also be present at varying frequencies [31]. Some patients with Dent disease 2 have also presented with non-renal symptoms such as mild intellectual impairment [2], hypotonia, cataracts, and growth defects [5,26], and these symptoms are likely to be milder than those who have Lowe syndrome.

Diagnosis

In the absence of other known causes of proximal tubular dysfunction, Dent disease should be suspected in patients who present with the following criteria [11]: (1) LMW proteinuria (elevation of urinary excretion of β2-microglobulin and/or retinol-binding protein at least 5-fold above the upper limit of normality); (2) hypercalciuria (>4 mg/kg in a 24-hour collection or >0.25 mg calcium per mg creatinine on a spot sample); and (3) at least one of the following: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, or CKD [5]. A family history indicating an X chromosome-linked inheritance of one or more of the clinical symptoms discussed above supports the diagnosis, with pathogenic variants recognition in either *CLCN5* or *OCRL1* confirming disease. However, not all affected patients have a pathogenic variant in one of these two genes, and some patients with confirmed pathogenic variants in *CLCN5* or *OCRL1* will not fulfill all three of the above clinical criteria. Therefore, while the identification of pathogenic variants in genes can confirm the diagnosis of Dent disease in someone with suggestive clinical symptoms, a negative genetic test cannot rule out a diagnosis.

Treatment

As with many other genetic diseases, the treatment of Dent disease focuses on symptom relief rather than a causative process [26]. Although the evidence to support the effectiveness of most of the current therapies is poor, current treatments of Dent disease are aimed at decreasing the levels of hypercalciuria and its complications and slowing the CKD progression

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[31]. Treatment of hypercalciuria mainly consists of a low-sodium diet and thiazide diuretics, the use of which has not been evaluated in randomized controlled trials. However, it has been shown to significantly reduce urinary calcium excretion in the short term [32] despite it also being related to significant adverse effects, such as hypovolemia and hypokalemia, related to primary tubulopathy [33]. Thus, thiazide diuretics in Dent disease should be used with caution and only with recurrent stone formation. Similarly, the management of rickets with vitamin D should proceed with caution since it can accrete hypercalciuria and therefore, only be indicated for patients with symptomatic bone disorder [20]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are widely used drugs for the treatment of proteinuria [25,34]. Even though ACEI and ARB should not theoretically be effective against tubular proteinuria, they have nonetheless been shown to reduce proteinuria in patients with Dent disease [9,10]. Blanchard et al. [10] suggest that the existence of histological glomerular injury and/or heavy proteinuria might provide grounds for the treatment of ACEI and ARB. However, the long-term outcomes of ACEI and ARB were not studied in detail.

Korean patients with Dent disease

According to the data of a multicenter study for the Korean Society of Pediatric Nephrology, a total of 55 male patients who had genetically confirmed Dent disease were collected from 2002 to 2021 in Korea (unpublished). The data sharing is permitted by the co-authors. The patients' median age at clinical diagnosis was 8.1 years, and the initial symptoms leading to a diagnosis of Dent disease were proteinuria (91%), hematuria (5%), family screening (3.6%), nephrocalcinosis (1.8%), growth retardation (1.8%), and polyuria (1.8%). In total, 49 of the 55 patients carried pathogenic variants of the *CLCN5* gene (Dent disease 1), and the remaining six patients showed pathogenic variants of the *OCRL1* gene (Dent disease 2) which is similar to the

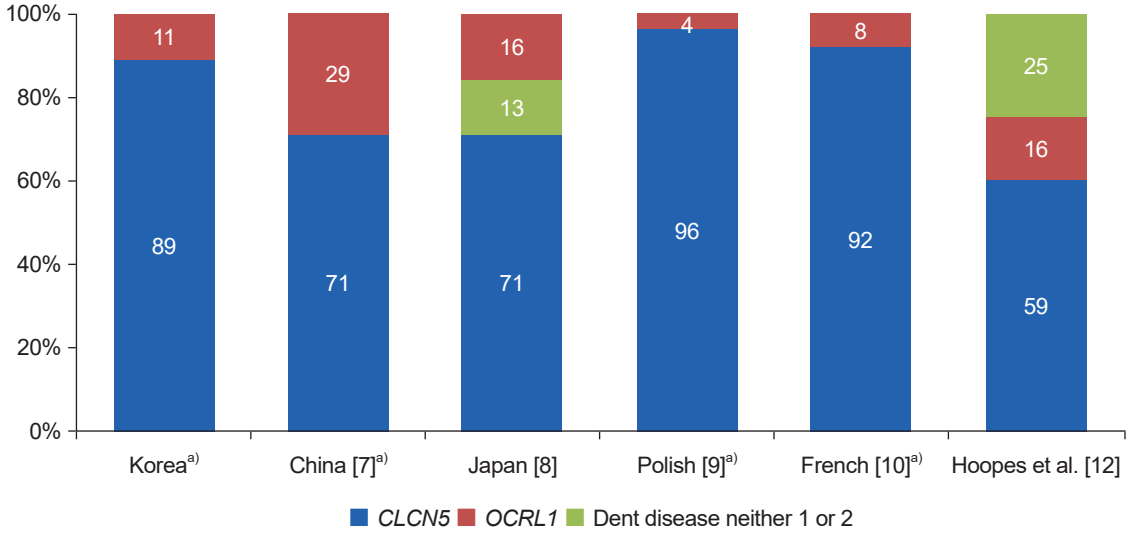

Fig. 2. Genetic heterogeneity in Dent disease. [a)]Only patients with a molecular diagnosis of Dent disease were included in the analysis.

Table 1. Frequency of clinical presentations in the global literature

Global literature	Low-molecular-weight proteinuria	Hypercalciuria	Nephrocalcinosis	Nephrolithiasis	Chronic kidney disease
Korea	100 (55/55)	43.4 (23/53)	29.6 (16/54)	5.45 (3/55)	5.66 (3/53)
China [7]	100 (32/32)	65.6 (21/32)	43.8 (14/32)	9.38 (3/32)	12.5 (4/32)
Japan [8]	100 (61/61)	46.3 (25/54)	37.7 (20/53)	-	7.55 (4/53)
Poland [9]	100 (15/15)	86.4 (19/22)	56.5 (13/23)	13.0 (3/23)	-
France [10]	100 (93/93)	92.0 (81/88)	42.3 (44/104)	32.4 (24/74)	-
Claverie-Martin et al. [20]	100	89	76	-	42

Values are presented as percent (number/number).

Polish and French studies (Fig. 2) [7-10,12]. All patients had LMW proteinuria, although hypercalciuria and nephrocalcinosis/nephrolithiasis were found in 43.4% and 34.5% of the patients, respectively. Hypercalciuria is a less constant presentation owing to the difference in definitions or various presentations of clinical features depending on the legions [7-10,20]. The clinical phenotypes in Korean patients with Dent disease do not differ significantly from the occurrence of various clinical symptoms in Asia patients with Dent disease (Table 1). However, the occurrence of hypercalciuria, nephrocalcinosis, nephrolithiasis, and CKD is higher in Europe and America than in Korean patients with Dent disease [7-10,20]. The estimated GFR (eGFR) at diagnosis and eGFR at an average follow-up of 7 years are comparable (106 mL/min/1.73 m^2 vs. 108 mL/min/1.73 m^2). The annual eGFR decline rate is similar to the previous report [10], with an annual decline in eGFR of 1.1 mL/min/1.73 m^2. Initial therapy consisted of thiazides in five patients, ACEI and ARB in 25 patients, and potassium citrate in four patients. At the last follow-up, three patients took thiazide, 10 patients took ACEI/ARB, and three patients took potassium citrate.

Conclusions

Dent disease is an uncommon X-linked recessive kidney disease that is often underdiagnosed. Although the identification of genetic pathogenic variants can support the diagnosis of Dent disease, not all affected patients have a pathogenic genetic variant. Clinicians should suspect Dent disease in male patients with LMW proteinuria or with idiopathic nephrocalcinosis, nephrolithiasis, or CKD.

Conflicts of interest

Eun Mi Yang 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.

Funding

This study was supported by grants from Chonnam National University Hospital Biomedical Research Institute (BCRI20008).

Acknowledgements

I am grateful to our colleagues Heeyeon Cho (Sungkyunkwan University School of Medicine), Min Hyun Cho (Kyungpook National University), Kyoung Hee Han (Jeju National University), Hee Gyung Kang (Seoul National University College of Medicine), Ji Hyun Kim (Seoul National University Bundang Hospital), Ji Yeon Song (Pusan National University Children's Hospital), and Se Jin Park (Daejeon Eulji Medical Center) for providing access to the patient's clinical reports (in alphabetical order).

Author contributions

All the work was done by EMY and SHC.

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ChiKD CHILDHOOD KIDNEY DISEASES

Review Article

Child Kidney Dis 2023;27(2):76-81
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.021

Tolvaptan: a possible preemptive treatment option in children with autosomal dominant polycystic kidney disease?

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Tolvaptan is a highly selective vasopressin receptor 2 antagonist that regulates cyclic adenosine monophosphate levels to inhibit both epithelial cell proliferation and chloride ion excretion, two mechanisms known to induce cyst expansion in autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan is currently the preferred treatment of rapidly progressive disease ADPKD in adult patients; however, since cyst formation in ADPKD begins early in life, (frequently in utero), and significant disease progression with cyst expansion occurs in the first decade, tolvaptan may be advantageous as a preemptive treatment in children with ADPKD. Tolvaptan has already been used to successfully treat refractory edema or hyponatremia in children; this literature review provides insight into the biochemical basis of its action to contextualize its use in the pediatric population.

Keywords: Child; Polycystic kidney, autosomal dominant; Tolvaptan

Introduction

Tolvaptan is a highly selective vasopressin receptor 2 (V2R) antagonist that acts by regulating cyclic adenosine monophosphate (cAMP) levels to inhibit both epithelial cell proliferation and chloride ion excretion, two mechanisms responsible for inducing cyst expansion in autosomal dominant polycystic kidney disease (ADPKD) [1,2]. The TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) trial [3] and the REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) trial [4] concluded that tolvaptan delays the increase in total kidney volume (TKV) and the decline in renal function in adult patients with ADPKD. Therefore, tolvaptan is currently the preferred treatment option for rapidly progressing ADPKD in adult patients in Japan, Canada, the EU, the USA, and Korea. Clinicians consider ADPKD to be essentially an adult-onset disease because serum creatinine levels typically remain within the normal range during childhood, and symptoms of end-stage kidney disease (ESKD) typically develop only in the fifth or sixth decade. However, cyst formation in ADPKD begins early in life, frequently in utero; notably, significant disease progression with renal cyst formation and expansion occurs in the first decade. Therefore, ADPKD cannot be isolated to adults only. This review tries to find out whether tolvaptan can be the option of preemptive treatment in children with ADPKD.

Received: October 25, 2023; Revised: November 20, 2023; Accepted: December 1, 2023

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Tolvaptan in adult patients with ADPKD

The polycystin complex (polycystin-1, polycystin-2, and fibrocystin/polyductin) is located in the primary cilia as membrane-associated proteins; it translates mechanical stimulation of the cilia into calcium entry, which triggers calcium-induced calcium release from the endoplasmic reticulum [2]. In ADPKD, polycystin levels are reduced below a critical threshold which disturbs the intracellular calcium homeostasis and enhances cAMP accumulation by increasing adenylyl cyclase type 6 (AC6) activity. This further stimulates epithelial cell proliferation activated by mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling and chloride-driven fluid excretion driven by the cystic fibrosis transmembrane conductance regulator (CFTR) and ultimately induces cyst expansion in ADPKD [2]. In addition, arginine vasopressin acts by binding to V2R, which stimulates AC6 as a GS protein-coupled receptor that increases intracellular cAMP levels [1]. In this regard, tolvaptan acts as a highly selective V2R antagonist that regulates cAMP levels to inhibit both epithelial cell proliferation by MAPK/ERK signaling and chloride-driven fluid excretion by CFTR in ADPKD (Fig. 1).

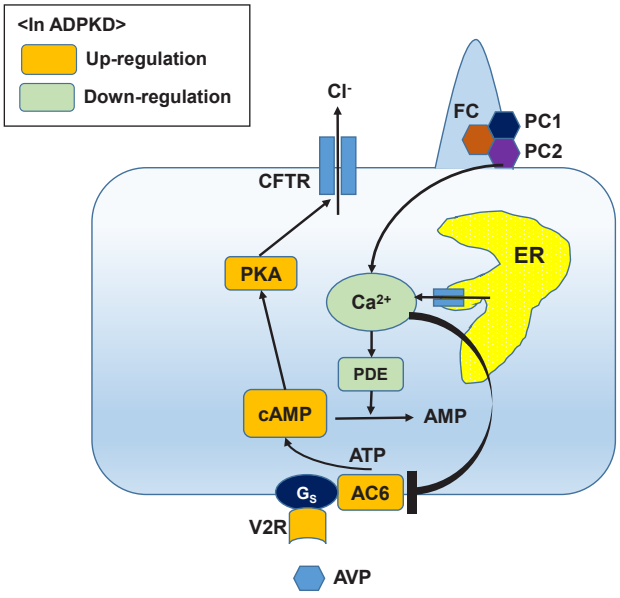

Fig. 1. Schematic pathway of chloride-driven fluid excretion in polycystic kidney disease. ADPKD, autosomal dominant polycystic kidney disease; FC, fibrocystin; PC1, polycystin-1; PC2, polycystin-2; ER, endoplasmic reticulum; CFTR, cystic fibrosis transmembrane conductance regulator; PKA, protein kinase A; PDE, phosphodiesterase; AMP, adenosine monophosphate; cAMP, cyclic AMP; ATP, adenosine triphosphate; AC6, adenylyl cyclase type 6; V2R, vasopressin receptor 2; AVP, arginine vasopressin.

In 2012, Torres et al. [3] published the results of a three-year, phase-III, multicenter, double-blind, placebo-control study on 1445 ADPKD patients (aged 18–50 years) with a TKV of >750 mL and an estimated creatinine clearance of ≥60 mL/min. The tolvaptan treatment group demonstrated only a 2.8% increase in the TKV compared to 5.51% in the placebo treatment group, showing a significant treatment effect. Likewise, the reduction in renal function, as evaluated using reciprocal serum creatinine, was significantly delayed in the treatment group as compared to the placebo treatment (−2.61 vs. −3.81; $P<0.001$). These results provided a cornerstone for the selection of tolvaptan as a treatment for ADPKD (TEMPO 3:4 trial) [3]. However, there was a significant increase of adverse events in the patients who received tolvaptan. These adverse events were related to elevation of liver-enzyme levels and increased aquaresis such as polyuria, thirst, nocturia, and polydipsia [3].

Five years later, Torres et al. [4] conducted follow-up studies of the TEMPO 3:4 trial and published them as the REPRISE trial. The trial included a total of 1,370 patients with ADPKD aged either 18–55 years with an estimated glomerular filtration rate (eGFR) of 25–65 mL/min/1.73 m^2 or 56–65 years with an eGFR of 25–44 mL/min/1.73 m^2. The patients were subjected to a 1:1 random allocation with tolvaptan and placebo and observed for 12 months. This study was more advanced than the TEMPO 3:4 trial. The authors concluded tolvaptan led to a significant delay in the rate of decrease in renal function, and long-term treatment was safe, which was corroborated via additional extended study [5].

In 2021, comparative results of the REPRISE trial and the aforementioned open-label extension trial were published. A post hoc analysis was done which retrospectively investigated patients with very low residual renal function (eGFR, 15–29 mL/min/1.73 m^2), which reported that both the extension and initiation of tolvaptan treatment were significantly effective in subjects with very low renal function. Therefore, tolvaptan offers beneficial therapeutic effects in patients diagnosed with ADPKD regardless of residual kidney function [6].

A pooled longitudinal analysis published in 2022 analyzed the results of eight clinical studies using tolvaptan and five clinical studies without tolvaptan, drawing attention to verifying the effectiveness of tolvaptan [7]. Over a long follow-up period of 5.5 years, tolvaptan was found to delay renal function loss by an eGFR of 1.01 mL/min/1.73 m^2 compared to the standard of the case group. Overall, the therapeutic effect of tolvaptan has been

extensively studied, which forms the basis of several treatment guidelines for its use in ADPKD [8-12].

Tolvaptan: experiences with pediatric use

Tolvaptan has been widely used in children for various indications other than ADPKD, such as severe edema and hyponatremia [13-22]. The first account of tolvaptan use in children is from Japan in 2014–an 8 years old girl diagnosed with steroid-resistant nephrotic syndrome received tolvaptan for one week for severe edema. This led to a significant increase in the urine volume without a concomitant increase in urine protein [13]. Since then, various cases have reported the effectiveness and safety of tolvaptan in pediatric patients in conditions involving hyponatremia, such as the syndrome of inappropriate antidiuretic hormone, for regulating body fluids in congestive heart failure, or after open heart surgery [14-20]. In a prospective study involving tolvaptan use in pediatric patients with nephrotic syndrome and severe edema, Meena et al. [21] reported a significant increase in urine volume by co-administering tolvaptan for 48 hours in patients who did not respond adequately to 48 hours of furosemide treatment.

In 2022, Piffer et al. [22] conducted a systematic literature review of 26 papers that reported vaptan-based treatment experiences for edema and hyponatremia published since 2008. The review included 115 pediatric patients with vaptan-based treatment, of which 63 were treated for hyponatremia and 52 for edema. Although vaptan-based treatment did not show superior results to conventional treatments for edema and hyponatremia, it showed substantial therapeutic effects, and only a few side effects, highlighting its safety in children.

Possible preemptive use of tolvaptan in pediatric ADPKD patients

ADPKD is often recognized as a disease confined to adults owing to the perception that most patients are asymptomatic during childhood. However, the following facts suggest that it is necessary to recognize that ADPKD requires early diagnosis and treatment in children. First, children with ADPKD are likely to have an overestimation of eGFR because of glomerular hyperfiltration for a considerable period. Therefore, the eGFR may not be an appropriate indicator of the progression of ADPKD during childhood. Second, the formation and expansion of renal cysts in ADPKD patients are already underway from the fetal period; also, the associated kidney damage starts from childhood. Therefore, TKV may not be the optimum prognostic indicator of ADPKD during childhood. Third, about 2%–5% of all ADPKD patients have severe clinical findings comparable to autosomal recessive polycystic kidney disease. Various clinical symptoms, such as frequency, polyuria, hematuria, urinary tract infection, renal stones, abdominal pain, hypertension, and proteinuria may be evident, but pediatric guidelines for managing them have not yet been established. Therefore, conclusive efforts are warranted to integrate pediatric ADPKD patients, who are currently excluded, into the purview of treatment using tolvaptan [23-25].

There are a few additional considerations. Since many patients dropped out of the TEMPO 3:4 trial due to drug side effects, clinicians should be cautious of the possible side effects of tolvaptan use. Children are more vulnerable to dehydration or electrolyte imbalance caused by the aquaretic effects of tolvaptan; likewise, hepatotoxicity is also a known side effect [26]. Therefore, appropriate counter-measures and monitoring should also be applied with tolvaptan use. Furthermore, not all patients with ADPKD progress to ESKD, so patient screening is extremely important. Currently, TKV is used as a valid predictive indicator in adult patients with rapidly progressive disease; however, the same cannot be applied to children. Thus, it is important to discover new biological markers that can be used as valid predictive indicators [27].

To date, tolvaptan has been rarely used in children. In 2017, Gilbert et al. [28] first reported tolvaptan use in a newborn with ADPKD with a family history of the disease. The patient developed pulmonary dysplasia due to huge kidneys at birth along with obstruction of the inferior vena cava, showing symptoms comparable to ADPKD. The infant was treated with 0.5 mg/kg/day of tolvaptan from 3 months of age which was increased to 1 mg/kg/day; the infant showed normal growth up to 12 months of age.

In 2021, a study published a post hoc analysis of the adolescents and young adults (aged 18–24 years) of the TEMPO 3:4 trial conducted in 2012 [29]. Of a total of 1,445 patients aged 18–50 years, 63 patients met the age criteria; 50 out of 63 patients were identified as having rapid progression (22 placebo group patients and 28 in the tolvaptan group). The authors noted that the change in TKV in the tolvaptan group was significantly lower than that of the placebo group, suggesting the possibility of using tolvaptan even in the younger age group.

In 2019, a multicenter, prospective study was conducted

https://doi.org/10.3339/ckd.23.021

Table 1. Recommendations for follow-up in children with ADPKD

Follow-up	Recommendation
Regular follow-up (every 1–3 yr; without HTN or proteinuria)	· Measure BP and urine protein excretion (at least once a year) · Perform ABPM at least once from age 5 yr · Consider repeated ultrasound depending on the clinical course and the age of the patient · Enquire about further at-risk siblings · Address psychosocial issues · Advise lifestyle modification (physical activity, maintenance of normal weight, low-salt diet, high water intake, avoidance of excessive protein intake)
Advanced follow-up (with HTN or proteinuria)	· Perform ABPM to confirm HTN · Use RAAS inhibitors as 1st line therapy and follow-up (target BP: below 75th percentile or <125/72 mmHg if age >16 yr) · Screen for end-organ damage (eye, heart)

ADPKD, autosomal dominant polycystic kidney disease; HTN, hypertension; BP, blood pressure; ABPM, ambulatory blood pressure monitoring; RAAS, renin-angiotensin-aldosterone system.

by Schaefer et al. [30] to evaluate the effects and side effects of tolvaptan in children with ADPKD. The study consisted of two types: phase A was planned as a 1-year, randomized, double-blinded, placebo-controlled multicenter trial, and phase B as a 2-year open-label extension trial. The study included pediatric ADPKD patients aged 4–17 years (weight ≥20 kg; eGFR ≥60 mL/min/1.73 m^2) diagnosed with ADPKD based on family history or genetic testing; at least 10 cysts (>4 for patients under 12 years of age) were identified for inclusion in the study.

In 2023, Mekahli et al. [31] published the results of this prospective study. A total of 91 patients participated in the study (48 in the tolvaptan group and 43 in the placebo group). The authors noted that the spot urine osmolality and specific gravity measured 1 week after drug administration were significantly lower in the tolvaptan group, confirming the efficacy of tolvaptan in pediatric patients. However, unfortunately, there was no significant difference in the changes in height-adjusted TKV over the year. It was reported that aquaretic adverse events were more common in the tolvaptan group compared to the placebo group (65% vs. 16%, respectively) and there were no elevated transaminases or drug-induced liver injuries [31].

Monitoring in children with ADPKD (before the tolvaptan era)

Certain issues need to be addressed before clinically using tolvaptan in pediatric ADPKD patients. At present, it is advisable to refer to the results of studies that have been published recently while following the international consensus statement [32]. First, a child with renal cysts and a family history of ADPKD or diagnosed with ADPKD through genetic testing must be checked for related symptoms, such as urinary tract infection, renal stones, hematuria, and abdominal pain. Blood pressure monitoring and urine protein excretion should be regularly performed every 1–3 years. In addition, it is important to ensure other siblings are tested, but general tests for extrarenal manifestations are not recommended. Patients must be educated on sufficient water intake, low-salt diet, exercise, smoking cessation, and weight control to improve lifestyle habits. Patients with confirmed hypertension or proteinuria should undergo regular ambulatory blood pressure monitoring and be strictly managed using renin-angiotensin-aldosterone inhibitor as the first-line therapy. Lastly, it is important to check for end-organ damage, including eye and heart (Table 1) [24,32].

Conclusion

Tolvaptan is a widely used treatment option to improve the prognosis of adult ADPKD patients, but there are several problems precluding its use in children. It is also true that the experience with tolvaptan use in children has been generally favorable without leading to significant hepatotoxicity compared to adults. Therefore, future studies must explore the preemptive use of tolvaptan in pediatric ADPKD patients.

Conflicts of interest

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

Funding

None.

Author contributions

All the work was done by HSB and MHC.

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ChiKD CHILDHOOD KIDNEY DISEASES

Review Article

Child Kidney Dis 2023;27(2):82-88
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.016

Anemia in children with chronic kidney disease

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Chronic kidney disease (CKD) causes numerous changes that destabilize homeostasis, of which anemia is one of its important complications. Anemia significantly reduces the quality of life in children with CKD and plays a crucial role in the progression of cardiovascular disease such as left ventricular hypertrophy, a major cause of mortality in those with advanced CKD. The treatment of anemia is a pivotal factor in reducing morbidity and mortality rates in children with CKD, representing one of the methods for enhancing patients' quality of life.

Keywords: Anemia; Children; Kidney disease

Introduction

Chronic kidney disease (CKD) can lead to various changes that disrupt homeostasis, with anemia as its important complication. Anemia in kidney failure was recognized in 1836 by Richard Bright, an English physician and early pioneer in kidney disease research, who noted that "healthy faces fade over time" [1]. Likewise, in 1839, toxicologist Robert Christison said, "By far the most remarkable character of the blood in the advanced stage of the Bright's disease is a gradual and rapid reduction of its coloring matter or hematosin" [2]. As kidney disease progresses, anemia prevalence increases [3]. According to the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), the prevalence of anemia is defined as 73%, 87%, and over 93% in pediatric CKD stages 3, 4, and 5, respectively [4]. Anemia is a significant factor in reducing the quality of life in children suffering from CKD, and it plays a crucial role in the progression of cardiovascular disease such as left ventricular hypertrophy, a leading cause of mortality among children with advanced CKD [5-9]. In addition, anemia in pediatric CKD significantly increases the risk of hospitalization and mortality compared with no anemia [10-12]. Therefore, this review aims to enhance our understanding of anemia in pediatric CKD and provide a comprehensive overview of its appropriate treatment.

Pathogenesis of anemia in CKD

Since the 1950s, with the kidney being recognized as a key regulator of erythropoiesis and the primary source of erythropoietin (EPO) production, EPO deficiency has emerged as the major probable cause of anemia in CKD [13,14]. CKD-related anemia is a multifactorial process resulting from relative EPO deficiency, uremia-induced inhibition of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis [15]. Additionally, factors such as inflammation, infection, blood loss, hyperparathyroidism, and nutritional deficiency play a role in causing anemia in CKD (Table 1) [15-18]. Recent studies have identified that the accumulation of iron-regulatory protein

Received: September 26, 2023; Revised: October 18, 2023; Accepted: October 22, 2023

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hepcidin, which was upregulated in CKD, is a main contributor to disordered iron homeostasis and anemia in CKD by impairing dietary iron absorption from the gastrointestinal tract and iron mobilization from body stores [15,19,20]. As glomerular filtration rate and inflammation decrease, hepcidin levels are expected to rise. Thus, hepcidin may be a potentially modifiable medium for anemia in CKD, and treatment strategies targeting hepcidin are currently being studied [21-23]. Therefore, evaluating these multiple factors and establishing an appropriate treatment plan are necessary to successfully treat anemia in CKD.

Defining anemia in CKD

Defining and assessing anemia in pediatric CKD is not as straightforward as it is in adults. Normal hemoglobin levels vary by age, sex, and race in both adults and children [5,24,25]. Previous versions of the Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines (2000) simply applied the adult hemoglobin cutoff value (<11.0 g/dL) to children, which was eventually found to significantly underestimate the prevalence of anemia in patients with CKD under 18 years old [17,26,27]. Hence, such guidelines were updated in 2006 to reflect age-dependent criteria for anemia in CKD [5]. These most recent KDOQI guidelines cite reference values for children according to the data from the National Health and Nutrition Examination Survey III. They recommend diagnosing anemia when hemoglobin levels fall below the 5th percentile based on age- and sex-specific criteria and initiating appropriate evaluation for anemia. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines also based the diagnostic criteria for CKD-related anemia on age, as shown in Table 2 [28].

