Review

IgA vasculitis with nephritis: an overview of the pathogenesis and clinical characteristics

Y. Zhang[1,2], G. Xu[1]

[1]Department of Nephrology, the Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China;
[2]Grade 2021, the Second Clinical Medical College of Nanchang University, Nanchang, Jiangxi, China.

Yuxin Zhang, MD
Gaosi Xu, MD, PhD

Please address correspondence to.
Gaosi Xu
1 Minde Road,
Donghu District,
Nanchang 330006, China.
E-mail: gaosixu@163.com

Received on May 29, 2024; accepted in revised form on July 22, 2024.

Clin Exp Rheumatol 2025; 43: 728-741.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2025.

Key words: IgA vasculitis, IgA vasculitis with nephritis, pathogenesis, renal fibrosis

Funding: this study was supported by the National Natural Science Foundation of China (No. 82060138), the Key Projects of Jiangxi Natural Science Foundation (No. 20224ACB206008), the Key Projects in the Second Affiliated Hospital of Nanchang University (no. 2022efyB01), and the Thousand Talents Plan project of introducing and training high-level talents of innovation and entrepreneurship in Jiangxi Province (no. JXSQ2023201030).

Competing interests: none declared.

ABSTRACT

IgA vasculitis with nephritis (IgAVN) is closely related to IgA nephritis (IgAN) and IgA vasculitis (IgAV), but the clinical characteristics and exact pathogenesis of IgAVN remain unclear. In the present study, we have reviewed 8 clinical trials with different treatments and found that most IgAVN patients had partial recovery after treatments while few patients (26.5%) recovered completely within 6 months. Adding cyclophosphamide to mycophenolate mofetil was beneficial in children with severe kidney damage but was not effective in adults with serious organ damage (p=0.847). Tonsillectomy reduced the recurrence rate (p=0.03). In 18 reported cases we summarised, intravenous methylprednisolone pulse (MEP) combined with immunosuppressants (66.7%) and MEP combined with oral prednisolone (27.8%) were the two most commonly utilised treatments, and rituximab (40%) was the most frequently used monoclonal antibody. Mechanistically, activated cytotoxic T lymphocytes, natural killer cells, macrophage and completements contributed to the inflammation and endothelial cell apoptosis in IgAVN patients. Galactose-deficient IgA1 may be a threshold for IgAVN. The bulk formation of immune complexes and the decreased clearance rate led to the deposition of immune complexes. In severe cases, coagulation cascade would be triggered and thus caused renal fibrosis.

Introduction

Immunoglobulin A vasculitis (IgAV) was the most common vasculitis in children with an incidence of 20.4 cases/100,000 per year (1). Immunoglobulin A vasculitis with nephritis (IgAVN) was one of the most common and severe complications of IgAV, about 30% of IgAV patients developed nephritis (2). Microscopically, IgAVN patients exhibited the deposition of immune complexes and complements, along with crescents and renal fibrosis. The prognosis of IgAVN patients was associated with the severity of renal damage (2), and 13% of the patients developed severe renal failure (creatinine clearance <30 ml/min) (3). Furthermore, it had been observed that Asian patients tended to exhibit a higher frequency of severe kidney lesions and worse outcomes compared to Caucasians (4). Interestingly, tonsillectomy has not been shown to confer protection in the Caucasian population (4).

Currently, the pathogenesis of IgAVN remains unclear. Studies found that Immunoglobulin A nephritis (IgAN) and IgAVN could developed successively in the same patient (5) and in different sets of twins (6), indicating there was a close correlation between IgAN and IgAVN. Galactose-deficient IgA1 (Gd-IgA) played an important role in IgAN and IgAVN patients, but its role in IgAV patients remained controversial (7, 8). Compared to IgAN, the endothelial injury inflammation was more prominent in IgAVN patients (8). Immune complexes were detected in all these three diseases, but their deposition varied.

This article reviewed up-to-date latest treatments in clinical trials of IgAVN and clinical characteristics of IgAVN patients, aiming to explore the treatment, prognosis and pathogenesis of IgAVN.

