

Nephrological disorders and neurological involvement in pediatric primary Sjogren syndrome: a case report and review of literature

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Case Report

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Abstract

Background: Sjögren syndrome(SS) is a rare disease in pediatrics, and little attention has been paid to the clinical feature in these patients. To date, there are few cases concern about neurological and nephrological disorders in childhood Sjögren syndrome. We describe a case of Sjögren syndrome in a 12-year-old girl who developed neurological disorders and interstitial nephritis and review the literature currently available on this topic. Case presentation: A 12-year-old girl was admitted to our hospital for arthritis and glucosuria. She was required to do labial gland and renal biopsy, because the positive for anti-nuclear antibody and anti-Sjögren syndrome B(anti-SSB) antibody. Then the biopsy was performed revealing the lymphocytic infiltrate in the small area and renal tubular interstitial damage,thus the diagnosis of Sjögren syndrome with tubular interstitial damage was made. Three months later, she presented again with headache, fever, nausea, vomiting and was recovered without drug therapy. Based on the patient's medical history, laboratory and imaging examination, and treatment, we speculate that the disorders of the nervous system were caused by the Sjögren syndrome. The girl has stable renal function and no residual nervous system damage in the next 1.5 years, but she underwent low dose prednisone therapy because of persistent renal glucosuria. Conclusion s: Nephrological disorders and neurological involvement are rare manifestations of Sjögren syndrome in children, and rarely presented as the initial symptoms. It should be suspected in children presenting with unexplained renal diseases, neurological abnormalities, or unexplained fever. Although there is no guidelines on the diagnosis and treatment of children Sjögren syndrome are currently available, early recognition and the appropriate treatment of renal damage and neurologic involvement would improve prognosis and prevent complications. Keywords : Neurologic manifestations, Kidney diseases, Sjogren's syndrome, Children

Background

Sjögren syndrome (SS) is a complex autoimmune disease characterized by inflammation of the lacrimal and salivary glands leading to keratoconjunctivitis sicca and xerostomia with up to half of affected adults developing additional extraglandular manifestations. It is one of the most common autoimmune rheumatic diseases in adults, and organ systems associated with extraglandular manifestations (EGMs) are frequently involved, including the nervous, pulmonary, and vascular system[1]. However, the incidence of primary SS in children is much lower than in adults, and the presentation of childhood Sjögren syndrome often differs between children and adults. To date, few cases of primary childhood SS combined with neurological disorders and nephrological damage have been reported in the literature. Here, we describe a case of juvenile Sjögren syndrome in a 12-year-old girl who developed arthralgia, neurological disorders, and interstitial nephritis.

Case Presentation

A 12-year-old girl presented to our clinic with left knee joint pain that had lasted for 7 days. The patient had no symptoms of fever, skin purpura, dry mouth, dry eyes, or parotitis. There was no past history of neck or face radiotherapy. Her physical examination revealed swelling in the left knee joint. Other physical findings were normal. Laboratory testing indicated normal complete blood counts and an erythrocyte sedimentation rate(ESR) of 33 mm (0–20 mm/h). The patient tested positive for glucosuria upon urine screening, but was negative for hematuria and proteinuria. Then, we administered an oral glucose tolerance test (OGTT) and measured glycosylated hemoglobin A-1c(HbA1c) to evaluate glucose intolerance. Eventually,she was diagnosed as having renal glucosuria (RG) with normal glucose tolerance and normal HbA1c. She also tested positive for anti-nuclear antibody(ANA) (1:100), anti-Sjögren syndrome B(anti-SSB/Ro), Perinuclear antineutrophil cytoplasmic antibody(P-ANCA)(1:10), and ESR (33 mm/h). Tests for anti-Sjögren syndrome A (anti-SSA/La), anti-Sm, anti-double stranded DNA(anti-dsDNA), anti-ribonucleoprotein(anti-RNP), anti-Scl70, anti-phospholipid, anti-Jo-1, anti-myeloperoxidase antineutrophil cytoplasmic antibody(anti-MPO-ANCA), rheumatoid factor (RF), anti-cyclic citrullinated peptide(anti-CCP) antibody, hepatitis B virus(HBV), hepatitis C virus(HCV), human immunodeficiency virus(HIV), IgG, IgA, IgM, C3, and C4 were negative or normal. Ophthalmological assessment revealed her schirmer's test was positive. Ultrasonography of shallow lymph glands showed enlarged lymph nodes in the bilateral parotid gland. Histopathological analysis of minor salivary gland biopsy showed a lymphocytic infiltrate around the ducts and acinus in the small area (> 50 lymphocytes/4mm²; Fig. 1). Renal biopsy showed tubular interstitial damage (Fig. 2). Light microscopy demonstrated previously unapparent proliferation of glomerular