Table 1. Cause of anemia in chronic kidney disease

Erythropoietin deficiency
Iron deficiency
Inflammation
Reduced erythrocyte survival duration
Infection
Acute or chronic blood loss
Hyperparathyroidism
Other hematologic disorder
Inadequate dialysis
Nutritional deficits

Treatment of anemia in CKD

The treatment of anemia is a pivotal factor in reducing morbidity and mortality rates in children with CKD and enhancing patients' quality of life. Although the recommended frequency for assessing anemia according to KDIGO and KDOQI guidelines may vary slightly according to the CKD stage and dialysis status, generally, for primary anemia prevention in pediatric CKD, clinicians are advised to monitor hemoglobin levels at least every 6 months to 1 year for anemia detection, and if anemia is diagnosed, the hemoglobin level should be monitored at least every 1 to 3 months [5,28]. For effective anemia treatment, the two most vital components, namely, exogenous erythropoiesis-stimulating agent (ESA) and iron supplementation, must be simultaneously administered. Adjunctive therapies to supplement other nutritional deficiencies and regulate bone mineral metabolism disorders can also be combined.

ESA therapy

Anemia management has dramatically transformed since recombinant human EPO was introduced in the late 1980s. The ESA therapy can significantly improve anemia symptoms in patients with CKD, reducing the need for blood transfusions [29,30]. After the U.S. Food and Drug Administration (FDA) approved the recombinant human EPO (epoetin alfa) in 1989, epoetin alfa became the standard treatment for EPO deficiency anemia. Subsequently, darbepoetin alfa was approved, offering the advantage of 2 to 3 times longer half-life than epoetin alfa [31]. Additionally, methoxy polyethylene glycol-epoetin beta, which has an even longer half-life, has been used [32]. The KDIGO guidelines recommend initiating ESA therapy in adult non-dialysis patients when hemoglobin is less than 10 g/dL and in adult dialysis patients when hemoglobin is 9–10 g/dL. However, no specific criteria are currently available for children with CKD, and making treatment decisions based on the potential benefits and side effects in each individual case is recommended. Furthermore, once ESA therapy is initiated, the recommended

Table 2. Diagnosing anemia in children with chronic kidney disease

Age	Hemoglobin concentration
0.5–5 yr	<11.0 g/dL
5–12 yr	<11.5 g/dL
12–15 yr	<12.0 g/dL
>15 yr	<13.0 g/dL in males <12.0 g/dL in females

target hemoglobin concentration for maintenance therapy in pediatric patients is approximately 11–12 g/dL [28]. After the initiation, hemoglobin concentration should be measured weekly until it stabilizes and reaches the target level. The most appropriate goal during the first month of treatment is an increase in hemoglobin concentration of approximately 1 g/dL. An increase of more than 1 g/dL during the first 2 weeks of monitoring should be considered as excessive, and the ESA dose should be reduced by approximately 25% to 50% [28].

Risk of ESA treatment

One of the most recognized side effects of ESA is hypertension, which is of particular significance because of its role as both a cardiovascular risk factor and a mediator of kidney disease progression [30,33]. However, given the ease of managing hypertension through ESA dose adjustments, discontinuation of the medication is rarely necessary. The more serious side effects are related to the increased risk for thrombotic complications and cardiovascular events [34,35]. Rapid increase in hemoglobin concentration must be avoided to reduce such thrombotic risks; additionally, particular caution should be exercised in patients who have recently experienced thrombotic events or have coagulation disorders [36,37].

Target hemoglobin concentration of ESA treatment

The biggest issue arising since the introduction of ESA therapy was the standard for determining the target hemoglobin concentration [38]. Partial correction of severe anemia versus complete normalization of hemoglobin concentration through ESA therapy and their impact on the quality of life have been investigated for quite some time [39]. Most of the studies demonstrated that achieving complete normalization of hemoglobin concentration did not further improve the quality of life. Instead, more importantly, the risk for cardiovascular and thrombotic events increased [38,40,41]. In addition, ESA therapy that aims to completely normalize the hemoglobin concentration has been associated with an increased risk for complications rather than therapeutic benefits. The reason why cardiovascular complication risk increases upon the complete normalization of hemoglobin concentration remains unclear, but researchers hypothesize that this phenomenon can be explained by the increase in blood viscosity at higher hemoglobin concentrations and the increase of vascular endothelial wall stress [35]. This risk may not be caused by the elevation of hemoglobin concentration per se but rather the very high ESA dose required to normalize such concentration. Therefore, the FDA recommends maintaining ESA treatment to achieve a therapeutic effect by using the lowest ESA dose needed.

Hyporesponsiveness of ESA treatment

Although uncommon, approximately 5% to 10% of patients treated with ESA experience ESA hyporesponsiveness intermittently or chronically during ESA therapy [42]. Maintaining a hemoglobin concentration above 10 g/dL without the use of high ESA doses may be difficult for these patients. Hence, the cause of hyporesponsiveness must be investigated. Its common causes include iron deficiency, blood loss, inflammation, infection, hyperparathyroidism, and other hematologic disorders [17,42,43]. Identifying and correcting these factors first is important.

Iron therapy

The most commonly identified reason for poor response to ESA therapy in pediatric CKD with anemia is iron deficiency [44]. ESA therapy itself increases the demand for iron and may reveal or exacerbate decreased iron availability [45]. Similar to many other studies involving adult patients, supplementing iron in children undergoing ESA therapy can reduce the required ESA dose per the achieved unit of hemoglobin level [46,47]. Hence, patients with CKD must be periodically evaluated for iron status and maintained with appropriate iron agents if necessary. The goal of iron therapy is not only to replenish depleted iron but also to prevent iron store depletion, avoid iron-deficiency erythropoiesis, and maintain the target hemoglobin level. The KDIGO anemia guidelines recommend assessing the iron status at least every 3 months during ESA therapy and targeting serum ferritin levels at 100 ng/mL or more and transferrin saturation at 20% or more for the maintenance of iron therapy [28]. Iron therapy is administered either orally or intravenously, depending on the dosage and dialysis status of children with CKD [48]. Children in the non-dialysis or peritoneal dialysis CKD group mostly receive oral iron agents, whereas those undergoing hemodialysis are more likely to require intravenous formulations to allow sufficient iron stores for ongoing erythropoiesis [49]. For oral iron agents, the recommended dose of elemental iron ranges from 2–3 mg/kg/day to 6 mg/kg/day, with a maximum daily dose of 150–300 mg, divided into 2–3 doses [50,51]. To maximize gastrointestinal absorption, children are advised to take iron supplements on an empty stomach and to avoid concomitant intake with any

https://doi.org/10.3339/ckd.23.016

calcium-containing binding agents [52]. Although oral iron supplements are cost effective and easy to administer, their efficacy in maintaining adequate iron stores for erythropoiesis is limited because of poor gastrointestinal absorption and poor compliance. Furthermore, oral iron supplementation often falls short in keeping up with the chronic blood loss associated with chronic hemodialysis in pediatric patients [17]. According to studies, intravenous iron supplementation showed significantly better responses in terms of serum ferritin and hemoglobin level increase, iron storage, and reduced required ESA doses than oral iron supplementation [47,49]. Studies verifying the efficacy of intravenous iron in children with nonhemodialysis CKD have also been reported [53,54]. Despite the advantages of intravenous iron administration, concerns remain because of its potential association with various clinical side effects, such as hypotension, tachycardia, and gastrointestinal symptoms, in addition to inducing iron overload–related oxidative stress [55,56]. Therefore, adequate monitoring of dosages, frequency, effectiveness, and safety is essential.

Oral HIF-PHIs

Considering the risk of developing complications such as hypertension and cardiovascular events, and other adverse events associated with existing ESA medications, experiments with new drugs aimed at reducing these complications have been conducted. A new class agent of anemia treatment for patients with CKD is the hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) [57-59]. The HIF-prolyl hydroxylase domain (PHD) pathway regulates the cellular response to hypoxia, which is also involved in anemia. HIF is transcription factor that regulates the production of EPO and is decomposed by prolyl hydroxylase under normal oxygen saturation conditions. But when oxygen is insufficient, the hydroxylation reaction cannot occur and HIF is stabilized. The HIF-PHD axis coordinates hypoxia response across multiple cell types and tissues. In addition to kidney and liver EPO production, HIF regulates iron metabolism and promotes erythrocyte precursor cell maturation and proliferation in bone marrow. HIF-PHI not only activated endogenous EPO production by inhibiting HIF-PHD, but also increases iron reuse in the liver by inhibiting hepcidin, and promotes erythropoiesis by enhancing iron availability [57-59]. Randomized, double-blind, phase 3 trial studies were conducted in adult dialysis participants with CKD-related anemia to evaluate the efficacy, safety, and pharmacokinetics between HIF-PHI and ESA therapy; results showed that the HIF-PHI agent was not inferior to ESAs in terms of correcting anemia and cardiovascular outcomes [60,61]. Based on these results, the HIF-PHI agents are currently being administered with FDA approval in adult patients undergoing dialysis for CKD, and phase 3 trial studies are underway for patients with CKD not undergoing dialysis [62,63]. Studies on the efficacy and safety of HIF-PHI, particularly daprodustat, in pediatric patients with CKD are also currently underway [64]. Unlike ESAs, which are injectable only, HIF-PHI agents are oral medications. When ESA treatment is actually used for a long period of time, most children complain of stress because the injection is too painful for them, thereby worsening their quality of life. The development of new oral agents will play a crucial role in relieving children's stress about administering injections.

Table 3. Treatment of anemia in children with chronic kidney disease

Treatment	Compound	Concern
ESA	Epoetin alfa	Hypertension
	Darbepoetin alfa	Thrombotic events
	Methoxy polyethylene glycol-epoetin beta	Cardiovascular risk
Iron	Intravenous: iron sucrose, ferric gluconate, iron dextran	Hypotension
	Oral: ferrous sulfate, ferrous gluconate, ferrous fumarate, ferric maltol, ferric citrate	Tachycardia
		Gastrointestinal symptoms
Oral HIF-PHIs	Daprodustat	Hypertension
	Roxadustat	Thromboembolic events
	Vadadustat	Cardiovascular risk
	Enarodustat	
Red blood cell transfusion		Allosensitization
		Volume overload
		Hyperkalemia

ESA, erythropoiesis-stimulating agents; HIF-PHIs, hypoxia-inducible factor prolyl hydroxylase inhibitors.

Red blood cell transfusion

Red blood cell transfusions should be used cautiously in patients with CKD, especially in children who are mostly considering future kidney transplantation, to minimize the development of allosensitization, which may affect transplant outcomes [28]. Despite the use of ESA and iron therapies, red cell transfusion is sometimes unavoidable when acute bleeding or severe anemia symptoms occur. Red blood cell transfusion can provide rapid improvement in symptoms related to anemia clinically, but in patients with CKD, particular attention must be paid to various risks, such as volume overload, hyperkalemia, citrate toxicity, hypothermia, coagulopathy, and immunologic reactions [65]. Therefore, red blood cell transfusion is a treatment option for patients with chronic anemia whose ESA treatment is not sufficiently effective due to conditions such as hemoglobinopathy, bone marrow failure, and ESA resistance. It may also be considered in patients who require rapid hemoglobin correction preoperatively [28]. As in adults, red blood cell transfusion, along with immunosuppressant administration, before kidney transplantation may lead to a better transplant outcome among children [66]. Finally, treatment of anemia in children with CKD was summarized in Table 3.

Conclusion

Anemia is an important complication associated with several adverse outcomes in children with CKD. EPO deficiency and iron deficiency act as the most important etiological factors of anemia; thus, ESA therapy with iron supplementation is the best treatment for CKD-related anemia. Providing the appropriate treatment for this type of anemia is crucial because it can not only minimize discomfort in daily life (e.g., school attendance) by improving the quality of life, cognitive function, and cardiovascular function but also reduce hospitalization risk, rapid aggravation of kidney failure, and mortality.

Conflicts of interest

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

Funding

None.

Author contributions

All the work was done by MJP and MHC.

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https://doi.org/10.3339/ckd.23.016

ChiKD CHILDHOOD KIDNEY DISEASES

Review Article

Child Kidney Dis 2023;27(2):89-96
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.018

Nutcracker syndrome in children: review of symptom, diagnosis, and treatment

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Renal nutcracker syndrome (NCS) is the entrapment of the left renal vein between the abdominal aorta and superior mesenteric artery. Although uncommon in pediatric patients, early diagnosis is crucial to avoid potential severe complications, such as anemia or renal vein thrombosis. NCS presents a variety of symptoms, most commonly including "Triade's symptoms"–hematuria, proteinuria, and flank pain. Diagnosis and treatment include invasive and noninvasive management, although due to a lack of pediatric clinical studies, management is widely variable. Conservative diagnosis and treatment are recommended as a first-line option for pediatric patients; however, invasive surgical treatment may be recommended based on symptom severity. This review aims to provide a comprehensive overview of NCS in children to better understand the widely variable incidence, occurrence, and management from early on to allow for early-onset management.

Keywords: Aorta, abdominal; Mesenteric artery, superior; Renal nutcracker syndrome; Renal veins

Introduction

Renal nutcracker syndrome (NCS) is a rare pediatric disease that is defined as the symptomatic entrapment of the left renal vein (LRV). In the anterior form, the LRV is compressed between the aorta and mesenteric artery (Fig. 1), or less commonly between the aorta and vertebral column, known as posterior NCS. Common symptoms include hematuria, proteinuria, and flank pain, known as "Triade's symptoms," although there is still wide variability in clinical presentation among children [1-3]. Symptoms are believed to result from increased pressure within the renal vein and the kidney's venous drainage system. This elevated pressure is believed to harm the thin-walled septa between the veins and the collecting system in the renal fornix, leading to hematuria or proteinuria [2]. However, pathological evidence supporting this hypothesis is still lacking [4].

Although the terms "nutcracker phenomenon (NCP)" and "NCS" were used interchangeably in earlier literature, NCP specifically refers to the anatomical structure without the occurrence of symptoms [1,4,5]. The first pathological description of this anatomical structure was attributed to the anatomist Grant in 1937 [1], following the first clinical report of the phenomenon by El-Sadr and Mina in 1950 [6]. The term "NCS" is commonly attributed to the Belgian physician de Schepper [7], although it

Received: October 11, 2023 ; Revised: December 8, 2023 ; Accepted: December 9, 2023

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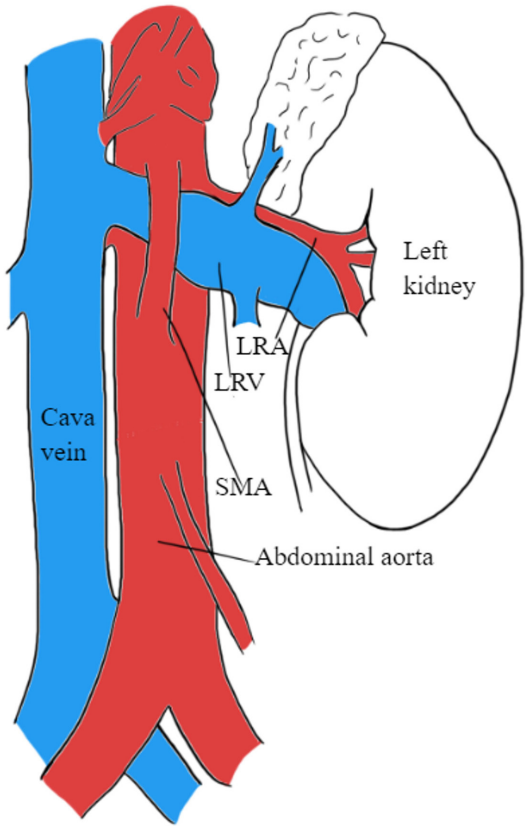

Fig. 1. Illustration of renal nutcracker syndrome, depicting the compression of the LRV between the abdominal aorta and the SMA. LRA, left renal artery; LRV, left renal vein; SMA, superior mesenteric artery.

was initially used by Chait et al. in 1971 [8].

While there is extensive research on NCS in adults [2,4], the incidence, diagnostic criteria, and treatment remain undefined in the pediatric cohort due to its rarity in children [9]. The exact incidence of NCS in children remains unknown [4]; however, a peak age period of diagnosis was observed between ages 10 and 14 years [10,11]. Timely identification of NCS is crucial due to the potential occurrence of more severe complications such as severe anemia or renal vein thrombosis resulting from hematuria [12]. Given the wide variability of NCS in the pediatric population, this literature review aimed to provide a better comprehensive understanding and overview of the disease in children.

Symptoms and clinical features

A wide range of symptoms has been observed in children with NCS due to the varying hemodynamic consequences of LRV compression [13]. LRV compression raises the retrograde venous pressure, impacting other associated vessels and leading to various clinical manifestations [14].

The most common symptoms observed in children with NCS are hematuria (micro- and macrohematuria), proteinuria (mainly orthostatic), and flank pain [3,5,9,13,15]. Additional studies observed symptoms such as renovascular hypertension, unspecified abdominal pain, dysmenorrhea, nephrolithiasis, calciuria, fatigue, testicular or scrotal pain, and varicocele [3,11,16,17]. Symptoms also often worsen with physical exercise [2,3].

Hematuria is the most frequently observed symptom in pediatric patients [3,7,18], occurring due to increased venous pressure leading to varicose veins rupturing and consequently bleeding into the renal collecting system [9,16]. Hematuria has been reported as the most frequent symptom in 75% of pediatric patients with NCS [3]. Children often experience microscopic hematuria asymptomatically, compared to adults, who more often experience hematuria with pain [11]. Additionally, a systematic review on pediatric NCS analyzing published literature from 1990 to 2020 described hematuria as the most commonly experienced symptom, observed in approximately 55% of children with NCS. This was followed by proteinuria and flank pain, observed in approximately 50% and 19% of children, respectively [9].

Although NCS can develop in individuals of all age groups, a higher incidence is observed in underweight or lean children aged 10 to 14 years, with a slight prevalence among females [14]. In a systematic review assessing 423 children with NCS (218 males and 205 females), the mean age of the study participants was 12 years [9].

Diagnosis and diagnostic criteria

Due to the rarity of NCS in children and a limited number of published studies, standardized diagnostic criteria for NCS in pediatric patients are lacking. Diagnosis often relies on exclusion criteria and utilizes conservative and invasive techniques [19].

In adults, renal venography is the first-line diagnostic examination [20,21]; other standard diagnostic techniques include renal Doppler ultrasonography (USG), magnetic resonance angiography, computed tomography (CT), and multislice helical CT angiography [22-25]. In contrast, many noninvasive diagnostic techniques, such as Doppler USG, magnetic resonance

https://doi.org/10.3339/ckd.23.018

imaging (MRI), or CT, are initially recommended for children [26-28]. As varicocele is often observed simultaneously with NCS in approximately 33% of male pediatric patients, Doppler USG is further recognized as an effective diagnostic technique [3]. Additionally, urinalysis helps identify potential NCS manifestations, including repeated hematuria (gross or microscopic), calciuria, and orthostatic proteinuria [9,29].

In children, recommended noninvasive examinations such as abdominal USG and Doppler studies are reported to have a sensitivity and specificity of approximately 82.3% and 89%–100%, respectively [3]. In the general population of patients with NCS, an aortomesenteric (AOM) angle of <35° is significantly characteristic of diagnosis (Figs. 2, 3) [30]. A previous study involving 205 pediatric patients reported an AOM angle of <25° in approximately 9% of asymptomatic pediatric patients with NCS [31]. Additionally, a study including 39 pediatric patients with orthostatic proteinuria reported that a ratio greater than 0.6 between the AOM angle in the upright and supine positions could be diagnostic of NCS [32]. However, additional criteria and further studies are required to validate the exact cutoff angle [20,33].

The diameter of LRV and peak velocity ratio in the AOM and hilar portions can also serve as diagnostic criteria for NCS in children (Figs. 2, 3) [3,9]. According to a study in 2002, a ratio greater than 4.2 for the diameter of LRV and 4.0 for the peak velocity ratio can be used as cutoff values to diagnose NCS [22]. A study enrolling a group of 12 pediatric patients published in 2006 recommended a peak velocity cutoff value of 4.7 (with specificity of 90% and sensitivity of 100%) [23]. Consequently, a study in 2007 including 216 pediatric patients with isolated

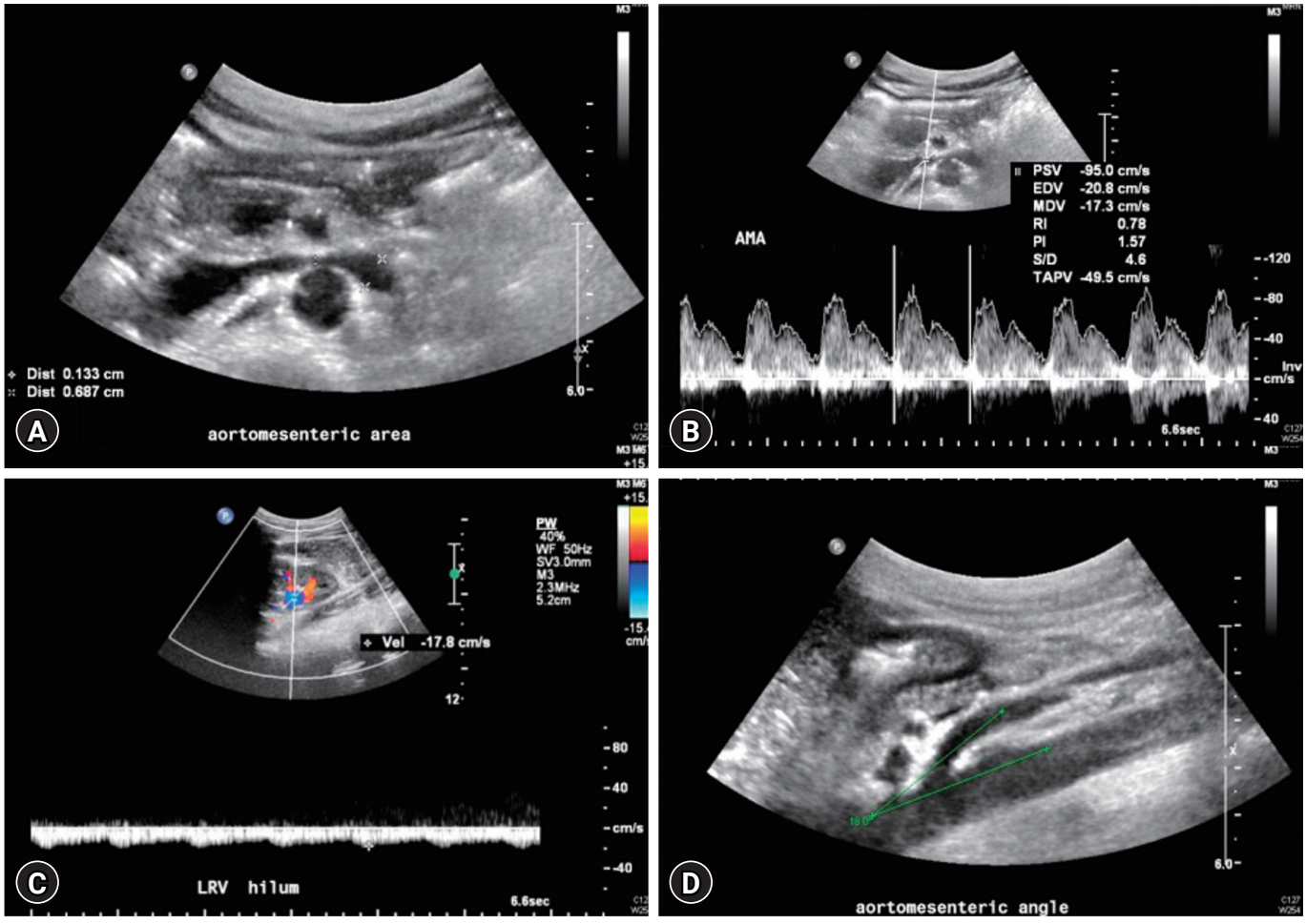

Fig. 2. Images of Doppler ultrasonography. (A) The diameters of left renal vein in the aortomesenteric portion (0.13 cm) and the hilar portion (0.69 cm). (B) The peak velocity in the aortomesenteric portion (95 cm/sec). (C) The peak velocity in the hilar portion (18 cm/sec). (D) The aortomesenteric angle (18°). Reused from Min et al. Child Kidney Dis 2018;22:75-80 [30].

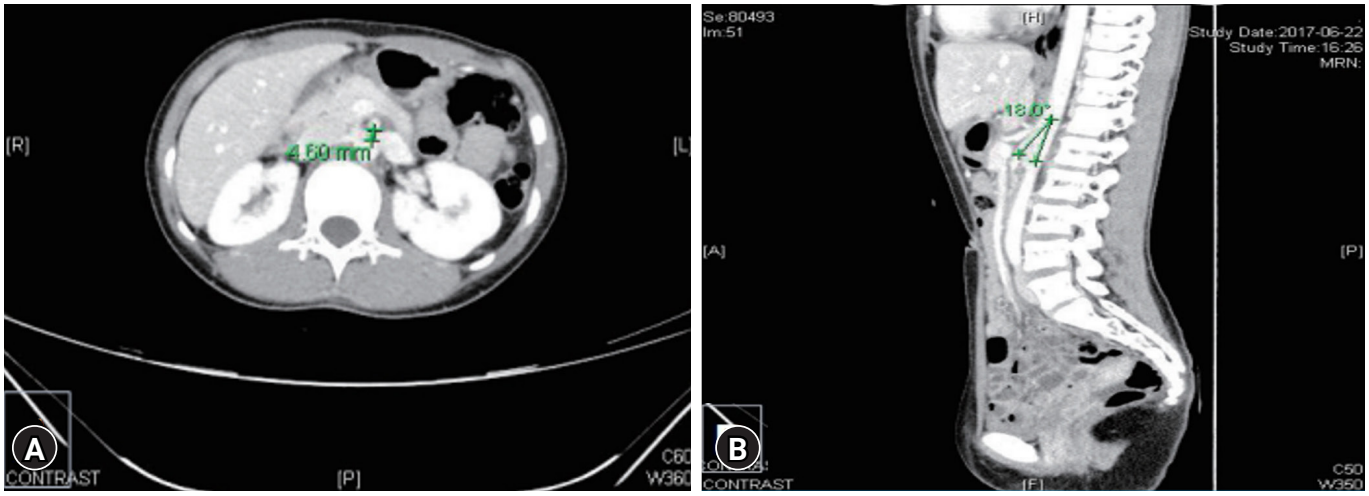

Fig. 3. Abdomen and pelvis computed tomography (enhancement). (A) Left renal vein was compressed by the aorta and the superior mesenteric artery (aorto-superior mesenteric artery distance: 4.6 mm). (B) Aortomesenteric angle was 18° in the sagittal plane. Reused from Min et al. Child Kidney Dis 2018;22:75-80 [30].

hematuria that reported NCS in approximately 33% of patients recommended a peak velocity ratio of at least 4.1 [24]. These varying results highlight the need for further research to validate peak velocity or LRV ratio cutoff values in diagnosing NCS.

Although conservative techniques are often recommended for diagnosis, invasive diagnostic techniques such as intravascular USG or phlebography are performed under circumstantial cases to assess the obstruction severity [9,28,29]. These invasive techniques may involve catheterization to measure the pressure gradient between the inferior vena cava (IVC) and LRV. The typical pressure gradient between IVC and LRV in the general population is <1 mmHg [28]. When the pressure gradient exceeds 3 mmHg, a definitive diagnosis of NCS is established [21,25,28]. Renal biopsies, venography, arteriography, cystoscopy, and intravenous urography are additional invasive techniques used in children [9].

