Current Treatment Options in Pediatrics (2023) 9:338–355
DOI 10.1007/s40746-023-00284-z

Pediatric Nephrology (BP Dixon and E Nehus, Section Editors)

Kidney Manifestations of Rheumatological Diseases in Children

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Published online: 16 November 2023

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Keywords Glomerulonephritis · Vasculitis · Systemic lupus erythematosus · Rheumatology · Paediatrics

Opinion statement

Paediatric rheumatological diseases are a group of multi-systemic inflammatory diseases affecting children and young people. The kidneys constitute a target organ during the acute presentation and life course of several multi-systemic inflammatory conditions including childhood systemic lupus erythematosus (cSLE), IgA vasculitis and ANCA-associated vasculitis. Unlike adults with rheumatic diseases, who may have prior concomitant kidney disease, children are more likely to have an acute, potentially reversible inflammatory process that typically requires prompt immunosuppressive treatment. Despite broad-spectrum immunosuppression, kidney outcomes remain suboptimal, with children progressing to irreversible chronic kidney disease and ultimately kidney failure, requiring

kidney replacement therapy or transplantation. In cSLE, for example, the kidney failure rate is 1–14% depending on the length of follow-up, with the average age of requiring a kidney transplant reported to be 24 years, thus illustrating the importance of follow-up into adulthood. Advances in improving the outcomes for these patients remain slow, and the recruitment of children to drug trials can be challenging. The aim of this review article is to summarise the key paediatric rheumatic diseases that commonly involve the kidney to highlight the epidemiology and current kidney outcomes. Useful information is also provided on suggested screening to detect the presence of active kidney inflammation and improvements in this field for the future.

Introduction

Paediatric rheumatological diseases are a group of multi-systemic inflammatory diseases affecting children and young people. The most common childhood rheumatic condition is juvenile onset arthritis (JIA) that has an incidence of up to 20 per 100,000 child population, in contrast to childhood systemic lupus erythematosus (cSLE) that has an incidence of about 0.2 per 100,000 child population [1, 2]. Primary vasculitis, whilst rarer, has been found to account for approximately 2–10% of paediatric rheumatology workload captured from registry data in North America [3]. The kidneys constitute a target organ during the acute presentation and the disease course of multi-systemic inflammatory conditions such as primary vasculitis and cSLE, and unlike adults, where there may be pre-existing concomitant kidney disease, children are more likely to have an acute, potentially reversible inflammatory process that requires prompt intervention [4]. There remains much unknown about the pathophysiology of these conditions, and due to the rarity of these diseases in children, recruitment to drug trials can be challenging, resulting in the use of data extrapolated from adult studies and slow improvements in clinically meaningful outcomes for children. In general, children with inflammatory diseases are at a greater risk of accelerated cardiovascular consequences, and this risk rises with the presence of persisting proteinuria and/or low glomerular filtration rate (GFR) [5]. There is therefore a lot to be gained by focusing on improving kidney outcomes in childhood-onset rheumatic diseases. The aim of this review article is to summarise the epidemiology and kidney outcomes of paediatric rheumatic diseases that commonly involve the kidney, including cSLE, IgA vasculitis, ANCA-associated vasculitis (AAV) and those where kidney involvement is less commonly involved such as polyarteritis nodosa (PAN). The article also provides additional information on screening to detect the presence of active kidney inflammation to guide clinicians.

Childhood-onset systemic lupus erythematosus (cSLE)

cSLE is a chronic, lifelong autoimmune multi-systemic disorder that has an onset in childhood in about a fifth of all diagnosed patients [6]. Common clinical features of cSLE include joint pain, malaise, fatigue, fever, weight loss and the characteristic 'butterfly' malar rash [7]. The median age at presentation is 12–13 years in childhood-onset disease. Although rare, cSLE has an incidence of around 0.2–3 cases per 100,000 childhood population and the prevalence is reported to be 2–34 per 100,000; however, these figures vary across the world and according to ethnicity, with cSLE being more prevalent

in Asian, Afro/Caribbean and Hispanic individuals [2]. In children, the gender difference is less striking than in adult-onset SLE (aSLE), where around 90% of patients are female; in cSLE, the male to female ratio is around 1:5, with a drift in post-pubertal teenagers towards a gender distribution more similar to adults [2]. Three different classification criteria have been developed and validated in adult-onset disease but need further evaluation in cSLE [8–10]. The SLICC criteria importantly allow the classification of patients who have histological evidence of lupus nephritis (LN) plus positive antibodies even in the absence of other clinical features. Whilst not fully understood, it is believed that a combination of genetic predisposition, immune dysregulation and environmental and hormonal factors contribute to the production of self-antibodies against the nuclear components of cells that drive the early pathophysiology of this disease. Childhood SLE is associated with a more aggressive clinical course than aSLE, greater severity of complications and higher morbidity and mortality [2, 11].

Frequency and diagnosis of kidney involvement

Kidney manifestations, termed lupus nephritis (LN), range from the presence of microscopic urine abnormalities to acute kidney failure [12]. LN is more commonly seen in cSLE than in aSLE, with reported rates of 50–82% in children and 20–40% in adults [13–15], with the highest incidence being reported in children of non-Caucasian ethnicity [16]. KDIGO alongside European guidelines advise that urinalysis (dipstick and sediment), proteinuria estimation, blood tests (serum creatinine, albumin and eGFR) and serology (anti-dsDNA and complement specifically) be performed to screen for kidney involvement at presentation and subsequent clinical reviews. Proteinuria severity can fluctuate, even in cases of severe active nephritis, and may appear relatively minor at times. Hence, repeated investigations over time are important in guiding clinical management decisions [17, 18]. A kidney biopsy should be considered in cases with reproducible proteinuria of > 0.5 g/24 h (equivalent to a urine protein to creatinine ratio > 50 mg/mmol) and/or impaired estimated glomerular filtration rate (eGFR) [19, 20]. The biopsy threshold for proteinuria is somewhat lower than for other causes of glomerulonephritis due to the likelihood of detecting LN at these levels. LN is diagnosed histologically according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system (Table 1) [21]. The histological class of LN has been shown to correlate with disease severity, long-term kidney outcome and morbidity [22] and is used to guide treatment [18].