mesangial cells, increases in mesangial matrix, tubular interstitial and acinus damage, renal tubule epithelial cell swelling and degeneration, focal tubular atrophy, and tubular epithelial cell fusion (< 5%), while an interstitial lymphoplasmacytic infiltrate was not obvious. Electron microscopy revealed partial foot process fusion and no other significant ultrastructural abnormalities. Immunofluorescence showed no deposition of immunoglobulins (IgG, IgA, and IgM) or complement (C3, C4, and C1q), and the kappa and lambda chains were also negative. Based on the 2012 American College of Rheumatology Classification (ACR) criteria for Sjögren syndrome and kidney biopsy, she was diagnosed as primary Sjögren syndrome (pSS) with tubular interstitial damage. Her treatment consisting of celebrex (200 mg/d) and hydroxychloroquine (100 mg/d) was administered during the first week, with hydroxychloroquine (200 mg/d) and sulfasalazine enteric-coated tablets (400 mg/d) during the next half year of treatment. After the first 2 months of treatment, the girl's joint pain was in complete remission and the complete blood counts and erythrocyte sedimentation rate were all normal. Three months later, she developed temporal headache, which was intermittent, being worst in the afternoon and relieved in the morning. The next day, she began to have a fever of 38.8°C with nausea and vomiting. With worsening symptoms, the patient came to our hospital directly, where an MRI scan of the brain was normal (Fig. 3). Her physical examination showed superficial sensation disorder in the upper limbs and Kernig signs. Complete blood counts, c-reactive protein, procalcitonin, and the erythrocyte sedimentation rate were all unremarkable. For further investigation, lumbar puncture was performed, which revealed normal cerebrospinal fluid (CSF) pressure (> 125 mmH₂O). High leucocyte counts of 30 cells 10⁶ L with lymphocytic predominance (60%), a CSF glucose level of 3.1 mmol/L, a chlorine level of 126.1 mmol/L, and a CSF protein level of 206 mg/L were noted. Cytology of the CSF showed large lymphocytes and occasional histiocytic cells with normal morphology. Bacterial culture of the CSF was negative. Virus antibody testing of the CSF was negative for herpes simplex 1 and 2, cytomegalovirus, echovirus, coxsackievirus, and Epstein-Barr virus. Cryptococcus neoformans and Mycobacterium tuberculosis were also not found in the CSF. After these test results, she was diagnosed with aseptic meningoencephalitis but we could not exclude the possibility of viral meningitis. Therefore, the patient was treated with intravenous acyclovir. However, due to drug allergy, we stopped acyclovir treatment early. After three days, her headache and rash were significantly relieved. Based on the patient's medical history, CSF examination, and treatment, we speculate that the disorders of the nervous system were more likely caused by the pSS. During the follow up of 1.5 years, her renal function was stable and no residual nervous system damage was apparent. She underwent low dose prednisone therapy (5–10 mg/d) for half a year because of persistent renal glucosuria.

Discussion And Conclusions

We aimed to review all full-text, peer-review publications reporting childhood Sjögren syndrome with kidney or nerve damage. Records were identified from the PubMed, EMBASE databases. The search terms were primary Sjögren syndrome, child, children, and childhood. Results were limited to case reports written in English. The search date was December 23, 2019.

The initial search yielded 511 articles, after excluding the duplicate articles and reading titles and abstracts, 61 papers were then read in detail. Finally, 20 case reports were included in the literature review after extracting and analyzing the data from the articles (Fig. 4). The information that was extracted from the papers were as follows: references and year, age and gender of patient, symptoms at onset, dry eyes or mouth, parotitis, neurologic manifestation, renal damage, elevated ANA, presence of anti-SSA and SSB antibodies, ESR, RF, hyperglobulinemic, schirmer test, CSF, renal and salivary gland biopsy and immunomodulatory therapy (Table 1)[2–21].