Comorbidities and complications

Comorbidities frequently observed in pediatric patients with NCS include varicocele, chronic fatigue syndrome or idiopathic chronic fatigue, superior mesenteric artery (SMA) syndrome, and Wilkie's syndrome [34-39]. Table 1 describes the comorbidities observed in pediatric patients with NCS from previously published studies.

Varicocele is characterized by the enlargement of veins within the scrotum and exhibits a direct association with NCS in male children [34]. In cases where NCS is present, it can contribute to the development or exacerbation of varicocele [40]. A study involving 3,042 patients with varicocele, including 858 LRV entrapment cases, reported a risk ratio of 43.3 for LRV entrapment-associated varicocele recurrence [34].

Table 1. Comorbidities observed in pediatric patients with nutcracker syndrome

Comorbidity	Author (year)	Patient characteristics
CFS, CF	Takahashi et al. (2000) [35]	9 NCS children
Varicocele	Li et al. (2018) [34]	858 NCS and 2,184 control
	Reddy et al. (2020) [14]	13-year-old boy
SMA syndrome	Lin et al. (2020) [36]	15-year-old male
	Du et al. (2022) [37]	14-year-old female
Wilkie's syndrome	England and Li (2021) [38]	15-year-old male
	Gungorer et al. (2022) [39]	17-year-old male

CFS, chronic fatigue syndrome; CF, chronic fatigue; NCS, nutcracker syndrome; SMA, superior mesenteric artery.

Furthermore, occasional associations have been observed between chronic fatigue syndrome and NCS, characterized by elevated LRV-IVC pressure gradients. Fatigue symptoms have shown a positive correlation with high peak velocity ratios through Doppler USG; in some instances, these symptoms have improved postoperatively [41-43]. This association was also reported in a study that observed nine pediatric patients with severe NCP and chronic fatigue syndrome or chronic fatigue [35]. Additionally, two case studies have reported the coexistence of NCS with SMA syndrome in a 15-year-old male and a 14-year-old female [36,37]. Wilkie's syndrome has also been recorded to occur concurrently with NCS in two case studies with 15-year-

https://doi.org/10.3339/ckd.23.018

old and 17-year-old males [38,39].

Additional complications unrelated to NCS but observed in pediatric patients with NCS include immunoglobulin A nephropathy, immunoglobulin M nephropathy, intussusception, Henoch-Schönlein purpura, right retrocaval ureter, urolithiasis, LRV duplication, renal abscess, midline congestion syndrome, celiacomesenteric trunk anomaly, intestinal malrotation, and spontaneous spermatic vein thrombosis [44-55].

Treatment

Two main treatment approaches for NCS include conservative and surgical treatments. In adults, surgical treatment is often considered the initial therapy of choice. Conversely, in pediatric patients, a conservative approach, often involving a watch-and-wait strategy, is typically recommended for a minimum duration of 2 years [40,56,57]. The choice between conservative and nonconservative management is controversial and often depends on the clinical status and severity of symptoms [58].

The recommendation for conservative management in children is supported by previous studies that have demonstrated the spontaneous resolution of symptoms as children undergo physical development. According to a comprehensive systematic review, out of 138 pediatric patients who received conservative treatment for NCS, approximately 95% achieved complete resolution or symptom improvement (43% or 52%, respectively) [9]. Regarding hematuria in pediatric patients with NCS, after a mean follow-up of 1.5 years, 75% of pediatric patients experienced a complete resolution of hematuria. This study also recorded a significant increase in patient height and weight and a significant decrease in LRV and peak velocity ratios, suggesting how body mass index (BMI) may be a potential hemodynamic factor for the spontaneous resolution of hematuria [59].

Although the exact mechanism behind the spontaneous resolution of symptoms remains unclear, adolescent growth and an increase in BMI may be indicators for the prognosis of NCS. A study involving 23 children with NCS showed a significant correlation between BMI and the regression of hematuria and proteinuria symptoms. The study reported an initial average BMI of 16.9 kg/m^2, significantly increasing to 18.6 kg/m^2 during the follow-up period [16]. An increase in body weight in adolescents often modifies the position of the left kidney, allowing for a decrease in pressure on the LRV [4,16]. Additionally, the physical growth of the patient can prompt fibrous tissue proliferation at the origin of the SMA, partially relieving the compression at the AOM angle [40].

Although conservative treatment is highly recommended, when severe NCS symptoms persist, various surgical and endovascular treatments techniques may be applied. Common surgical treatments include the LRV, SMA, or left gonadal vein transposition, kidney autotransplantation, endovascular stent placement, laparoscopy, and shunt operation [60-65]. Among them, LRV transposition is considered the gold standard surgical treatment for uncompensated NCS. Other surgical options depend on the patient's specific case and context, such as symptoms severity, stage of the syndrome, and patient age [9,66]. For example, in a cohort of 53 male pediatric patients diagnosed with NCS and varicocele, spermatic-inferior epigastric vein anastomosis was performed. Approximately 96% and 49% of patients experienced improved NCS and scrotal bulge symptoms postoperatively [67]. Another example of case-specific operative treatment was recorded in managing NCS in a 16-year-old female. In situ, gonadal vein valvotomy and side-to-side gonado-iliac bypass were performed, resulting in a complete resolution in the patient [68]. Furthermore, in a case study of a 14-year-old female with NCS, orthostatic proteinuria resolved after angiotensin-converting enzyme inhibition therapy, although this treatment may affect renal hemodynamics in children [15,69].

In summary, NCS treatment varies depending on the patient's specific context. However, further clinical studies with long-term follow-up are required to evaluate the effectiveness of different treatment approaches.

Conclusions

Early diagnosis of NCS is crucial to prevent severe complications such as anemia or renal vein thrombosis. NCS symptoms vary widely, including hematuria, proteinuria, and flank pain. Due to pediatric NCS's rarity, diagnostic criteria are not well-established, although common noninvasive diagnostic techniques include Doppler USG, MRI, and CT for initial diagnosis. Comorbidities associated with NCS in pediatric patients include chronic fatigue syndrome, chronic fatigue, varicocele, SMA syndrome, and Wilkie's syndrome. Treatment options for NCS range from conservative management to surgical interventions. Further research and clinical studies with long-term follow-up are necessary to establish standardized diagnostic criteria and evaluate the efficacy of different treatment ap-

proaches for NCS in pediatric patients. These studies should additionally focus on evaluating the accuracy of noninvasive techniques, exploring the impact of associated comorbidities, and assessing the efficacy and safety of different treatment approaches. A better understanding of NCS in children will enable early management and improved outcomes.

Conflicts of interest

Se Jin Park and Jae IL Shin are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, and decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

Conceptualization: DSK, JIS
Data curations: DSK, SJP
Formal analysis: DSK, SJP, JIS
Investigation: DSK, SJP
Methodology: DSK, SJP, JIS
Project administration: SJP, JIS
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Writing-review & editing: DSK, SJP, JIS
All authors read and approved the final manuscript.

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https://doi.org/10.3339/ckd.23.018

ChiKD CHILDHOOD KIDNEY DISEASES

Original Article

Child Kidney Dis 2023;27(2):97-104
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.006

Efficacy and safety of losartan in childhood immunoglobulin A nephropathy: a prospective multicenter study

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Purpose: Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) are frequently employed to counteract the detrimental effects of proteinuria on glomerular diseases. However, the effects of ARBs remain poorly examined in pediatric patients with immunoglobulin A (IgA) nephropathy. Herein, we evaluated the efficacy and safety of losartan, an ARB, in pediatric IgA nephropathy with proteinuria.

Methods: This prospective, single-arm, multicenter study included children with IgA nephropathy exhibiting proteinuria. Changes in proteinuria, blood pressure, and kidney function were prospectively evaluated before and 4 and 24 weeks after losartan administration. The primary endpoint was the difference in proteinuria between baseline and 24 weeks.

Results: In total, 29 patients were enrolled and received losartan treatment. The full analysis set included 28 patients who received losartan at least once and had pre- and post-urinary protein to creatinine ratio measurements (n=28). The per-protocol analysis group included 22 patients who completed all scheduled visits without any serious violations during the study period. In both groups, the mean log (urine protein to creatinine ratio) value decreased significantly at 6 months. After 24 weeks, the urinary protein to creatinine ratio decreased by more than 50% in approximately 40% of the patients. The glomerular filtration rate was not significantly altered during the observation period.

Conclusions: Losartan decreased proteinuria without decreasing kidney function in patients with IgA nephropathy over 24 weeks. Losartan could be safely employed to reduce proteinuria in this patient population. *ClinicalTrials.gov trial registration (NCT0223277)*

Keywords: Angiotensin receptor antagonists; Child; Glomerulonephritis, IGA; Losartan; Prospective studies

Received: March 9, 2023; Revised: October 5, 2023; Accepted: October 6, 2023

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Introduction

Immunoglobulin A (IgA) nephropathy is the most common glomerular disease and is often diagnosed in children and young adults. Given that a considerable proportion of IgA nephropathy progresses to chronic kidney disease (CKD), especially when proteinuria is ≥1 g/day, the therapeutic goal is to reduce proteinuria. Blockage of the renin-angiotensin system (RAS) to reduce proteinuria has been the mainstay of IgA nephropathy treatment [1-4], along with various immunosuppressive medications [5-7].

The RAS is a hormonal system that plays a crucial role in blood volume and systemic vascular resistance. Activation of RAS results in increased blood pressure and sodium and water retention, subsequently increasing the effective circulating volume. RAS blockade reduces systemic and intraglomerular hydrostatic pressures by inhibiting angiotensin II-mediated efferent arteriolar vasoconstriction. Renal angiotensin II plays a major role in the development of renal fibrosis that progresses to end-stage renal failure, and the degree of proteinuria is known to be a risk factor for progression to kidney failure [8-10]. The ability of angiotensin II receptor blockers (ARBs) to reduce proteinuria, thereby delaying CKD progression, has been well-examined in diabetic nephropathy with proteinuria [11], leading to the approval of losartan and irbesartan for this indication. In IgA nephropathy, ARBs are frequently employed in combination with other therapeutic agents [12,13], and in adults, low-dose losartan was proven to reduce proteinuria [14]. Also, the blockade of RAS alone appears to be effective in children with proteinuria induced by kidney disease [15]. Among ARB, losartan has been approved by the U.S. Food and Drug Administration (FDA) for delaying CKD progression in proteinuric diabetic nephropathy along with irbesartan, although only losartan has been approved for children >5 years of age.

Angiotensin-converting enzyme inhibitors (ACEIs) are often selected as the first choice of RAS blocking agent; however, some patients fail to tolerate ACEIs and are switched to ARBs. A high incidence of ACEI-induced side effects such as dry cough has been documented in East Asia [16]. Therefore, ARBs have a relatively high clinical significance in this region. However, the use of ARBs for proteinuric glomerulopathy other than diabetic nephropathy remains off-label. In addition, the efficacy of ARB alone remains unexplored among pediatric patients with IgA nephropathy. In the present study, we performed a prospective multicenter study to confirm the efficacy and safety of losartan in reducing proteinuria in normotensive childhood IgA nephropathy with persistent proteinuria in Korea.

Methods

Subjects

Herein, children aged 24 months to 18 years who were diagnosed with IgA nephropathy based on kidney biopsies performed at participating hospitals were enrolled if they fulfilled the following two conditions: (1) estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2, and (2) a mean urine protein to creatinine ratio (UPCR) in the first morning urine sample of 3 consecutive days of ≥0.3. Patients with the following conditions were excluded: hypertension, allograft kidney transplantation, renal artery stenosis, confirmed primary hyperaldosteronism, history of hypersensitivity reactions to ARB, pregnancy, lactation, treatment with immunosuppressive agents such as steroids or calcineurin inhibitors, or taking antihypertensive drugs other than ACEIs or ARBs for blood pressure regulation. The number of subjects required to assess the efficacy of losartan in reducing proteinuria was calculated to be 28, assuming the following: level of significance α=0.05, type 2 error β=0.10, power of the test 80%, drop-out rate 10%, and magnitude of protein reduction 35.8%, according to the study by Webb et al. [17].

Methods

Study design

This study was approved by the Korean FDA and Institutional Review Boards of all participating institutions and conducted according to the Declaration of Helsinki. The trial was registered with ClinicalTrials.gov under the trial registration number NCT02232776. As a placebo-controlled study was assumed to be unethical, this study was designed as a single-arm study. The enrollment of study subjects was conducted from September 2014 to October 2016, with participation from seven centers in Korea. Patients who agreed to participate in the study were screened after obtaining written consent from the subjects and their legal representatives and enrolled if they met the pre-determined inclusion and exclusion criteria. At 2, 4, 12, and 24 weeks after initiating losartan, patients were assessed for proteinuria in the first morning urine, blood pressure, and potential side effects. Complete blood count and serum chemistry tests were performed at 12 and 24 weeks. Blood pressure was measured on two occasions, with a 1- to 3-minute interval between measurements, using the oscillometric method. The

https://doi.org/10.3339/ckd.23.006

mean value obtained from these measurements was used for analysis. Losartan was initiated at a dose of 0.7 mg/kg/day, taken once daily. At the 2- and 4-week follow-ups, the losartan dose was increased if proteinuria persisted given the absence of side effects, up to a maximum dose of 1.5 mg/kg/day or 100 mg/day. Complete remission was defined as a UPCR of <0.2, and partial remission was defined as a UPCR reduction of >50%. Proteinuria was evaluated using the first-morning UPCR. The eGFR was calculated using the bedside Chronic Kidney Disease in Children (CKiD) formula.

The primary endpoint was the change in proteinuria at 6 months after treatment. The secondary endpoints were as follows: (1) changes in proteinuria 1 month after dosing, (2) complete remission rate at 6 months, (3) partial remission rate percentage 6 months after administration, and (4) changes in eGFR at 6 months after dosing.

Statistical analysis

Subjects who had taken losartan at least once and had pre- and post-UPCR were grouped into the full analysis set (FAS) group. Subjects who completed all scheduled visits without any serious violations were grouped into the per-protocol (PP) group. Patients were excluded from the PP group if they had (1) hypertension requiring additional antihypertensive drugs or hypotension necessitating ARB discontinuation, (2) an eGFR of <60 mL/min/1.73 m^2, and (3) non-compliance with the visit schedule. For statistical analysis, the FAS group was used as the main analysis group and the PP group as the auxiliary group. Primary and secondary endpoints and adverse events, such as kidney dysfunction, hyperkalemia, angioedema, and changes in blood pressure, were analyzed. The UPCR was analyzed using a natural logarithm to satisfy the assumption of normality. The paired *t*-test was used when the difference in the log UPCR at the 6-month follow-up before and after the medication satisfied the assumption of normality, and the Wilcoxon signed-rank test was employed when the assumption of normality was not satisfied. Categorical data are presented as frequencies and percentages, and 95% confidence interval (CIs) were estimated. Continuous data are presented as mean±standard deviation or median (interquartile range [IQR]).

Results

Patients' characteristics

In this prospective study, 29 subjects with biopsy-proven IgA nephropathy were enrolled and received losartan treatment at the median age of 12.2 years (IQR, 10.1–15.0 years). Among them, the UPCR was not assessed in one patient after receiving losartan, who was excluded from the FAS group (n=28). This group is defined as the intent-to-treat (ITT) population (Fig. 1). In the ITT group, three patients had hypertension before losartan administration, one patient exhibited a decreased eGFR <60 mL/min/1.73 m^2 at the 2-week visit after initiating losartan, and two did not complete the visit schedule; therefore, they were excluded from the PP group (n=22). Table 1 summarizes the basic clinical characteristics of the ITT group. The median disease duration was 3.12 years (IQR, 0.51–4.42 years). At enrollment, the median baseline proteinuria was 0.72 mg/mg (IQR, 0.48–0.95 mg/mg) in the FAS group.

Outcomes

In the ITT group, the mean log UPCR value before losartan administration was −0.34, which significantly decreased to −0.80 at 6 months of administration (*P*=0.003). In the PP group, we noted a significant decrease in the mean log UPCR value at 6 months of administration (*P*=0.02) (Fig. 2). In both groups, the mean log UPCR was significantly reduced 1 month after ad-

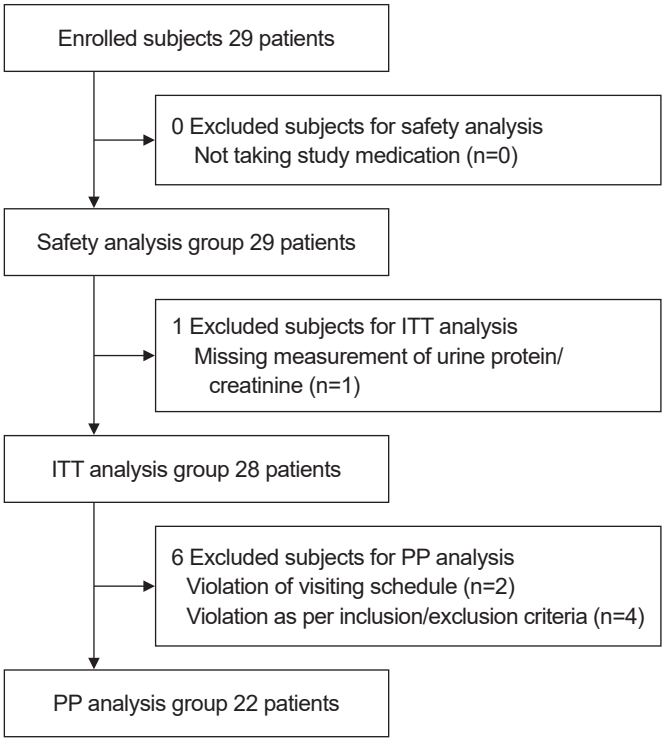

Fig. 1. Study disposition. ITT, intention to treat; PP, per-protocol.

ministration when compared with that before administration (Fig. 2). Following 6 months of treatment, proteinuria disappeared (UPCR was less than 0.2) in 14.3% (95% CI, 4.02%–32.7%) and 13.6% (95% CI, 2.90%–34.9%) of patients in the ITT and PP groups, respectively. Six months after treatment, a >50% reduction in UPCR was observed in 39.3% (95% CI, 21.2%–57.4%) and 36.7% (95% CI, 16.3%–56.5%) of the FAS and PP groups, respectively. The eGFR values before and after losartan administration did not differ significantly (Table 2).

Safety

During the study period, nine (31.0%) of the 29 subjects who received losartan treatment experienced one or more adverse events. Overall, 26 adverse events were reported, of which one was a significant adverse reaction involving a cutaneous abscess that occurred in a 12-year-old male subject; however, there was no causal relationship with the drug (Table 3). No hyperkalemia or angioedema was observed during the study period. Following 6 months of losartan treatment, the median values for altered systolic and diastolic blood pressure were −2.50 mmHg (IQR, −5.50 to 9.00 mmHg) and −3.0 mmHg (IQR, −7.00 to 4.50 mmHg), respectively. There was a slight decrease in blood pressure, although symptoms such as dizziness were not observed (Table 4).

Table 1. Baseline characteristics of patients

Characteristic	Value (n=28)
Age (yr)	12.0±3.32 (6–18)
Male (male:female)	20:8
Height (cm)	152.8±18.3 (114.8–196.3)
Weight (kg)	51.1±16.9 (20.2–85.9)
Heart rate (beats/min)	83.4±16.2 (60–120)
Systolic blood pressure (mmHg)	112.1±11.3 (95–134)
Diastolic blood pressure (mmHg)	67.8±8.61 (42–83)
Estimated GFR (IDMS)	116.3±31.6 (64.2–194.4)
Urine protein/creatinine (mg/mg)	0.82±0.45 (0.32–1.87)
Urine microalbumin/creatinine (mg/mg)	0.58±0.41 (0.04–1.48)

Values are presented as mean±standard deviation (range).
GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry.

Discussion

The ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) study and that by Webb et al. have confirmed the efficacy of RAS blockade for reducing proteinuria in children [17,18]. The ESCAPE study has revealed that strict blood pressure control can effectively delay the progression of CKD with proteinuria in children receiving ACEIs [18]. However, in the ESCAPE study, similar to several other studies conducted in adults, the efficacy of RAS inhibition for suppressing proteinuria was not examined independently from the effect of blood pressure reduction mediated by RAS inhibition on proteinuria. In addition,

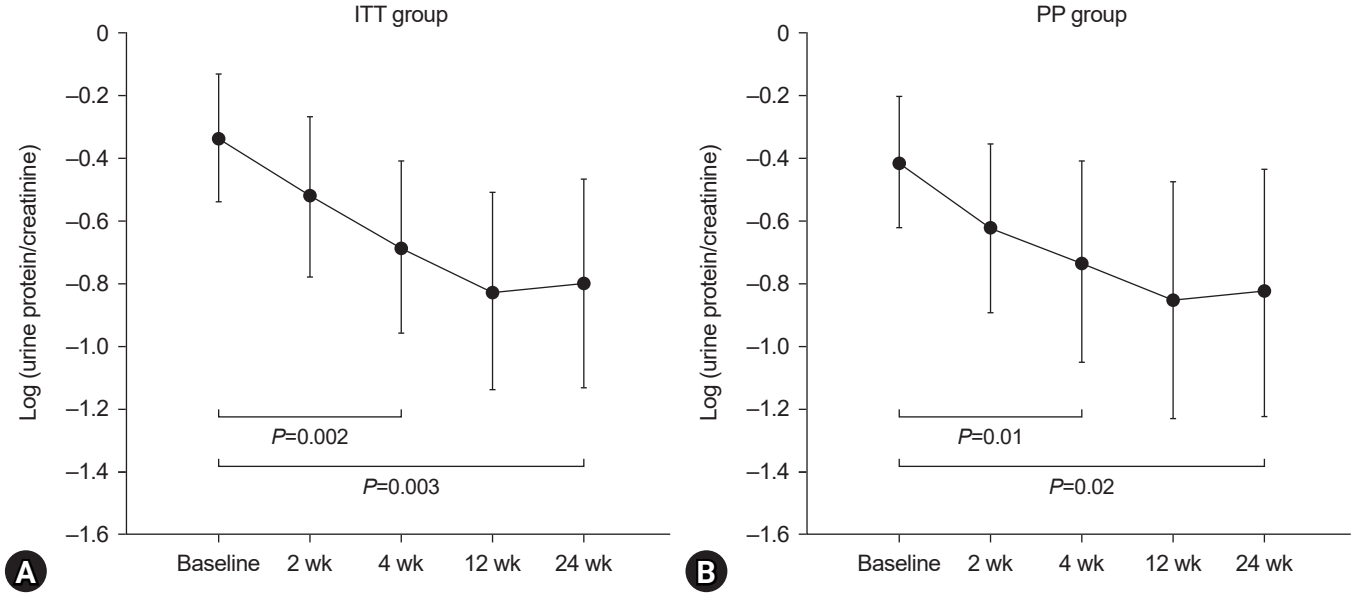

Fig. 2. Change of proteinuria. ITT, intention to treat; PP, per-protocol.

https://doi.org/10.3339/ckd.23.006

Table 2. Changes in the estimated glomerular filtration rate

Group	Baseline	6 mo	Δ 6 mo–baseline	*P*-value
ITT				0.97
Mean±SD	116.3±31.6	116.1±26.0	−0.17±21.4	
Median (range)	116.9 (64.2 to 194.4)	114.5 (49.8 to 156.1)	0.23 (−50.6 to 47.2)	
PP				0.17
Mean±SD	126.7±26.8	121.1±23.8	−5.57±18.2	
Median (range)	122.5 (90.3 to 194.4)	120.9 (77.6 to 156.1)	−2.57 (−50.6 to 29.7)	

ITT, intention to treat; PP, per-protocol; SD, standard deviation.

Table 3. Reported adverse events and serious adverse events (n=26)

Adverse events	No. (%)
Upper respiratory tract infection	13 (50.0)
Gastrointestinal symptoms	4 (15.4)
Allergic conjunctivitis	3 (11.5)
Headache	2 (7.69)
Allergic rhinitis	2 (7.69)
Acute otitis externa	1 (3.85)
Cutaneous abscess	1 (3.85)
Hyperkalemia, cough, arrhythmia, facial edema	0

Table 4. Changes in BP

	BP changes[a)]	*P*-value
△Systolic BP (mmHg), mean (range)	−2.50 (−25.0 to 30.0)	0.89
△Diastolic BP (mmHg), mean (range)	−3.00 (−14.0 to 24.0)	0.52

BP, blood pressure.
[a)]Change from the screening BP to 24-week BP.

the underlying diseases of the study participants were heterogeneous. In the present study, the efficacy of RAS inhibition on proteinuria in pediatric IgA nephropathy was evaluated independently of the antihypertensive effect of losartan. According to the study by Webb et al. [17], losartan could effectively reduce proteinuria in pediatric patients with CKD when compared with a calcium channel blocker, amlodipine or placebo. Although amlodipine and placebo increased proteinuria by 1.4%, losartan reduced proteinuria by 35.8%. In addition, several prospective studies have evaluated the efficacy and safety of ACEIs with or without ARB in children [19-21].

A randomized controlled trial assessing pediatric patients with IgA nephropathy in Japan has supported lisinopril monotherapy in reducing proteinuria when compared with combination therapy with lisinopril and losartan. The cumulative disappearance rate of proteinuria at 24 months was 89.3% with combination therapy and 89% for monotherapy, without differences in safety [19]. Conversely, the long-term efficacy of losartan and enalapril treatment revealed that the reduction in proteinuria at 3 years was 30.0% for losartan and 40.5% for enalapril [20]. These studies have shown that either ACEI or ARB therapy can be effective in pediatric patients with IgA nephropathy.

In the present study, we aimed to evaluate the efficacy and safety of losartan in children with IgA nephropathy and provide medical evidence for the use of losartan in children with proteinuric kidney disease in Korea. Losartan is an angiotensin II type I receptor blocker that blocks the angiotensin system, inhibits kidney damage, and reduces urinary proteinuria. To the best of our knowledge, this is the first prospective clinical study to examine the potential of losartan monotherapy in children with IgA nephropathy. Our study supports the finding that losartan could effectively reduce proteinuria in pediatric patients with IgA nephropathy.

IgA nephropathy is known to exhibit a relatively benign clinical course in children when compared with that in adults [22-25]. In a Japanese study, although adult IgA nephropathy was found to progress to kidney failure in 10%–20% and 50% of patients within 10 and 20 years, respectively, kidney survival rates at 10- and 20-year were 95% and 82%, respectively, in children [23]. In a retrospective study assessing 99 pediatric patients with IgA nephropathy and 125 adult patients with IgA nephropathy, pediatric patients were more likely to display minimal histologic lesions, and 10-year kidney survival was 87% in children when compared with 48% in adults [26]. In children, the probability of spontaneous remission without treatment was found to be higher than the predicted probability [27]. Most subjects in this study also showed improvements in proteinuria with losartan treatment.

A recent study from Korea has shown that 65 (5.6%) of 1,154 pediatric patients with IgA nephropathy developed CKD stage 3-5 during a median follow-up of 5 years. In total, 947 patients were treated with RAS blockers with or without additional immunosuppressive drugs, and 207 patients (17.9%) received

no pharmacologic treatments. Considering proteinuria, the authors found that 839 patients (72.7%) achieved remission. Moreover, remission was found to be an independent prognostic factor that negatively correlated with the progression of CKD stage 3-5 (hazard ratio, 0.19; 95% CI, 0.06–0.26; *P*<0.001) [28]. Accordingly, these findings highlight that the prognosis of children with IgA nephropathy in Korea is relatively good, and achieving remission indicates a favorable outcome of IgA nephropathy.

