EDUCATIONAL REVIEW

Kidney manifestations of pediatric Sjögren's syndrome

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Abstract

Approximately 1% of all patients with Sjögren's syndrome (SS) are children. Unlike the adult form, in which sicca syndrome is the main presentation, in children, the most common clinical finding is recurrent enlargement of the salivary glands. In pediatric SS, extraglandular manifestations represent a significant feature and, among these, kidney manifestations are relevant. Kidney involvement is observed in 5–20.5% of children with SS, most frequently tubulointerstitial nephritis. This injury can lead to serious phenotypes, including distal kidney tubular acidosis with the development of severe hypokalemia, which can lead to ECG abnormalities, weakness, and hypokalemic periodic paralysis. Kidney implications in pediatric SS also include nephrolithiasis, nephrocalcinosis, and various types of glomerular damage, which often require immunosuppressive therapies. Laboratory findings are usually comparable to adults, including hyperglobulinemia and high rates of antinuclear antibodies (ANA, 63.6–96.2%), and anti-Ro/SSA (36.4–84.6%). The current classification criteria for SS are inaccurate for the pediatric population, and more specific criteria are needed to improve the diagnostic rate. Due to the rarity of the disease, strong recommendations for treatment are lacking, and several therapeutic strategies have been reported, mostly based on glucocorticoids and disease-modifying antirheumatic drugs, with different outcomes. The aim of this paper is to provide an overview of the kidney implications of pediatric SS based on the latest evidence of the medical literature.

Keywords Pediatric Sjögren's syndrome · Kidney · Renal · Tubulointerstitial nephritis · Primary Sjogren's syndrome

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disorder that predominantly affects the exocrine glands, with frequent multi-organ involvement. In the adult population, the inflammation of salivary and lacrimal glands represents the main feature of the disease, leading to the development of sicca syndrome with xerostomia and xerophthalmia, resulting in dry mouth and eyes. Two forms of SS can be distinguished: primary SS (pSS) is recognized as an isolated disease, whereas secondary SS is associated with other underlying autoimmune disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis [1]. The pathophysiology of SS is not entirely understood.

Host and environmental factors lead to abnormal activation of both innate and adaptive immunity in genetically predisposed individuals [2, 3]. Lymphocytes and specific autoantibodies all contribute to the pathogenesis of chronic inflammation, leading to the formation of germinal centers in affected tissue and an increased risk of non-Hodgkin's lymphoma and other malignancies [2–4]. Although SS is commonly observed in adults, mainly due to secondary forms, a childhood onset can rarely occur [2, 3, 5–10]. Indeed, pediatric SS is believed to account for approximately 1% of all SS patients and, 10 years ago, less than 200 cases of pediatric SS had been described [6, 11–16]. Typical clinical findings in children with SS include recurrent parotid swelling and, often, significant extraglandular manifestations (EGMs) (Fig. 1) [16, 17]. Due to the systemic spectrum of the disease, autoinflammation can affect every tissue and organ, resulting in a clinical phenotype that is highly heterogeneous [15, 17]. Kidney involvement is regarded as a relevant feature in pediatric SS, with an estimated prevalence of 5–20.5% (Table 1) [2, 3, 7–10, 16–21]. However, due to the disease's rarity, epidemiological and clinical data regarding the kidney manifestations of