Management and kidney outcome

The treatment target for LN should be the achievement of complete remission [18]. If a complete response is achieved, patients are far less likely to have subsequent flares. Figure 1 outlines the typical treatments used

Table 1. International society of nephrology/renal pathology society 2003 classification of lupus nephritis (LN) [21]

Class	Name		Light microscopy	Immunofluorescence
I	Minimal mesangial LN		Normal	Mesangial immune deposits
II	Mesangial proliferative LN		Mesangial hypercellularity or mesangial matrix expansion	Mesangial immune deposits
III	x	A Active lesions	Segmental or global glomerulonephritis (<50% of glomeruli)	Diffuse subendothelial immune deposits
		A/C Active and chronic lesions		
		C Chronic lesions		
IV	Diffuse LN	A Active lesions	Segmental or global glomerulonephritis LN (>50% glomeruli)	Diffuse subendothelial immune deposits
		A/C Active and chronic lesions		
		C Chronic lesions		
V	Membranous LN			Global or segmental subepithelial immune deposits
VI	Advanced sclerosing LN		LN (>90% globally sclerosed glomeruli without residual activity)	

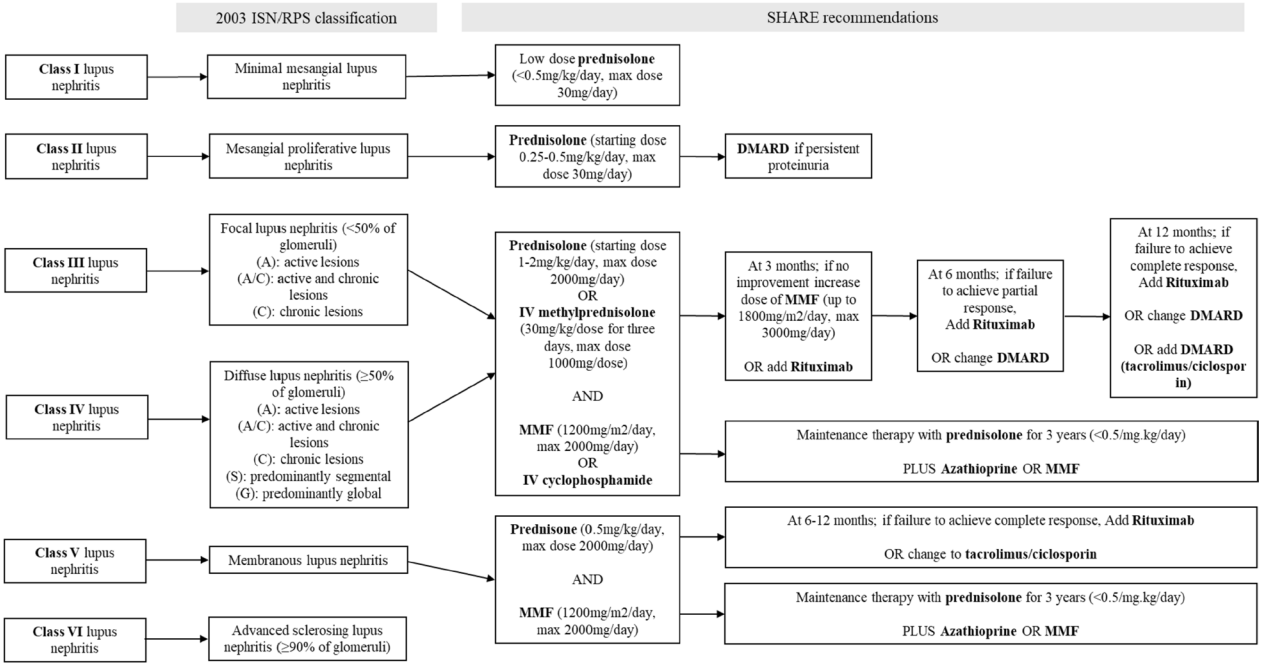

Fig. 1 Overview of 2003 ISN/RPS classification criteria for lupus nephritis and SHARE recommendations for management [18, 21].

according to the histological class of LN derived from European agreed guidelines [18]. Supportive treatments such as proteinuria management using angiotensin-converting enzyme (ACE) inhibitors, antihypertensive treatments, the use of hydroxychloroquine and minimising thrombotic risk are also important. In children with LN, 40–60% will achieve complete remission. Data on progression to chronic kidney disease (CKD) in children is limited, with a reported rate of 3.8% in 6.6 years of follow-up, with most cases being CKD stage 2 [23]. The risk of kidney failure is 1–14% depending on follow-up, and the median age for requiring a kidney transplant is 24 years. With regards to outcomes, a Chinese cohort study involving 92 children with SLE reported a mortality rate in childhood-onset LN of 2.1/1000 patient-years, with kidney failure and CKD occurring in 3% and 5% of patients respectively [24]. A large multicentre cohort study demonstrated increased renal morbidity in children and a clinically significant twofold greater mortality in cSLE patients when compared to aSLE, although it did not reach statistical significance (19.4% vs. 10.4%, $p = 0.337$) [25]. Predictors of poorer kidney outcomes in LN include increased serum creatinine concentrations, baseline proteinuria and histological features of activity and chronicity. The outcome data for LN demonstrates the importance of the need for a very long-term follow-up of patients with cSLE, even after they transition into adult care.

IgA vasculitis (Henoch-Schönlein purpura)

Immunoglobulin A vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is a leukocytoclastic small-vessel vasculitis, and it is by far the most common vasculitis in children with an incidence of 3 to 27 cases per 100,000 children [26]. The peak age of incidence in children is between 4 and 7 years old [26]. The pathogenesis of IgA vasculitis is incompletely understood, but it is thought to be associated with the production of galactose-deficient IgA1 from the mucosa of the oral cavity and/or gastrointestinal (GI) tract. IgAV presents as a purpuric, symmetrical, non-blanching rash on the lower limbs, and it is associated with any combination of the following triad: joint involvement (arthralgia/arthritis), GI involvement and kidney involvement (nephritis) [27]. It is generally accepted that the 2008 EULAR/PRINTO/PRES criteria should be used to classify IgAV because it has been validated specifically in children, with a sensitivity of 100% and a specificity of 87% (Table 2) [28].