Few studies have established that losartan can be safely used in children and adolescents [18,29]. Dizziness or headache is common due to drug-related adverse reactions, which can be reversed by appropriate dose adjustment, and sometimes due to side effects, in which case the medication may be withdrawn for a short period and subsequently re-initiated [18]. Compared with ACEIs, losartan can be safely employed in terms of potential side effects [20,30]. However, when combined with tacrolimus, careful attention should be paid to hyperkalemia and metabolic acidosis. In addition, hyperkalemia may occur when losartan is combined with ACEI in CKD, and potassium concentration should be observed [21,31]. Herein, we observed no adverse events, such as decreased blood pressure, reduced GRF, or hyperkalemia, during the 24-week study period. There were no instances of relatively common side effects such as angioedema or hyperkalemia, which may be attributed to the limited number of subjects in the study. In the present study, losartan was initiated at a dose of 0.7 mg/kg/day, once daily, and was gradually increased (12.5–25.0 mg/day) up to a maximum dose of 1.5 mg/kg/day or 100 mg/day. For children, doses were initially estimated using adult doses, and the dose of losartan used in the present study is known to be safe for children and adolescents [17,19,20,32]. Considering children <6 years of age undergoing treatment for hypertension, doses of 0.1 to 0.7 mg/kg are effective, and doses of 1.4 mg/kg can be used without difficulty [32].

The present study was the first prospective, multicenter study conducted in Korea. However, its limitations need to be stated, including the relatively short study period, a small number of study subjects, and a single-arm design. An additional limitation of this study lies in the absence of consideration of histopathological findings for IgA nephropathy. The inclusion criteria encompassed children between 24 months and 18 years of age. However, since all enrolled participants were 6 years or older, the assessment of efficacy and safety in patients below this age threshold is limited.

In conclusion, this study represents the first multicenter study for the use of losartan in pediatric patients with IgA nephropathy within our country. The results of this study demonstrate that losartan treatment led to a substantial reduction in proteinuria among children with IgA nephropathy, all while exhibiting a favorable safety profile devoid of severe adverse events. As such, these findings support the effective and safe application of losartan in managing IgA nephropathy in pediatric populations.

Ethical statements

This study was approved by the Korean FDA and Institutional Review Boards of all participating institutions including Seoul National University (IRB No. H1407113596), and conducted according to the Declaration of Helsinki. Informed consent was obtained.

Conflicts of interest

Eujin Park, Eun Mi Yang, Jin Soon Suh, Jae Il Shin, Hae Il Cheong, and Hee Gyung Kang are editorial board members of the journal but were 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.

Funding

This research was supported by a grant (14172MFDS178) from the Ministry of Food and Drug Safety in 2014.

Author contributions

Conceptualization: HH, YHA, HGK, SHK
Data curation: EP, HJC
Formal analysis: KHH, JWL
Funding acquisition: HGK, ISH, HIC
Investigation: HJC, KHH, MHC, JWK, SYK, KHK, HWP
Methodology: JSS, JIS, MHC, HGK
Project administration: JWK, KHK
Visualization: HH, YHA
Writing–original draft: HH, YHA
Writing–review & editing: HGK, SHK
All authors read and approved the final manuscript.

https://doi.org/10.3339/ckd.23.006

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https://doi.org/10.3339/ckd.23.006

ChiKD CHILDHOOD KIDNEY DISEASES

Original Article

Child Kidney Dis 2023;27(2):105-110
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.011

Hypokalemia as a risk factor for prolonged QT interval and arrhythmia in inherited salt-losing tubulopathy

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Purpose: To analyze electrocardiograms (ECGs) of patients with a salt-losing tubulopathy (SLT) and to determine the frequency and risk factors for long QT and arrhythmia.
Methods: A total of 203 patients aged <19 years with SLT, specifically Bartter syndrome and Gitelman syndrome, who had a 12-lead ECG were included in this retrospective study. We analyzed the presence of an arrhythmia or prolonged corrected QT (QTc) on ECGs obtained for these patients. Demographic and laboratory data were compared between patients with abnormal and normal ECG findings.
Results: Out of the 203 SLT patients, 38 (18.7%) underwent electrocardiography and 10 (40.0%) of 25 patients with inherited SLT had abnormal ECG findings, including prolonged QTc and arrhythmias. The abnormal ECG group had significantly lower serum potassium levels than the normal group (median [interquartile range]: 2.50 mmol/L [2.20–2.83] vs. 2.90 mmol/L [2.70–3.30], *P*=0.036), whereas other serum chemistry values did not show significant differences. The cutoff level for a significant difference in QTc interval was serum potassium level <2.50 mmol/L. One cardiac event occurred in a 13-year-old boy, who developed paroxysmal supraventricular tachycardia and underwent cardiac ablation. No sudden cardiac deaths occurred in this cohort.
Conclusions: The incidence of ECG abnormalities in patients with inherited SLT was 40.0%, whereas the ECG screening rate was relatively low (18.7%). Therefore, we recommend ECG screening in patients with inherited SLT, especially in those with serum potassium level <2.50 mmol/L.

Keywords: Arrhythmias, cardiac; Bartter syndrome; Electrocardiography; Gitelman syndrome; Hypokalemia

Introduction

Bartter syndrome (BS) refers to an inherited salt-losing tubulopathy (SLT) characterized by a defect in salt reabsorption in the thick ascending limb of the loop of Henle [1]. Gitelman syndrome (GS) shares metabolic abnormalities with BS [2] and is caused by a defect in the thiazide-sensitive sodium/chloride cotransporter in the distal convoluted tubule, resulting in SLT [3]. These conditions may result in hypokalemia, metabolic alkalosis, activated plasma renin, and normal or low blood pressure [4]. Fluctuations in potassium levels can significantly affect the electrical characteristics of the heart muscles. Hypokalemia can lead to the development of ventricular arrhythmias, resulting in life-threatening conditions. Hypokalemia also causes electrocardiographic changes, such as QT interval prolongation, ST-segment depression, flat or low-amplitude T waves, and

Received: July 4, 2023; Revised: August 25, 2023; Accepted: August 31, 2023

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often prominent U waves [5]. Patients may experience presyncope, vertigo, ataxia, or blurred vision [6-8].

The frequency of cardiac arrhythmia or sudden death is unknown. To date, cardiac arrhythmia or death associated with BS and GS has been reported in six cases in the literature: three as cardiac arrhythmia and three as sudden cardiac death [7-11]. Therefore, the cardiac manifestations of BS and GS can be fatal. Hypokalemia, hypomagnesemia [7], QT dispersion, and JT dispersion [12] have been suggested as risk factors for cardiac arrhythmia in SLT. However, no large-scale studies have been conducted to date.

Therefore, the purpose of this study was to assess the frequency of electrocardiographic abnormalities and identify associated risk factors in patients diagnosed with inherited SLT.

Methods

Patients

Patients visiting Seoul National University Children's Hospital between January 1991 and May 2022 who were younger than 19 years of age and who underwent 12-lead electrocardiography with a diagnosis of an SLT were included in this retrospective study. Inherited SLT encompassed BS and GS. The exclusion criteria included non-nephrogenic electrolyte imbalance and other genetic diseases (Fig. 1).

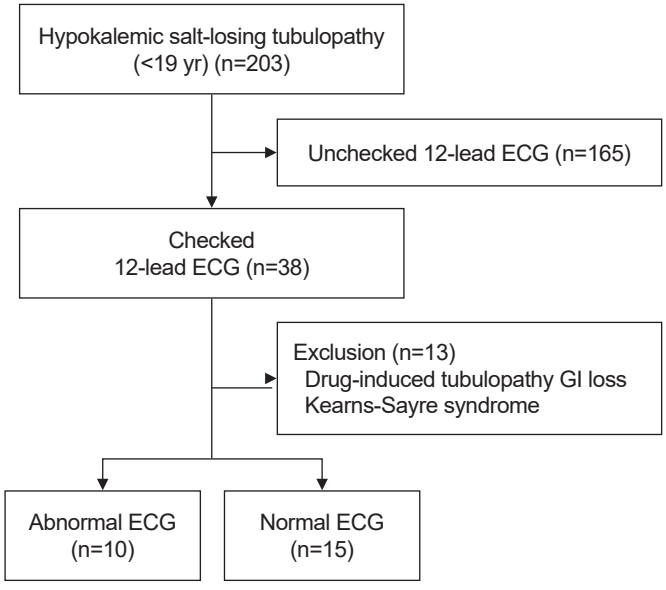

Fig. 1. Patient flowchart. ECG, electrocardiography; GI, gastrointestinal.

Electrocardiogram

All electrocardiograms (ECGs) obtained for eligible patients during the study period were analyzed. QT intervals were measured in leads II, V5, and V6, and the longest value was used. The QT interval was adjusted for heart rate using the Bazett formula ($QTc=QT/RR^{0.5}$; all units are ms). ECGs findings were categorized as abnormal if they included a prolonged corrected QT (QTc) or an abnormal rhythm. Abnormal rhythm was defined as the absence of sinus rhythm. All patients' data of QTc were classified based on recommended QTc interval value from Goldenberg and Moss [13]. For classification, those with a prolonged QTc were grouped in the abnormal ECG group, whereas those with normal and borderline QTc values were grouped into the normal ECG group. For group comparisons, one ECG per patient was selected, with the criterion being an abnormal rhythm or the longest QTc.

Clinical manifestations

Clinical information, including sex, age, height, weight, and body mass index (BMI), as well as serum sodium, potassium, calcium, and magnesium levels, were compared between the two groups. Age, height, weight, and BMI were analyzed closest to the time of ECG measurement, and laboratory findings including serum electrolyte and creatinine levels were analyzed within 24 hours of ECG measurement.

Statistics

Statistical analyses were performed using SPSS version 27.0 (IBM Corp.). Continuous variables are presented as medians (interquartile range [IQR]). Between-group comparisons were conducted using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. Statistical significance was set at a *P*-value below 0.05.

Results

A total of 203 patients were diagnosed with SLT at Seoul National University Children's Hospital during the study period. Among them, 38 (18.7%) had available ECG data. Patients with non-nephrogenic tubulopathies such as chemotherapy-induced tubulopathy, electrolyte imbalance derived from the gastrointestinal tract, and other known genetic diseases were excluded from the study (n=13). Ultimately, the study group comprised 25 individuals.

The number of ECGs performed varied for each patient

https://doi.org/10.3339/ckd.23.011

(median, 2; range, 1–127). A total of 172 ECGs were obtained from eligible patients, of which 80 were classified as normal and 92 as abnormal. One patient had 127 ECGs (49 normal, 78 abnormal) alone due to a paroxysmal supraventricular tachycardia (PSVT) event and prolonged hospitalization; therefore, we excluded this patient. Thereafter, there were 31 normal ECGs and 14 abnormal ECGs. ECGs were mostly performed due to hypokalemia or symptomatic conditions such as poor oral intake, diarrhea, vomiting, and muscle cramps; besides these conditions, ECGs were also performed before the thiazide loading test to diagnose SLT (n=4) and for pre-operative evaluation (n=3).

To compare the characteristics and biochemical profiles of patients according to ECGs, one ECG was assigned to each patient. This resulted in 15 patients, including one patient with PSVT in the normal ECG group and 10 patients in the abnormal ECG group (Fig. 1). No significant differences were noted between the normal and abnormal ECG groups in terms of sex, age, weight, height, or BMI (Table 1). A comparison of serum chemistry values is shown in Table 1. The median serum potassium levels were 2.90 mmol/L (IQR, 2.70–3.30 mmol/L) in the normal ECG group and 2.50 mmol/L (IQR, 2.20–2.83 mmol/L) in the abnormal ECG group, showing a significant difference between the two groups (P=0.036). No significant differences were noted in the serum sodium, chloride, total calcium, magnesium, or total carbon dioxide levels between the two groups.

We also compared the general features and biochemical values based on serum potassium levels (Tables 2, 3). When comparing serum potassium levels below 3.00 mmol/L and above 3.00 mmol/L, no statistical significance was noted for any indicator (Table 2). However, when comparing serum potassium levels below 2.50 mmol/L and above 2.50 mmol/L, a significant difference was noted in the QTc interval. Between

Table 1. Comparison of patient characteristics and biochemical values

Characteristic	Normal ECG group (n=15)	Abnormal ECG group (n=10)	P-value
Sex (male: female)	8:7	6:4	1.000
Age (yr)	10.4 (5.25–17.6)	4.27 (0.51–14.8)	0.160
Weight (kg)	34.0 (12.6–50.5)	12.2 (6.25–42.0)	0.160
Height (cm)	135.3 (97.6–155.5)	89.9 (68.2–153.6)	0.212
BMI (kg/m^2)	16.9 (13.9–22.1)	14.7 (12.4–19.1)	0.472
Sodium (mmol/L)	139.0 (132.0–139.0)	136.0 (132.0–138.3)	0.311
Potassium (mmol/L)	2.90 (2.70–3.30)	2.50 (2.20–2.83)	0.036
Chloride (mmol/L)	96.0 (92.0–101.0)	90.5 (84.8–100.0)	0.238
Calcium (mg/dL)	9.90 (9.60–10.2)	9.85 (9.60–10.4)	0.892
Magnesium (mg/dL)	1.50 (1.35–1.85)	1.70 (1.28–2.18)	0.697
Total CO_2 (mg/dL)	27.0 (24.0–32.0)	29.0 (26.0–35.5)	0.215

Values are presented as median (interquartile range).
ECG, electrocardiography; BMI, body mass index; CO_2, carbon dioxide.

Table 2. Comparison of characteristics and biochemical values by potassium level (≥3.0 mmol/L vs. <3.0 mmol/L)

Characteristic	Serum potassium (≥3.0 mmol/L) (n=6)	Serum potassium (<3.0 mmol/L) (n=19)	P-value
Sex (male: female)	4:2	10:9	0.661
Age (yr)	11.6 (5.70–15.4)	5.78 (3.01–17.5)	0.555
Weight (kg)	38.9 (15.6–46.8)	20.6 (8.70–50.5)	0.475
Height (cm)	134.8 (92.0–155.9)	114.0 (81.0–155.0)	0.731
BMI (kg/m^2)	15.3 (13.3–20.9)	15.3 (13.3–21.6)	1.000
Sodium (mmol/L)	138.5 (136.5–140.3)	137.0 (132.0–139.0)	0.303
Chloride (mmol/L)	97.5 (92.8–103.8)	93.0 (87.0–100.0)	0.246
Calcium (mg/dL)	9.95 (9.83–10.1)	9.90 (9.60–10.5)	0.926
Magnesium (mg/dL)	1.65 (1.35–2.03)	1.70 (1.35–2.00)	0.897
Total CO_2 (mg/dL)	28.5 (23.0–31.3)	28.0 (25.5–33.5)	0.494
QTc (ms)	436.0 (413.0–462.3)	442.0 (411.0–492.0)	0.514

Values are presented as median (interquartile range).
BMI, body mass index; CO_2, carbon dioxide; QTc, corrected QT interval.

Table 3. Comparison of characteristics and biochemical values by potassium level (≥2.5 mmol/L vs. <2.5 mmol/L)

Characteristic	Serum potassium (≥2.5 mmol/L) (n=19)	Serum potassium (<2.5 mmol/L) (n=6)	*P*-value
Sex (male: female)	10:9	4:2	0.661
Age (yr)	7.08 (3.02–17.5)	11.6 (2.82–16.3)	0.887
Weight (kg)	20.6 (8.70–43.4)	34.0 (10.2–81.3)	0.514
Height (cm)	112.0 (79.3–153.5)	145.4 (82.9–163.0)	0.343
BMI (kg/m^2)	15.3 (13.2–21.2)	16.6 (13.7–30.1)	0.581
Sodium (mmol/L)	138.0 (132.0–139.0)	138.0 (134.3–140.5)	0.687
Chloride (mmol/L)	93.0 (88.0–100.0)	96.5 (82.0–104.8)	0.877
Calcium (mg/dL)	10.0 (9.60–10.4)	9.80 (9.08–10.1)	0.400
Magnesium (mg/dL)	1.70 (1.40–2.10)	1.50 (1.28–1.83)	0.424
Total CO_2 (mg/dL)	27.5 (24.0–32.3)	28.5 (24.0–37.0)	0.506
QTc (ms)	435.0 (403.0–468.0)	491.0 (439.5–586.8)	0.030

Values are presented as median (interquartile range).
BMI, body mass index; CO_2, carbon dioxide; QTc, corrected QT interval.

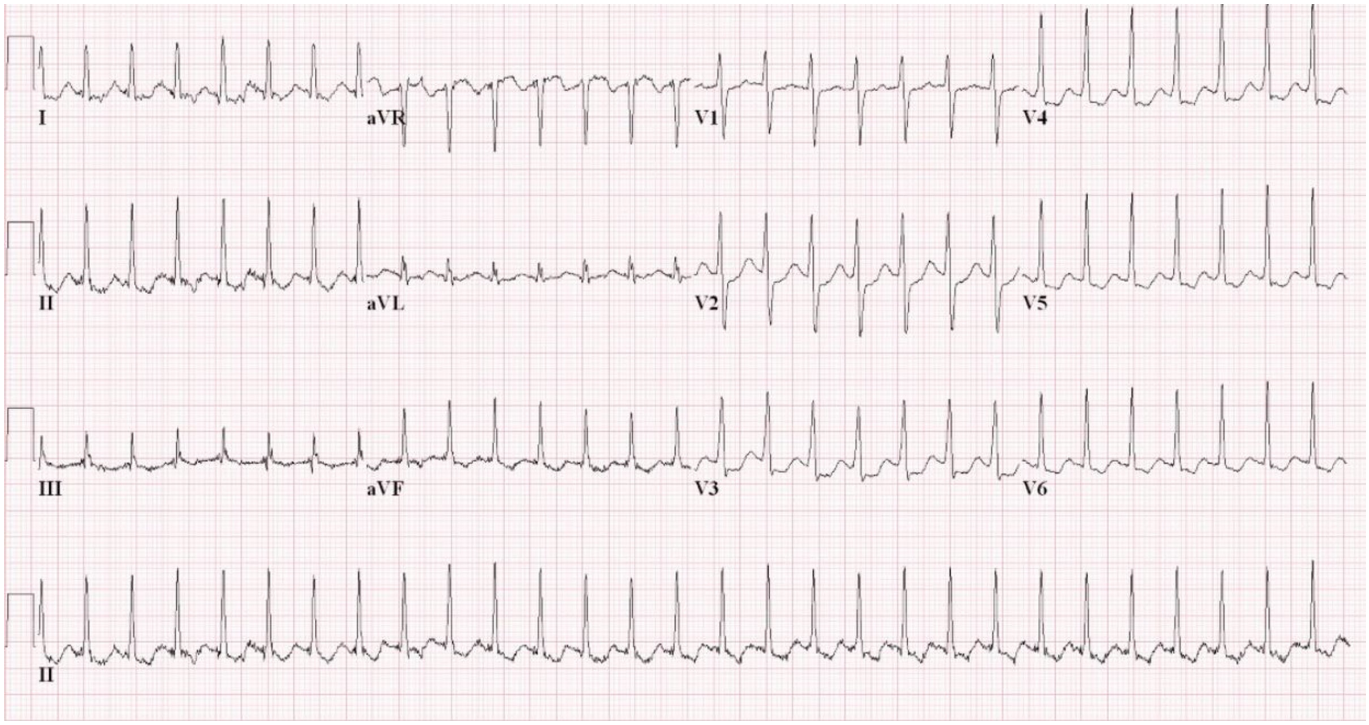

Fig. 2. A 12-lead electrocardiography with narrow QRS tachycardia.

the group with a serum potassium level ≥2.50 mmol/L (n=19) and the group with a level <2.50 mmol/L (n=6), the median QTc interval was 435.0 ms (IQR, 403.0–468.0 ms) and 491.0 ms (IQR, 439.5–586.8 ms), respectively, showing a significant difference (*P*=0.030).

One patient presented with PSVT (Fig. 2); he was a 13-year-old boy with severe hypokalemia (2.20 mmol/L) and normal serum magnesium (1.70 mmol/L). The patient's father had a history of sudden cardiac death of an unknown cause. The patient underwent cardiac ablation. The patient harbored a confirmed *CLCNKB* mutation and was diagnosed with type III BS. He was the only patient who underwent a cardiac intervention for PSVT, specifically cardiac ablation. To date, PSVT has not recurred; however, due to recurrent severe hypokalemia, long-term inpatient treatment was administered, including potassium replacement and other medications, including potassi-

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um-sparing diuretics and a thiazide, with regular electrolyte level and ECG monitoring.

Fourteen patients (56.0%) were currently being followed up in the nephrology or pediatric departments at this center, but the remaining patients were either transferred (n=4) or lost to follow-up (n=7). Only two individuals had normalized QTc, three still had prolonged QTc, and five had no follow-up ECG; therefore, normalization was unknown. Three patients progressed to chronic kidney disease with a long-term prognosis regardless of the ECG findings. No sudden cardiac death was observed in any patient during the study period.

Discussion

This retrospective study assessed the frequency of electrocardiographic abnormalities and explored the associated risk factors in patients diagnosed with inherited SLT. The study findings revealed that 40.0% of the patients with SLT had a prolonged QTc interval, and one of the 25 patients experienced a cardiac arrhythmia in the form of PSVT. The incidence of prolonged QTc is not well established in BS [1], whereas it can be as high as 50.0% in GS [3].

Cortesi et al. [7] suggested that SLT itself increases patients' vulnerability to arrhythmia, especially in case of severe hypokalemia. Baseline ECG checks should be conducted for patients with BS and GS [14]. However, the rate of ECG screening for SLT was found to be low (18.7%) in our study cohort. Therefore, it is important to enforce regular ECG screening to enable early detection of any potential arrhythmia or QTc prolongation in patients with SLT. We found significant differences in serum potassium levels between the normal and abnormal ECG groups, indicating an association between serum potassium levels and prolonged QTc or arrhythmia. This aligns with the findings of previously reported cases that consistently emphasized the association between hypokalemia and occurrence of cardiac arrhythmia or death in individuals with BS and GS [7-11]. The target serum potassium level of 3.00 mmol/L for the general population may not be applicable to patients with SLT. According to Konrad et al. [1] and Blanchard et al. [3], maintaining a serum potassium level of 3.00 mmol/L may require an increased dose of potassium supplements and other medications, possibly leading to a decrease in medication compliance in patients with severe SLT. Consistent with a previous report [7], the present study analyzed the potassium cutoff level for QTc prolongation, which was a serum potassium level of 2.50 mmol/L. A prolonged QT interval is known to increase the risk of developing ventricular arrhythmias [13]. Therefore, achieving and maintaining this target serum potassium level in SLT is crucial to avoid arrhythmia.

The recommended treatment to maintain an optimum serum potassium level is as follows. A potassium supplement containing potassium chloride must be administered, starting with 1–2 mmol/kg/day, and titration must be tailored to the individual patient while considering symptoms and side effects. In the case of severe hypokalemia, intravenous supply is essential. Simultaneously, the patients are strongly encouraged to consume potassium-rich foods [1,2]. Patients with BS are usually also administered nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin (1–4 mg/kg/day divided in 3–4 doses), ibuprofen (15–30 mg/kg daily in 3 doses), and celecoxib (2–10 mg/kg/day divided in 2 doses), and there is insufficient evidence to recommend specific NSAIDs. In addition, for abnormal electrolyte status, potassium-sparing diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and thiazides may be helpful, but their routine use is not recommended, as they may result in hypovolemia [1]. In the case of GS patients, indomethacin is rarely used, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are occasionally used, but should be discontinued if there is a risk of hypovolemia [2].

This study has some limitations. First, while the number of patients diagnosed with SLT was relatively high, the low number of ECGs available for patients resulted in limited patient recruitment. In the future, more ECGs should be performed to increase the statistical power. Second, the number of ECGs and intervals varied widely among individuals, making it statistically challenging to analyze each ECG individually. We also evaluated ECG abnormalites other than prolonged QTc, such as ST depression, flat T-wave, and prominent U wave. However, since those abnormalities were only identified in a small number of patients, we based our comparison on QTc prolongation alone. In the presence of abnormal ECG findings, regular ECG follow-ups are necessary for assessing risk factors. Third, because of the retrospective nature of this study, all patients had different follow-up periods; therefore, it was not possible to compare long-term outcomes. Lastly, this study does not provide evidence to determine whether BS and GS themselves increase the risk of arrhythmias or if the higher incidence of arrhythmias is solely due to hypokalemia.

In conclusion, as hypokalemia is strongly correlated with pro-

longed QTc, it is important to maintain serum potassium levels above 2.50 mmol/L and to be aware of symptoms such as acute diarrhea or vomiting, which can cause hypokalemia. As the incidence of abnormal ECG findings was found to be quite high (40.0%) in our study, it may be beneficial to conduct ECG screening for every BS and GS patient. If an abnormality is found during ECG screening, regular follow-up ECGs are required, and further cardiologic evaluation should be considered.

Ethical statements

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. H-2306-115-1439) and complied with the principles of the Declaration of Helsinki. The informed consent was waived because of the retrospective nature of this study.

Conflicts of interest

Hee Gyung Kang 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 conflict of interest relevant to this article was reported.

Funding

This research was supported and funded by Seoul National University Hospital Lee Kun-Hee Child Cancer &Rare Disease Project, Republic of Korea (grant number: 23C-026-0100) and the Seoul National University Hospital Research Fund, Republic of Korea (grant number: 0320222120).

Acknowledgments

We would like to express our deepest gratitude to the all patients in this study.

Author contributions

Conceptualization: YHA, HGK
Data curation: SRK, YHA, HGK, NC
Investigation: SRK
Methodology: YHA, SRK
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Writing-review and editing: HGK, NC

All authors read and approved the final manuscript.

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https://doi.org/10.3339/ckd.23.011

ChiKD CHILDHOOD KIDNEY DISEASES

Original Article

Child Kidney Dis 2023;27(2):111-116
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.020

Association of body weight and urinary tract infections during infancy: a nationwide comparative matched cohort study

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Purpose: This article was to investigate the association between urinary tract infections (UTIs) and high weight status in infancy.
Methods: We conducted a nationwide matched cohort study from January 2018 to December 2020 using data from the Korean National Health Insurance System and the Korean National Health Screening Program for Infants and Children. We analyzed the association between UTI diagnosis codes and high weight status (which was defined as being in the 90th percentile or higher of weight-for-age).
Results: We found that 22.8% of infants with UTIs exhibited high weight status, compared to 20.0% of non-UTI infants (P<0.001). Per our multivariable analyses, the adjusted odds ratio for high weight status was 1.09 (95% confidence interval, 1.06–1.13).
Conclusions: UTI in the first 12 months of life was associated with a weight-for-age percentile of ≥90. Our findings corroborate those of previous single-center studies and emphasize the importance of careful monitoring for this at-risk group.

Keywords: Body weight; Infant; Urinary tract infections

Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections in children [1], and their incidence stands at approximately 7.0% in febrile infants aged under 24 months [2]. Although UTIs have been considered to have a relatively benign course, potential complications such as kidney scars may develop. Kidney scarring, which occurs in approximately 15% of children following UTIs, can result in long-term severe consequences such as chronic kidney disease [3]. Consequently, conscious efforts to prevent UTIs and the accurate identification of their underlying risk factors are critical.