Treatments and efficacy in clinical trials of IgAVN

We searched on PubMed and Web of Science, with the combination of the following terms: "IgA vasculitis with nephritis", "treatments" and "clinical

trials" updated to May 29, 2024. The complete search strategy was shown in Supplemental material. Studies written in English and had the details of treatments and efficacy of IgAVN were included, but traditional Chinese medicine-related treatments were excluded.

There were 8 clinical trials on IgAVN concerning different treatments and efficacy with detailed information, as described in Table I. One study recruited 66 children with a median age of 8.9 years and illustrated that the percentage of patients with proteinuria decreased significantly from 80.3% to 11.5% within three months, while complete remission (CR) was only attained in 13 of 66 cases (26.5%) within 6 months of steroids and immunosuppressants (9). Geng *et al*. indicated that there was not significant difference in the efficacy of mycophenolate mofetil (MMF) and cyclophosphamide (CYC) in IgAVN children with nephrotic syndrome (p=0.074) after 12 months of follow-up (10).

A controlled study assessed the efficacy of intravenous methylprednisolone pulse (MEP) in combination with CYC, median 24 hour proteinuria in both groups decreased to 0.2 g/d. 26 (89.7%) patients treated with MEP alone had partial remission (PR), with 22 (88%, p=0.847) in the combination treatment, indicating that there was no benefit from adding CYC to MEP (11). Similar findings were also reported in Tarshish et al.'s study (12). However, other studies suggest the opposite, indicating that mycophenolate mofetil (MMF) combined with cyclophosphamide (CYC) may be beneficial in children with severe kidney diseases (13-15). IgAVN of at least IVb was proven in 37 patients aged 0-17. Crescents occurred in 60.7± 2.3% of 17 patients received CYC + MEP and 55.5±6.5% in 20 patients received MEP only. Proteinuria in patients received CYC was lower than that received MEP commencing 2 months into treatments. After the treatments, patients who received CYC had a larger reduction in median proteinuria from baseline than those who just received MEP (13).

In one trial treated with MEP and tonsillectomy, PR in MEP was 100%, while PR in MEP combined with tonsillectomy was 29 of 31 (93.5%, p=0.02). However, no patients relapsed after tonsillectomy, whereas 10 of 40 (25%, p=0.03) patients treated with only MEP relapsed (16). The decrease in recurrence rate was also found in IgAVN patients who received tonsillectomy (17). All IgAVN patients treated with MEP only relapsed while 33 of 48 (68.8%, p=0.02) patients relapsed after tonsillectomy. 47 of 49 (95.5%) IgAN patients had proteinuria CR after tonsillectomy with 25 of 49 (51.0%, p<0.001) in MEP only. 45 of 49 (91.8%) patients had haematuria remission after tonsillectomy and 23 of 39 (46.9%, p<0.001) patients in MEP treatment group. Similar findings were reported in a study showing that tonsillectomy was linked to higher rate of CR and lower rate of estimated glomerular filtration rate (eGFR) deterioration (18). However, a retrospective assessment found that tonsillectomy with MEP had no advantages compared with MEP alone at 12 months (19). Additionally, a study demonstrated that Caucasian patients who underwent kidney transplantation had a good allograft survival (64.0%), and 8 of 19 (42.1%) patients relapsed, with a recurrence incidence of 0.05/patient/year (20).

Additionally, Jauhola *et al*. compared the efficacy of cyclosporine A (CSA) and MEP in severe IgAVN patients, patients treated with CSA all achieved PR in 3 months and none of them needed extra immunosuppressive treatments, while only 7 (53.8%) patients with MEP had PR, indicating CSA was effective in severe IgAVN patients (21). Another study recruited 7 patients, 5 of whom had already undergone 1 to 3 immunosuppressive therapies, and all patients responded to CSA within an average of 1.4 months, suggesting CSA maybe useful for severe treatment-resistant patients (22).