Frequency and diagnosis of kidney involvement

IgAV nephritis (IgAVN) is the main cause of morbidity in patients with IgAV [29], and it can affect 40–50% of children [27, 30]. It can present with a spectrum of manifestations ranging from microscopic haematuria with or without proteinuria that typically self-resolves over subsequent weeks to an acute nephrotic or nephritic syndrome which is more severe and less common [31]. Due to the risk of nephritis, all patients with IgAV should be routinely monitored for at least 6 months using urinalysis testing as a minimum (for

Table 2. EULAR/PRINTO/PRES criteria for IgAV and classification definition. Patients must have purpura/petechiae and of the following: abdominal pain, histopathology, arthritis or arthralgia and kidney involvement [28]

Criterion	Glossary
Purpura (mandatory criterion)	Purpura or petechiae with lower limb predominance
AND either of the following	
(1) Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding
(2) Histopathology	Typically leukocytoclastic vasculitis with a predominant IgA deposit or proliferative glomerulonephritis with a predominant IgA deposit
(3) Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion
	Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion
(4) Kidney involvement	Proteinuria > 0.3 g/24 h or > 30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample
	Haematuria or red blood cell casts: > 5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥ 2 + on dipstick

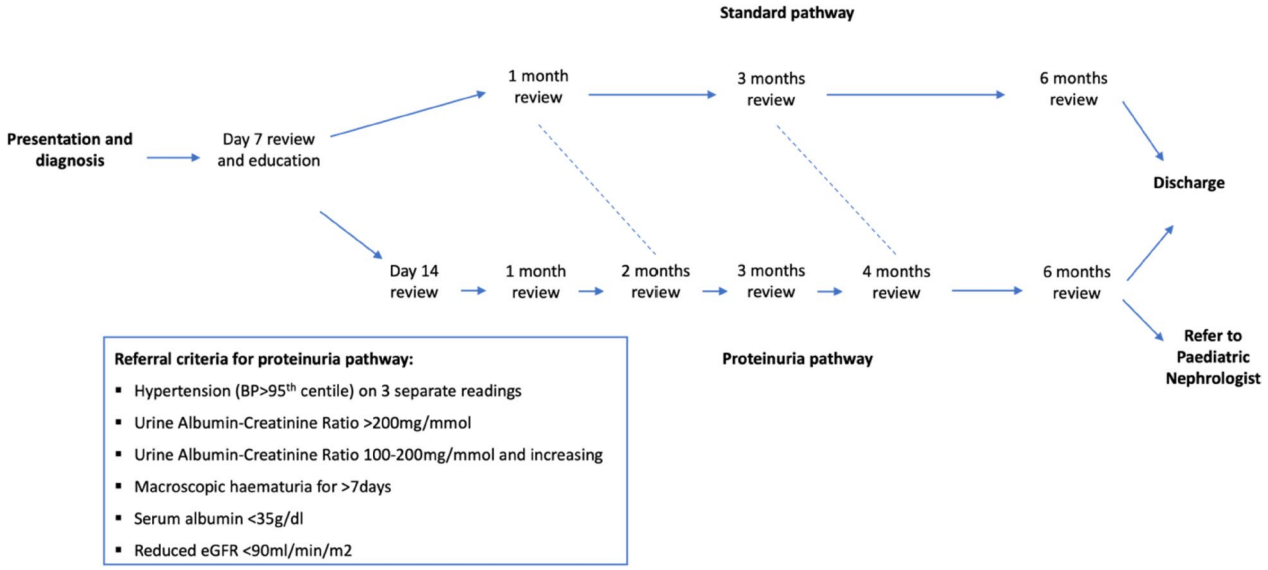

Fig. 2 Proposed follow-up pathway for children with IgA vasculitis, adapted from Watson et al. [33].

Table 3. Suggested definitions of the severity of kidney involvement IgAV nephritis, adapted from Ozen and colleagues [31]

Severity of IgAV nephritis	Definition
Mild	Normal GFR[a] and mild[b] or moderate[c] proteinuria
Moderate	<50% crescents on kidney biopsy and impaired GFR[d] or severe persistent proteinuria[e]
Severe	>50% crescents on kidney biopsy and impaired GFR[c] or severe persistent proteinuria[e]

GFR, glomerular filtration rate; *UP:UC*, urine protein to urine creatinine ratio; *UA:UC*, urine albumin to urine creatinine

[a]Normal GFR: > 80 ml/min/1.73 m^2

[b]Proteinuria: UP:UC ratio < 100 mg/mmol (in an early morning urine sample)

[c]Moderate proteinuria: UP:UC ratio 100–250 mg/mmol (in an early morning urine sample)

[d]Impaired GFR: < 80 ml/min/1.73 m^2

[e]Severe persistent proteinuria: UP:UC ratio > 250 mg/mmol for 4 weeks, UP:UC ratio > 100 mg/mmol for 3 months, and UP:UC ratio > 50 mg/mmol for 6 months

example, weekly for the first 4–6 weeks and then monthly) alongside BP measurements at diagnosis and if investigations reveal evidence of nephritis [31, 32]. The key goal is early detection of kidney involvement, and published examples of monitoring templates exist within the literature, as reproduced in Fig. 2 [33]. The severity of kidney involvement was classified by the SHARE initiative based on urinary findings and/or renal histology (Table 3) [31]. In children with suspected evolving IgAVN, usually detected due to rising

proteinuria, a kidney biopsy is indicated to confirm the diagnosis and classify the extent of inflammation to guide treatment choices. Indications for consideration of a kidney biopsy include persisting proteinuria with a urine protein to creatinine ratio > 250 mg/mmol (approx. equivalent to 2.5 g/day) for 4 weeks, acute kidney injury and nephrotic or nephritic syndrome [31]. The proteinuria threshold for when to biopsy remains higher in this condition compared to other forms of glomerulonephritis due to the high rates of spontaneous remission. Histological features include immunofluorescence demonstrating predominant IgA1 deposits in the mesangium region often alongside glomerular deposits of C3. Histological classification is based on the International Study of Kidney Disease in Children (ISKDC) (Table 4), with potential benefit from additional activity and chronicity descriptors [34].