Infantile obesity, once considered benign and without significant concerns, has more recently been linked to childhood obesity; the body mass index (BMI) value of an infant is reported to be associated with their BMI value at the age of 5 years [4]. Considering the substantial role of adipose tissue in immune responses, deviations in adipose tissue quantities could potentially impact the immune system, resulting in increased susceptibility to infections [5]. Indeed, in the United States, an analysis of an inpatient database comprising subjects aged 2 to 20 years demonstrated a significantly increased risk of UTIs

Received: October 24, 2023; Revised: December 4, 2023; Accepted: December 8, 2023

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among obese females [6]. However, there is a paucity of specific data concentrating on the infantile period (during which UTIs are most prevalent). Two separate studies involving young children have been reported, both indicating an association between obesity and UTIs, although they were both single-center retrospective studies [7,8]. Infants may have prolonged contact with feces due to the lack of toilet training, leading to a higher incidence of ascending infantile UTIs. In addition to immune system alterations caused by adipose tissue, it is suspected that obese infants may have an abundance of internal bacteria in their perineal area due to its large contact surface, although this has not been confirmed by previous studies. In prior studies, a correlation was demonstrated between obesity and an increase in *Escherichia coli* within the gut microbiota, the most prevalent pathogen associated with UTIs [9,10]. Despite the existence of these predisposing factors, there is still a paucity of research specifically focusing on infantile UTIs and their association with body weight status. Recently, Yim et al. [11] conducted a nationwide cohort study to identify the association between body weight status and UTI development among children aged 4 to 71 months, in which they found that body weight status was associated with the development of UTIs among children aged 2 to 6 years.

In this nationwide population-based matched cohort study, we aimed to identify the association between body weight status and UTI during infancy, using data from the Korean National Health Information Database (NHID) and the Korean National Health Screening Program for Infants and Children (NHSPIC) data.

Methods

We conducted a nationwide population-based matched cohort study of Korean children born between January 1, 2017, and December 31, 2019, using NHID and NHSPIC data. Briefly, NHID data are provided by the Korean National Health Insurance System (NHIS), a Korean Ministry of Health and Welfare-affiliated mandatory healthcare system covering 99.4% of the 51 million people in South Korea. Korean NHSPIC is a health screening program for infants and children during well-baby check-up visits [12,13]. All children are eligible to participate in the NHSPIC seven times: i.e., at the ages of 4–6 months (1st), 9–12 months (2nd), 18–24 months (3rd), 30–36 months (4th), 42–48 months (5th), 54–60 months (6th), and 66–71 months (7th). Each program entails physical examination, anthropometric parameter (including height and weight) measurements, questionnaires, and anticipatory guidance for their age. The rate of participation in NHSPIC among all Korean children was 83.0% in 2020 [14], which implies that the results of NHSPIC can adequately represent the health status of Korean children.

Children eligible for this study were those who had claims data for UTIs at any time before reaching 12 months of age and who participated in the first NHSPIC examination between January 2018 and December 2020. UTIs were identified according to ICD-10 codes, which include acute pyelonephritis (APN) (N10), acute cystitis (N30.0, N30.8, N30.9, and B37.4), and unspecified UTI (N39.0 and P39.3). Controls were children who had visited the well-baby clinic and undergone the 1st NHSPIC examination without being diagnosed with UTIs. They were matched one-to-one with the study participants based on their birth year, birth month, and sex. Children with complex chronic conditions were excluded, derived from the Pediatric complex chronic conditions classification system version 2 [15].

Weight status, measured between 4 and 6 months of age, was dichotomized as at or above the 90th percentile and below the 90th percentile. We considered the following variables as covariates: sex, prematurity, parents' socioeconomic status, and place of residence (categorized into capital, metropolitan, and rural). Data regarding income and area of residence were obtained from the NHIS qualification data, and information about prematurity was sourced from the 1st NHSPIC questionnaire. Categorical variables were presented as counts and percentages. We compared infants with UTI and those without UTI using a chi-square test. To investigate a potential association between high weight and UTI status, we performed a multivariable logistic regression analysis. We conducted two sensitivity analyses: first, we included the status of vesicoureteral reflux (VUR) and constipation as covariates (since they are known risk factors for UTIs) in sensitivity analysis model 1. Additionally, we excluded infants diagnosed with VUR from sensitivity analysis model 2. VUR was defined as having a diagnosis code of N13.7 or Q62.7, while constipation was defined as having a diagnosis code of K59.0. All statistical analyses were performed using R-project version 4.2.6 (R Foundation for Statistical Computing). The threshold for statistical significance was set at $P<0.05$.

Results

Baseline characteristics

A total of 153,453 children who experienced UTIs in infancy

https://doi.org/10.3339/ckd.23.020

and received the 1st NHSPIC between January 1, 2018, and December 31, 2020, were enrolled. Among them, children with complex chronic conditions were excluded (n=17,927), leaving 135,526 infants affected by UTIs and 133,526 matched children not affected by them who were eligible for the main analysis (Fig. 1). Among them, 139,583 (51.9%) were boys and 3.88% (10,435) were born prematurely (Table 1).

Association between body weight status and UTI experience

Among infants with UTI experience, high weight (which was defined as weight-for-age ≥90th percentile) was significantly more prevalent than it was among infants without UTI experience (22.8% vs. 20.0%, *P*<0.001) (Table 1). Additionally, there were significant differences in sex, place of residence, and income status between those with UTI experience and those without it. Our multivariable logistic regression analysis revealed that high weight status remained significantly associated with UTI experience after adjusting for covariates, with an adjusted odds ratio (OR) of 1.09 (95% confidence interval [CI], 1.06–1.13) (Table 2).

Sensitivity analysis

The results of the multivariable analysis, which included VUR and constipation as covariates (model 1), and the analysis that excluded infants diagnosed with VUR (model 2), are shown in Table 3. Both sensitivity analyses demonstrated a statistically significant association between high weight and UTI experience after adjusting for covariates.

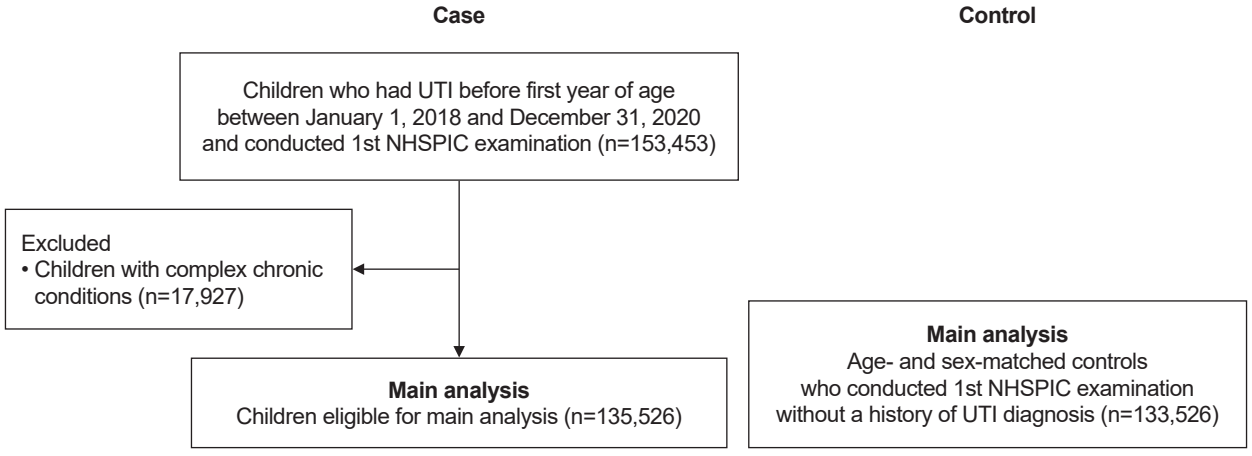

Fig. 1. Flow diagram for study participants. UTI, urinary tract infection; NHSPIC, National Health Screening Program for Infants and Children.

Table 1. Baseline characteristics of the study population

Characteristic	No UTI (n=133,526)	UTI (n=135,526)	Total (n=269,052)	*P*-value
Male sex, No (%)	66,282 (49.6)	73,301 (54.1)	139,583 (51.9)	<0.001
Place of residence, No (%)				<0.001
Capital	20,960 (15.7)	19,085 (14.1)	40,045 (14.9)	
Metropolitan	34,936 (26.2)	34,952 (25.8)	69,888 (26.0)	
Rural	77,630 (58.1)	81,489 (60.1)	159,119 (59.1)	
Income status, No (%)[a]				<0.001
<20 percentiles	13,439 (10.3)	13,916 (10.5)	27,355 (10.4)	
20 to <40 percentiles	11,296 (8.46)	11,843 (8.94)	23,139 (8.60)	
40 to <60 percentiles	23,426 (17.9)	24,792 (18.7)	48,218 (18.3)	
60 to <80 percentiles	44,671 (34.3)	45,666 (34.5)	90,427 (34.4)	
≥80 percentiles	37,750 (28.9)	36,212 (27.3)	73,962 (28.1)	
Preterm birth, No (%)	5,275 (3.95)	5,160 (3.81)	10,435 (3.88)	0.056
Weight-to-age more than 90 percentile, No (%)	26,767 (20.0)	30,944 (22.8)	57,711 (21.4)	<0.001

UTI, urinary tract infection.
[a]People with a special occupation such as military personnel was excluded in the income status analysis.

Table 2. Association between urinary tract infection experience and weight status

Variable	Adjusted OR (95% CI)	*P*-value
High weight[a)]	1.09 (1.06–1.13)	<0.001
Male sex	1.59 (1.55–1.64)	<0.001
Income status		0.713
<20 percentiles	Reference	
20 to <40 percentiles	1.00 (0.94–1.07)	
40 to <60 percentiles	1.04 (0.99–1.10)	
60 to <80 percentiles	1.04 (0.99–1.09)	
≥80 percentiles	0.99 (0.94–1.04)	
Place of residence		<0.001
Capital	Reference	
Metropolitan	1.04 (0.99–1.08)	
Rural	1.13 (1.08–1.17)	
Prematurity	1.00 (0.93–1.08)	0.993

OR, odds ratio; CI, confidence interval.
[a)]High weight was defined as a weight-to-age percentile of ≥90. Covariates were as follows: sex, income status, place of residence, and prematurity.

Table 3. Sensitivity analysis

	Adjusted OR (95% CI)	*P*-value
Model 1[a)]		
High weight	1.09 (1.06–1.13)	<0.001
VUR	13.6 (10.6–17.6)	<0.001
Constipation	0.84 (0.49–1.42)	0.514
Model 2[a)]		
High weight	1.09 (1.05–1.13)	<0.001

OR, odds ratio; CI, confidence interval; VUR, vesicoureteral reflux.
[a)]Model 1 was conducted after including VUR and constipation as covariates, in addition to the ones in the main analysis. Model 2 was conducted after excluding infants diagnosed with VUR.

Discussion

In this study, we identified a statistically significant association between UTI occurrence during infancy and weight status. This association remained statistically significant even after adjusting for covariates and conducting various sensitivity analyses. The findings suggest that infants with a body weight-for-age above the 90th percentile may be more susceptible to infantile UTIs compared to those with weight-for-age values below the 90th percentile.

While congenital anomalies of the kidney and urinary tract, including VUR, are well-established risk factors for infantile UTIs, and circumcision and breastfeeding are well-known protective factors, a variety of environmental factors remain relatively underexplored. Various cross-sectional studies have identified obesity as a risk factor for UTIs in young children (encompassing children aged 2–6 years). However, research specifically focusing on infants aged below one year (who constitute the most susceptible group) is limited. Renko et al. [16] conducted a meta-analysis based on four studies, concluding that obesity predisposes to a higher risk of UTIs (OR, 2.23; 95% CI, 1.37–3.63), with two of them focusing on young children. Hsu et al. [7] reported that obesity was strongly associated with the presence of febrile UTI, and obese children (weight-for-age above the 95th percentile) aged 2 years or younger had a higher risk of developing a UTI than non-obese children (OR, 1.92; 95% CI, 1.15–3.21 in overweight [weight-for-age above the 85th percentile] children and OR, 2.46; 95% CI, 1.54–3.93 in obese children). Yang et al. [8] found that among children under 3 years, those classified as overweight or obese were significantly more predisposed to febrile UTIs (OR, 1.84; 95% CI, 1.11–3.05). However, both these studies were single-center studies. Recently, Yim et al. [11] reported that obesity in children less than 6 years of age were associated with subsequent UTIs during a 3-year follow-up period (hazard ratio, 1.13; 95% CI, 1.10–1.16), using the same platform of Korean NHID. However, obesity in children aged 4 months to 2 years did not show a clear association with subsequent UTIs (hazard ratio, 1.00; 95% CI, 0.97–1.03). In our paper, we conducted a cross-sectional comparison of weight status between infants with UTIs and non-UTI infants, and this yielded significant results [11].

Childhood obesity contributes to various pathophysiological changes, including heightened inflammation, altered adipokine signaling, metabolic shifts, and epigenetic modifications, all of which significantly impact immune response [17,18]. It is plausible to speculate that similar associations between weight status and UTI occurrence exist in young children for these reasons. However, direct measurements of associated changes in immunity have not been extensively investigated, which necessitates further research. Infants are generally more susceptible to ascending UTIs compared to older children. This vulnerability is attributed to factors such as a shorter urethra and a lack of toilet training. The absence of proper toileting increases the contact time between colonic bacteria and the urethral opening, which is a critical contributor to UTI development. In cases where obesity increases the surface area of contact between feces and skin within the diaper, the intensity of this contact is likely augmented. Previous studies have demonstrated an association between obesity and gut microbiota imbalance [9,10]. Gao et al. [9] revealed that obese children exhibit a higher abundance of *E. coli* compared to non-obese children. Additionally,

https://doi.org/10.3339/ckd.23.020

an animal model study showed that the gut commensal *E. coli* exacerbates obesity and insulin resistance in mice [10]. Given that ascending UTIs are attributed to gut microbiota, the increase in *E. coli* within gut microbiota associated with obesity may exert more pronounced effects on infants. Nevertheless, these aspects remain relatively unexplored and necessitates further in-depth investigation and related studies.

A significant advantage of our study is the comprehensive, nationwide inclusion of children with UTIs. Given that the NHSPIC participation rate exceeded 80%, this study offers more reliability than investigations conducted at a single center. However, our study had some limitations. First, the categorization of the patient group was solely based on the diagnostic codes for APN, cystitis, and unspecified UTI, potentially leading to a detection bias. Second, due to limitations in our data source, we were unable to assess specific clinical manifestations like fever or severity such as the occurrence of urosepsis. These details would have been instrumental in the identification of any potential additional risks associated with high weight within these subgroups. Furthermore, given the limited power of our conclusion (adjusted OR, 1.09), the clinical significance of this finding would not be substantial, emphasizing the need for further research. Lastly, undetected covariates may influence the results due to the observational nature of the study.

In conclusion, UTIs occurring in the first 12 months of life were associated with a weight-for-age percentile of ≥90. This finding supports prior single-center study outcomes and indicates the need for meticulous monitoring of this vulnerable group.

Ethical statements

This study was reviewed and approved by the Public Institutional Review Board designated by the Korean Ministry of Health and Welfare (IRB No. P01-202207-01-029). The requirement for informed consent was waived because of the nature of the study.

Conflicts of interest

Ji Hyun Kim and Hee Gyung Kang are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. There are no other conflicts of interest to declare.

Funding

None.

Author contributions

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Data curation: PGP
Formal analysis: PGP
Investigation: PGP
Methodology: YHA, HGK
Visualization: JHK
Writing-original draft: PGP
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All authors read and approved the final manuscript.

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https://doi.org/10.3339/ckd.23.020

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Case Report

Child Kidney Dis 2023;27(2):117-120
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.017

Renal artery stenosis presenting as congenital nephrotic syndrome with hyponatremic hypertensive syndrome in a 2-month-old infant: a case report

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Here, we present the case of a 2-month-old male infant with hyponatremic hypertensive syndrome resulting from stenosis of the right proximal and mid-renal arteries. The patient exhibited nephrotic-range proteinuria, low serum albumin, increased serum creatinine, and elevated renin and aldosterone levels. Doppler ultrasonography and computed tomography angiography revealed decreased vascular flow in the small right renal artery. Following a successful percutaneous balloon angioplasty, the patient experienced a decrease in blood pressure and normalization of serum electrolyte levels within a few days. However, it took 3 months for the proteinuria to resolve completely. This case is significant as it represents the first reported instance of a neonate presenting with clinical features resembling congenital nephrotic syndrome caused by renal artery stenosis that was successfully treated with percutaneous renal angioplasty.

Keywords: Case reports; Hypertension; Hyponatremia; Nephrotic syndrome; Renal artery stenosis

Introduction

Hyponatremic hypertensive syndrome (HHS) is characterized by hypertension, hyponatremia, and hypokalemia, which are attributed to unilateral stenosis or occlusion of the renal artery [1]. Approximately 16% of adults with unilateral renal artery stenosis have been reported to suffer from HHS [2]. The prevalence of HHS in children is not well known, but it is considered a rare disease [3,4]. However, a previous study reported that HHS was observed in 28% of pediatric patients with renovascular hypertension in a single center [2]. Patients with HHS may develop central nervous system symptoms such as convulsions, altered mental status due to hypertension, and combined hyponatremia [3,5]. Patients may also experience polyuria, polydipsia, and nephrotic-range proteinuria [2]. In most cases, the disease can be managed by addressing the underlying cause, controlling blood pressure, and providing supportive care for dehydration and hyponatremia [1]. Herein, we report a case of

Received: October 8, 2023; Revised: November 6, 2023; Accepted: November 16, 2023

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HHS in a 2-month-old infant who presented with nephrotic syndrome and improved after percutaneous balloon angioplasty.

Case report

A 2-month-old male infant with no specific birth history presented to the hospital with general weakness, vomiting, and poor oral intake for 5 days. At the time of admission, the patient's initial body weight was 6.6 kg, which was 400 g lower than usual, and mottled skin was observed. His blood pressure was severely elevated, measuring 143/107 mmHg. Laboratory tests revealed proteinuria in the nephrotic range, with a urine protein-to-creatinine ratio of 107 mg/mg, as well as a low serum albumin level of 2.6 g/dL, low serum sodium level of 123 mmol/L, increased serum creatinine level of 0.8 mg/dL, and elevated renin and aldosterone levels of >80 ng/ml/hr (0–3 years reference range: <16.6 ng/mL/hr) and 206 ng/dL (1–11 months reference range: 6.5–86.0 ng/dL). The patient developed atonic seizures and perioral cyanosis on the second day after admission. The patient received intravascular anticonvulsants, antihypertensive medications, and a 3% saline solution. Kidney Doppler ultrasonography revealed hypotrophy of the right kidney, decreased vascular flow due to narrowing of the right renal artery, and compensatory hypertrophy of the left kidney. Brain magnetic resonance imaging, electroencephalogram and tests for viral infections (toxoplasmosis, rubella, cytomegalovirus, herpes, human immunodeficiency virus, and syphilis) performed on this patient were all negative, and the next-generation sequencing panel for diagnosing podocytopathy-related gene mutations was negative. The patient had no significant family history related to thrombosis or stenosis. The patient underwent renal computed tomography angiography, and the results showed that the left renal artery was intact; however, the proximal ostium of the right renal artery was not clearly visible, and there was a suspected small right renal artery (Fig. 1A-C). The patient underwent percutaneous abdominal aortography and balloon angioplasty to improve right renal artery stenosis. Aortography revealed several focal stenoses in the right proximal and mid-renal arteries, suggesting thrombi accompanied by a focal filling defect (Fig. 1D). Through balloon angioplasty, the blood flow was improved by treating the stenosis. After the procedure, the patient's general condition improved, blood pressure decreased, and antihypertensive medication was tapered. After the procedure, serum albumin, sodium, renin, aldosterone, and creatinine levels were restored to normal. Proteinuria decreased after treatment, but nephrotic-range proteinuria persisted. There were no abnormal findings on antithrombin, protein C, protein S, antiphospholipid antibody, or factor 5, 7, 8, or 10 tests for detecting thrombophilia. Administration of low-molecular-weight heparin was initiated to manage the patient's residual renal artery thrombi, which was then switched to warfarin. Nineteen days after the procedure, the patient was discharged with warfarin and antihypertensive drugs. The proteinuria disappeared after 3 months without antiproteinuric medication. Six months later, a follow-up renal computed tomography angioplasty confirmed that the residual thrombosis had disappeared; therefore, warfarin was discontinued.

Discussion

Our case represents the first reported case of a neonate presenting with massive proteinuria, hypoalbuminemia, and hypertension caused by renal artery stenosis that was successfully treated with percutaneous renal angioplasty. These clinical features should be differentially diagnosed from congenital nephrotic syndrome.

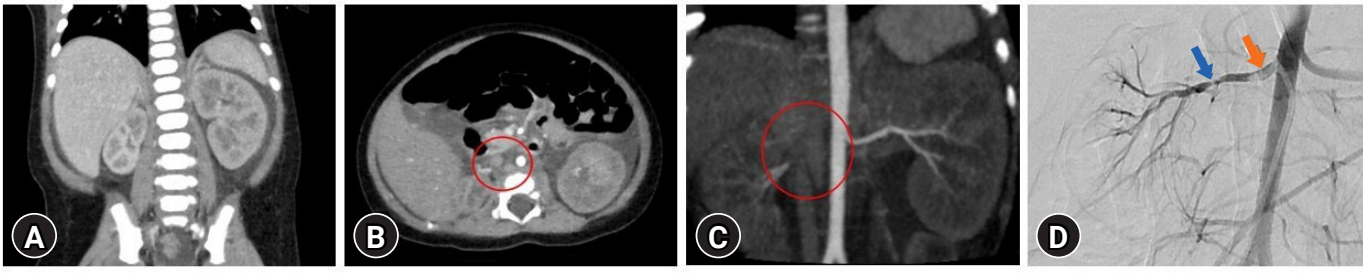

Fig. 1. (A) Renal computed tomography (CT) angiography showing asymmetric small size of right kidney with compensatory left renal hypertrophy. (B, C) Renal CT angiography showing the invisible of the right renal artery proximal portion (red circle). (D) Abdomen aortography showing the right renal artery proximal filling defect (red arrow) and mid-portion stenosis (blue arrow).

https://doi.org/10.3339/ckd.23.017

Congenital nephrotic syndrome is a heterogeneous group of disorders characterized by nephrotic-range proteinuria and hypoalbuminemia, which typically manifests in infants younger than 3 months. It is a rare disease classified into primary congenital nephrotic syndrome, caused by genetic defects in podocyte proteins such as nephrin and podocin, and secondary congenital nephrotic syndrome, caused by infections (e.g., syphilis, toxoplasmosis, cytomegalovirus, rubella, hepatitis B, and human immunodeficiency virus) or maternal alloimmune disease (e.g., maternal systemic lupus erythematosus) [6]. Several case reports have demonstrated that HHS resulting from renal artery stenosis and thrombosis can lead to massive proteinuria and/or hypoalbuminemia [2,5,7,8]. Neonatal cases of nephrotic syndrome and HHS caused by renal arterial stenosis are rare. When ischemia occurs in the unilateral kidney, overstimulation of the renin-angiotensin-aldosterone system in the ischemic kidney causes hypertension in HHS. Additionally, hyperfiltration in the contralateral kidney leads to secondary polyuria, renal electrolyte loss, including natriuresis, and hypovolemia. The pathophysiology of massive proteinuria in HHS has not been clearly elucidated. Some theories include ultrafiltration, focal segmental glomerular sclerosis development, and podocyte injury associated with angiotensin II [2,9,10]. Therefore, patients with renal artery stenosis should be considered HHS due to renal artery hypertension. Renovascular hypertension in children is one of the most common causes of secondary hypertension. In previous studies, HHS was confirmed in about 1/4 of renovascular hypertension [2], so we should be careful not to underdiagnose HHS by reviewing the patient's clinical features and laboratory findings.

Patients diagnosed with HHS typically undergo treatment with antihypertensive medication and supportive care and may require invasive procedures and surgery to alleviate symptoms. Previously reported cases of neonates with HHS have been managed with medication and/or nephrectomy [4,5,11,12]. In our case, the patient underwent successful percutaneous balloon angioplasty, which preserved the function of the affected kidney. To our knowledge, this is the first report on using percutaneous balloon angioplasty to treat HHS in neonates. Percutaneous balloon angioplasty is an effective intervention for improving hypertension and correcting electrolyte imbalance in patients with HHS [2,8,13,14]. Angioplasty is considered the optimal choice for preserving kidney function in patients with renal artery stenosis, especially in children with a longer lifespan.

In our patient, multiple thrombi with renal artery stenosis were observed. The occurrence of thrombosis in neonates is rare. A German registry reported the incidence of symptomatic renal vein thrombosis in neonates to be at least 2.2 per 100,000 live births and renal artery stenosis is even more uncommon. This can be related to factors such as indwelling catheter insertion, for example, umbilical artery catheterization as well as disseminated intravascular coagulation, impaired liver function, fluctuations in cardiac output, and congenital heart diseases in neonates [5,15]. Our patient had no history of thrombosis, and thrombophilic conditions were excluded based on laboratory tests. However, it remains unclear whether renal artery thrombosis results in renal artery stenosis or whether hypoplastic kidney itself affects artery stenosis. However, renal artery stenosis and nephrotic syndrome can also cause thrombosis. Monitoring for additional thrombotic events is necessary in the future. At the last follow-up at 3 years of age, the patient did not experience any other thrombotic events.

Our patient presented with neurological symptoms at treatment initiation. HHS induces secondary hyperreninemia and hyperaldosteronism, further exacerbating salt and water loss and leading to malignant hypertension [2,4,13]. This condition has been associated with progressive target organ damage in children, including encephalopathy and intracranial hemorrhage. Central nervous system symptoms occur in approximately half of patients with HHS and are caused by encephalopathy resulting from severe hypertension and hyponatremia [2,3,5,7,8,12]. While most patients recover when electrolyte imbalance and hypertension improve, some patients may still have residual central nervous system sequelae [5,7]. Therefore, early detection and timely treatment of HHS are crucial for preventing neurological sequelae.

In our case, the presence of HHS provided clues regarding the underlying condition. Early diagnosis and appropriate management of HHS are essential to mitigate the risk of complications associated with persistent malignant hypertension and electrolyte imbalance in neonates.

Ethical statements

This case was reviewed and approved by the Institutional Review Board of Seoul National University Hospital and a waiver the requirement to obtain any informed consent (IRB No. H-2306-190-1444).

Conflicts of interest

Hee Gyung Kang and Ji Hyun Kim are editorial board member of the journal but were 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.

Funding

None.

Author contributions

Conceptualization: HGK
Data curation: DK, SHL
Investigation: DK
Methodology: YHA, HGK, JHK, SHL
Project administration: YHY, HGK, JHK, SHL
Visualization: YHA, HGK, JHK
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Writing-review & editing: YHA, SHL
All authors have read and approved the final manuscript.

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https://doi.org/10.3339/ckd.23.017

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Case Report

Child Kidney Dis 2023;27(2):121-126
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.022

Angiotensin receptor blocker induced fetopathy: two case reports and literature review

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The administration of angiotensin type 2 receptor blockers (ARBs) during pregnancy is known to cause ARB fetopathy, including renal insufficiency. We aimed to analyze the outcomes of two patients who survived ARB fetopathy and perform an accompanying literature review. Case 1 was exposed antenatally from a gestational age of 30 weeks to valsartan because of maternal pregnancy-induced hypertension. The patient presented with oliguria immediately after birth, and renal replacement therapy was administered for 24 days. Seven years after birth, renal function was indicative of stage 2 chronic kidney disease (CKD) with impaired urinary concentration. Case 2 had a maternal history of hypertension and transient ischemic attack and was treated with olmesartan until 30 weeks of pregnancy. Renal replacement therapy was performed for 4 days since birth. After 8 years, the patient is with CKD stage 2, with intact tubular function. Recent reports suggest that ARB fetopathy might manifest as renal tubular dysgenesis and nephrogenic diabetes insipidus, in contrast to mild alterations of glomerular filtration. Tubular dysfunction may induce CKD progression and growth retardation. Patients with ARB fetopathy should be monitored until adulthood. The ARB exposure period might be a critical factor in determining the severity and manifestations of fetopathy.