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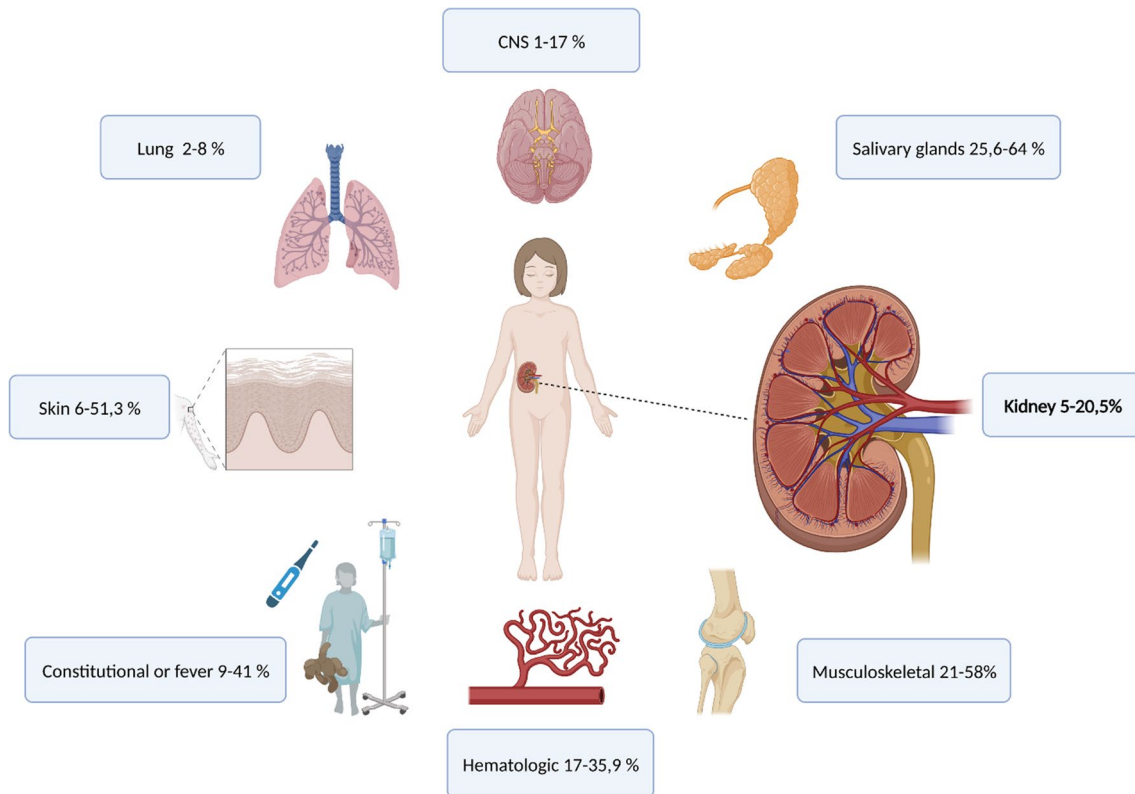
Fig. 1 Glandular and extraglandular manifestations in pediatric Sjögren's syndrome. Kidney is involved in 5–20.5% of affected children [3, 7–10, 16, 20]. CNS, central nervous system

pediatric SS are limited [6, 7, 17]. The most common kidney injury in affected children is tubulointerstitial nephritis (TIN), which can clinically manifest as renal tubular acidosis (RTA), hematuria, glycosuria, hypokalemia, and impaired urinary concentrating ability [3, 6, 17, 22]. Furthermore, nephrolithiasis, nephrocalcinosis, and various types of glomerulonephritis (GN) have been reported, often requiring immunosuppressive treatments [6, 23].

Pathophysiology

A genetic predisposition and aberrant activation of the immune system are responsible for the development of glandular and EGMs in SS [24]. In affected patients, there is an abnormal activation of CD4 + T cell-derived and NK cells, mostly caused by an altered interferon (IFN)-λ signaling pathway upon stimulation by pro-inflammatory cytokines such as IL-12, IL-23, and IL-33 [24]. Moreover, IL-17 and IL-22, predominantly secreted by Th17 cells, promote inflammation via IL-6 and tumor necrosis factor (TNF)-α and, indirectly, BAFF production. This results in MHC-II overexpression, increased lymphocytic infiltration, and, controversially, an overproduction of multiple autoantibodies,

including anti-Ro/SSA and anti-La/SSB [24]. In addition, it has been proposed that certain genes involved in the Wnt/β-catenin signaling pathway may be involved in the pathogenesis of SS [24]. In patients with kidney involvement, the histologic findings are predominantly represented by an interstitial infiltration of T cells, B lymphocytes, and plasma cells [25]. Notably, a younger onset age in adults correlates with a higher prevalence of B-cell-mediated glandular and EGMs, including kidney involvement [25]. The high incidence of lymphopenia observed in a substantial number of patients is accompanied by lymphoplasmacytic infiltrates in the kidney interstitium [25]. In patients with kidney involvement, the association with lymphomas and the key role of IL36g and cryoglobulins may be crucial factors to understand in the future [25].

Clinical features

Pediatric SS is an extremely uncommon disorder that predominantly affects older children and adolescents, with a strong female predominance (80–87%), comparable to that observed in adult patients [7–10, 16]. In adults, SS is typically diagnosed between 30 and 50 years of age, whereas

Table 1 Relevant issues in pediatric Sjögren's syndrome

Relevant issue	Percentage
Pediatric Sjögren's syndrome	≈ 1% of total cases
Primary forms	Nearly all cases
Secondary forms	Very rare
Female to male ratio	4:1
Laboratory findings:	
ANA	63.6–96.2%
Anti-Ro/SSA	36.4–84.6%
Anti-La/SSB	27.3–65.4%
Glandular manifestations:	Up to 80%
Recurrent salivary gland enlargement	Up to 64%
Dryness and sicca syndrome	34–80%
Extraglandular manifestations:	Up to 58%
Kidney involvement	5–20.5%
Tubulointerstitial involvement	Nearly all cases
Tubulointerstitial nephritis	Up to 80%*
RTA (dRTA > pRTA, mixed forms)	Common°
Nephrolithiasis and nephrocalcinosis	Rarely documented
Glomerular damage	Rarely documented
Mild glomerular lesions	
Glomerulosclerosis	
Glomerulonephritis	