Primary Sjögren syndrome is an autoimmune disorder that causes inflammation and injury to the exocrine glands[22], predominantly the lacrimal and salivary glands, resulting in dry eyes and mouth (sicca syndrome). There are few reports on childhood primary Sjögren syndrome, because SS is more common in adults than in children. The female to male ratio in adults is 9:1, and joint problems were present in 30%-50%, while the incidence of kidney disease varies from 0.3% to up to 33.5%, depending on the study[23–27]. Other extraglandular diseases, such as cutaneous vasculitis, pulmonary manifestations, and peripheral nervous system manifestations occur in less than 10%[22]. In children, the sex ratio was 83-92.3% female[28, 29], and the most frequent symptom was parotid swelling, which was present in 42.3–53%, while central nervous system symptoms were present in 8.7%, and renal manifestations were present in 9.9%-11.5%. Central nervous system and renal damage is uncommon in pediatric cases. We report a case of childhood pSS presenting with interstitial nephritis and neurological disorders.

We reviewed all full-text articles on childhood primary Sjogren syndrome and focused on cases of pediatric pSS with kidney or nerve damage (Table 1). In the review, 20/22 children were female, and 10/22 children had neurologic manifestations, often prior to the diagnosis of pSS. We reported a case in a female pediatric patient that had fever and superficial sensation disorder in the limbs months after pSS was diagnosed. Neurologic disorders included the peripheral nervous system (PNS) and the central nervous system (CNS), and involved fever, headache, mental disorder, gaze deviation, lethargy, muscle weakness, urinary incontinence, hypalgesia, difficulty with ambulation, or ptosis. Until now, no studies have been performed on the epidemiology and characteristics of neurological damage in children with pSS. The prevalence of neurologic manifestations in adults ranges between 28% and 67.5% according to the different study populations and the definition or methods for the detection of neuropathy[30–32]. The studies showed that 46%–80% of adult patients with neurological symptoms developed such symptoms prior to the diagnosis of pSS[30, 31]. The frequency of constitutional symptoms and lung involvement was significantly higher in pSS with neurological involvement than in pSS without neurological involvement, and the articular symptoms were significantly less frequent in pSS with neurological involvement[33]. At present, the pathogenic mechanisms for most forms of neurological involvement in pSS have not been elucidated. However, several mechanisms have been considered to explain this involvement. In the development of PNS involvement in pSS patients, vascular or peripheral inflammatory infiltrates with or without necrosis may be found, and vasculitis of the vasa nervorum has also been proposed as a pathogenic mechanism[34–38]. These CNS disorders may be explained by three pathogenic factors. The first hypothesis involves the direct infiltration of the CNS by mononuclear cells[39]. The second hypothesis involves vascular injury that may be related to the presence of antineuronal antibodies and anti-Ro antibodies[40]. Finally, researchers[41–43] suggest that the underlying mechanism of CNS lesion development in pSS involves ischemia secondary to small vessel vasculitis.

In renal manifestations, the main damage in childhood pSS is tubulointerstitial nephritis (TIN), and the clinical features of renal involvement are proteinuria, hematuria, glucosuria, or alkaline urine. A literature review of pediatric pSS showed that renal manifestations were present in 9.9%, including renal tubular acidosis (RTA), membranous glomerulonephritis (MGN), hypokalemia, and interstitial nephritis[28]. Glomerular damage is rare, and we only found three cases, one report a case of pSS with mesangial proliferative glomerulonephritis and IgA deposits[8], another report a girl with pSS complicated by MGN[15], the last one reported a case of pauci-immune crescentic glomerulonephritis[12]. It has been proposed that the course of renal impairment might be shorter in the interstitial nephritis group, and the incidence of cryoglobulinemia and low C4 might be higher in the glomerulonephritis (GN) group[9]. The prevalence of renal involvement in adult pSS has been reported to range from 1% in some large retrospective registries, to 5–14% in most European studies, and > 30% in a cohort of 573 Chinese patients[44]. Unlike children, the renal damage in adults is manifested by overt or latent distal RTA, nephrogenic diabetes insipidus, and rarely, proximal RTA[27, 44, 45]. The frequency of GN in adults varies from 16.6 to 58.2% depending on race, center, and number of cases[23, 24, 46–48]. In renal biopsies of GN, membranoproliferative glomerulonephritis (MPGN) secondary to cryoglobulinaemia is the most common type, and other pathological types include membranous nephropathy, IgA nephropathy, focal segmental glomerulosclerosis, minimal change disease, unspecified proliferative glomerulonephritis, crescentic glomerulonephritis, and global glomerulosclerosis[44]. A large cohort of adult pSS patients revealed that patients with TIN have a better prognosis and clinical outcome, while patients with GN have a less favorable prognosis and a higher risk of developing lymphoma, which is related to cryoglobulinemia.