Keywords: Angiotensin-converting enzyme inhibitors; Angiotensin receptor antagonists; Case reports; Diabetes insipidus, nephrogenic; Renal insufficiency, chronic

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays an essential role in the development of fetal kidneys [1]. All components of the RAAS, including angiotensin II receptor type 1 (AT1) and type 2 (AT2), exist in the developing kidneys [1]. Angiotensin II, an active form of angiotensin I converted by angiotensin-converting enzyme, promotes cellular growth through angiotensin II receptors, especially AT1. Administration of RAAS blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), during the second and third trimesters of pregnancy has been reported to cause oligohydramnios, neonatal respiratory failure, renal insufficiency, and skeletal abnormalities, including limb contracture and hypocalvaria [1]. This condition is referred to as an ACEI/ARB fetopathy. Fetal exposure to ACEI/ARB results in decreased glomerular numbers and tubular atrophy, which manifest as a decreased glomerular filtration rate and impaired urinary concentration, respectively [1,2]. Most affected patients show poor survival and progress to end-stage kidney disease [2,3]. However, few studies have examined the long-term renal prognosis of ACEI/ARB fetopathy owing to poor survival rates. The current study aimed to present the long-term outcomes of two patients who survived ACEI/ARB fetopathy, to discuss tubular dysfunc-

Received: November 7, 2023; Revised: December 18, 2023; Accepted: December 18, 2023

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tion of fetopathy, and to suggest possible factors affecting the clinical course of fetopathy.

Case report

Case 1

A 7-year-old boy was born at a gestational age (GA) of 39 weeks, with a birth weight of 3,360 g (50th–75th percentile). His mother had a history of pregnancy-induced hypertension and valsartan was administered from the second trimester of pregnancy until delivery. Oligohydramnios was observed at 30 weeks of gestation. On the 4th day after birth, the patient was transferred to our center because of persistent anuria and azotemia. At the time of admission, his vital signs were as follows: blood pressure 64/38 mmHg, heart rate 142 beats/min, respiratory rate 52 breaths/min, and body temperature 36.6 °C. A physical examination revealed no remarkable findings. Initial laboratory results showed blood urea nitrogen (BUN) and creatinine (Cr) of 20.5 mg/dL and 4.85 mg/dL, but neither electrolyte imbalance nor acidosis was detected. Urinalysis showed no abnormal findings, while renal parenchymal echogenicity was increased on sonography. However, the patient's body weight increased over time, azotemia became aggravated (Cr, 5.01 mg/dL), and hyponatremia developed (Na, 129 mmol/L). Peritoneal dialysis was initiated on the 2nd day of admission, and urination was observed on the 4th hospital day (HD). The modality of renal replacement therapy (RRT) was changed to continuous RRT (CRRT) on HD 5 for volume control but returned to peritoneal dialysis after 2 days due to platelet consumption. The RRT was maintained for a total of 24 days. The patient exhibited no other complications, and the last laboratory finding before discharge of HD 38 showed a BUN and Cr of 13.8 mg/dL and 1.71 mg/dL (Fig. 1A). He has been undergoing regular checkups for 7 years.

Case 2

An 8-year-old boy was born at a GA 36 weeks with a birth weight of 2,560 g (25th–50th percentile). His mother had a history of hypertension, diabetes mellitus, and transient ischemic attack. She was treated with olmesartan until an incidental diagnosis of pregnancy at an estimated GA 30 weeks. A history of oligohydramnios was not available as appropriate antenatal care was not provided. The patient's Apgar scores were 4 and 8 at 1 and 5 minutes, respectively. Mechanical ventilation and inotropics were applied for meconium aspiration and neonatal hypotension (mean blood pressure 20–30 mmHg). On the 2nd day after birth, pneumothorax was detected. The anuria persisted for 4 days. The patient was transferred to this center 4 days after birth because of anuric acute kidney injury (AKI). The patient's vital signs and initial laboratory findings upon transfer were as follows: blood pressure 60/52 mmHg, heart rate 145 beats/min, respiratory rate 44 breaths/min, body temperature 36.5 °C, BUN/Cr 45.2/6.18 mg/dL, Na-K-Cl 126-5.90-81.0 mmol/L, and Ca-P-Uric acid 9.40-7.10-19.3 mg/dL. Blood gas analysis revealed a pH of 7.37, partial pressure of carbon dioxide (pCO_2) of 38.7 mmHg, and HCO_2 of 22.2 mmol/L. Urinalysis showed no abnormal findings, while renal parenchymal echogenicity was increased on sonography. CRRT was initiated immediately after the admission and was maintained for 4 days. Urination was observed on the 2nd day after admission (Fig. 1B). During hospitalization, the patient was diagnosed with hemorrhagic periventricular leukomalacia and cerebellar hemorrhage. He was discharged on HD 31 and after 8 years of regular follow-up, the patient was transferred to another hospital near his residence.

Long-term renal outcomes

Table 1 briefly describes the long-term outcomes of the two cases. Both patients maintained favorable growth. For renal functions, their glomerular filtration rate did not recover to normal range which is over 90 mL/min/1.73 m^2 even after discharge. Also, ultrasonographic findings were persistently compatible with those of chronic kidney disease (CKD), exhibiting abnormal renal parenchymal echogenicity and poor corticomedullary differentiation. Glycosuria and proteinuria, implying proximal tubular dysfunction, were not detected in either of the patients. However, case 1 was sustained impaired urinary concentration (urine osmolality 101 mOsm/kg) since birth, suggesting distal tubular dysfunction although his growth was within the normal range. Confirmatory tests such as water restriction test for nephrogenic diabetes insipidus (NDI) were not conducted considering the normal aldosterone/renin level. He had started amlodipine use 2 years prior to this report for hypertension without secondary causes. Case 2, on the other hand, exhibited preserved tubular function but neurological sequelae, including delayed development and intellectual disability, associated with perinatal cerebral insult.

Discussion

Recently, Miura et al. [2] published a paper presenting clinical manifestations of tubular dysfunction in ARB fetopathy. Two

https://doi.org/10.3339/ckd.23.022

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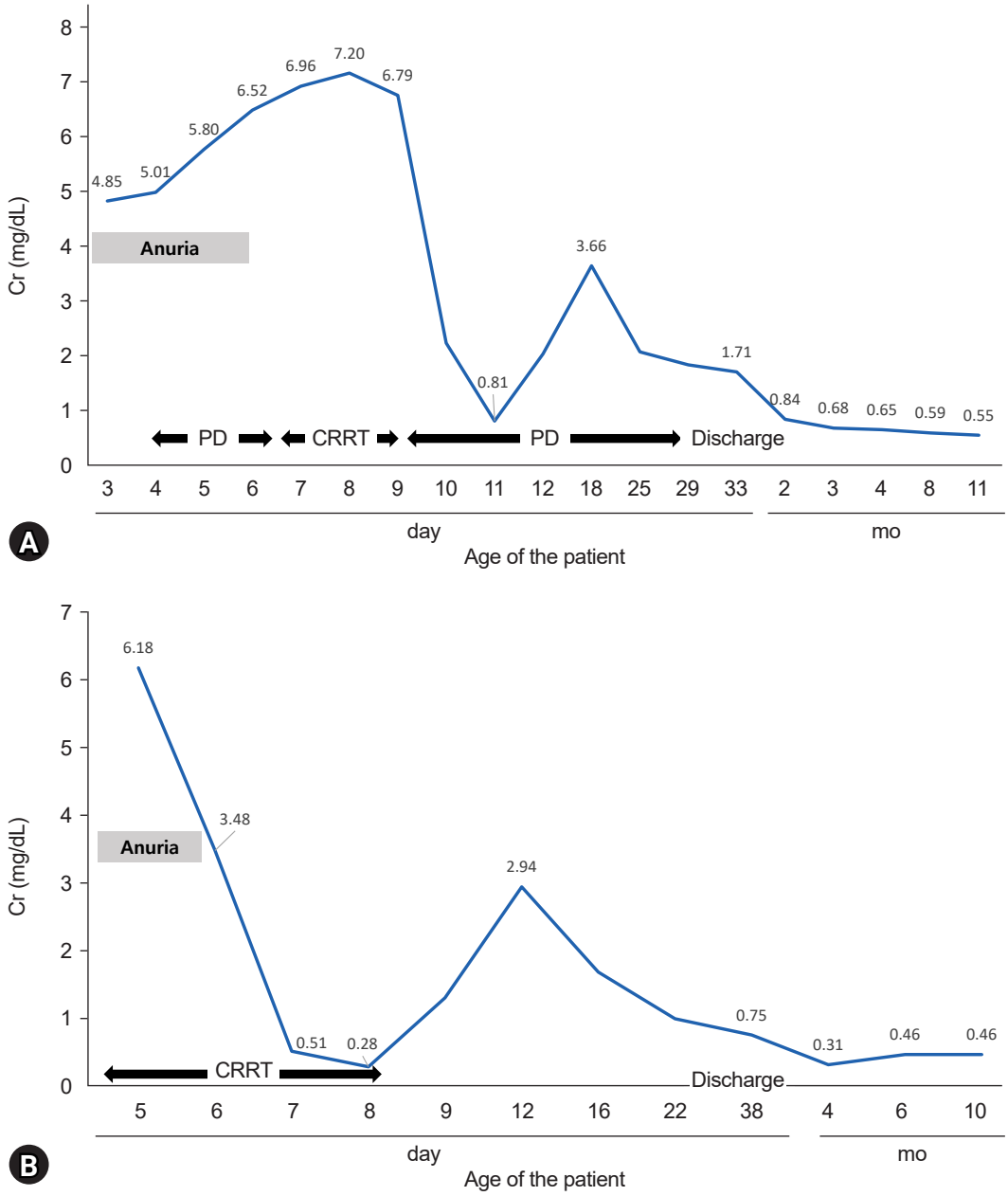

Fig. 1. (A) Case 1 was administered PD for anuric AKI on the 2nd day of hospitalization. Renal replacement therapy, including CRRT, was continued for 24 days. The patient was discharged on hospital day of 38. (B) Case 2 was initiated CRRT for anuric AKI on the first day of hospitalization. CRRT was administered for 4 days. The patient was discharged on hospital day of 31. Cr, creatinine; PD, peritoneal dialysis; CRRT, continuous renal replacement therapy; AKI, acute kidney injury.

patients, after recovering from neonatal AKI, presented with polyuria and polydipsia, and were diagnosed with salt-losing NDI (Table 2). Gang et al. [3] reported a pathologic confirmation of renal tubular dysgenesis (RTD) in ARB fetopathy (Table 2). A kidney biopsy performed during exploratory laparotomy confirmed small and undifferentiated tubules which is compatible with RTD. Exposure to ACEI/ARB decreases the perfusion of fetal kidneys during nephrogenesis and causes pathological changes in the kidneys [4]. This secondary RTD is fatal in affected neonates.

So far, the research presented by Bullo et al. [4] in 2012 is the largest systematic review of ACEI/ARB fetopathy. The 12 cases of ARB fetopathy from the research with at least one available long-term clinical data are listed in Table 2 [2-13]. Among the 12

cases, only five patients were evaluated for renal tubular functions and three out of the five patients had clinical manifestations related to tubular dysfunctions such as growth retardation and renal tubular acidosis (Table 2). On the other hand, glomerular function is relatively followed with attention. This study spotlight the tubular dysfunction derived from ARB fetopathy which leads to growth retardation and deterioration of CKD in affected infants. Pediatric patients who survive ARB fetopathy should be under regular monitoring of tubular function as well as glomerular function.

In 2012, Spaggiari et al. [14] suggested that discontinuation of ACEI/ARB before 34–36 weeks of gestation normalizes the amniotic fluid level and does not cause renal impairment. Correspondingly, Bullo et al. [4] demonstrated that ACEI/ARB fetopathy occurs significantly less frequently in first-trimester exposure to ACEI/ARB when compared with exposure during second and third trimesters or the entire pregnancy. Recently in 2021, Oh et al. [5] compared a case with another previously reported case of ARB fetopathy (Table 2). In case 13, maternal use of telmisartan was discontinued when a 35-week pregnancy was incidentally diagnosed which was 10 days before delivery. Nevertheless, only mild NDI was noted and resolved after 6 months. Another case in comparison was prenatally exposed to candesartan just before delivery, from gestational week of 35 to 36, which resulted in anuria with neonatal hypotension. Their clinical course differed according to the exposure period of ARB.

In this study, case 1 was exposed to ARB during the latter period of pregnancy, whereas case 2 was affected earlier. In the long-term, case 1 demonstrated abnormal urine concentration while case 2 exhibited intact tubular function (Table 1). Although both patients had anuric AKI in the neonatal period, long-term renal complications had more distinct and long-lasting effects in patients with later exposure. Comparably, in previously reported cases, exposure to ARB during period including third trimester of pregnancy causes more severe clinical presentation of fetopathy and poor long-term renal outcomes as shown in Table 2. The following pathophysiology of fetal kidney development also supports these clinical implications: (1) AT1, which is crucial for kidney development, predominates over AT2 in time through kidney development, and (2) ARB is highly selective for AT1. Since kidney development persists until approximately 3 years after birth, neonates and infants are also contraindicated for ACEI/ARB.

In contrast to the second and third trimesters, fetal exposure to ACEI/ARB during the first trimester is often described as relatively safe. However, fetopathy also occurs following first-trimester exposure to ACEI/ARB and it is only the severity that differs [15]. Additionally, according to Quan [1], the use of RAAS blockers especially ACEI, early in pregnancy can cause multisystemic congenital anomalies. Prenatal exposure to ACEI reduces the activation of both AT1 and AT2. This action contributes to early cellular proliferation and growth driven by AT2

Table 1. Long-term outcomes of two patients with ARB fetopathy

Variable	Case 1	Case 2
Exposed medication	Valsartan	Olmesartan
ARB-exposed period (wk)	GA 30–39	GA 0–30
Growth and development	Height 10th–25th percentile Weight 10th–25th percentile (normal development)	Height 5th–10th percentile Weight 25th–50th percentile (delayed development, intellectual disability)
eGFR (mL/min/1.73 m^2)	71.3 (CKD stage 2)	65.8 (CKD stage 2)
Glycosuria/proteinuria	(–/–)	(–/–)
Ultrasonography	Increased renal parenchymal echogenicity Poor corticomedullary differentiation	Increased renal parenchymal echogenicity Poor corticomedullary differentiation
Urine specific gravity	1.01	1.01
Urine osmolality (mOsm/kg)	101	517
Plasma aldosterone/renin ratio	5.51	Not done
Kidney biopsy	Not done	Not done
24-hr ABPM	Awake average: 131/96 mmHg Asleep average: 129/88 mmHg	Not done
Current medication	Amlodipine	None

ARB, angiotensin II receptor blocker; GA gestational age; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; 24-hr ABPM, 24-hour ambulatory blood pressure monitoring.

https://doi.org/10.3339/ckd.23.022

Table 2. Characteristics and renal outcomes of previously reported ARB fetopathy comparing with current cases

Case	ARB exposure		Features of ARB fetopathy					Renal (glomerular/tubular) outcomes		
	Type	Period (GW)	Oligo-hydramnios	Neonatal hypotension	Respiratory failure	Skeletal involvement	Renal insufficiency	Follow-up period	Glomerular	Tubular
1	Valsartan	30–39	+	–	–	–	+[b]	7 yr	CKD (stage 2)	Abnormal concentration
2	Olmesartan	0–30	NA	+	+	–	+[b]	8 yr	CKD (stage 2)	Normal
3 [4,6]	Losartan	0–8[a]	+	–	–	–	–	18 mo	NA	FTT
4 [4,7]	Valsartan	0–20[a]	+	–	–	–	–	6 mo	Normal	Normal
5 [4,8]	Valsartan	0–25[a]	+	–	–	+	+	30 mo	CKD (stage 2)	Normal
6 [4,9]	Losartan	0–27[a]	+	–	+	–	–	3 mo	NA	NA
7 [4,10]	Losartan	0–29	+	+	+	+	+	14 mo	Normal	RTA FTT
8 [4,6]	Candesartan	0–31	+	NA	NA	+	+	NA	CKD (NA)	NA
9 [4,11]	Candesartan	0–31	+	+	+	+	+	34 mo	Normal	NA
10 [4,9]	Losartan	0–31	+	–	–	+	–	2 yr	Normal	NA
11 [5]	Candesartan	0–31	+	+	+	+	+[b]	6 yr	CKD (stage 2)	NDI
12 [4,12]	Olmesartan	0–33	+	–	+	+	+	1 yr	CKD (stage 2)	NA
13 [4,9]	Valsartan	0–34	+	–	+	–	+[b]	1 mo	NA	NA
14 [5]	Telmisartan	0–35	–	–	+	+	–	20 mo	Normal	Transient partial NDI
15 [3]	Olmesartan	0–36	+	+	+	–	+[b]	25 day	ESKD	RTD
16 [4,13]	Valsartan	0–36	+	+	+	–	+	NA	NA	Abnormal concentration
17 [4,9]	Valsartan	28–36	+	NA	+	+	+	8 mo	CKD (NA)	NA
18 [2]	Candesartan	33–37	+	+	+	–	+[b]	2 yr	CKD (stage 3)	NDI

ARB, angiotensin II receptor blocker; GW, gestational weeks; NA, not available; CKD, chronic kidney disease; FTT, failure to thrive; RTA, renal tubular acidosis; NDI, nephrogenic diabetes insipidus; ESKD, end-stage kidney disease; RTD, renal tubular dysgenesis.
[a]Exposure period not including the third trimester, which is GW of 28–40. [b]Supported with renal replacement therapy.

https://doi.org/10.3339/ckd.23.022

which disrupts early embryogenesis. Therefore, maternal ACEI/ARB use should be discontinued immediately after recognizing possible fetopathies. Also, physicians should be aware of the discrete clinical impacts of ACEI and ARB.

This study had several limitations. Since the study was a retrospective observation, limited clinical data were available, and detailed evaluations of tubular dysfunction were not performed. Additional research is needed on the clinical correlation between the affected tubular segments and renal manifestations in relation to the severity-determining factors of ACEI/ARB fetopathy.

Exposure to ACEI/ARB during pregnancy results in evident renal insufficiency, including NDI and RTD. Patients with ACEI/ARB fetopathy should be monitored until adulthood, as tubular dysfunction induces growth retardation and CKD progression. This study emphasizes the potential risk of ACEI/ARB fetopathy and reiterates the importance of physician alertness.

Ethical statements

The Institutional Review Board of the Samsung Medical Center approved this study (IRB No. 2022-12-073-001). The need for informed consent was waived by all participants.

Conflicts of interest

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

Funding

None.

Author contributions

All the work was done by JJ and HC.

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https://doi.org/10.3339/ckd.23.022

ChiKD CHILDHOOD KIDNEY DISEASES

Case Report

Child Kidney Dis 2023;27(2):127-132
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.014

A case of cystinuria with a heterozygous *SLC3A1* mutation presenting with recurrent multiple renal stones in a 14-year-old boy

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Cystinuria, a genetically inherited disorder, is a rare cause of kidney stones. It is characterized by impaired transport of cystine and amino acids in the proximal renal tubule and the small intestine. Most patients develop cystine stones throughout their lifetime. Recurrent renal stones need to be extracted by repeated urologic interventions. Treatment options of cystinuria for preventing stone recurrence are limited and poorly tolerated. In this study, we report a pediatric case of cystinuria with a heterozygous *SLC3A1* mutation diagnosed by stone analysis, measurement of urine cystine excretion, and genetic analysis. There were recurrent renal stones despite repetitive shock wave lithotripsy and retrograde intrarenal surgery. However, the rate of stone formation seemed to be slower after D-penicillamine was added into adequate hydration and urinary alkalinization.

Keywords: Case reports; Cystinuria; SLC3A1 protein, human; Urolithiasis

Introduction

Cystinuria (OMIM 220100) is an inherited disorder characterized by impaired transport of dibasic amino acids including cystine in the brush border membrane of the proximal renal tubule and the small intestine [1]. Because of the low solubility of cystine at normal urinary pH, cystine stones can be caused by high urinary cystine excretion [1-3]. Cystine stones often occur in the second or third decade of life. It can also occur during infancy or childhood occasionally [1]. Its incidence rate in the pediatric age group has increased up to 6%–8% of all stones [4]. However, according to the recent urinary stone composition data from South Korea [5], cystine stones occurred rarely in the Korean population, which accounted for only 0.35% of the total stone composition. Mutations in the *SLC3A1* and *SLC7A9* genes are known to be responsible for cystinuria. Homozygotes or mixed heterozygotes of these two genes are associated with increased urinary cystine excretion and kidney stone formation [6]. Generally, treatment options of cystinuria for preventing stone recurrence are limited and poorly tolerated. Given its prevalence by age, studies about pediatric patients of cystinuria confirmed by genetic analysis are relatively rare. In this study, we report a rare case of a 14-year-old boy with cystinuria caused by a heterozygous mutation in the *SLC3A1* gene with recurrent multiple kidney stones. The rate of stone formation seemed to be slower after D-penicillamine was added into conservative management.

Received: September 11, 2023; Revised: October 16, 2023; Accepted: October 16, 2023

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Case report

A 14-year-old boy was referred to our hospital because of recurrent renal stones with gross hematuria and flank pain. Five years ago, he had sudden onset of sharp pain in his back and lower abdomen with brown-colored urine. After diagnosis of renal stones by urologists, he underwent repeated shock wave lithotripsy every 6 months. However, stones kept occurring alternately on both kidneys with a shortened period of every 3 to 4 months and increases in size and numbers. Retrograde intrarenal surgery of left kidney and that of both kidneys were done to remove large kidney stones at 18-month intervals. There was no family history of urolithiasis or other renal diseases. His body mass index was 20.2 kg/m^2 (32 percentiles) and his blood pressure was 118/61 mmHg (75 percentiles). He did not have any medical history of urinary tract infection. He had taken potassium citrate (10 mEq/dose, 3 times a day) for 6 months. Initial laboratory evaluation was as follows: white blood cell count of 10.6×10^3/μL, hemoglobin level of 14.4 g/dL, platelet count of 273×10^3/μL, blood urea nitrogen of 11.7 mg/dL, creatinine (Cr) of 1.01 mg/dL, sodium of 141 mmol/L, potassium of 4.4 mmol/L, chloride of 105 mmol/L, calcium of 9.8 mg/dL, phosphorus of 3.3 mg/dL, cystatin C of 0.99 mg/L (reference, 0.53–0.95 mg/L), and estimated glomerular filtration rate (eGFR) of 101 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Cr-cystatin equation. Urinalysis showed pH 6.0, +/– protein, and >60 red blood cells/high-power field. Urinary levels of calcium, uric acid, citric acid, and oxalate were 32 mg/day (reference, 100–300 mg/day), 355 mg/day (reference, 250–750 mg/day), 573 mg/day (reference, 320–1,240 mg/day), and 27 mg/day (reference, <50 mg/day), respectively. A renal sonogram and abdomen computed tomography showed multiple, hyperechoic stones on both kidneys without hydronephrosis (Fig. 1). The diagnosis of cystinuria was confirmed by highly elevated urinary levels of cystine and dibasic amino acids. Urinary concentrations of cystine, ornithine, lysine, and arginine were 943 μmol/g Cr (reference, 25–125 μmol/g Cr), 1,387 μmol/g Cr (reference, 31–91 μmol/g Cr), 5,907 μmol/g Cr (reference, 153–634 μmol/g Cr), and 3,212 μmol/g Cr (reference, 31–109 μmol/g Cr), respectively. Chemical stone analysis using colorimetric method was positive for cystine composition. Urine alkalinization with potassium citrate (30 mEq/day), oral hydration (>3 L/day),

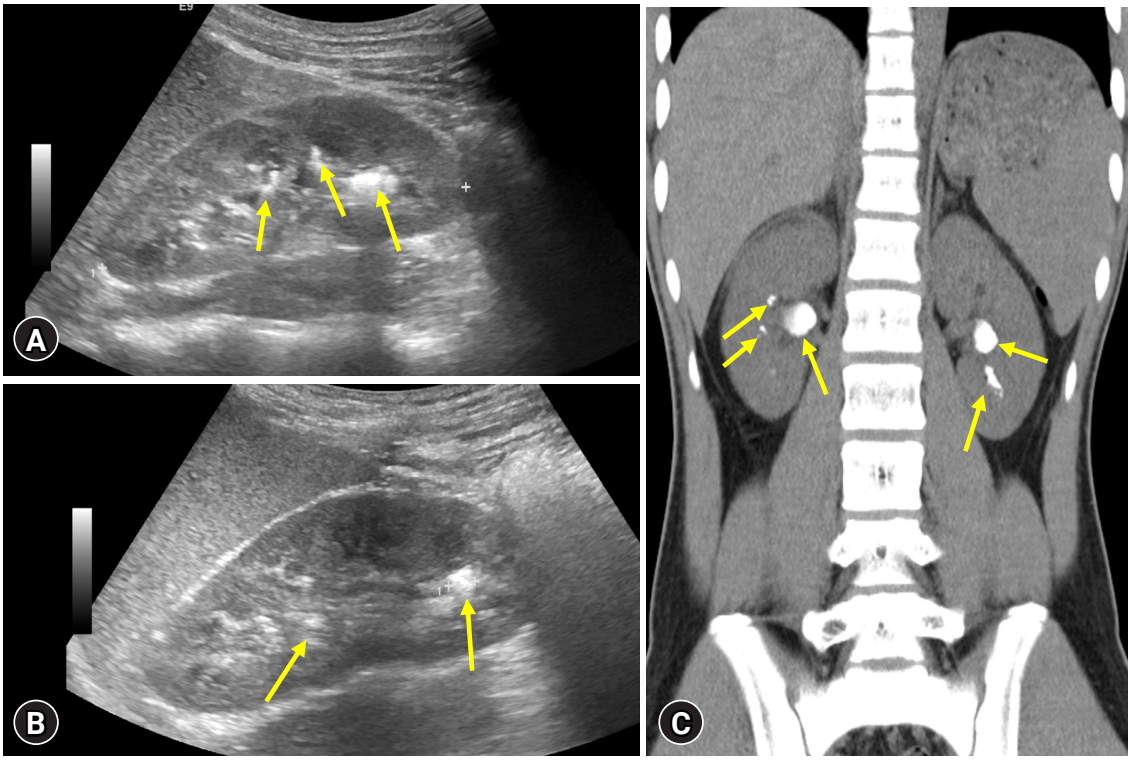

Fig. 1. Renal ultrasonography and abdominal computed tomography showing multiple kidney stones. (A) Right kidney. (B) Left kidney. (C) Multiple hyperechoic stones in bilateral pelvicalyceal system (arrows). The largest sizes of renal stones on right kidney and left kidney were 1.53 cm and 0.62 cm, respectively.

https://doi.org/10.3339/ckd.23.014

and a low-protein (<20 g/day) and low-salt (<2 g/day) diet were initiated for the management of cystinuria simultaneously. Despite repeated interventions and supportive care, stones recurred continuously. In addition, metabolic alkalosis occurred intermittently due to prolonged high-dose citrate therapy. After regular follow-ups for a year, he and his parents underwent genetic analysis using whole exome sequencing and heterozygous *SLC3A1* gene mutations [NM_000341.4:c.1820del (p.Leu607HisfsTer4)] were found in the patient and his mother (Fig. 2). Due to recurrence of kidney stones, captopril (12.5 mg/day), the first angiotensin-converting enzyme inhibitor that has a sulfhydryl ligand that forms bond with cysteine, was added in addition to standard fluid and alkalization therapy. However, after a month, multiple kidney stones started to recur again. Captopril was stopped since it seemed not to be effective. Instead, D-penicillamine (250 mg/day) was started and he got percutaneous nephrolithotripsy to remove stones at the same time. After that, renal stones were reduced without newly visible stones. There was no gross or microscopic hematuria for 6 months. Serum cystatin C level gradually increased in the last 2 years (0.99, 1.03, 1.00, 1.22 mg/L) and the latest eGFR using the CKD-EPI Cr-cystatin equation was 87.0 mL/min/1.73 m^2. The patient's clinical course over the 2 years of treatment is shown in Fig. 3.