Management and kidney outcome

Management recommendations for IgAVN are determined by the histological features and clinical disease severity in terms of proteinuria and kidney function. First-line treatment for histological class III or above with persisting clinical features is usually oral corticosteroids together with a disease-modifying antirheumatic drug (DMARD) as a steroid-sparing agent [31]. Patients with persistent proteinuria (> 3 months) should be treated with an ACE inhibitor or angiotensin receptor blocker [31]. For children with IgAV, the use of prophylactic corticosteroid treatment during the initial presentation to prevent the onset of nephritis is not indicated, as several randomised controlled studies have shown no significant benefit [17, 35]. Most children with IgAVN will make a complete recovery without any treatment; therefore, the risk of long-term kidney failure in all children presenting with IgAV is relatively low (1–7%), even in those with minor isolated urine abnormalities [29, 31, 36]. However, this risk significantly increases by 12 times in children who present with nephrotic and/or nephritic syndrome (up to 19.5% would develop permanent kidney impairment) [31, 36]. In children who had a kidney biopsy for IgAVN, about 66% will have a normal outcome, and a third will develop long-term proteinuria with progression to eventual CKD over

Table 4. The grading system of the International Study of Kidney Disease in Children (ISKDC) classification for pathological scoring of IgAVN in children [34]

ISKDC grade	Features
Grade I	Minimal changes, normal light microscopy
Grade II	Mesangial proliferation
Grade III	Crescents < 50% of the glomeruli. A, Focal; B, diffuse
Grade IV	Crescents 50–75% of the glomeruli. A, Focal; B, diffuse
Grade V	Crescents > 75% of the glomeruli
Grade VI	Membranoproliferative glomerulonephritis

20 years [27]. Histological factors that are associated with progression to kidney failure include tubular atrophy, interstitial fibrosis, glomerular sclerosis and crescents, especially in patients presenting with mixed nephrotic and nephritic syndrome [34, 37].

ANCA-associated vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAVs) is an umbrella term for a group of rare multi-systemic small and medium-vessel vasculitides including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [38]. These diseases are associated with a fulminant presentation in children, often with multiple organ involvement and subsequently recurrent disease relapses. AAVs are extremely rare in childhood, with an estimated incidence of 0.45 cases/million children/year (GPA and MPA) according to a French nationwide study [39]. However, a Canadian study reported a much higher incidence of GPA of 6.39 cases/million children/year, suggesting that there may be geographical variation or inaccuracies in the epidemiological data due to the low number of cases [40]. The precise incidence of MPA and EGPA in childhood remains unknown. There are no validated diagnostic criteria for GPA, MPA or EGPA in children. For GPA, the EULAR/PRINTO/PRes-endorsed 2008 classification criteria should be used in the paediatric population [41]. MPA and EGPA are defined in the Chapel Hill (2012) nomenclature and can be used in children for research purposes but are not validated clinically [41, 42].

Frequency and diagnosis of kidney involvement

In children with AAVs, kidney manifestations are very common and heavily contribute to morbidity and mortality. GPA is commonly associated with high levels of anti-PR3 antibodies depicted by cytoplasmic staining of neutrophils (cANCA), whereas MPA and EGPA are more frequently associated with anti-MPO antibodies that cause perinuclear staining of neutrophils (pANCA) [41]. Kidney involvement is most common in children with MPA (75–90% at presentation) and follows a more aggressive clinical course than either GPA or EGPA [43]. Kidney involvement in GPA is seen in around 75% of patients at presentation, and half of these patients will present with reduced kidney function (eGFR < 60 ml/min/m^2). In children with AAV, nephritis will present with clinical features such as haematuria and proteinuria, hypertension and oedema [43]. Initial kidney screening should include renal function tests, urinalysis (dipstick with an estimation of proteinuria if necessary) and BP measurements. Twenty-four-hour BP and four-limb BP measurements may be considered depending on the presenting symptoms [41]. Rapidly progressive glomerulonephritis with acutely deteriorating kidney function is common at presentation in AAV. Pauci-immune necrotising glomerulonephritis

(PINGN), the most common cause of crescentic glomerulonephritis, is a severe manifestation of AAV that presents with a very rapid decline in kidney function, often leading to irreversible kidney failure [44]. Patients with PINGN or ANCA-associated glomerulonephritis (AAV-GN) without other organ involvement are said to have renal limited vasculitis (RLV). The 'gold standard' method for confirming AAV-GN is a kidney biopsy [43]. According to the paediatric AAV-GN classification, histological categories should be grouped into focal, crescentic, mixed and sclerotic [45]. There are no internationally agreed thresholds acting as indications for when to conduct a kidney biopsy in AAV; however, due to the high risk of rapid disease progression and kidney failure, it is of the authors' opinion that delays in receiving treatment should be avoided.

Management and kidney outcome

The management of paediatric AAVs is based on the adult European Vasculitis Study (EUVAS) guidelines [41]. Induction regimens are determined by the extent and severity of the disease. For a severe, life-threatening or refractory disease with kidney involvement, rituximab, IV cyclophosphamide, plasma exchange and/or intravenous immunoglobulin (IVIG) should be considered after IV methylprednisolone in an attempt to achieve rapid remission [41, 43]. A multi-centre study evaluating the outcomes of 46 children with AAV reported a 55% rate of CKD at 1 year after diagnosis, of which 20% of patients had CKD stages 3–5 and 17% had kidney failure requiring dialysis or a kidney transplant [46]. After 5 years of follow-up, the rate of dialysis or kidney transplantation had risen to 22%, indicating that most morbidity occurs at presentation or in the first few years. The authors also reported a 6.5% mortality rate, demonstrating the concerning outcomes for children with this condition compared to other inflammatory diseases. A smaller study involving 8 patients reported long-term outcomes after a median of 19 years; 1 patient had developed kidney failure, 1 had died and the median eGFR in the other 6 children was 76 ml/min/m2 (equivalent to CKD stage 2) [47].