From the review, except the girl we reported, 20 of 21 children were positive for ANA and anti-SSA, while, 8 out of 20 were anti-SSB negative. This result is consistent with previous observations that the positive rate of ANA and anti-SSA is higher than anti-SSB in adults and children[32, 49, 50]. From a systematic review of primary Sjogren syndrome in pediatric populations, the presence of anti-SSA (Ro), anti-SSB (La), and anti-nuclear antibodies (ANA) was positive in 36.4–84.6%, 27.3–65.4%, and 63.6–96.2%, respectively[50]. New research showed that patients positive for both anti-SSA and anti-SSB had a substantially higher risk of cerebral infarction and venous thromboembolism than the general population[51].

Meanwhile, we also found an interesting phenomenon, hyperglobulinemia presented in 12 cases, and 11/12 were IgG, only 3 cases were IgA. High IgG levels are a common feature of SS and might reflect greater B cell activation[52]. Research showed that patients with high IgG levels had a higher prevalence of purpura and immunological markers (ANA, RF, anti-SSA, and anti-SSB)[53]. All of the 3 cases with high IgA had renal damage, so we speculated whether IgA participated the pSS and kidney

disease at the same time. Plasma cells producing IgA rather than IgG or IgM are dominantly observed in the salivary glands of SS patients [54]. Enrichment of anti-SS-B IgA antibodies in the saliva of patients with SS may suggest enhanced local synthesis of anti-SS-B IgA [55]. The presence of IgA autoantibodies against M3 muscarinic acetylcholine receptors is also considered to be a pathophysiological factor of primary SS[56]. These findings suggest that abnormal immunity of IgA production may be attributable to SS, but unfortunately immunofluorescent findings of the 3 children indicated no deposition of IgA. More extensive investigations will be needed to support the hypothesis.

All the patients in our report received immunomodulatory therapy including glucocorticoid, azathioprine, rituximab, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, and methotrexate. At present, the treatment of childhood pSS presenting with renal and nerve damage lacks large-scale evidence-based medicine and is mostly based on clinical experience. Although the long-term outcome of renal damage in pediatric pSS is usually good, glucocorticoids were often used in pediatric cases with RTA and TIN, and chronic immunosuppression is needed for the glomerular involvement often associated with a progressive course[5, 7, 57]. Long term outcomes may be related to the improvement in overall survival rate, renal survival rate, and complete remission rate of renal disease in childhood pSS treated with immunosuppressive therapy. From our review, steroids (1 mg/kg/day) were often used as the initial immunosuppressive treatment in pediatric pSS patients with TIN or GN. However, the outcome of children presenting with neurological diseases in the review is relatively less favorable. All the cases here reported residual neurologic manifestations, even though these children received steroids (1–2 mg/kg/day) or other immunosuppressive therapies. Kornitze[3] reviewed reported cases of childhood Sjogren syndrome with CNS complications in which 10 of 10 cases received steroid therapy and 7 of 10 patients had residual neurological deficits at follow-up. The effectiveness of glucocorticoids combined with other immunosuppressants in children still requires further study.

The frequency of renal damage and neurologic involvement in childhood pSS is much lower than in adults, and the clinical symptoms may be significantly different than what is seen in adults. If children present with unexplained renal diseases, neurological abnormalities, and unexplained fever, pSS should be considered. Special serological screening tests should be added to routine laboratory tests, while kidney biopsy may contribute to assessing the extent of renal damage and the need for immunomodulatory therapy. Early recognition and the appropriate treatment of renal damage and neurologic involvement would improve prognosis and prevent complications. Long term follow-up is essential for these children due to the possibility of rapid progression.