Discussion

Here we report a case of cystinuria with a heterozygous *SLC3A1* gene mutation in an adolescent boy with recurrent multiple renal stones. Cystinuria was diagnosed by stone analysis, measurement of urine cystine excretion, and genetic analysis. While repeated urologic interventions were needed, D-penicillamine was found to be effective in decreasing the rate of stone formation without any side effects in our case.

Cystinuria is an inborn congenital disorder characterized by impaired transport of dibasic amino acids including cystine which is relatively insoluble at the physiological pH of urine [1]. As a result, it can produce cystine stones, causing pain, hematuria, infection, and renal failure in rare cases. The diagnosis of cystinuria is based on confirmation of a hexagonal cystine crystal with a microscopic examination of urine. However, this can only be observed in about 25% of patients. The most obvious diagnostic method is to confirm an increase in cystine excretion in 24-hour urine tests. However, since it is difficult to collect 24-hour urine in infants, one-time urinary cystine to Cr ratio can help diagnose it [7]. Cystine stones are very large in size, and they recur frequently. Thus, they are difficult to treat with interventions. Therefore, early diagnosis and preventive treatment are important. Current medical management to reduce stone formation for cystinuria includes adequate hydration (>3 L/day), low sodium (<2 g/day) and protein (<20 g/day) diet, and urine alkalinization (up to pH 7.5) [8]. If these measures fail, cystine-binding thiols such as tiopronin and D-penicillamine, captopril, and crystal growth inhibitors can be considered [8]. Due to recurrent episodes of renal stones, patients with cystinuria are at high risk of developing chronic kidney disease [9].

Although genetic testing is not always required for the diagnosis of cystinuria, it might be helpful in diagnosing patients with atypical clinical presentation and genetic counseling. Previous studies have shown that cystinuria is caused by mutations in the *SLC3A1* gene (located on chromosome 2p21) encoding neutral and basic amino acid transport protein rBAT

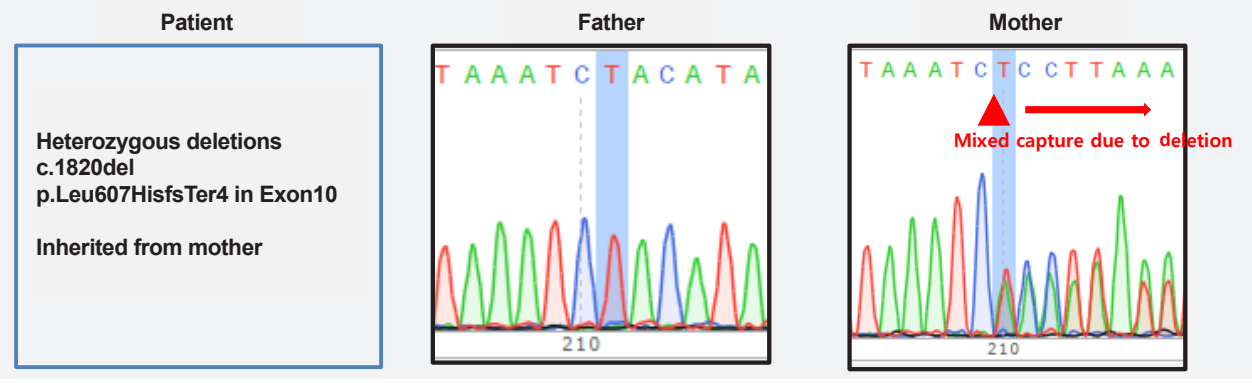

Fig. 2. Electropherogram showing the heterozygous *SLC3A1* gene mutation.

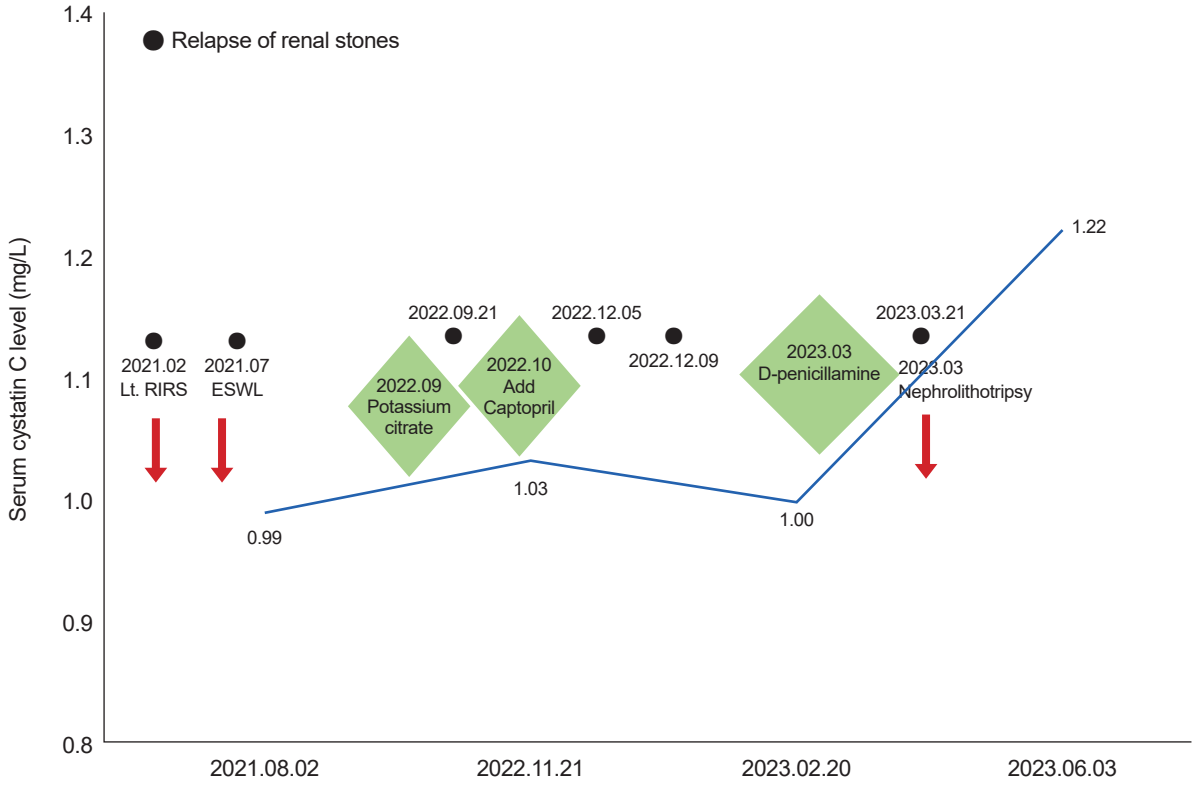

Fig. 3. Clinical course of the patient over 2 years of treatment. RIRS, retrograde intrarenal surgery; ESWL, extracorporeal shock wave lithotripsy.

and the *SLC7A9* gene (located on chromosome 19q13) encoding b(0,+)-type amino acid transporter 1 [6]. According to mutation types of these two genes, cystinuria can be classified into type A (two mutations on *SLC3A1*), type B (two mutations on *SLC7A9*), and type AB (one mutation on each of *SLC3A1* and *SLC7A9*) [1,6]. Jeong et al. [10] identified six new mutations in mutational analysis of Korean cystinuria patients, and the mutations in the *SLC3A1* gene were more frequently observed in the Korean population. Our case belongs to type A cystinuria since the patient's genetic analysis showed a heterozygous *SLC3A1* gene mutation. While type AB patients are known to have a mild phenotype, the disease severity in relation to the type of cystinuria cannot be correlated in pediatric patients [1,7]. A recent study of genotypic and phenotypic analyses of Korean pediatric patients with cystinuria did not find a significant association between clinical course and genotype [7]. In that report [7], the prevalence of cystinuria was higher in females with a median onset age of 1.5 years. Only one patient with a heterozygous *SLC7A9* mutation had a family history of renal stones. Among eight patients, except for one patient with a single heterozygous *SLC3A1* mutation who was treated with oral sodium bicarbonate only, seven patients were treated with tiopronin combined with potassium citrate or captopril. Most patients had to undergo repeated urologic interventions similar to our case. However, symptoms of cystinuria of our patient developed at a relatively older age. In particular, the onset age of a patient with a heterozygous *SLC3A1* gene mutation in the study of Kim et al. [7] was 1.3 years. While the patient showed therapeutic effect with conservative management only, our patient had to constantly change treatment strategies because of recurrent renal stones.

It has been widely recognized that the most effective therapy in patients with cystinuria is to prescribe thiol-containing compounds including α-mercaptopropionyl glycine (α-MPG) and D-penicillamine [8]. Thiol compounds contain sulfhydryl groups, which undergo a disulfide exchange reaction with cysteine, generating two molecules of cysteine bound to thiols. The solubility of the complex is 50 times higher than cystine [8]. Tanzer et al. [11] have reported a case of cystinuria in a 1-year-old girl with a heterozygote for *M467T* mutation within the *SLC3A1* gene. She underwent repeated nephrolithotomy and

https://doi.org/10.3339/ckd.23.014

received α-MPG. Tangnararatchakit et al. [12] have also shown successful management with D-penicillamine in 4-year-and 6-month-old girls with cystinuria after recurrent stone removals. Most pediatric cases did not have a history of familial kidney diseases. They initially presented with symptoms of fever, abdominal pain, and vomiting [7,11,12]. Although repeated urologic interventions were done with conservative treatment, renal stones frequently recurred. Therefore, cystine-binding thiol drugs or captopril in addition to urine alkalinization were added. These concurrent treatments led to success with disappearance of renal stones in follow-up examinations. Similar to these cases, treatment for cystinuria was also difficult in our case. Drugs sometimes had to be discontinued or replaced by other drugs in consideration of the patient's treatment compliance, drug side effects, and treatment effects. Conservative management with potassium citrate was not effective. Therefore, we added captopril to induce formation of captopril–cysteine disulfide known to be 200 times more soluble than cystine [8]. However, the dose of captopril could not be sufficiently given due to the risk of hyperkalemia. There was a concern for the development of hyperkalemia since we were also using potassium citrate in our patient. As a result, multiple renal stones recurred and urological procedures had to be repeated. Then D-penicillamine was administered by gradually increasing its dose. There has been no recurrence of newly formed renal stones for 6 months. D-penicillamine forms penicillamine-cysteine disulfide through thiol-disulfide exchange reaction so that cystine could not be crystallized in the urine. Halperin et al. [13] have revealed the efficacy of D-penicillamine which enables significantly less urinary tract surgery for stone removal and reduces episodes of renal colic. However, it can cause changes in appetite, skin mucosal lesions, proteinuria, systemic lupus erythematosus, and blood abnormalities such as leukocytosis and thrombocytopenia [1,14]. Due to these side effects, patients' drug compliance is often low. In order to increase patient's compliance with treatment, it is important to determine the appropriate dose of the drug that can minimize the concentration of cysteine in urine while reducing side effects of the drug. In addition, regular blood tests and urine tests are needed to monitor drug's side effects as well as progress of the disease. In spite of dietary and conservative treatments mentioned earlier, if the treatment response is refractory, α-MPG (tiopronin) can be applied to reduce free cystine concentration. It has a similar mechanism of action to D-penicillamine with fewer side effects, including nausea, vomiting, diarrhea, skin rash, etc. Jung et al. [9] have shown that α-MPG can reduce individual stone formation rate in cystinuric patients showing toxicity of D-penicillamine. As tiopronin is currently unavailable in South Korea [9], we used D-penicillamine instead of tiopronin.

Previous studies [1,14] have shown that patients with cystinuria are at risk of acute kidney damage and rapidly progressing chronic renal failure. Prot-Bertoye et al. [15] have suggested that recurrent renal stones with cystinuria extracted by repeated interventions might deteriorate kidney function with an eGFR of <60 mL/min/1.73 m^2. Furthermore, a few patients can progress to end-stage kidney disease. The key mechanism of impaired renal function in cystinuria is insolubility of cystine in the tubular fluid and urine. At the histological level, cystine crystals can cause obstruction in ducts of Bellini and lead to interstitial inflammation/fibrosis [11]. In our patient, the level of cystatin C, a useful biomarker for eGFR over serum Cr, gradually increased in the last 2 years. Continuous close monitoring for kidney function and therapy to prevent cystine stone events are of utmost importance.

In summary, cystinuria is a relatively rare disease in children. It is difficult to diagnose early due to its non-specific symptoms. In addition, although medical treatment is inevitable because of a low therapeutic effect only with dietary and conservative treatment, there are many difficulties considering drug's side effects and patients' compliance to treatment. Here, we report a rare case of a 14-year-old boy with cystinuria caused by a heterozygous *SLC3A1* mutation showing recurrent multiple renal stones. The rate of stone formation seemed to be slower after D-penicillamine was added. Since there were frequent urological procedures and relapses of urinary stones in our patient, continuous monitoring for kidney function is needed. In the future, studies including multicenter and large-sized participants are needed for successful preservation of renal function and comprehensive management approach in patients with cystinuria.

Ethical statements

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2023AS0226). Informed consent was waived due to its retrospective study design.

Conflicts of interest

Hyung Eun Yim, an Editor-in-Chief of the journal, was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization: HEY
Data curation: MHS, HEY
Formal analysis: HWC, HEY
Methodology: HWC, MHS, HEY
Project administration: HEY
Visualization: HWC, HEY
Writing - original draft: HWC, HEY
Writing - review & editing: HWC, MHS, HEY
Approval of final manuscript: all authors.

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https://doi.org/10.3339/ckd.23.014

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Case Report

Child Kidney Dis 2023;27(2):133-138
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.23.013

Nutcracker syndrome combined with immunoglobulin A nephropathy: two case reports

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Nutcracker syndrome (NCS) is a disease caused by compression of the left renal vein between the superior mesenteric artery and the abdominal aorta. Immunoglobulin A (IgA) nephropathy (IgAN) is characterized by the predominance of IgA deposits in the glomerular mesangial area. Hematuria and proteinuria can be present in both diseases, and some patients can be concurrently diagnosed with NCS and IgAN; however, a causal relationship between the two diseases has not yet been clarified. Here, we report two pediatric cases of NCS combined with IgAN. The first patient presenting with microscopic hematuria and proteinuria was diagnosed with NCS at the initial visit, and the second patient was later diagnosed with NCS when proteinuria worsened. Both patients were diagnosed with IgAN based on kidney biopsy findings and treated with angiotensin-converting enzyme inhibitors and immunosuppressants. A high index of suspicion and timely imaging or biopsy are essential for the proper management of NCS combined with glomerulopathy.

Keywords: Case reports; Glomerulonephritis; Immunoglobulin A; Renal nutcracker syndrome

Introduction

The nutcracker phenomenon (NCP), also known as left renal vein (LRV) entrapment, is defined as compression of the LRV between the superior mesenteric artery and abdominal aorta. Nutcracker syndrome (NCS) describes LRV entrapment with clinical manifestations, such as micro- to macroscopic hematuria, proteinuria, flank pain, abdominal pain, and varicocele [1]. Although the prevalence of NCS is unknown, it is increasingly being diagnosed owing to the development of diagnostic techniques [2,3]. Meanwhile, immunoglobulin A (IgA) nephropathy (IgAN) is the most common glomerulonephritis (GN) worldwide and leading cause of chronic kidney disease and end-stage kidney disease. Recurrent hematuria, with or without proteinuria, has also been reported in IgAN [4]. Although it is a rare presentation, several cases of coexisting NCS and IgAN have been reported [3,5-7]. In a Japanese study, the prevalence of NCP in 146 patients with IgAN was 6.8% [8]. Despite these reported cases, the relationship between these two diseases has not yet been clarified. Furthermore, it is difficult to diagnose and treat these patients appropriately. In this study, we report two pediatric cases of NCS combined with IgAN to suggest a relationship between the two diseases and emphasize their clinical significance.

Received: August 8, 2023; Revised: September 12, 2023; Accepted: September 30, 2023

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Case report

Case 1

An 11-year-old boy visited our hospital for the evaluation of proteinuria and microscopic hematuria, which were confirmed during a school health check-up. Two years prior, only microscopic hematuria was found during a school health check-up. The patient had no relevant family history. His body mass index (BMI) was 17.8 kg/m^2 (25th percentile) and blood pressure was 113/76 mmHg (73rd percentile). Laboratory test results, including complete blood cell counts, electrolytes, and biochemistry tests, were unremarkable. Complement C3 and C4 levels were within the normal range; however, serum IgA level was elevated at 229 mg/dL (reference range: 53–204 mg/dL). Results for anti-double-stranded DNA, antinuclear antibody, and antineutrophilic cytoplasmic antibody were negative. Urinalysis revealed 2+ protein and 5–9 red blood cells/high-power field (RBCs/HPF). Random urinary protein-to-creatinine ratio (UPCR) in the early morning was 0.64, and protein amount in 24-hour urinalysis was 477 mg (14 mg/m^2/hr). The protein measured in supine and erect positions for 12 hours was 157 mg (9.4 mg/m^2/hr) and 193 mg (11.6 mg/m^2/hr), respectively. Urine dysmorphic RBC testing was negative. On initial kidney Doppler ultrasonography, the blood flow velocity of the LRV at the renal hilum and aortomesenteric portion was 28.8 and 161.7 cm/s, respectively. The peak velocity ratio (PVR) was 5.61; therefore, the patient was diagnosed with NCS. He was treated with enalapril, and a kidney biopsy was performed due to worsened proteinuria with a UPCR of 0.70. Light microscopy revealed segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis (≤25%) (Oxford classification: M1, E0, S1, T0, C0). IgA (3+), lambda (3+), kappa (2+), fibrinogen (2+), IgM (1+), and C3 (1+) levels in the mesangial regions were observed using immunofluorescence. Mesangial and paramesangial electron-dense deposits and focal foot process effacement (10%) were confirmed by electron microscopy. This result was consistent with IgAN. Deflazacort was initiated, but after 2 months, proteinuria was aggravated, with a 24-hour urine protein amount of 762 mg (23 mg/m^2/hr). Subsequently, azathioprine was administered, and proteinuria and hematuria improved. Azathioprine and deflazacort were discontinued 2 and 4 years later, respectively, and the patient is now being treated with enalapril alone. Five years after the kidney biopsy, urinalysis showed a specific gravity of 1.04, 2+ protein, and 0–1 RBCs/HPF. UPCR was 0.14, and protein levels in the 24-hour urine were 289 mg (7.62 mg/m^2/hr). Proteinuria has been waxing and waning until recently. Based on recent laboratory findings, serum cystatin C level increased from 0.82 to 0.95 mg/L (0.53–0.95 mg/L). Cystatin C-based estimated glomerular filtration rate was 99 mL/min/1.73 m^2. Kidney Doppler ultrasonography was repeated, and NCS was confirmed (PVR, 6.37) (Fig. 1A-C). The patient's clinical course is shown in Fig. 1D.

Case 2

A 7-year-old boy presented to our hospital with proteinuria and microscopic hematuria, which were confirmed during a school health check. His father had a history of thin glomerular basement membrane (GBM) disease, which was diagnosed during high school. His BMI was 16.4 kg/m^2 (50th percentile) and his blood pressure was 101/64 mmHg (56th percentile). Laboratory test results, including complete blood cell count, electrolytes, and biochemistry tests, were unremarkable. Other blood examination results, including complement C3 and C4, IgA, anti-double-stranded DNA, antinuclear antibody, and antineutrophilic cytoplasmic antibody tests, were also normal. Urinalysis revealed 2+ protein and 30–60 RBCs/HPF. The UPCR was 0.59, and protein amount in 24-hour urinalysis was 250 mg (11.3 mg/m^2/hr). The percentage of dysmorphic urine RBCs in the specimen was 80%. The patient was treated with enalapril for the suspected GN. After 6 months, follow-up urinalysis revealed a UPCR of 0.17 and 10–29 RBCs/HPF. The amount of protein in the 24-hour urinalysis was 98 mg (4.4 mg/m^2/hr), and dysmorphic RBCs were not observed. Subsequently, enalapril was discontinued, and the patient was followed up. After 3 years, proteinuria with microscopic hematuria worsened. Urinalysis revealed 3+ protein and 30–60 RBCs/HPF. The UPCR was 1.30, and the protein content in the 24-hour urine was 1,215 mg (34.4 mg/m^2/hr). The patient was again treated with enalapril. A kidney biopsy could not be performed due to the parents' reluctance. Kidney Doppler ultrasonography was performed. The blood flow velocity of the LRV at the renal hilum and aortomesenteric portion was 24.3 and 141.7 cm/s, respectively. The PVR was 5.83; therefore, the patient was diagnosed with NCS. Genetic testing for Alport syndrome using next-generation sequencing (*CD151*, *COL4A3*, *COL4A4*, *COL4A5*, *COL4A6*, *FN1*, *MYH9*, and *PXDN*) was negative. Despite maintaining enalapril, proteinuria with microscopic hematuria waxed and waned; therefore, deflazacort was initiated. Based on follow-up laboratory findings, the IgA level was continuously elevated at 232 mg/dL (53–204 mg/dL). One year later, repeat kidney Doppler ultrasonography showed NCS, with the PVR increasing to 7.16. After deflazacort was ini-

https://doi.org/10.3339/ckd.23.013

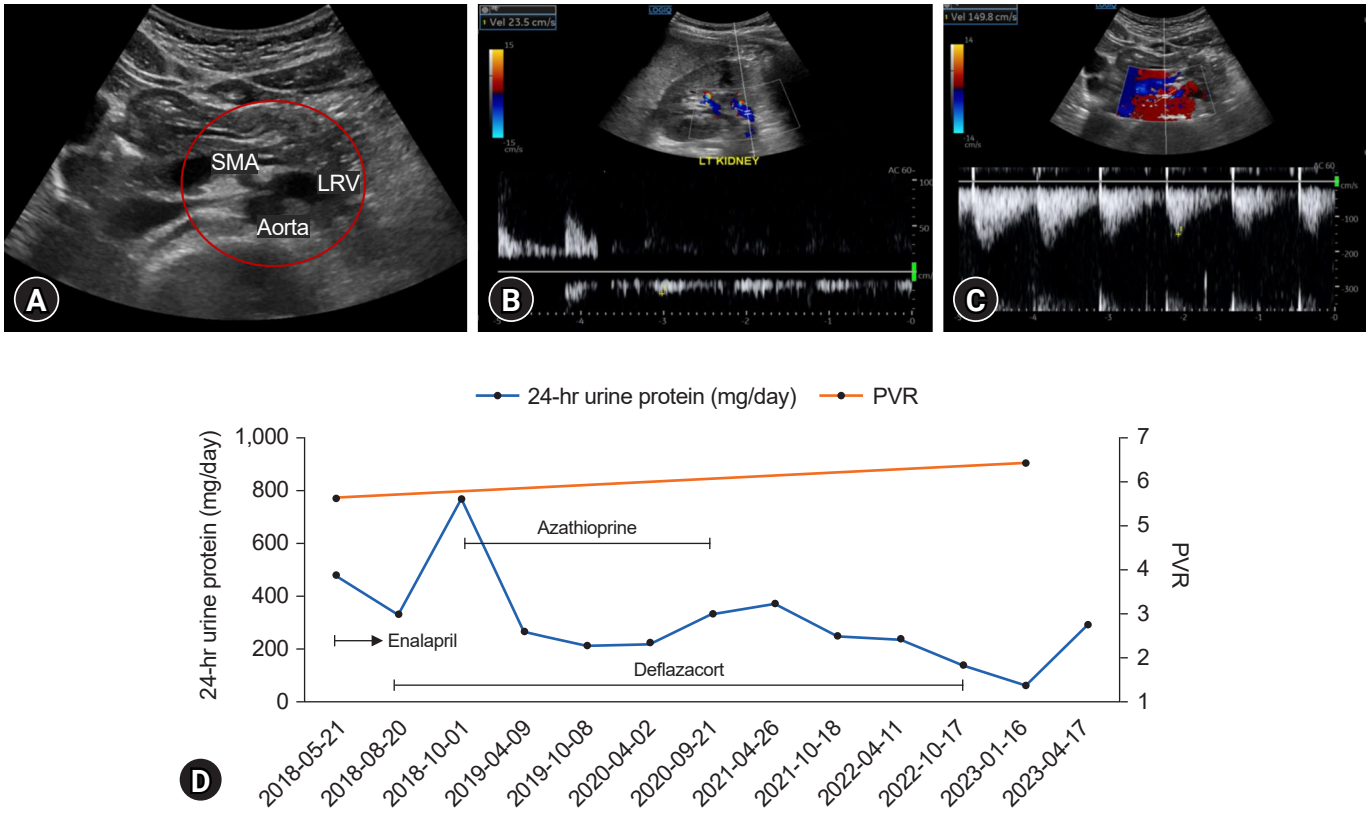

Fig. 1. Renal Doppler ultrasound and clinical course of case 1. (A) Left renal vein (LRV) entrapment between the abdominal aorta and superior mesenteric artery (SMA). (B) Peak velocity at the renal hilum, 23.5 cm/s. (C) Peak velocity at the aortomesenteric portion, 149.8 cm/s. (D) Follow-up 24-hour urine protein and peak velocity ratio (PVR).

tiated, proteinuria with microscopic hematuria improved, but proteinuria worsened after the patient and his parents decided to discontinue the medication (24-hour urine protein, 222–757 mg/day). Cystatin C level increased from 0.93 to 1.07 mg/L (0.53–0.95 mg/L) during the past year. Cystatin C-based estimated glomerular filtration rate was 86 mL/min/1.73 m^2. Finally, his parents agreed for kidney biopsy, 5 years after the onset of the initial manifestations. Light microscopy revealed focal to diffuse mesangial proliferation and mild tubular atrophy. No glomeruli were globally sclerotic (Oxford classification: M1, E0, S0, T0, C0). IgA (3+), C3 (2+), kappa (2+ to 3+), lambda (3+), and fibrinogen (3+) levels in the mesangial regions were determined using immunofluorescence. Electron microscopy revealed an irregular contour and thickness of the GBM (115–308 nm; mean, 197 nm) with multiple mesangial electron-dense deposits. IgAN was confirmed by renal biopsy (Fig. 2A-C). He is currently undergoing outpatient follow-up and maintaining enalapril and deflazacort therapy. The patient's clinical course is shown in Fig. 2D.

Discussion

Herein, we report two cases of NCS combined with biopsy-proven IgAN in pediatric patients. Few studies have described the coexistence of NCS and IgAN with pathological and radiological confirmation, particularly in children. Cases of NCS combined with IgAN can occur and should not be overlooked because of the associated morbidity.