To date, it was still lack of high quality of large sample randomised clinical trials, and the main objects of treatments were suppressing inflammation, reducing proteinuria and relieving kidney damage. Typically, only those with severe nephritis needed to be actively treated. Prednisolone remain the most commonly used therapy in patients with nephropathy progressing, especially for those in the early-stage and had not developed renal fibrosis (23, 24). There were also emerging combination therapies, such as MEP combined with immunosuppressants, but whether the additional combined therapy was more effective still needed further research (11, 13). Additionally, Fujinaga *et al*. pointed out that treatments for severe IgAVN patients with extensive life expectations should focus both relieving symptoms and achieving CR without continues renin-angiotensin system (RAS) inhibitor therapy (25). Prevention of developing nephritis was a primary concern in IgAV patients without nephritis (26). Notably, corticosteroids could effectively treat the extrarenal symptoms of IgAV, but their efficacy in preventing the progression in nephritis was limited (27).

Clinical characteristics of patients with IgAVN

The majority of the current clinical research focused on treating children because children had higher rate of incidence. In Table I, a total of 347 (83.0%) children and 71 (17.0%) adults were recruited, comprising 226 (54.1%) male and 192 (45.9%) female. In Table I, adults exhibited higher creatinine levels (99.8 *vs*. 68.4 μmol/l) and a lower eGFR rate (67.3 *vs*. 107.3 ml/min/1.73 m^2), suggesting that the severity of conditions in adults may be more pronounced.

Additionally, a literature search on PubMed and Web of Science for relevant reports updated to May 29, 2024, was performed, using the combination of the following terms "IgA vasculitis", "therapy" and "cases". The complete search strategy was demonstrated in the Supplemental material. Studies written in English, reported cases of IgAV with renal involvement as the major characteristic and had sufficient data on treatments and outcomes were included.

There were 18 reported IgAVN cases, and we summarised them in Table II, including 6 (33.3%) patients with recurrence and 12 (66.7%) without recurrence. 13 were adults with an average age of 32.8 and 5 were children with an

Table I. Comparison of data in clinical trials of IgAVN.