Other childhood rheumatic conditions that may involve the kidneys

Polyarteritis nodosa (PAN)

Polyarteritis nodosa (PAN) is a rare type of vasculitis caused by damage to small and medium-sized arteries. Due to its rarity, little epidemiological data exists, and the true incidence of PAN in children is unknown. Childhood-onset PAN presents with clinical symptoms associated with cutaneous, intestinal, musculoskeletal and kidney inflammation, such as muscle pain, weight loss, fever and hypertension [48]. Kidney manifestations of PAN at presentation include hypertension, proteinuria, haematuria and

impaired kidney function. A UK-based single-centre retrospective study of 69 children treated over a period of 32 years found that 13 (19%) children with PAN had kidney involvement at presentation and 10 (15%) children had a significant decrease in eGFR [48]. The EULAR/PRINTO/PRES criteria for childhood-onset PAN state that patients must have histopathology or angiographic abnormalities plus one of the following: skin involvement, myalgia/muscle tenderness, hypertension, peripheral neuropathy or kidney involvement [28]. A targeted tissue biopsy should be performed when PAN is suspected; however, caution is needed due to the risk of aneurysm rupture and haemorrhage [41]. Catheter digital subtraction arteriography is the gold standard investigation for PAN in childhood but can only be performed in specialist paediatric centres [41]. The severity and extent of childhood-onset PAN vary significantly, and management can be challenging. First-line management for PAN typically involves the use of corticosteroids and either mycophenolate mofetil or cyclophosphamide [49].

Takayasu arteritis (TA)

Takayasu arteritis (TA) is a large-vessel vasculitis predominantly affecting the aorta and its main branches [50]. The estimated annual incidence of TA in all ages is between 0.3 and 3.3 per million population, and it is highest in females of childbearing age [50]. The incidence of paediatric-onset TA is not well established. In children and adolescents, TA presents with non-specific symptoms in the early latent phase including fever, arthralgia, headaches, hypertension and weight loss. The diagnosis of TA in children can be challenging, involving a combination of clinical, laboratory, imaging and histological criteria. The EULAR/PRINTO/PRES classification for paediatric-onset TA relies heavily on vascular imaging [28]. Unless early treatment is commenced, irreversible blood vessel damage can occur, leading to stenosis, fibrosis and potential thrombus or aneurysm formation; thus, it typically presents with features of end-organ damage, such as stroke, leg claudication or kidney infarction [50]. A study involving 179 patients with TA, of whom 25 patients had paediatric-onset TA, found that children had increased inflammatory markers, a greater extent of vascular injury and more critical clinical manifestations when compared to adults [51]. The most common kidney complication of TA in children is renovascular hypertension, caused by renal artery stenosis [50]. Rarely, renal artery stenosis may also result in renal artery aneurysms that can rupture and cause life-threatening bleeding [52]. No consensus exists for treatment, but biologic agents such as TNFα, IL-6 and JAK inhibitors may have a role, and early reports support their effectiveness. Antiplatelet therapy is often used despite no evidence supporting its role [50]. In children with renal artery stenosis, interventional revascularisation procedures such as percutaneous transluminal renal angioplasty (PTRA), kidney auto-transplantation and surgical bypass may be performed with reasonable success [53].

Systemic sclerosis

Juvenile-onset systemic sclerosis (jSSc) is characterised by skin sclerosis and the involvement of blood vessels and internal organs. Scleroderma renal crisis is a rare but serious complication of SSc that can lead to rapid deterioration of kidney function. Kidney involvement is uncommon in all jSSc cohorts (4–13%), with renal crisis being extremely rare (< 4%) [54]. Patients present with severe hypertension reduced eGFR, haematuria and haemolytic anaemia, and the diagnosis is confirmed through a kidney biopsy [54].

Sjogren syndrome

Sjogren syndrome (SS) is a chronic systemic autoimmune disease characterised by chronic lymphocytic infiltration of the exocrine glands, predominantly the lacrimal and salivary glands, resulting in characteristic mouth and/or eye dryness (sicca symptoms) and leading to progressive glandular destruction. Childhood-onset SS (cSS) is rare, with an unknown incidence, and only a few hundred cases have been reported in the literature [55]. Children often present due to parotitis or non-specific symptoms such as arthralgia [55]. Clinicians rely on clinical judgement and experience, guided by adult criteria, to diagnose cSS [56]. Kidney involvement in cSS is rare and estimated to affect 10% of paediatric patients [57, 58]. It mainly presents as tubular interstitial nephritis (TIN) due to lymphocytic infiltration with tubular dysfunction, resulting in renal tubular acidosis (RTA, usually distal), hypokalaemia, nephrocalcinosis or renal Fanconi syndrome. Glomerulonephritis is rare but has been described [59]. Even though the long-term kidney outcome in cSS is typically favourable, the ongoing need for immunosuppression due to kidney involvement is linked to a poorer prognosis [58, 59].

IgG4-related disease

IgG4-related disease (IgG4-RD) is a rare fibro-inflammatory condition characterised by tumour-like lymphoplasmacytic infiltrations, typically exhibiting tissue fibrosis and extremely elevated serum IgG4 levels. Epidemiological paediatric data are lacking, and 82 cases of childhood-onset IgG4-RD have been reported in the literature [60]. There are no diagnostic criteria for paediatric IgG4-RD, but the revised comprehensive diagnostic criteria,

validated in adults, can be used, comprising 3 domains (clinical and radiological features, serological raised serum IgG4 > 135 mg/dL and pathological features) [61]. Kidney manifestations in children are rare and reported in 6–32% of patients aged < 25 years old [60]. It mainly occurs in the form of TIN, sometimes membranous glomerulonephritis or obstructive acute kidney injury due to retroperitoneal fibrosis [62]. Despite being extremely rare, a diagnosis should be considered in children with laboratory evidence of kidney damage/decline in kidney function or abnormalities in kidney imaging with known pre-existing disease or clinical suspicion of IgG4-RD [62]. The disease can cause end-organ damage if left untreated and usually responds to corticosteroids.