NCS can develop at any age, although mostly in the second and third decades of life [9]. The clinical manifestations of NCS include hematuria, orthostatic proteinuria, left flank pain, and, although rarely, pelvic congestion symptoms [1]. Hematuria and proteinuria are generally considered to be caused by elevated LRV pressure, resulting in the rupture of thin-walled collateral veins into the calyceal fornix [9]. NCS is diagnosed using various tools, such as kidney Doppler ultrasonography, computed tomography, magnetic resonance imaging, and retrograde left renal venography [2]. The first imaging tool for suspected NCS was kidney Doppler ultrasonography, with a sensitivity and

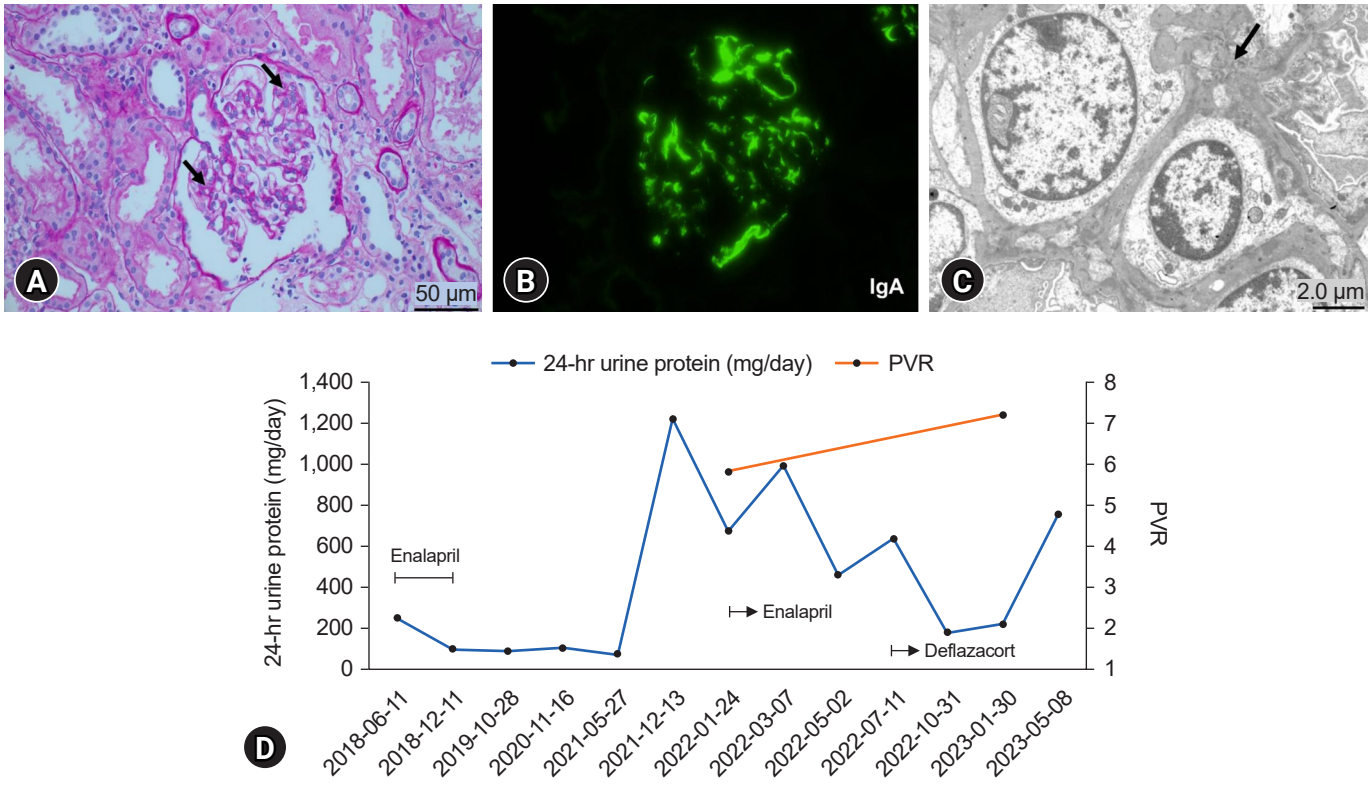

Fig. 2. Renal biopsy findings and clinical course of case 2. (A) A glomerulus with focal to diffuse mesangial proliferation (black arrows) (periodic acid-Schiff stain, ×400). (B) Strong immunoglobulin A (IgA) staining in mesangial regions (×400). (C) Electron-dense deposits in the mesangium (black arrow) (×4,000). (D) Follow-up 24-hour urine protein and peak velocity ratio (PVR).

specificity of 82.3% and 89% to 100%, respectively. However, there are no optimal cutoffs for PVR for diagnosing NCS in children due to the small LRV sampling area and measurement variability according to the patient positioning [10]. Park et al. [11] suggested that a cutoff value greater than 4.0 for the PVR should be used as a sonographic criterion to diagnose NCS in children. In our study, two patients were diagnosed with NCS through Doppler ultrasonography with a cutoff value greater than 4.0 for PVR. Meanwhile IgAN, characterized by predominant IgA deposits in glomerular mesangial areas, is the most common form of GN worldwide. Similar to NCS, the clinical features of IgAN can also present as macroscopic hematuria, asymptomatic microscopic hematuria with or without proteinuria, nephrotic syndrome, and, rarely, acute kidney injury [4]. Although the coexistence of NCS and IgAN is rare, several cases have been reported [3,5-8]; however, a clear correlation is yet to be confirmed. Ozono et al. [5] reported the case of two young adults with NCP complicated by IgAN. Compared to 10 patients showing only NCP, those with NCP and IgAN showed dysmorphic RBCs, suggesting glomerular hematuria, aggravation of hematuria after upper respiratory infections, persistence of proteinuria, urinary granular casts, and elevation of serum IgA levels. Subsequently, Shin et al. [3] reported a case of NCS combined with IgAN in a 9-year-old girl with gross hematuria. In a Japanese study [8], 10 of 146 patients with IgAN showed LRV entrapment, and all patients had dysmorphic urinary RBCs. Recently, a case of coexisting NCP and superior mesenteric artery syndrome in a patient with IgAN was reported [6]. In our study, the two boys were diagnosed with NCS and IgAN. Case 1 had a history of microscopic hematuria 2 years ago, and case 2 had a familial history of thin GBM disease. In case 1, serum IgA levels were elevated in the initial laboratory findings, and urine dysmorphic RBCs were not found. The serum IgA level in case 2 was initially normal but was continuously elevated during the follow-up examination, and dysmorphic RBCs were observed on urinalysis. While case 1 was diagnosed with NCS on initial kidney Doppler ultrasonography, kidney biopsy showed IgAN. In case 2, NCS was confirmed when proteinuria was aggravated 4 years after the initial presentation. The kidney biopsy findings were consistent with IgAN. A causal relationship between NCS

https://doi.org/10.3339/ckd.23.013

and IgAN may exist because of their relatively common combinations.

Several studies have investigated how NCS can induce glomerular changes and are related to IgAN. According to the proposed hypothesis of the IgAN pathogenesis, increased amounts of galactose-deficient IgA1 are recognized as autoantigens by autoantibodies (mostly of the immunoglobulin G subclass) to form pathological immune complexes, some of which are deposited in the glomeruli and induce kidney injury [4]. Various pathological findings of IgAN are present in addition to IgA deposits in the mesangial areas on immunofluorescence. They are classified according to the Oxford classification as mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and cellular crescents [4]. In a study by Ha and Lee [12], kidney biopsy showed moderate mesangial hypercellularity and increased mesangial matrix in a patient diagnosed with NCS. These authors suggested that the mesangial lesions might have been induced by the angiotensin II (Ang II) effect caused by NCS. Keane and Raij [13] also found that the accumulation of phlogogenic macromolecules caused by Ang II in the glomerular mesangium may induce mesangial expansion and eventual glomerulosclerosis. Given that vascular endothelial cells actively participate both in innate and adaptive immune responses [14], LRV entrapment in NCS may cause venous congestion and endothelial activation, contributing to impairment of the immune system. Notably, in a recent large cohort study examining the association between NCP and GN, the prevalence of LRV entrapment was higher in patients with IgAN and IgA vasculitis with nephritis (Henoch-Schönlein purpura nephritis) after adjusting for age, sex, and BMI. Furthermore, glomerular IgA and galactose-deficient IgA1 deposition was more common in patients with lupus nephritis and IgAN-unrelated diseases with LRV entrapment than in those without LRV entrapment [7].

Kidney biopsy can be an important tool for the definite diagnosis of GN. In the present case, kidney biopsies were performed to diagnose possible combined GN. Since it is difficult to diagnose complicated IgAN in patients with NCS based on clinical and laboratory findings, kidney biopsy should be considered when proteinuria or hematuria is aggravated in patients with NCS. Conversely, kidney Doppler sonography can be performed in patients with an unusual clinical course of GN. While proteinuria with hematuria was initially reduced after immunosuppressant administration in case 1, proteinuria has since been waxing and waning and persisted for a long time relative to the kidney biopsy findings. As NCS persists, prolonged proteinuria can be attributed to both IgAN and NCS. In case 2, NCS was diagnosed when proteinuria was aggravated. Since he was not initially evaluated for the presence of NCS, we could not confirm how NCS contributed to the development and progression of IgAN. However, his proteinuria and hematuria were relatively severe in comparison to the kidney biopsy findings and persisted despite taking immunosuppressants. NCS continued on follow-up ultrasonography. Considering the mechanism by which NCS can influence glomerular changes mentioned earlier, NCS may have affected our patients' disease courses. Furthermore, Shimada et al. [15] reported that renal congestion caused tubulointerstitial and glomerular injury in a rat model. In our cases, cystatin C levels were elevated, and considering the renal congestion associated with renal function decline, this observation can be attributed to NCS. Although additional studies are needed, our cases suggest that renal venous congestion due to LRV entrapment could induce proteinuria and hematuria, leading to renal damage.

Conservative care is the first-line treatment of NCS in children. In a systematic review, improvement or complete resolution was observed in nearly 95% of patients treated with a conservative approach over 24 months [10]. Compared with NCS, the clinical course of IgAN is variable, ranging from an asymptomatic non-progressive disease to a highly aggressive disease. Poor prognosis is correlated with proteinuria ≥1 g/day, sustained hypertension, and severe renal involvement. Angiotensin-converting enzyme inhibitors and Ang II receptor blockers can effectively control proteinuria and hypertension. Combined immunosuppressive therapy can be considered in patients with persistent proteinuria or worsened kidney function [4]. Since IgAN is a significant cause of chronic kidney disease, and NCS and IgAN have a different treatment and prognosis, it is important to diagnose these two diseases at an early stage and determine appropriate management to improve clinical prognosis in the future.

In summary, our study's finding of NCS combined with IgAN may be coincidental; however, the relationship between the two disease entities is supported by our patients' clinical courses and previous studies. Future multicenter studies involving large sample sizes are needed to clarify the relationship between NCS and GN, independent to IgAN. Despite NCS diagnosis, considering the presence of combined GN in case of aggravated proteinuria or hematuria is crucial for appropriate management. Furthermore, clinicians must be aware of combined NCS

when the clinical course of GN is uncommon. Likewise, a high suspicion and timely imaging or biopsy are essential for the accurate diagnosis of NCS combined with glomerulopathy.

Ethical statements

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2023AS0135), and informed consent was waived due to the retrospective study design.

Conflicts of interest

Eujin Park and Hyung Eun Yim are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization: HEY
Data curation: SHK, MHS, EP, HEY
Investigation: SHK
Methodology: SHK, MHS, EP, HEY
Project administration: HEY
Visualization: SHK
Writing-original draft: SHK
Writing-review & editing: SHK, MHS, EP, HEY
All authors have read and approved the final manuscript.

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https://doi.org/10.3339/ckd.23.013

ChiKD CHILDHOOD KIDNEY DISEASES

Instructions For Authors

Revised 2023. 02. 20

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A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. ChiKD allows authors to submit preprints to the journal. It is not treated as duplicate submission or duplicate publication. ChiKD recommends that authors disclose the existence of a preprint with its DOI in the letter to the Editor during the submission process. Otherwise, a plagiarism check program—Similarity Check (Crosscheck) or Copy Killer—may flag the results as containing excessive duplication. A preprint submission will be processed through the same peer-review process as a usual submission. If a preprint is accepted for publication, the authors are recommended to update the information on the preprint site with a link to the published article in ChiKD, including the DOI at ChiKD. It is strongly recommended that authors cite the article in ChiKD instead of the preprint in their next submission to journals.

7. Peer review policy

All papers, including those invited by the editor, are subject to peer review. ChiKD has adopted a double-blind peer review policy, where the author identities remain anonymous to the reviewers, and vice versa, and the identities of the reviewers and authors are visible to (decision-making) the editor throughout the peer review process. The Editorial Board selects reviewers based on expertise, publication history, and past reviews. During the peer review process, reviewers can interact directly or exchange information (e.g., via submission systems or email) with only an editor, which is known as "independent review." An initial decision will normally be made within 2 weeks after the reviewers agree to review a manuscript. No information about the review process or editorial decision process is published on the article page.

All manuscripts from editors, employees, or members of the editorial board are processed in the same way as other unsolicited manuscripts. During the review process, submitters will not engage in the selection of reviewers or the decision process. Editors will not handle their own manuscripts even if the manuscripts are commissioned. The conflict of interest declaration should be added as follows.

Conflicts of interest: Eujin Park has been an editorial board member of Childhood Kidney Diseases since 2021 but has no role in the decision to publish this article. No other potential conflicts of interest relevant to this article were reported.

MANUSCRIPT SUBMISSION AND PEER REVIEW PROCESS

1. Online submission

All manuscripts should be submitted via the e-submission system available at http://submit.chikd.org/. Manuscripts should be submitted by the corresponding author, who should indicate the address, phone number, and e-mail address for correspondence on the title page of the manuscript. The revised manuscript is to be submitted through the same web system under the same identification numbers. Once an author has registered and logged into your account, the online system will lead the user through the steps of the submission process in order. All articles submitted to the journal must comply with these instructions. Failure to do so will result in the return of the manuscript and possible delay in publication. For assistance, please contact us via e-mail (chikd@chikd.org) or telephone (+82-10-4391-0788).

2. Peer review process

ChiKD reviews all received materials. All papers are evaluated by a double-blind, peer-review process. Manuscripts are sent

to the two (or more) most relevant investigators, who review the content. The acceptance criteria for all papers are based on the quality and originality of the research and its clinical and scientific significance. An initial decision will normally be made within 2 weeks after the reviewers agree to review a manuscript, and the reviewers' comments will then be sent to the corresponding authors. Revised manuscripts must be submitted online by the corresponding author. Failure to resubmit the revised manuscript within 4 weeks of the editorial decision is regarded as a withdrawal. The editorial office should be notified if additional time is needed or if an author chooses not to submit a revision. The editorial committee makes decisions concerning editing, revision, and acceptance or rejection, and editing may include shortening an article, reducing the number of illustrations or tables, or changing the paper's format or the order of the manuscript. The editor selects referees, and the results of reviews will be classified as follows:

- Accepted: The manuscript will be forwarded to the publisher without further corrections.
- 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.
- Rejection: When one out of the two (or more) reviewers rejects the manuscript, the final decision is made by the editorial committee.

3. Peer review process for handling submissions from editors, employees, or members of the editorial board

All manuscripts from editors, employees, or members of the editorial board are processed in the same way as other unsolicited manuscripts. During the review process, submitters will not engage in the selection of reviewers or the decision process. Editors will not handle their own manuscripts even if the manuscripts are commissioned.

4. Conditions of publication

All authors are required to affirm the following statements prior to their manuscript being considered:

(1) If the manuscript does not have a new result or conclusion, then it should not have the same title as a previously published article.
(2) Once a case has been published in an original paper, it may not be reproduced as a case report. However, the Editorial Board may consider making an exception and accepting a report in circumstances in which a novel diagnostic method, a novel therapeutic trial, or a previously unknown accompanying condition is found.
(3) Clinical trials on drugs with commercial implications will be evaluated by the proper subcommittee before being reviewed for publication.
(4) Case reports of previously published cases will not be accepted. The editorial board will make an exception only if the case is very rare. The index of ChiKD should be reviewed before submitting a case report.
(5) Rejected manuscripts may not be resubmitted.
(6) If the author does not address the comments made by the reviewer or if the manuscript does not follow the guidelines provided, it will be rejected.

MANUSCRIPT PREPARATION

The details of manuscript preparation differ according to the publication type, including reviews, original articles, case reports, editorials, and correspondence. Other types can be discussed with the Editorial Board.

1. Publication type

ChiKD publishes special articles, reviews, mini-reviews, original articles, case reports, editorial, and correspondence.

1) **Special articles:** Special articles provide the scientific insight for any important topic in medicine, research, ethics, or healthcare. They may also address guidelines and consensus statements, recommendations or statements from task forces. Original articles, reviews, and mini-reviews are possible formats for special articles, but the details of manuscript format can be flexible depending on the contents. Most special articles are invited by the editors; however, unsolicited submissions may also be considered for publication.
2) **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.

3) **Mini-reviews:** Mini-reviews provide a concise review or critical summary for a specific topic related to pediatric nephrology. Most mini-review articles are invited by the editors; however, unsolicited submissions may also be considered for publication. Mini-review articles are accepted after peer review. They should have the following format: 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 3,000 words. A maximum of 2 tables or 2 figures is allowed. The number of references is limited to 50.
4) **Original articles:** These are papers containing the results of clinical or laboratory investigations, which are sufficiently well documented to be acceptable to critical readers. The original articles should be organized in the following order: title page, structured abstract of no more than 250 words and keywords, main text (introduction, methods, results, discussion), references, tables, figures, and figure legends. Maximum length: 4,000 words of text (not including the abstract, tables, figures, and references). A maximum of 6 tables or 6 figures is allowed. The number of references should not exceed 40.
5) **Case reports:** Case reports should be organized in the following order: title page, unstructured abstract of no more than 200 words) and keywords, main text (introduction, case report, discussion), references, tables, figures, and figure legends. The length of the text, excluding references, tables, and figures, should not exceed 2,500 words. A maximum total of 6 tables and figures may be included. The number of references is limited to 15.
6) **Editorials:** Editorials should be commentaries on articles published recently in the journal. Editorial topics could include active areas of research, fresh insights, and debates. The order of the submitted manuscript should include a title page, discussion, conflict of interest, acknowledgments (if applicable) and references. The text should be limited to 1,500 words and 10 references. A maximum total of 2 tables and figures may be included.
7) **Correspondence:** Correspondence (letters to the editor) may be in response to a published article, or a short, free-standing piece expressing an opinion. A brief case report can be published as a letter to the editor. Correspondence should be no longer than 1,000 words of text and 10 references. Letters can be edited by the Editorial Board. Responses by the author of the subject paper may be provided in the same issue or next issue of the journal. Replies by authors should not exceed 500 words of text and 5 references. A maximum total of 2 tables and figures may be included.

Table 1 shows the recommended maximums of manuscripts according to publication type.

Table 1. Recommended maximums for articles submitted to ChiKD

Type of article	Abstract (words)	Text (words)	References	Tables & figures
Review	200	5,000	100	No limits
Mini-review	200	3,000	50	2 Tables, 2 figures
Original article	250	4,000	40	6 Tables, 6 figures
Case report	200	2,500	15	Total 6
Editorial	No	1,500	10	Total 2
Correspondence	No	1,000	10	Total 2
In reply	-	500	5	Total 2

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. For an extensive revised paper, reviewer or editor can request an English editing certificate again. The editors reserve the right to return a manuscript to the author if the quality of English is poor.
- The manuscript must be submitted in MS Word format (doc or docx).
- The text of the manuscript, including tables and their footnotes and figure legends, 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 for percentage (%) and degree (°).
- 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 sex 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 nonrandomized 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

We recommend using the template provided at http://www.chikd.org/authors/authors.php to format the manuscript.

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 institutional affiliation(s) of the author(s); (4) the running title, of 10 words or less; (5) the e-mail address, telephone number of the corresponding author; and (6) notes. If several authors and institutions are listed, it should be made clear with which department and institution each author is affiliated. For a multicenter study, each individual's affiliation should be indicated using a superscript Arabic number 1,2,3.... The corresponding author or first author should be clearly designated. In a separate paragraph, an address for correspondence including the name of the corresponding author address (institutional affiliation, city, zip code, and country), and e-mail address should be given. The running title should not be a declarative or interrogative sentence. Notes (disclaimers) include ethics approval and consent to participate, conflict of interest, funding, authors' contributions, additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

2. Abstract and keywords

1) **Abstract:** Original articles provide a structured abstract of less than 250 words, which should be divided into the following sections:

- **Purpose:** A single sentence describing why the study was done and the type of study carried out. Clinical studies should include the setting (e.g., practice or hospital).
- **Methods:** The total number of species of animals or subjects, with (where relevant) the method of selection. For in vitro studies, specify the cell and tissue used, the assays or assessments carried out, and the statistical tests applied.
- **Results:** The main results obtained, providing means (±SD or SE) or medians (with ranges) and significance levels, where necessary. Clinical data should include any withdrawals.
- **Conclusions:** Implications based on the methods and results presented.

Abbreviations, if needed, should be kept to an absolute minimum, and given with proper identifications.

2) **Keywords:** Authors should provide, and identify as such, up to 5 keywords or short phrases that will assist indexers in cross-indexing the article and can be published with the abstract. Use terms from the Medical Subject Headings (MeSH) list of Index Medicus; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used. Keywords should be listed in alphabetical order and the first letter of a keyword should be capitalized (e.g., Hematuria; Nephrotic syndrome).

3. Main text

1) **Introduction:** The introduction should contain enough references to the most pertinent papers to inform readers and describe others' relevant findings. It also includes the specific question driving the authors' particular investigation.
2) **Methods:** We endorse the principles articulated in the Declaration of Helsinki and expect that all investigations involving human materials have been performed in accordance with these principles. Animal experiments must be reviewed and approved by an appropriate committee (Institutional Animal Care and Use Committee) for the care and use of animals. Studies involving pathogens requiring a high degree of biosafety should pass the review of a relevant Institutional Biosafety Committee. The approval of the experimental protocol should be described in the Methods section. An explanation of the experimental methods should be concise and sufficient for repetition by other qualified investigators. Procedures that have been published previously should not be described in detail; however, new or significant modifications of previously published procedures need full descriptions. The sources of special chemicals or preparations should be given (i.e., name of company). The methods of statistical analyses and the criteria used to determine statistical significance (i.e., the significance level) should be described. Case reports, case histories, or case descriptions do not contain separate Methods or Results sections.
3) **Results:** This part should be presented logically using text, tables, and illustrations. Excessive textual repetition of table or figure content should be avoided.
4) **Discussion:** The data should be interpreted concisely without repeating materials already presented in the Results section. Speculation is permitted, but it must be supported by the authors' presented data and be well-founded.

4. References

In the text, references should be cited with Arabic numerals in brackets, numbered in the order cited. In the references section, the references should be numbered and listed in order of appearance in the text. Authors are responsible for the accuracy and completeness of their references and correct text citations.

- List all authors up to six in number. If there are more than six authors, list the first six and add "et al." to the last author's name.
- Papers in press may be listed among the references with the journal name and tentative year of publication.
- Unpublished data or personal communications can be listed only with the author's written permission.
- Other types of references not described below should follow the Recommendations of ICMJE (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Journal article:

1. Jung J, Lee JH, Kim KS, Song SH, Moon DH, Yoon HM, et al. Management strategies for congenital isolated hydronephrosis and the natural course of the disease. Child Kidney Dis 2022;26:1-10.
2. Aier A, Pais P, Raman V. Psychosocial aspects of children with chronic kidney disease and their families. Clin Exp Pediatr 2021 Nov 10 [Epub]. https://doi.org/10.3345/cep.2021.01004

Book or book chapter:

3. Volpe JJ. Neurology of the newborn. 5th ed. Saunders/Elsevier; 2008.
4. Hong CE. Textbook of pediatrics. 9th ed. Korea Textbook Publishing Co.; 2008.
5. Pan ES, Cole FS, Weinttrub PS. Viral infections of the fetus and newborn. In: Taeusch HW, Ballard RA, Gleason CA, editors. Avery's diseases of the newborn. 8th ed. Elsevier Saunders; 2005. p. 495–529.

Website

6. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals [Internet]. International Committee of Medical Journal Editors; 2021 [cited 2022 Jan 10]. Available from: http://www.icmje.org/recommendations/

5. Table(s)

Tables should be typed double-spaced on separate pages within the manuscript, and they should be titled and numbered in Arabic numerals in the order of their first citation in the text. Each column should be given a short heading. Only the first letter of the first word in each row and column should be capital letters. If numerical measurements are given, the unit of measurement should be included in each heading. The sta-

tistical significance of observed differences in the data should be indicated by the appropriate statistical analysis. All abbreviations should be defined in footnotes. For special remarks, superscripts a), b), c)... should be used. No more than 6 tables are needed. Tables should follow the references on separate pages.

6. Figure(s)

The author is responsible for submitting prints that are of sufficient quality to permit accurate reproduction, and for approving the final color galley proof. ChiKD assumes no responsibility for the quality of the photography as it appears in the journal. Symbols, arrows, or letters used in photographs should contrast with the background. A legend for each light microscopic photograph should include the name of the stain and magnification (i.e., H&E, ×400); electron microscopic photography should have an internal scale marker. All kinds of figures may be reduced, enlarged, or trimmed for publication by the editor. No more than 6 figures are needed. All legends for figures should be double-spaced. Figure legends should follow tables on separate pages. Do not use a separate sheet for each legend. Figure legends should describe briefly the data shown and explain any abbreviations or reference points in the photograph. The figures should be numbered in the form Fig. 1, Fig. 2, and Fig. 3. Related figures should be combined into one figure, with each subfigure denoted by the letters, A, B, C, and so on, following the Arabic number of the main figure (i.e., Fig. 1A; Fig. 1B, C; Fig. 1A–C). Figures should be submitted in the TIFF or EPS file formats. If the only possible file format is JPEG, it must be in the highest quality with minimum compression. It is recommended to size original figure widths to 4 inches wide. The minimum requirements for digital resolution are:

- 900 DPI/PPI for black and white images, such as line drawings or graphs.
- 300 DPI/PPI for picture-only photographs.
- 600 DPI/PPI for photographs containing pictures and line elements, i.e., text labels, thin lines, arrows.

MANUSCRIPT PROCESSING AFTER ACCEPTANCE

1. Final version

After a paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. TIFF and PDF formats are preferred for the submission of digital files of photographic images. Files containing figures must be named according to the figure number (ex: Fig. 1. tiff). Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, they should be renumbered to reflect such changes so that all tables, references, and figures are cited in numeric order.

2. Manuscript corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 working days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

3. Galley proof

After corrections have been made, an accepted manuscript will be sent to the publisher for printing. The proof may be revised more than once by the corresponding author, if needed. The author should double-check for corrections in the content, title, affiliation, capitalization, locations of figures, and references. Corresponding authors are responsible for further corrections made after printing.

4. Confirmation of acceptance

Once the manuscript is at the publisher, confirmation of acceptance by ChiKD will be issued. Upon registering for the board exams, a receipt of confirmation can be ordered for an accepted manuscript.

5. Post-publication discussions

Post-publication discussions can be held through letters to the editor. If any readers have concerns about any articles published, they can submit a letter to the editor related to the arti-

cles. If any errors or mistakes are found in an article, they can be corrected through an erratum, corrigendum, or retraction.

CONTACT INFORMATION

Questions regarding manuscript submission may be sent to:

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Checklist

- ☐ A covering letter stating the material has not been published previously, and will not be submitted for publication elsewhere, and stating conflicts of interest of all listed authors, if any.
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- ☐ The ORCID iDs of all authors should be provided.
- ☐ The manuscript must be written in MS Word (docx).
- ☐ Double-spaced typing with 12-point font.
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- ☐ Title page with the article title, authors' full name(s) and affiliation(s), corresponding author's e-mail, running title (less than 10 words), and notes, if any.
- ☐ Abstract up to 250 words for an original articles and up to 200 words for reviews and case reports. Up to 5 keywords as in MeSH.
- ☐ All table and figure numbers are found in the text.
- ☐ References are listed in a proper format. All references listed in the references section are cited in the text and vice versa.
- ☐ The number of references is limited to 100 (for reviews), 40 (for original articles), 15 (for case reports), or 10 (for editorials and letter to the editor).
- ☐ A maximum number of figures or tables is inserted.
- ☐ Figures as separate files, in TIFF, EPS, PSD, JPEG, or PPT format.
- ☐ Included a title for each table and figure (a brief phrase no longer than 10 to 15 words) and explanatory legend as needed.

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