Authors and year	2022 Butzer *et al*. (9)	2021 Geng *et al*. (10)	2020 Umeda *et al*. (16)	2011 Jauhola *et al*. (21)	2010 Pillebout *et al*. (11)	2008 Moroni *et al*. (20)	2004 Kawasaki *et al*. (13)	2004 Tarshish *et al*. (12)
Patients' selection criteria	Age 0-18 years proven by biopsy	Age 0-18 years, 24 h proteinuria reached the level of nephrotic syndrome	Age 0-18 years, no recurrent tonsillitis	Age 2-16 years, grade III–VI in biopsy	Age 18-84 years proven by biopsy	Had received a kidney transplantation, Caucasian	Age 0-17 years, IgAVN of at least IVb	Age >12 weeks <16 years, eGFR of at least 35 ml/min/1.73 m^2, biopsy ≥ grade III
Number of patients	66	T/C (33/35)	T/C (31/40)	T/C (11/13)	T/C (25/29)	19	T/C (17/20)	T/C (28/28) Non-trial 23
M/F	33/33	T (17/16), C (21/14)	T (17/14), C (17/23)	T (8/3), C (7/6)	T (17/8), C (17/12)	13/6	T (8/9), C (9/11)	42/37
Age (years, median/mean)	8.9 (6.1-11.4)	T 8.1 (6.8-11.2), C 8.3 (7.0-11.6)	T 6.4 (5.1-7.5), C 7.7 (6.2-10.7)	9.4	T (52.8±18.5), C (60.7±11.0)	29±12	T (7.9±3.1), C (8.0±2.8)	T (7.68±3.22), C (8.02±2.99), Non-trial (8.17±3.04)
Treatments	MEP, PSL, MMF, CYC, CSA, ACEi, AT1 antagonists	T: MMF, PSL, ACEi C: CYC, PSL, ACEi	T: Tonsillectomy, MEP C: MEP	T: CSA, ACEi C: MEP, ACEi	T: MEP, PSL, CYC C: MEP, PSL	CYC, Tacrolimus, AZA, MMF, MEP, Sirolimus	T: MEP, CYC C: MEP	T: CYC, supportive therapy C: supportive therapy
Microscopic haematuria, n (%)	20 (30.8)	T 10 (30.3), C 8 (22.9)	T 5 (16.1), C 4 (10.0)	T 11 (100), C 13 (100)	T 22 (95.7), C 23 (88.5)	-	-	-
Proteinuria	3.7 (1.9-6.4) g/g creatinine	T 112 (69.8-150.5) mg/kg, C 87 (62.0-253.0) mg/kg	-	-	T 3.6 (0-12) g/24h C 3.2 (0-21) g/24h	0.3±0.2 g/24h	T (181±85) mg/m^2/h C (154±13) mg/m^2/h	T (134.8±78.3) mg/m^2/h C (128.1±70.4) mg/m^2/h
eGFR (ml/min/ 1.73 m^2, median)	86.7 (75.3-118.0)	T 122.0 (108.0-147.0) C 127.5 (108.3-161.0)	T 109.2 (93.9-122.9) C 121.7 (113.0-138.2)	-	T 76 (9-132) C 60 (10-125)	-	-	T 93.9±35.6 C 103.4±48.5
Serum albumin (g/L)	33 (30-39.2)	T 33.0 (24.9-37.4) C 32.8 (26.4-37.3)	T 36 (29-41) C 34 (29-37)	-	T 30 (13-48) C 28 (13-37)	-	T (27±6) C (29±4)	T 2.45±0.82 C 2.46±0.85
Serum creatinine	-	-	-	-	T 88 (61-903) µmol/l C 110 (53-668) µmol/l	(13±4) g/l	T (71±48) µmol/l C (63±32) µmol/l	-
Crescents	48 (72.7%)	-	-	-	-	-	T (60.7±12.3%) C (55.5±6.5%)	T (36.0±31.2%) C (31.7±29.0%)
Hypertension, n (%)	15 (22.7)	T 3 (9.1) C 1 (2.9)	T 0 C 1 (2.5)	-	T 6 (24.0) C 15 (51.7)	16 (84.0)	-	-
Blood pressure (mmHg, mean)	-	-	-	-	T 130/74 C 134/77	-	T (87±10) C (83±14)	T (112±27.61) C (109±29.92)
Follow-up	6 months	1 year	T 3.4 (2.7-4.8) year C 7.7 (5.9-9.9) year	2 years	T 59.8 months C 60.9 months	(9.1±8.25) year	-	6 years
Outcomes	13 (26.5%) CR	T 27 (81.8%) CR C 27 (77.1%) CR	T 29 (94%) PR C 40 (100%) PR	T 11 (100%) PR C 7 (53.8%) PR	T 22 (88.0%) PR, 1 (4.0%) worsened C 26 (89.7%) PR	The actuarial 15-year patient survival was 80%, the death-censored graft survival was 64%	Proteinuria was 10±5 mg/m^2/h in patients treated with MEP and CYC, 29±29 mg/m^2/h in only MEP	T 13 (46.4%) CR, 8 (25.6%) PR C 14 (50%) CR, 6 (21.4%) PR
Recurrence	-	T 1 (3.0%) C: 0	T 0 C 10 (25.0%)	-	-	8 (42.1%)	-	31 (39.2%)

IgAVN: IgA vasculitis nephritis; T: treatment group; C: control group; MMF: mycophenolate mofetil; PSL: oral prednisolone; CYC: cyclophosphamide; CSA: cyclosporine A; AZA: azathioprine; ACEi: angiotensin converting enzyme inhibitor; AT1: angiotensin II receptor subtype 1; IgAN: IgA nephritis; MEP: intravenous methylprednisolone pulse; eGFR: estimated glomerular filtration rate; CR: complete recovery; PR: partial recovery.