Conclusion

The kidney is a target organ in a wide range of rheumatological diseases affecting children, most commonly seen in cSLE, IgAV and AAVs. It is less commonly seen in PAN, TA, systemic sclerosis, IgG4-related disease and Sjogren's syndrome. Kidney involvement is extremely rare in JIA and therefore not addressed in this review [63]. Although with varying degrees of rarity, clinicians should remain vigilant and aware of potential kidney manifestations of rheumatological diseases in children since they can result in significant morbidity in adulthood [64]. Advances have been made in standardising definitions to classify these diseases, and management strategies have been published to align care. Children should at least undergo a baseline urinalysis and blood pressure check as a minimum in diseases where kidney involvement is a recognised complication, and a summary of other kidney-specific investigations is presented in Table 5. Urinalysis is inexpensive and should ideally be repeated during each clinical review, even if negative previously. The kidney biopsy is an important investigation, and histological features will often guide treatment. The timing of conducting a biopsy will depend on the natural history of the disease, with more urgency in conditions that have a high risk of rapidly progressive glomerulonephritis. Despite current management strategies, children with rheumatological diseases continue to suffer from suboptimal rates of complete remission and poor long-term kidney outcomes. Further research is needed to fully understand the complex pathophysiology that drives these diseases to target the kidney and to discover better ways to intervene as we strive to improve long-term kidney outcomes for children.

Table 5. Investigations to evaluate kidney involvement in children with suspected or proven rheumatological disease

	Urine analysis	Bloods	Immunological tests	Imaging	Other
General screening	Urine dipstick UA:UC ratio or UP:UC ratio Urine microscopy for quantification of haematuria and evidence of active sediment	FBC ESR and CRP Clotting ± and prothrombotic screen U&Es, bone profile and LFTs CPK and LDH	Immunoglobulins Complement (C3 and C4) Anti-streptolysin O antibody titre (ASOT) ANA Anti-dsDNA ANCA and APS antibodies Anti-GBM antibody	Abdominal USS with Doppler measurements	Blood pressure measurement Height to calculate eGFR
Further specific investigations			Anti-PR3 and MPO titres if ANCA positive		Skin biopsy with IgA immunofluorescence Renal biopsy

GFR, glomerular filtration rate; *UP:UC*, urine protein to urine creatinine ratio; *UA:UC*, urine albumin to urine creatinine ratio

Acknowledgements

The authors would like to acknowledge all members of the Experimental Arthritis Treatment Centre for Children (EATC4C) and the National Institute of Health Research (NIHR) Alder Hey Clinical Research Facility for their support in delivering research indirectly related to this work.

Declarations

Conflict of Interest
Avni Patel, Julien Marro, Liza McCann and Louise Oni each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer
The views expressed in the manuscript are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health.

References and Recommended Reading

1. Costello R, McDonagh J, Hyrich KL, Humphreys JH. Incidence and prevalence of juvenile idiopathic arthritis in the United Kingdom, 2000–2018: results from the Clinical Practice Research Datalink. Rheumatology (Oxford). 2022;61(6):2548–54. https://doi.org/10.1093/rheumatology/keab714.
2. Smith EMD, Lythgoe H, Midgley A, Beresford MW, Hedrich CM. Juvenile-onset systemic lupus erythematosus: update on clinical presentation, pathophysiology and treatment options. Clin Immunol. 2019;209:108274. https://doi.org/10.1016/j.clim.2019.108274.
3. Weiss PF. Pediatric vasculitis. Pediatr Clin North Am. 2012;59(2):407–23. https://doi.org/10.1016/j.pcl.2012.03.013.
4. Alobaidi S, Alotaibi M, Al-Zahrani N, Al-Dhaheri F. Renal system and rheumatology. In: Almoallim H, Cheikh M, editors. Skills in rheumatology. Singapore: Springer Singapore; 2021. p. 309–28.
5. Dahman HAB. Challenges in the diagnosis and management of pediatric rheumatology in the developing world: lessons from a newly established clinic in Yemen. Sudan J Paediatr. 2017;17(2):21–9. https://doi.org/10.24911/sjp.2017.2.2.
6. Amaral B, Murphy G, Ioannou Y, Isenberg DA. A comparison of the outcome of adolescent and