The various percentages of both glandular and extraglandular manifestations are reported in Fig. 1. Glomerular involvement is described in Table 2

ANA antinuclear antibodies, *RTA* renal tubular acidosis, *dRTA* distal renal tubular acidosis, *pRTA* proximal renal tubular acidosis

*In a small series of pediatric patients who underwent a kidney biopsy

°According to a small series, dRTA accounts for up to 92% of all RTA. Hypokalemia, often with hypokalemic paralysis, and impaired urine-concentrating ability are the most frequently reported clinical findings

in children, the average age at diagnosis ranges from 12 to 14.2 years, and the primary form accounts for nearly all cases [2, 3, 7–9, 16, 18]. Pediatric SS is characterized by a variable phenotype whose characteristics and severity can vary markedly between patients [3, 13, 26]. The clinical findings of pediatric SS can be divided into glandular manifestations, which predominantly involve the parotid glands, and EGMs.

Glandular manifestations

The most common feature in childhood is recurrent parotid enlargement, which is present in up to 64% of patients, although submandibular gland swelling may also be observed [3, 7–10, 16, 20]. Bilateral or unilateral salivary gland enlargement is frequently accompanied by pain and tenderness and, unlike adults, has not been associated with

increased mortality rate [3, 27]. Dryness and sicca syndrome are also common findings in children, with prevalence rates ranging from 34 to 80% [2, 3, 7–10, 15, 16, 18]. Patients with sicca syndrome experience dry eyes and mouth, resulting in an inability to assimilate food, halitosis, mucositis, weight loss, decreased tear production, and keratoconjunctivitis sicca up to corneal ulcerations [3, 18, 28]. Despite the paucity of distinct epidemiological data, it has been reported that children with SS can suffer from recurrent vaginitis, pancreatitis, chronic dry wheezing, and dry skin [3, 18, 29].

Extraglandular manifestations

A deeper understanding of EGMs of pediatric SS is currently a major area of focus for pediatric rheumatologists [3, 9, 18]. Musculoskeletal manifestations are the most prevalent EGMs, ranging from 21 to 58% of cases. Their clinical spectrum includes myalgias, arthralgias, and severe forms of arthritis and myositis [9]. Arthralgias are the most prevalent musculoskeletal involvement in children, affecting 54% of patients, whereas nonerosive arthritis affects large joints in 24% of cases [3, 9]. In addition, constitutional symptoms, such as fever, affect up to 41% of children with SS [3, 7–10, 16, 20]. Fatigue and malaise are frequent symptoms, with an unknown etiopathogenesis that is likely influenced by both chronic pain and depression [3, 18]. Pulmonary manifestations have been reported in less than 8% of pediatric patients, with less severe complications than in adults [3, 8, 9, 16]. The main respiratory finding is interstitial lung disease, mainly resulting in chronic cough and, on rare occasions, dyspnea [3]. In addition, skin manifestations have been reported in up to 51.3% of children with SS, including dryness, Raynaud's phenomenon, cutaneous vasculitis, purpura, erythema nodosum, and cutaneous amyloidosis [3, 8, 18]. The gastrointestinal tract is primarily implicated in oral and pancreatic dysfunction. However, chronic diarrhea, nonalcoholic steatohepatitis, atrophic gastritis, and chronic gastritis have also been described in pediatric SS [3, 18, 30]. Neurologic complications have been reported in up to 17% of pediatric patients [8, 10, 16]. Interestingly, neuromyelitis optica spectrum disorder and SS have been recently investigated due to their unusual co-occurrence in childhood [3, 31–33]. Other central nervous system implications include encephalopathy and meningoencephalitis, resulting in headache, vomiting, chorea, paralysis, and seizures [3, 17, 34–36]. The peripheral nervous system can also be implicated, with polyneuropathy and mononeuritis [3, 18]. Hematologic complications affect 17–35.9% of children with SS, including mild chronic anemia, thrombocytopenia, and leukopenia, up to lymphomas [3, 18, 20, 37]. According to the literature, patients with pSS have a 10–44 fold greater risk of lymphoma than the general population, even higher than patients with SLE and RA [38]. Up to 10% of patients

with pSS develop low-grade B cell lymphoma, typically extranodal marginal zone lymphomas (eMZL) of mucosa-associated lymphoid tissue (MALT) [38, 39]. Interestingly, the development of eMZL is often related to cryoglobuline-mia and seems to be more frequent in adult pSS with kidney involvement than those without kidney manifestations [17, 40, 41]. There is controversy as to whether there is a higher incidence of lymphoma in patients with TIN or GN, with studies producing contradictory results [40, 41]. Kidney involvement in pediatric SS represents this paper's main argument and is described in detail in the following sections.