Abbreviations

SS: Sjögren syndrome; pSS: primary Sjogren syndrome; EGMs: extraglandular manifestations; ESR: erythrocyte sedimentation rate; OGTT: oral glucose tolerance test; HbA1c: glycosylated hemoglobin A-1c; RG: renal glucosuria; ANA: anti-nuclear antibody; anti-SSB: anti-Sjögren syndrome B; P-ANCA: perinuclear antineutrophil cytoplasmic antibody; anti-SSA: anti-Sjögren syndrome A; anti-dsDNA: anti-double stranded DNA; anti-RNP: anti-ribonucleoprotein; anti-MPO-ANCA: anti-myeloperoxidase antineutrophil cytoplasmic antibody; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid; PNS: peripheral nervous system; CNS: central nervous system; TIN: tubulointerstitial nephritis; RTA: renal tubular acidosis; GN: glomerulonephritis; MGN: membranous glomerulonephritis; MPGN: membranoproliferative glomerulonephritis

Declarations

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Authors' contributions

JZ wrote the first draft of the manuscript and contributed to patient management. YZ contributed to patient management and to the literature review. MZ and XG contributed to the literature review. ZZ performed the radiological studies. QC critically

revised the manuscript and supervised patient management. All the authors read and approved the final version of the manuscript.

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Ethics approval and consent to participation

Parental informed consent for publication was obtained.

Consent for publication

Written informed consent was obtained from the patient's legal guardians for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Tables

Case	2	3	4	5	6	7	8	9	10	11
Reference	Yerramilli [2]	Arora [3]	Yerramilli [4]	Yerramilli [5]	Yerramilli [6]	Jung [8]	Igawa [9]	Yerramilli [10]	Yerramilli [10]	Kagan [12]
Age (Gender)	6/E	11/B	11/B	11/B	11/B	11/F	12/F	11/F	16/F	12/F
Symptoms at onset	fever, lethargy, irritability, rash	hematuria, proteinuria	fever, lethargy, irritability, rash	fever, lethargy, irritability, rash	fever, lethargy, irritability, rash	AKI				
Dry eyes or mouth	N	N	N	N	N	Y	Y	Y	N	NM
Parotitis	N	N	N	N	N	N	Y	Y	Y	Y
Neurological disorders	gaze deviation	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia
Neurological symptoms	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia	amblyopia
Renal damage	N	N	dRTA	dRTA	dRTA	dRTA	dRTA	dRTA	dRTA	hematuria, proteinuria
ANP	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Anti-Ro/SSA	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Anti-Cc/SSB	Neg	Neg	Neg	Neg	Neg	Neg	Pos	Neg	Neg	Neg
ESR	NM	NM	NM	NM	NM	NM	Pos	Neg	NM	NM
RF	Pos	Neg	Pos	Pos	Pos	NM	NM	NM	Neg	Neg
Hypertension	N	N	N	N	N	N	IgG	NM	IgM	NM
Schirmer test	Neg	Pos	Neg	Neg	Neg	Pos	Pos	Neg	NM	NM
CSF	Pos	Pos	Pos	Pos	Pos	NM	NM	Neg	NM	NM
Renal biopsy	NM	NM	MIN	MIN	MIN	IgA	TIN	NM	NM	crescentic GN, TIN
Salivary gland biopsy	Pos	Pos	Pos	Pos	Pos	NM	Pos	Pos	NM	NM
Immunomodulation	GC	GC	GC	GC	GC	GC	GC	GC	GC	GC AZA
Outcome	normal renal function	normal renal function	normal renal function	normal renal function	normal renal function	normal renal function				
Follow up (yr)	3	0.5	NM	NM	NM	4m	NM	3w	NM	1

Case	13	14	15	16	17	18	19	2021
Ref: DeGuzman [13]	Skalova [14]	Yoshida [15]	Berman [16]	Zawadzki [17]	Kobayashi [18]	Chang [19]	Ohno [20]	1 patient
Age (yr)	16/F	13/M	10/F	15/F	10/F	11/F	15/F	8/E 61E/F
Symptoms at onset	muscular weakness	hematuria	fever	headache	gait disturbances	uveitis	fever	weakness
		proteinuria	dizziness	vomiting				arthralgia
DrN eyes or mouth	N	N	NM	NM	N	N	Y	NM Y
PaNtitis	NM	N	NM	NM	Y	Y	Y	NM N
Numbness in limbs								
Neurologic examination		static weakness	<u>dysmetria weakness</u>	<u>proprioception</u>				N N superficial sensat
slurred speech								impair
Renal damage	dRTA	hematuria	N	dRTA	dRTA	N	dRTA	dRTA
	proteinuria	proteinuria						glucosuria
ANeg	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
ANeg/SSA	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
ANeg/SSB	Pos	Pos	Pos	Pos	Neg	Pos	Neg	Pos
ESRM	Pos	NM	Pos	NM	Pos	Pos	Pos	Pos
RFNM	Pos	NM	Pos	NM	Pos	Pos	Pos	Pos
Hypos								
Immunoglobulinemic IgG		N	IgG	IgG IgA IgM	IgG IgM IgG	IgA	IgG	IgG
Schimmer test	NM	NM	NM	Neg	Pos	Neg	Pos	NM
CSF	Pos	NM	Pos	NM	NM	Pos	NM	NM
Renal biopsy	TIN	MGN	NM	TIN	TIN	NM	NM	NM
Salivary gland biopsy	NM	Pos	Pos	Pos	Pos	NM	Neg	NM
Immunomodulatory GC CSA	GC CSA	GC	GC CTX	GC CTX	GC CTX	GC	NM	GC
Outcome	recover	urine protein stable	hematuria	tubular acidosis	stable	stable	NM	symp
visual impairment								improved
difficulty walking								
Follow up (yr)	1m	2m	11m	14m	5	3	3	2m