average age of 11.6. Of them, male was 8 (44.4%) and female was 10 (55.6%). 3 (16.8%) had clinical symptoms of purpura, 7 (38.9%) had a history of hypertension. 16 (88.9%) patients had clinical symptoms of purpura, 7 (38.9%) had abdominal pain, 5 (27.8%) had arthritis, and 3 (16.7%) had oedema. All but one patient developed haematuria and proteinuria symptoms. Low creatinine clearance was seen in 2 patients who underwent creatinine clearance test, indicating probable renal function impairment. Of the 5 patients who underwent C-reactive protein (CRP) testing, all showed elevated levels of CRP. 3 of 11 (27.3%) showed elevated serum creatinine levels. 8 of 14 (57.1%) had reduced serum/plasma albumin levels.

Mesangial hyperplasia was the most common (61.1%) renal lesion in IgAVN (28). Crescents developed in 9 instances (50%) and glomerulosclerosis were found in 3 cases (16.7%). All patients who underwent immunofluorescence found IgA deposition, while some patients also had deposition of IgG, IgM, C3, C4, and fibrin.

At present, there are two main treatment methods, one is MEP combined with immunosuppressive therapy (66.7%), the other one is MEP combined with oral prednisolone (PSL)

Table II. Summary of reported cases of IgAVN.

n.	Author	Age/Sex	Medical history	Symptoms	Urinalysis	Blood test	Key diagnostic tests	Treatments	Outcomes
1	Khor *et al*. (117)	50/M	Chronic tobacco use, hypertension, chronic obstructive pulmonary disease, and alcoholic cardiomyopathy	Purpuric rash over bilateral upper, lower extremities, joint pain over bilateral hands and ankles	Proteinuria, haematuria	Serum albumin of 3.1 g/dL, serum erythrocyte sedimentation rate (ESR) 30 mm/h	Skin biopsy, renal biopsy, immunofluorescence study	oral lisinopril, PSL	Skin rash resolved, blood pressure was well-controlled, proteinuria improved
2	Mizerska-Wasiak *et al*. (118)	14/M	Had appendicitis and underwent an appendectomy	Symmetrical purpura on legs and buttocks, abdominal pain, joint swelling of elbow, wrist, ankle, and thumb occurred, renal function deteriorated	Proteinuria of 59.3 mg/dL, haematuria of 25-30 HPF	Creatinine level was 0.88 mg/dL, GFR 82 mL/min/1.73m^2	Renal biopsy, immunofluorescence study	PSL, MEP, azathioprine (AZA), ganciclovir, acyclovir, cyclophosphamide (CYC), MMF, isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA)	The general condition and renal function and renal function were improved
3	Hou *et al*. (119)	12/F	-	Leg purpura, abdominal pain, proteinuria, haematuria	Proteinuria, haematuria, estimated glomerular filtration rate (eGFR) was 116 mL/min/1.73m^2	Serum creatinine (SCr) was 51 mmol/L, serum albumin was 40.5 g/L	Renal biopsy, immunofluorescence study	MEP, leflunomide, captopril	Patient had no recurrence of skin rash or abdominal pain, renal functions are normal, proteinuria 8 mg/kg/day
4	Hou *et al*. (119)	12/M	Leg purpura for a month	Leg purpura, proteinuria, haematuria	Proteinuria, haematuria, eGFR was 124 mL/min/1.73m^2	SCr was 53.6 mmol/L, serum albumin was 40.7 g/L	Renal biopsy, immunofluorescence study	MEP, leflunomide, captopril	No recurrence of skin rash, no detectable urinary protein, renal functions are normal, and no hypertension
5	Hou *et al*. (119)	11/F	-	Leg purpura, bilateral swelling of the wrists and knees	Haematuria, proteinuria, eGFR was 121 mL/min/1.73m^2	SCr was 30.2 mmol/L, serum albumin was 37.9 g/L	Renal biopsy, immunofluorescence study	MEP, leflunomide, captopril	No recurrence of skin rash, no detectable urinary protein, renal functions are normal
6	Hou *et al*. (119)	11/F	-	Leg purpura, bilateral swelling of the wrists	Haematuria, proteinuria, eGFR was 119 mL/min/1.73m^2	SCr was 29.8 mmol/L, serum albumin was 39.2 g/L	Renal biopsy, immunofluorescence study	MEP, leflunomide, captopril	No recurrence of skin rash, no detectable urinary protein, renal functions are normal, and no hypertension
7	Hou *et al*. (119)	12/M	-	Leg purpura	Haematuria, proteinuria, eGFR was 120 mL/min/1.73m^2	SCr was 39.4 mmol/L, serum albumin was 33.9 g/L	Renal biopsy, immunofluorescence study	PSL, leflunomide, captopril	No recurrence of skin rash, no detectable urinary protein, renal functions are normal
8	Lundberg *et al*. (58)	19/F	Purpura	Purpura, abdominal pain, arthralgia	Proteinuria, haematuria, urine albumin:creatinine ratio (ACR) 538 mg/mmol	C-reactive protein (CRP) 28 mg/L, creatinine 99 µmol/L, p-alb 34 g/L	Skin biopsy, renal biopsy	MEP, PSL, RTX, OFAB	Albuminuria had been < 200 mg/day, creatinine had been normal
9	Lundberg *et al*. (58)	49/F	Asthma, severe eczema	Abdominal pain. Haematochezia, purpura, mild eosinophilia, oedema	U-sediment 11-20 ervs/hpf, no granular casts, the urine ACR was in the nephrotic range	Creatinine 102 µmol/L, p-alb 23 g/L, CRP 50 mg/L	Skin biopsy, renal biopsy	BSM, MEP, RTX, MMF, AZA	Creatinine improved, the urine ACR <250 mg/mmol
10	Lundberg *et al*. (58)	28/F	A family history of IgAVN, macrohematuria without rashes	Macrohematuria, fever, a skin rash on the buttocks in conjunction with a viral upper respiratory tract infection	Proteinuria, haematuria	Creatinine 217 µmol/L, p-alb 29 g/L, CRP 36 mg/L	Skin biopsy, renal biopsy	MEP, PSL, RTX	Proteinuria continued to decrease, the urine ACR was 8.8 mg/mmol
11	Lundberg *et al*. (58)	19/M	Kidney stone	Fever, sore throat, haematuria	Proteinuria, haematuria	Creatinine 228 µmol/L, p-alb 28 g/L, CRP 98 mg/L	Renal biopsy, histologic examination	MEP, RTX, MMF	Proteinuria, microhaematuria and creatinine began to increase