## Kidney involvement in children with Sjögren's syndrome

The prevalence of kidney involvement in pediatric SS is estimated between 5 and 20.5%, and both tubulointerstitial and glomerular damage have been described [7–10, 16, 20, 21]. The clinical spectrum is wide and can range from latent to life-threatening conditions, mostly due to electrolyte disturbances. However, TIN is the most prevalent form of nephropathy in both adults and children with SS [6, 17, 19, 22]. According to a recent large multicenter study, TIN accounts for up to 98% of kidney manifestations in adults with SS who underwent a biopsy, similar to pediatric reports [6, 17, 18, 42]. In pediatric SS, a kidney biopsy should be considered when significant kidney involvement is suspected, such as in the presence of impaired urinary concentrating ability, evidence of RTA, hypokalemic paralysis, idiopathic recurrent nephrocalcinosis/nephrolithiasis, and proteinuria, particularly if intense (> 2 g/day or urinary protein/creatinine ratio > 2), suggesting a glomerular disease.

Tubulointerstitial involvement

Chronic inflammation in TIN is caused by interstitial reactive lymphocytic infiltrates that are predominantly composed of B cells with sporadic T and NK lymphocytes, similar to the lymphocyte aggregates observed around the ducts of salivary and lacrimal glands, which are frequently organized into germinal center-like structures [6, 17, 19, 23]. When performed, kidney biopsy often reveals focal tubular atrophy, acinus damage, interstitial fibrosis, tubular epithelial cell degeneration, and fusion [17, 23]. In a recent review focusing on kidney involvement in pediatric SS, 10/21 patients underwent a kidney biopsy, and TIN was detected in 80% of cases [17]. TIN is often manifested by RTA, which is a well-known feature of kidney involvement in adult pSS, with estimated prevalence rates ranging from 62 to 73% [22, 43, 44]. Three major subtypes of RTA have been identified: proximal RTA (pRTA), which typically results