*F, female; M, male; Y, yes; N, no; m, months; w, weeks; NM, not mention; Neg, negative; Pos, positive; GC, glucocorticoid; AZA, azathioprine; RTX, rituximab; HCQ, hydroxychloroquine; CTX, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; CSA, cyclosporine A; TAC, tacrolimus.

Figures

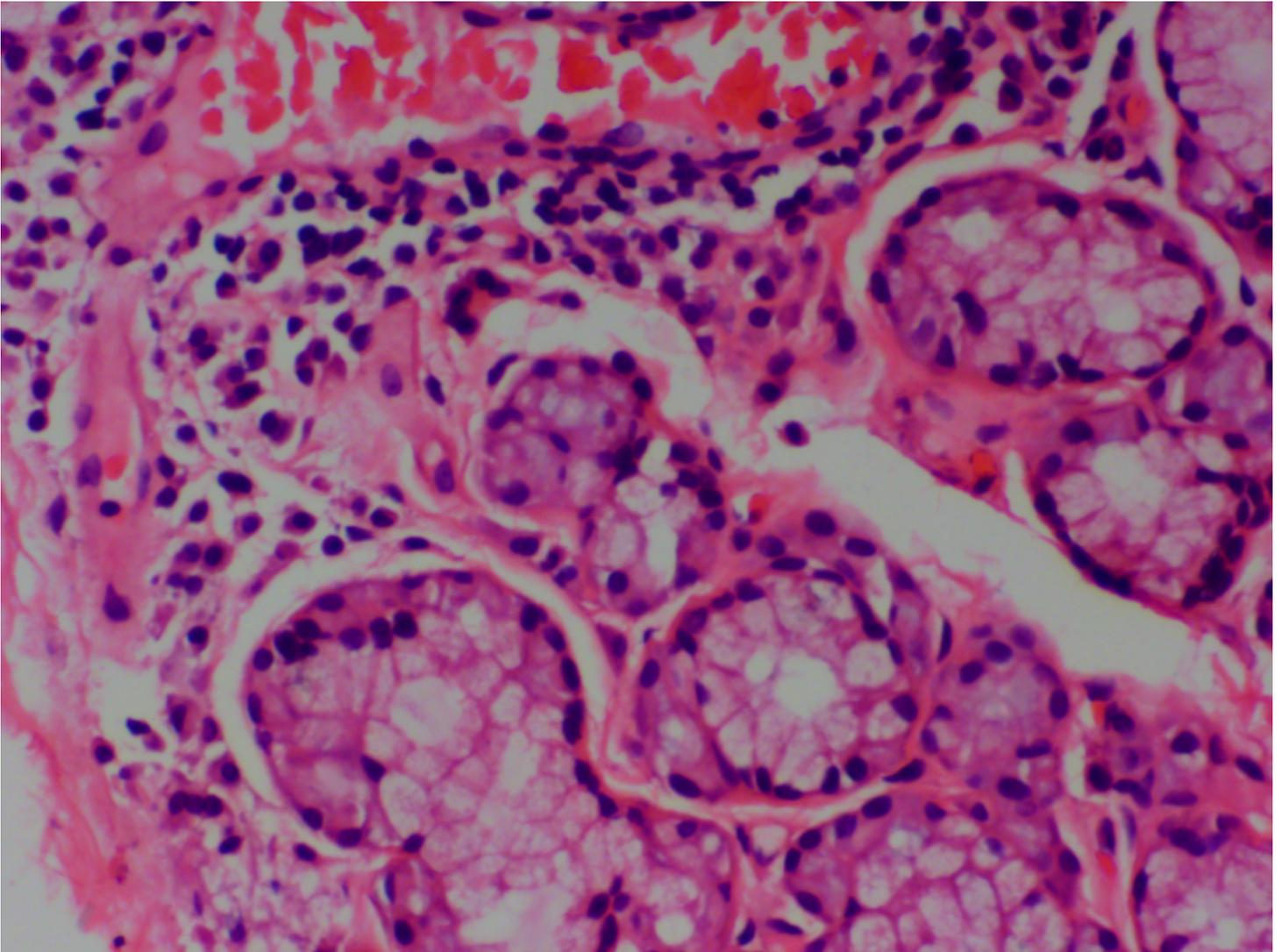


Figure 1

minor salivary gland biopsy

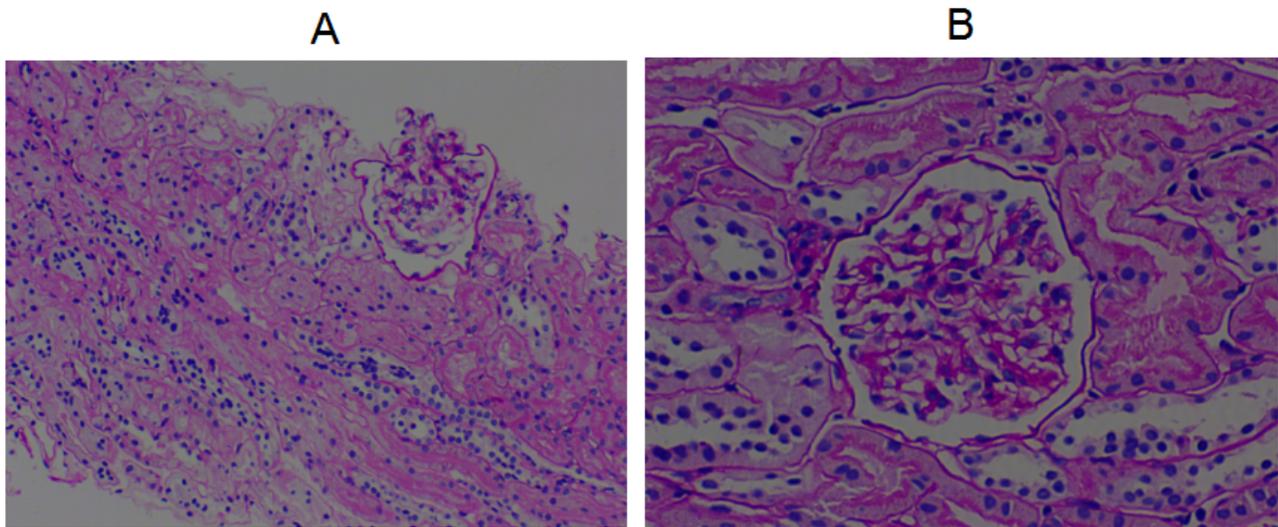


Figure 2. Kidney biopsy specimen. Light microscopy(Periodic Acid-Schiff stain, original magnification, $\times 100$, $\times 200$) demonstrated unapparent proliferation of glomerular mesangial cells, mesangial matrix increase,tubular interstitial and in acinus damage, renal tubule epithelial cell swell and degeneration, focal tubular atrophy, tubular epithelial cell fuse($<5\%$), interstitial lymphoplasmacytic infiltrate was not obvious.