n.	Author	Age/Sex	Medical history	Symptoms	Urinalysis	Blood test	Key diagnostic tests	Treatments	Outcomes
12	T. Yamakawa *et al*. (30)	29/F	IgAV	Purpura, abdominal pain, macrohematuria, proteinuria	Proteinuria, haematuria	-	Renal biopsy	MEP, tonsillectomy	Proteinuria gradually decreased to less than 140 mg/d, haematuria disappeared within 6 months, SCr level were stable (1.0-1.2 mg/dL)
13	Tanaka *et al*. (32)	29/F	-	Purpura, oedema of the lower legs	Proteinuria, haematuria	Serum concentration of albumin 2.8 g/dL, serum concentration of cholesterol 217 mg/dL	Renal biopsy, immunofluorescence study	MEP, CYC	Mild interstitial dilatation with tubular atrophy disappeared, the degree of deposition of IgA and IgM particles in the mesangium of the glomerulus reduced, hypercellularity in the capillaries improved
14	Ishiguro *et al*. (34)	68/F	-	Lower limb oedema, purpura, proteinuria	Proteinuria, haematuria, the protein:creatinine ratio (PCR) in the urine was 10.4 g/gCr, creatinine clearance was 67.6 mL/min	Serum albumin 1.8 mg/dL, IgG 301 mg/dL, IgA 144 mg/dL, IgM 46 mg/dL, C3 96 mg/dL, C4 35 mg/dL, CH50 46.2 U/mL	Renal biopsy, immunofluorescence study	Half-dose pulse steroid therapy, PSL, CYC, RTX	Proteinuria relieved, the serum CD19/20-positive B-cell count remained low
15	Pillebout *et al*. (29)	22/M	-	Arthralgia of the knees and ankles	Proteinuria (1.1 g/day), haematuria	SCr 95 μmol/L, serum albumin 44.9 g/dL, CRP 51 mg/L	Renal biopsy, immunofluorescence study	RTX	No new rash, no haematuria and proteinuria, SCr was 70 μmol/L, albumin 41.7 g/L, CRP 9 mg/L
16	Sugiyama *et al*. (31)	25/M	Upper respiratory tract infections	Purpura, abdominal pain, gross haematuria, arthralgias	Proteinuria, haematuria, creatinine 1.17 mg/dl, urea nitrogen 15.0 mg/dl, uric acid 9.6 mg/dl, creatinine clearance 56.0 ml/min, the urine volume 1,800 ml/day	Total protein 6.28 g/dL, albumin 3.31 g/dl, total cholesterol 271 mg/dl	Renal biopsy, immunofluorescence study	Tonsillectomy, MEP, PSL, antiplatelet drugs and enalapril	Proteinuria was 0.4 g/d, no microhaematuria was observed, the level of serum IgA decreased to 91.4 mg/dl
17	Kusuda *et al*. (33)	26/F	-	Purpura, abdominal pain and melena	Proteinuria, haematuria	IgG level decreased	Renal biopsy, immunofluorescence study	Heparin, MEP, IV-IG	Proteinuria disappeared
18	Schmaldienst *et al*. (35)	49/M	-	Colic and abdominal pain, arthralgias of the ankle and knee joints, purpura	Renal disease had not been noted at the onset of the disease	-	Renal biopsy	Oral antibiotics, high-dose prednisolone, cyclosporin A	Patient developed heavy proteinuria and haematuria during the high-dose steroid therapy and got complete remission after cyclosporin A