from defective bicarbonate reabsorption in the proximal convoluted tubule; distal RTA (dRTA); and rare mixed forms [18, 22]. The specific pathophysiology underlying dRTA in SS has not yet been completely understood, and both the lack of H(+)-ATPase in the cortical collecting tubule, with a subsequent failure of the proton pump, and a permeability defect, resulting in bicarbonate leakage into the tubular lumen, have been suggested [6, 45, 46]. In addition, TIN and nephrocalcinosis may worsen medullary ammonia transfer [6]. In adult SS, dRTA occurs in over 95% of RTA cases, with a global prevalence in pSS patients ranging from 4 to 39%, predominantly in middle-aged women [6, 43, 47]. In particular, the alpha-intercalated cells of the collecting duct fail to secrete a sufficient amount of hydrogen ions in the urine, leading to a non-anion-gap metabolic acidosis with alkaline urine [18, 19]. Other cations such as potassium, calcium, and phosphorus are secreted to maintain electroneutrality, resulting in hypokalemia, nephrolithiasis, and bone resorption (Fig. 2) [18, 48, 49]. Thus, RTA is considered one of the main kidney manifestations of TIN in pediatric SS [6, 17]. In a cohort of 12 pediatric patients with RTA and SS, RTA was most frequently associated with pSS and present from the onset (in 25% of patients) to 9 years after diagnosis, affecting older children and adolescents [22]. Notably, dRTA is the most common subtype of RTA also in pediatric SS, while pRTA and mixed forms have rarely been observed [6, 17, 22]. However, the global prevalence of RTA in pSS is estimated to be approximately 9% [6]. Interestingly, only 14 cases of RTA had been detected in pediatric SS in a report from 2020, and the majority of them had dRTA [6, 17, 22, 34]. In this cohort, the associated kidney diseases were diabetes insipidus and nephrocalcinosis in four and three cases, respectively, with both occurring simultaneously in one patient [6, 17, 22]. The main manifestations of RTA in pediatric SS are non-anion gap metabolic acidosis, dehydration, and hypokalemia with alkaline urine [6, 17, 22, 50]. Hypokalemia is believed to occur in up to 92% of children with RTA and SS, with the lowest reported serum values of 1.2 mEq/L, whereas serum bicarbonate had reached reported values of 9.6 mg/dL [22]. Despite the fact that severe hypokalemia can occur in such children, also with a prolonged QT interval, an asymptomatic course can be observed [6]. The most feared complication of severe hypokalemia in pediatric SS is hypokalemic periodic paralysis, which causes profound weakness or paralysis; according to small case series, this life-threatening condition has been reported in up to half of children with RTA and SS, predominantly female adolescents and older children [6, 17, 22, 47, 51, 52]. To date, including adults, about 60 cases of hypokalemic paralysis in SS patients with RTA, mostly dRTA, have been reported
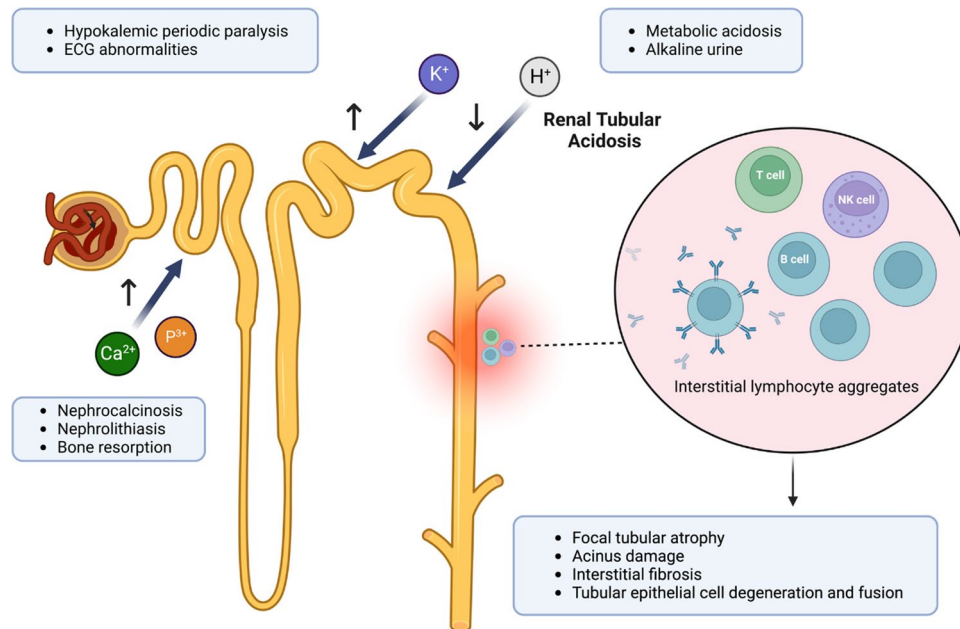
Fig. 2 Tubulointerstitial involvement. In tubulointerstitial involvement, kidney biopsy usually documents interstitial lymphocyte aggregates with multiple findings, such as focal tubular atrophy, acinus damage, interstitial fibrosis, tubular epithelial cell degeneration and fusion. Tubulointerstitial nephritis mainly presents with renal tubular acidosis with various degrees of polyuria and proteinuria. A failure of the proton pump, together with a permeability defect, are thought to be the cause of an impaired hydrogen secretion, resulting in non-anion-gap metabolic acidosis with alkaline urine. Thus, other cations such as potassium, calcium, and phosphorus are secreted to maintain electroneutrality. Hypokalemia can be mild or severe, leading to ECG abnormalities, weakness, up to hypokalemic periodic paralysis. The large amount of calcium and phosphorus secreted can be responsible for bone resorption, nephrolithiasis and nephrocalcinosis

[47, 51, 53–55]. Significantly, hypokalemic paralysis is regarded as the initial symptom in 7% of SS patients, according to a series of 130 individuals [43, 47].

Although several cases have been reported in adults, nephrocalcinosis is a very rare finding in SS children, and only two cases have been reported to date [6, 56]. Furthermore, nephrogenic diabetes insipidus has been described in pediatric SS, and affected patients can suffer from impaired urine-concentrating ability of varying degrees, including mild forms [6].