Figure 2

Renal biopsy

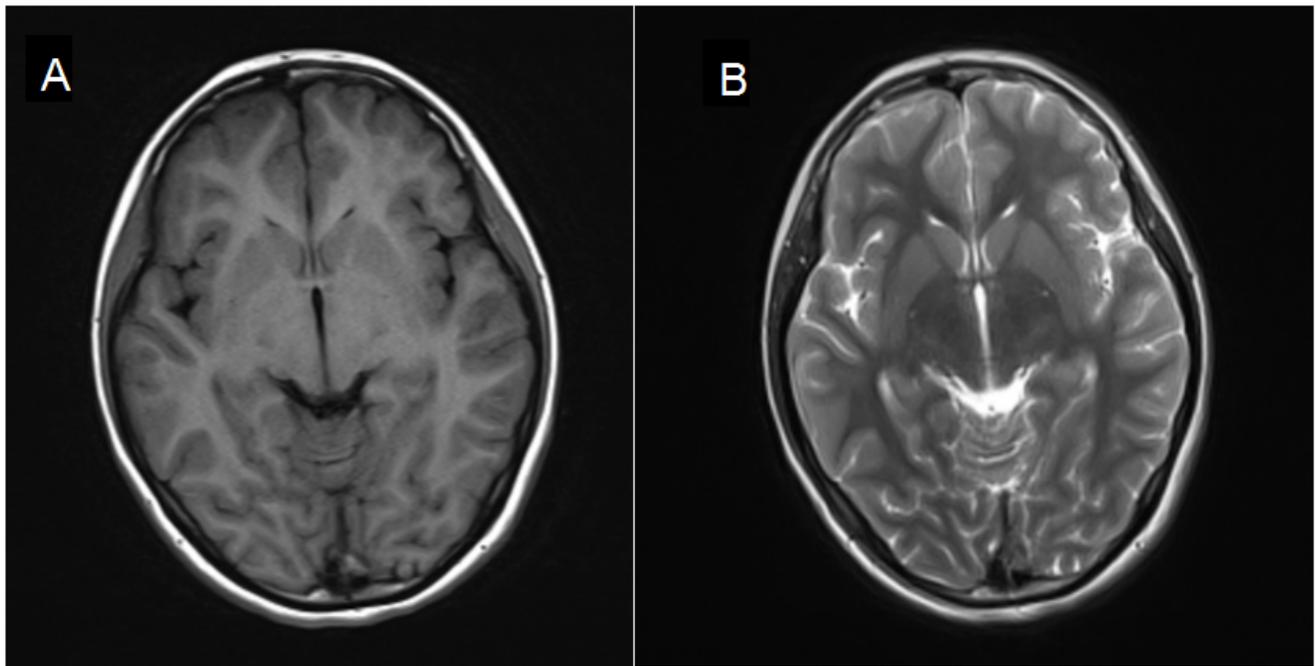


Figure 3. T1-weighted and T2-weighted image showing normal signal intensity in the parenchymal,brainstem and cerebellum. No abnormality was found in the shape, size and position of ventricle, cistern and sulci.

Figure 3

MRI scan of the brain

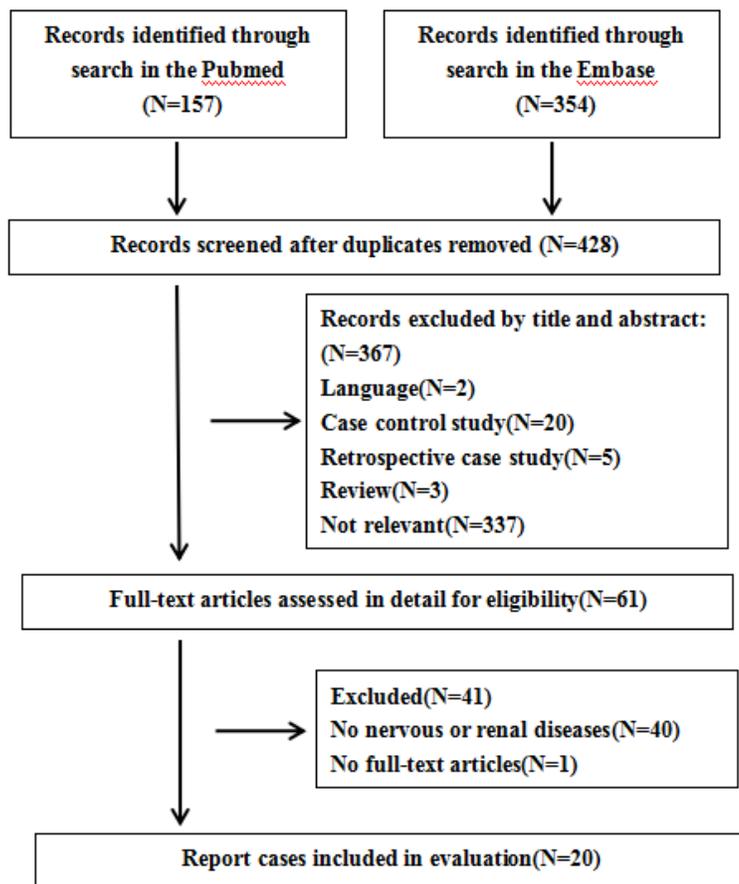


Figure 4

Case reports

Supplementary Files

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