ESR: serum erythrocyte sedimentation rate; PSL: oral prednisolone; MEP: intravenous methylprednisolone pulses; AZA: azathioprine; CYC: cyclophosphamide; INF: isoniazid; RMP: rifampicin; PZA: pyrazinamide; eGFR: estimated glomerular filtration rate; SCr: serum creatinine; ACR: urine albumin:creatinine ratio; CRP: C-reactive protein; p-alb: plasma albumin; RTX: rituximab; OFAB: methyl benzenesulfonate; MMF: mycophenolate mofetil; PCR: the protein:creatinine ratio; IV-IG: intravenous immunoglobulin.

treatment (27.8%). Rituximab (RTX, 40%), leflunomide (33.3%), MMF (20%) and CYC (20%) were used more frequently in immunosuppressive therapy and some patients received multiple immunosuppressants. One patient was treated with RTX only, and had a good improvement (29). 16 patients had been cured with 1 patient had not fully recovered and 1 lost follow-up. Additionally, cases showed that tonsillectomy combined with MEP may be beneficial to recurrent IgAVN patients (30, 31). For steroid-resistant IgAVN patients, CYC was effective for the formation of crescents and the immune complexes deposition (32), and high-dose intravenous immunoglobulin (IV-IG) should be considered (33). RTX (34) and cyclosporine A (35) might be helpful for patients with nephrotic syndrome.

The pathogenesis of IgAVN and IgAV

The pathogenesis of IgAVN

The pathogenesis of IgAVN remains unclear. There were 21 articles con-

Table III. Summary of literature concerning the pathogenesis of IgAVN.