Glomerular damage

Glomerular involvement in children with SS is extremely rare and frequently associated with immunosuppressive treatments [6, 17]. To the best of our knowledge, only eight cases of predominant glomerular damage have been reported in pediatric SS in the literature, excluding forms of lupus nephritis in secondary SS associated with juvenile SLE (Table 2). However, glomerular involvement is an uncommon finding in adults with SS [18]. In a large series of 95 adult patients with SS and kidney involvement who underwent a kidney biopsy, 23.2% were found to have glomerular damage, frequently in conjunction with TIN [57]. Multiple bioptic findings, including minimal change disease, focal segmental and global glomerulosclerosis, crescentic GN, membranous nephropathy, membranoproliferative glomerulonephritis, and IgA nephropathy, have been documented in such patients [17, 19, 40, 43, 58, 59].

Diagnostic algorithm

The absence of specific classification criteria for pediatric forms is a major issue [6, 60, 61]. Indeed, there is growing consensus that EGMs and systemic involvement are more common in pediatric SS than in the adult form. In addition, the early manifestations of pediatric SS are heterogenous, making early diagnosis challenging, resulting in underdiagnosis and prolonged diagnostic delays [6, 20, 21, 60]. The historical American–European Consensus Group (AECG) criteria for pSS were developed and validated between 1989 and 1996, and improved in 2002 [62]. The last revision of these classification criteria for pSS was validated in 2016 by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR), and represents the current diagnostic tool for the disease [63]. According to the 2016 ACR/EULAR consensus, (1) anti-Ro/SSA antibody positivity, (2) focal lymphocytic sialadenitis, pathogenic

Table 2 Glomerular damage in pediatric Sjögren's syndrome

Reference	Age at onset/gender	Kidney manifestations	Kidney biopsy	Treatment
Yoshida et al. [72]	13/F	Hematuria, proteinuria	MN	MZB, GC
Pessler et al. [22]	6/F	Polydipsia, polyuria, hyposthenuria	Extensive glomerulosclerosis and TIN	GC, CTX, MMF
Jung et al. [57]	11/M	Mild proteinuria, macroscopic hematuria	MesPGN With IgA deposits	GC
Ito et al. [75]	10/F	Hematuria, proteinuria	MesPGN and IgA deposits	GC
Ito et al. [75]	12/F	Hematuria, proteinuria	MesPGN and IgA deposits	None
Kagan et al. [73]	12/F	AKI	Pauci-immune crescentic GN	GC, PE, CTX, AZA
Liu et al. [21]	-	-	Mild glomerular lesions	-
Gong et al. [20]	-	-	Focal proliferative GN and mild TIN	-

MN membranous nephropathy, *MZB* mizoribine, *GC* glucocorticoid, *CTX* cyclophosphamide, *MMF* mycophenolate mofetil, *GN* glomerulonephritis, *MesPGN* mesangial proliferative GN, *IgAN* IgA nephropathy, *AKI* acute kidney injury, *PE* plasma exchange, *AZA* azathioprine, *TIN* tubulointerstitial nephritis

ocular findings measured with (3) the Ocular Staining Score and (4) the Schirmer's test, and (5) a lack of salivary flow rate represent the current classification criteria for SS [63]. In 1999, however, specific classification criteria for pediatric SS were proposed, with improvements on the diagnostic rate (in a series of 135 cases of pediatric SS, the diagnostic rate increased from 39 to 76% regarding the AECG criteria) [20, 60, 61]. Nonetheless, some characteristics are shared with the adult form of SS, such as reactive lymphocytic infiltration of the exocrine glands, anti-Ro/SSA and/or anti-La/SSB antibody positivity, antinuclear antibodies (ANA) positivity, polyclonal hypergammaglobulinemia, and high erythrocyte sedimentation rate (ESR) [6, 20]. According to a systematic review of the literature on pediatric pSS, ANA (63.6–96.2%), anti-Ro/SSA (36.4–84.6%), and anti-La/SSB (27.3–65.4%) are highly prevalent in children with SS [64]. In addition, hyperglobulinemia is a common finding in children with SS as a result of heightened B lymphocyte activation [17, 65]. Kidney involvement is not included in the 2016 ACR/EULAR criteria for SS classification but, as discussed above, kidney manifestations play an important role in pediatric SS, and manifest or latent dRTA had been included in the classification criteria proposed for pediatric pSS in 1999 [60]. In clinical practice, hematuria, proteinuria, and alkaline urine may suggest tubulointerstitial or glomerular damage in children. Specifically, tubulointerstitial inflammation can be suggested by an increased urinary excretion of β-2 microglobulin (β2M) at the diagnosis and during follow-up and its normalization can reflect improvement after therapy [6]. Blood exams should routinely be performed to detect increased ESR, non-anion gap metabolic acidosis, hypokalemia, and other electrolyte disfunctions, serum creatinine, serum proteins, and albumin. Kidney ultrasonography may

be performed to investigate nephrocalcinosis, nephrolithiasis, and other morphological abnormalities. Lastly, a kidney biopsy may be useful for determining the nature and extent of kidney damage and the need for a specific treatment (Fig. 3) [6, 17].