adult-onset systemic lupus erythematosus. Rheumatology. 2014;53(6):1130–5. https://doi.org/10.1093/rheumatology/ket488.
7. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Manifestations of systemic lupus erythematosus. Maedica. 2011;6(4):330–6.
8. Smith EMD, Rasul S, Ciurtin C, Al-Abadi E, Armon K, Bailey K, et al. Limited sensitivity and specificity of the ACR/EULAR-2019 classification criteria for SLE in JSLE?-Observations from the UK JSLE Cohort Study. Rheumatology (Oxford). 2021;60(11):5271–81. https://doi.org/10.1093/rheumatology/keab210.
9. Lythgoe H, Morgan T, Heaf E, Lloyd O, Al-Abadi E, Armon K, et al. Evaluation of the ACR and SLICC classification criteria in juvenile-onset systemic lupus erythematosus: a longitudinal analysis. Lupus. 2017;26(12):1285–90. https://doi.org/10.1177/0961203317700484.
10. Sag E, Tartaglione A, Batu ED, Ravelli A, Khalil SM, Marks SD, et al. Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicentre study. Clin Exp Rheumatol. 2014;32(3):440–4.
11. Mina R, Brunner HI. Update on differences between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Res Ther. 2013;15(4):218. https://doi.org/10.1186/ar4256.
12. Bankole AA, Nwaonu JN. The shifting landscape of lupus nephritis management: a review. Cureus. 2022;14(1):e20950. https://doi.org/10.7759/cureus.20950.
13. Hoover PJ, Costenbader KH. Insights into the epidemiology and management of lupus nephritis from the US rheumatologist's perspective. Kidney Int. 2016;90(3):487–92. https://doi.org/10.1016/j.kint.2016.03.042.
14. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh JE, et al. Disease activity, severity, and damage in the UK juvenile-onset systemic lupus erythematosus cohort. Arthritis Rheum. 2012;64(7):2356–65. https://doi.org/10.1002/art.34410.
15. Sassi RH, Hendler JV, Piccoli GF, Gasparin AA, da Silva Chakr RM, Brenol JC, et al. Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus. Clin Rheumatol. 2017;36(1):89–95. https://doi.org/10.1007/s10067-016-3478-4.
16. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus. 2011;20(13):1345–55. https://doi.org/10.1177/0961203311416694.
17 KDIGO. clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4s):S1-s276. https://doi.org/10.1016/j.kint.2021.05.021.
18. Groot N, de Graeff N, Marks SD, Brogan P, Avcin T, Bader-Meunier B, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis. 2017;76(12):1965–73. https://doi.org/10.1136/annrheumdis-2017-211898.
19. Groot N, de Graeff N, Avcin T, Bader-Meunier B, Brogan P, Dolezalova P, et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Ann Rheum Dis. 2017;76(11):1788–96. https://doi.org/10.1136/annrheumdis-2016-210960.
20. Gordon C, Amissah-Arthur M-B, Gayed M, Brown S, Bruce IN, D'Cruz D, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology. 2018;57(1):e1–45. https://doi.org/10.1093/rheumatology/kex286.
21. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65(2):521–30. https://doi.org/10.1111/j.1523-1755.2004.00443.x.
22. Yu F, Haas M, Glassock R, Zhao M-H. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. Nat Rev Nephrol. 2017;13(8):483–95. https://doi.org/10.1038/nrneph.2017.85.
23. Oni L, Wright RD, Marks S, Beresford MW, Tullus K. Kidney outcomes for children with lupus nephritis. Pediatr Nephrol. 2021;36(6):1377–85. https://doi.org/10.1007/s00467-020-04686-1.
24. Chan EY, Yap DY, Wong WT, Wong WH, Wong SW, Lin KY, et al. Long-term outcomes of children and adolescents with biopsy-proven childhood-onset lupus nephritis. Kidney Int Rep. 2023;8(1):141–50. https://doi.org/10.1016/j.ekir.2022.10.014.
25. Tucker LB, Uribe AG, Fernández M, Vilá LM, McGwin G, Apte M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus. 2008;17(4):314–22. https://doi.org/10.1177/0961203307087875.
26. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. 2022;18(1):22–34. https://doi.org/10.1038/s41584-021-00718-8.
27. Oni L, Sampath S. Childhood IgA vasculitis (Henoch Schonlein purpura)-advances and knowledge gaps. Front Pediatr. 2019;7:257. https://doi.org/10.3389/fped.2019.00257.
28. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final Classif Criteria. 2010;69(5):798–806.

https://doi.org/10.1136/ard.2009.116657%JAnnalsoftheRheumaticDiseases.
29. Chen JY, Mao JH. Henoch-Schönlein purpura nephritis in children: incidence, pathogenesis and management. World J Pediatr. 2015;11(1):29–34. https://doi.org/10.1007/s12519-014-0534-5.
30. Chan H, Tang YL, Lv XH, Zhang GF, Wang M, Yang HP, et al. Risk factors associated with renal involvement in childhood Henoch-Schönlein purpura: a meta-analysis. Plos One. 2016;11(11):e0167346. https://doi.org/10.1371/journal.pone.0167346.
31. Ozen S, Marks SD, Brogan P, Groot N, de Graeff N, Avcin T, et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis—the SHARE initiative. Rheumatology. 2019;58(9):1607–16. https://doi.org/10.1093/rheumatology/kez041%JRheumatology.
32. UK IgAV clinical practice guideline working group (Lead: Oni L: Best practice guideline for the management of complications associated with IgA vasculitis (HSP) in children and young people search strategy [unpublished]. 2022. https://ukkidney.org/renal-association/news/iga-vasculitis-guideline-rcpch-endorsed.
33. Watson L, Richardson AR, Holt RC, Jones CA, Beresford MW. Henoch Schonlein purpura–a 5-year review and proposed pathway. Plos One. 2012;7(1):e29512. https://doi.org/10.1371/journal.pone.0029512.
34. Koskela M, Ylinen E, Ukonmaanaho EM, Autio-Harmainen H, Heikkilä P, Lohi J, et al. The ISKDC classification and a new semiquantitative classification for predicting outcomes of Henoch-Schönlein purpura nephritis. Pediatr Nephrol. 2017;32(7):1201–9. https://doi.org/10.1007/s00467-017-3608-5.
35. Hahn D, Hodson EM, Craig JC. Interventions for preventing and treating kidney disease in IgA vasculitis. Cochrane Database Syst Rev 2023;2023(2):CD005128. https://doi.org/10.1002/14651858.CD005128.pub4.
36. Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: a systematic review. Arch Dis Child. 2005;90(9):916–20. https://doi.org/10.1136/adc.2005.074641.
37. Tan J, Tang Y, Xu Y, Yan S, Xu Y, Tan L, et al. The clinicopathological characteristics of Henoch-Schönlein purpura nephritis with presentation of nephrotic syndrome. Kidney Blood Press Res. 2019;44(4):754–64. https://doi.org/10.1159/000501459.
38. Calatroni M, Oliva E, Gianfreda D, Gregorini G, Allinovi M, Ramirez GA, et al. ANCA-associated vasculitis in childhood: recent advances. Ital J Pediatr. 2017;43(1):46. https://doi.org/10.1186/s13052-017-0364-x.
39. Sacri AS, Chambaraud T, Ranchin B, Florkin B, Sée H, Decramer S, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. Nephrol Dial Transplant. 2015;30(Suppl 1):i104–12. https://doi.org/10.1093/ndt/gfv011.
40. Grisaru S, Yuen GW, Miettunen PM, Hamiwka LA. Incidence of Wegener's granulomatosis in children. J Rheumatol. 2010;37(2):440–2. https://doi.org/10.3899/jrheum.090688.
41. de Graeff N, Groot N, Brogan P, Ozen S, Avcin T, Bader-Meunier B, et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides – the SHARE initiative. Rheumatology. 2018;58(4):656–71. https://doi.org/10.1093/rheumatology/key322%JRheumatology.
42. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11. https://doi.org/10.1002/art.37715.
43. Plumb LA, Oni L, Marks SD, Tullus K. Paediatric anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: an update on renal management. Pediatr Nephrol. 2018;33(1):25–39. https://doi.org/10.1007/s00467-016-3559-2.
44. McAdoo SP, Tanna A, Randone O, Tam FWK, Tarzi RM, Levy JB, et al. Necrotizing and crescentic glomerulonephritis presenting with preserved renal function in patients with underlying multisystem autoimmune disease: a retrospective case series. Rheumatology. 2014;54(6):1025–32. https://doi.org/10.1093/rheumatology/keu445%JRheumatology.
45. Noone DG, Twilt M, Hayes WN, Thorner PS, Benseler S, Laxer RM, et al. The new histopathologic classification of ANCA-associated GN and its association with renal outcomes in childhood. Clin J Am Soc Nephrol. 2014;9(10):1684–91. https://doi.org/10.2215/cjn.01210214.
46. Arulkumaran N, Jawad S, Smith SW, Harper L, Brogan P, Pusey CD, et al. Long- term outcome of paediatric patients with ANCA vasculitis. Pediatr Rheumatol Online J. 2011;9:12. https://doi.org/10.1186/1546-0096-9-12.
47. Mahi SL, Bahram S, Harambat J, Allard L, Merlin E, Belot A, et al. Pediatric ANCA vasculitis: clinical presentation, treatment, and outcomes in a French retrospective study. Pediatr Nephrol. 2023. https://doi.org/10.1007/s00467-022-05855-0.
48. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. Arthritis Rheum. 2013;65(9):2476–85. https://doi.org/10.1002/art.38024.
49. Brogan PA, Arch B, Hickey H, Anton J, Iglesias E, Baildam E, et al. Mycophenolate mofetil versus