Treatment options and outcome

Despite the lack of strong recommendations due to the rarity of the disease, adult patients with SS are treated with immunosuppressive drugs and nonpharmacologic measures [24, 66]. Artificial tears and punctal plugs may be beneficial for xerophthalmia, whereas intra-oral lubricating devices do not appear to be effective for xerostomia [66]. Low-dose glucocorticoids (GCs) may be helpful in moderate systemic activity forms, despite the frequent occurrence of adverse effects in long-term treatments [67]. Adult patients with SS are commonly treated with conventional disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine (HCQ; mainly for its efficacy in SLE), methotrexate (MTX; especially for musculoskeletal involvement), azathioprine (AZA), cyclosporine (CSA), and mycophenolate mofetil (MMF); however, the improvements are slight and controversial [68, 69]. In some cases, monoclonal antibodies may also be beneficial for adult SS, particularly rituximab, even though a reduction in fatigue and dehydration has not been conclusively demonstrated [70]. Inhibitors of IL-1, IL-6, and TNF-α did not show significant improvements; nevertheless, several ongoing studies are evaluating potential future treatment strategies [24].

According to a systematic review of the literature, multiple treatment strategies for children with SS have been
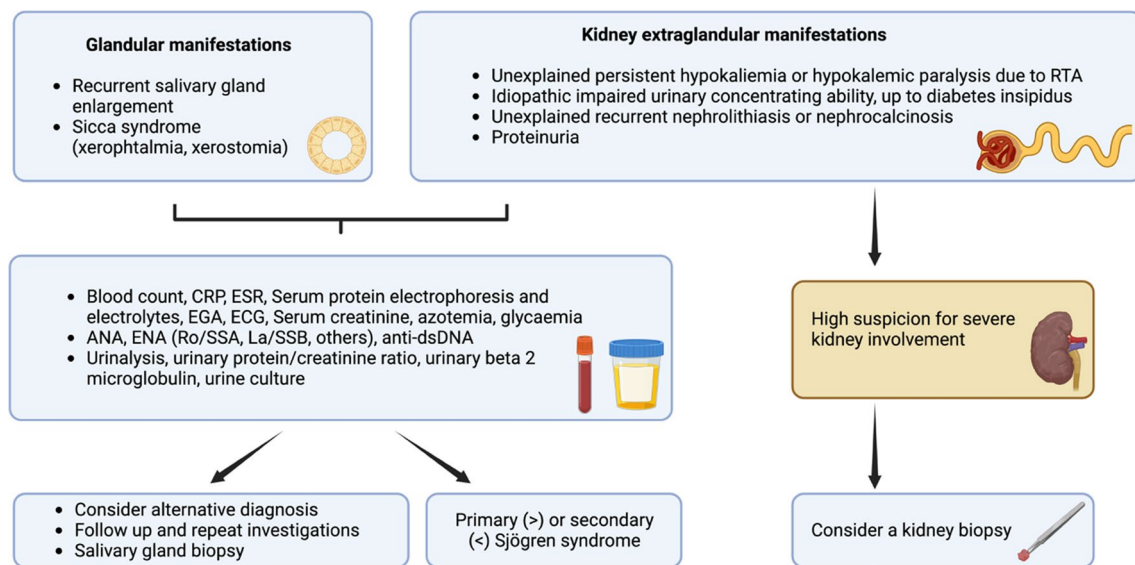
Fig. 3 Flow-chart illustrating a proposed diagnostic approach for pediatric Sjögren's syndrome, with a focus on kidney involvement. RTA, renal tubular acidosis

reported, all of which are based on scant evidence of efficacy from small series and case reports. Thus, there is a lack of good-quality studies and guidelines for a correct, evidence-based approach to pediatric SS, probably also due to the widely variable phenotype [26]. Such concerns may also be found in the current adult guidelines for the management of pSS, released by the British Society for Rheumatology in 2017 [26, 71]. GCs, DMARDs, including HCQ and MTX, and nonsteroidal anti-inflammatory drugs are the most common drugs used in patients with pSS [26]. Kidney involvement shares the same treatment limitations as other manifestations of the disease. GCs, mostly prednisone and methylprednisolone, are widely used in both tubulointerstitial and glomerular damage in children with SS [6, 17, 22, 26, 34, 50, 56, 72, 73]. Significantly, GCs are administered in about 52% of pediatric SS patients with EGMs, and one patient with hypokalemic paralysis due to dRTA required high doses of methylprednisolone (100 mg/day) [26]. Good improvement has been noted after the administration of oral prednisone in a consistent number of patients, but its efficacy alone is a controversial issue due to the frequent co-administration of other DMARDs [26]. According to the literature, 62% of children with SS have been treated with DMARDs, including HCQ (34%), MTX (5.8%), and others [26]. Kidney implications require a prompt treatment strategy. Stable kidney function has been detected after a multi-drug therapy with GCs, MMF, and AZA [6]. A combination of GCs and cyclophosphamide has also been reported in a few patients, with various outcomes [17, 46, 56, 74]. One patient with dRTA was successfully treated with GCs and CSA [52]. Kidney damage in children with SS has also been