cyclophosphamide for remission induction in childhood polyarteritis nodosa: an open-label, randomized Bayesian noninferiority trial. Arthritis Rheumatol. 2021;73(9):1673–82. https://doi.org/10.1002/art.41730.
50. Aeschlimann FA, Yeung RSM, Laxer RM. An update on childhood-onset Takayasu arteritis. Front Pediatr. 2022;10:872313. https://doi.org/10.3389/fped.2022.872313.
51 Bolek EC, Kaya Akca U, Sari A, Sag E, Demir S, Kilic L, et al. Is Takayasu's arteritis more severe in children? Clin Exp Rheumatol. 2021;39(129):32–8. https://doi.org/10.55563/clinexprheumatol/kr357t.
52. Gargah T, Harrath MB, Bachrouche H, Rajhi H, Abdallah TB, Lakhoua MR. First case of childhood Takayasu arteritis with renal artery aneurysms. Pediatr Rheumatol. 2010;8(1):21. https://doi.org/10.1186/1546-0096-8-21.
53. Aeschlimann FA, Twilt M, Yeung RSM. Childhood-onset Takayasu arteritis. Eur J Rheumatol. 2020;7(Suppl1):S58-s66. https://doi.org/10.5152/eurjrheum.2019.19195.
54. Foeldvari I, Klotsche J, Torok KS, Kasapcopur O, Adrovic A, Stanevicha V, et al. Are diffuse and limited juvenile systemic sclerosis different in clinical presentation? Clinical characteristics of a juvenile systemic sclerosis cohort. J Scleroderma Relat Disord. 2019;4(1):49–61. https://doi.org/10.1177/2397198318790494.
55. Basiaga ML, Stern SM, Mehta JJ, Edens C, Randell RL, Pomorska A, et al. Childhood Sjögren syndrome: features of an international cohort and application of the 2016 ACR/EULAR classification criteria. Rheumatology (Oxford). 2021;60(7):3144–55. https://doi.org/10.1093/rheumatology/keaa757.
56. Randell RL, Stern SM, Van Mater H, Schanberg LE, Lieberman SM, Basiaga ML, et al. Pediatric rheumatologists' perspectives on diagnosis, treatment, and outcomes of Sjögren disease in children and adolescents. Pediatr Rheumatol. 2022;20(1):79. https://doi.org/10.1186/s12969-022-00740-4.
57. Yokogawa N, Lieberman SM, Sherry DD, Vivino FB. Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria. Clin Exp Rheumatol. 2016;34(2):343–51.
58. Zhao J, Chen Q, Zhu Y, Zhao M, Liu J, Zhang Z, et al. Nephrological disorders and neurological involvement in pediatric primary Sjogren syndrome:a case report and review of literature. Pediatr Rheumatol. 2020;18(1):39. https://doi.org/10.1186/s12969-020-00431-y.
59. Bogdanović R, Basta-Jovanović G, Putnik J, Stajić N, Paripović A. Renal involvement in primary Sjogren syndrome of childhood: case report and literature review. Mod Rheumatol. 2013;23(1):182–9. https://doi.org/10.1007/s10165-012-0633-x.
60. de Sainte MB, Ebbo M, Grados A, Rebours V, Reumaux H, Briantais A, et al. A descriptive study of IgG4-related disease in children and young adults. Autoimmun Rev. 2022;21(4):103035. https://doi.org/10.1016/j.autrev.2022.103035.
61. Umehara H, Okazaki K, Kawa S, Takahashi H, Goto H, Matsui S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol. 2021;31(3):529–33. https://doi.org/10.1080/14397595.2020.1859710.
62. Capecchi R, Giannese D, Moriconi D, Bonadio AG, Pratesi F, Croia C, et al. Renal Involvement in IgG4-related disease: from sunlight to twilight. Front Med (Lausanne). 2021;8:635706. https://doi.org/10.3389/fmed.2021.635706.
63. Varma S. Juvenile rheumatoid arthritis with focal segmental glomerulosclerosis: a rare association. Pediatr Nephrol. 2010;25(10):2189–90. https://doi.org/10.1007/s00467-010-1504-3.
64. Anders H-J, Vielhauer V. Renal co-morbidity in patients with rheumatic diseases. Arthritis Res Ther. 2011;13(2):222. https://doi.org/10.1186/ar3256.

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