treated with HCQ, MTX, and rituximab, often with good improvement [17, 32, 50]. In order to correct acidosis and hypokalemia, alkali and electrolyte supplementation (such as potassium chloride or citrate) is usually required [6, 26]. Despite clinical improvement being reported following treatment with various drugs, this has not been studied in a controlled setting and may not be generalizable to all children with SS; therefore, no conclusions can be made regarding the efficacy of therapy. However, although the long-term prognosis of kidney involvement in pediatric pSS is usually favorable, chronic immunosuppression is often required, and even kidney failure has been described suggesting that SS may represent an underdiagnosed cause of kidney failure in children [17, 23].

Conclusions

EGMs are a common issue in children with SS, and among these, kidney involvement plays a relevant role. Kidney implications may include both tubulointerstitial and glomerular damage, and a biopsy may reveal multiple different findings. Pediatric SS should be suspected in older children and adolescents, especially females, with hematuria, proteinuria, or impaired urinary concentrating ability, associated with salivary gland swelling and positive rates of ANA and anti-Ro/SSA antibodies. In addition, rare but life-threatening conditions may be observed, including periodic hypokalemic paralysis. Although the prognosis of kidney involvement in pediatric SS is typically favorable, the risk of developing

lymphomas seems to be greater, prolonged immunosuppressive therapies are usually necessary, and kidney failure can occur. Thus, it is critical to improve our knowledge about kidney involvement in pediatric SS to provide a prompt diagnosis and improve the disease management.

Key summary points

1. Pediatric Sjögren's syndrome accounts for approximately 1% of all forms of SS, representing a rare autoimmune disease in childhood.
2. The main clinical feature in children with Sjögren's syndrome is salivary gland enlargement, although sicca syndrome is also commonly observed. On the other hand, extraglandular manifestations are more significant than in adults.
3. Tubulointerstitial nephritis is the most frequent kidney injury in affected children, leading to kidney tubular acidosis and electrolyte disturbances such as severe hypokalemia, which can lead to periodic hypokalemic paralysis.
4. Glomerular damage is less common than tubular interstitial involvement. Several types of glomerulonephritis have been observed at kidney biopsy, and immunosuppressive drugs are usually required.
5. Treatment strategies for the kidney implications of pediatric Sjögren's syndrome lack strong recommendations and are based on case reports and case series. Specific classification criteria for children are needed to increase the diagnostic rate and improve outcomes.

Multiple choice questions

Answers are given following the reference list.

1. Which of the following statements is true about pediatric Sjögren's syndrome?

   A) Sicca syndrome is the most significant feature.
   B) Kidney involvement is not relevant in affected patients.
   C) Kidney failure has been observed due to severe kidney involvement.
   D) Current classification criteria are accurate enough for the pediatric population.

2. What percentage of children with Sjögren's syndrome has kidney manifestations?

   A) 5–20.5%
   B) 1–5%

   C) 45–70%
   D) 0.5–2%

3. Which of the following manifestations of tubulointerstitial nephritis is the most feared in children?

   A) Macroscopic hematuria
   B) Mild impaired urinary concentrating ability
   C) Periodic hypokalemic paralysis
   D) Severe proteinuria

4. What is the most serious long-term complication in pediatric Sjögren's syndrome with kidney involvement?

   A) Recurrent nephrolithiasis
   B) Persistent proteinuria
   C) Diabetes insipidus
   D) Extranodal marginal zone lymphomas

5. Which of the following classification criteria for Sjögren's syndrome includes kidney manifestation?

   A) The 2016 ACR/EULAR criteria for all patients with Sjögren's syndrome
   B) The 1999 criteria for children and adolescents with Sjögren's syndrome
   C) The 2002 AECG criteria for all patients with Sjögren's syndrome
   D) None of these

Declarations

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Answers: 1. C; 2. A; 3. C; 4. D; 5. B