n.	Authors	Published year	Research method	Factors involved in the pathogenesis of IgAVN
1	Zhu *et al*. (49)	2023	Determine AZGP1 in the urine of IgAVN patients by diaPASEF	A damaged kidney will overexpress AZGP1, which may worsen the kidney damage
2	Wright *et al*. (39)	2023	Children with IgAV (37 without nephritis, 10 IgAVN) were recruited, 26 healthy children and 30 children with SLE were controls. ELISA was used to assess urinary C3, C4, C5 and C5a	Complements played roles in the pathogenesis of IgAVN
3	Marro *et al*. (120)	2022	ELISA was used to quantify the IgA concentrations in the urine and serum in 12 IgAVN, 35 IgAV without nephritis, 12 HC	Serum IgA1 was not associated with IgAVN
4	Irabu *et al*. (38)	2021	Patients underwent immunohistochemical analysis. The levels of AIM in the patients' serum and urine as well as HC were measured by ELISA	AIM played a role in the pathogenesis of IgAVN
5	Tang *et al*. (44)	2021	The s-Gd-IgA1 were assessed by lectin-based ELISA in 52 IgAN patients, 57 IgAVN patients, 26 IgAV patients, and 40 HC	Serum Gd-IgA1 played a role in the pathogenesis of IgAVN
6	Mizerska-Wasiak *et al*. (121)	2021	60 children (24 IgAN and 36 IgAVN) and 20 HC were recruited. Albuminuria, haematuria, serum creatinine, and IgA and C3 levels were measured at the beginning and end of follow-up, GFR was calculated	TNFR1 was not related to Gd-IgA1
7	Zhang *et al*. (45)	2020	Plasma IgA1 and Gd-IgA1 level were measured by ELISA in 112 IgAVN patients during renal biopsy	Gd-IgA1 was associated with the development and progression of IgAVN
8	Sugiyama *et al*. (8)	2020	s-Gd-IgA1 were measured by ELISA and KM55, g-Gd-IgA1 were detected by paraffin embedded sections stained with KM55 immunohistochemistry	s-Gd-IgA1 was associated with IL-6 elevation, g-Gd-IgA1 was associated with IL-8 elevation
9	Wu *et al*. (56)	2020	Serum TNF-α was determined by chemiluminescence immunoassay in 53 IgAVN patients, 53 IgAN patients and 53 HC	TNF-α was associated with IgAVN severity
10	Imai *et al*. (36)	2020	PBMCs were compared in 21 IgAV patients, 8 IgAVN patients and 20 HC. Renal biopsy samples and PBMCs were evaluated by immunohistochemistry analysis and flow cytometry. Serum CX3CL1 levels were evaluated by ELISA	Activated CTLs and NK cells played roles in the pathogenesis of IgAVN
11	Wang *et al*. (47)	2018	The glomeruli of 82 children were assessed by light microscopy and immunofluorescence	Glomerular fibrinogen deposition was associated with severe immune dysfunction, inflammatory response and glomerular injury
12	Saito *et al*. (41)	2016	The expression levels of TLRs mRNA in PBMCs of 20 patients with IgAVN, 49 patients with IgAN and 20 patients with thin basement membrane nephropathy were compared	The up-regulated expression of TLR mRNA in PBMCs was associated with the development of IgAVN
13	Hu *et al*. (37)	2016	25 IgAVN patients and 14 HC were enrolled. Flow cytometry was used to identify B cells subtype fractions in venous blood. ELISA was used to measure the serum interleukin levels	Bregs played roles in the pathogenesis of IgAVN
14	Tian *et al*. (48)	2015	The levels of plasma fibrinogen, d-dimer, and FDPs were measured in 89 children with severe IgAVN, before and after therapy	Fibrinolytic system may contribute to kidney damage
15	He *et al*. (50)	2015	The changes of serum proteomic profiles in 6 IgAV patients, 6 IgAVN patients and 7 HC were studies by high sensitivity nanoLC-MS/MS. Functional pathway analysis of differentially expressed proteins was performed by PANTHER and DAVID software. Several of the discovered differently proteins were subsequently confirmed by ELISA	Angiotensinogen played a role in the pathogenesis of IgAVN
16	Hilhorst *et al*. (65)	2011	20 IgAVN patients were recruited. Light and electron microscopy were used to examine renal biopsies for circulating IgA immune complexes. 40 IgAN patients were examined as controls	IgAVN was a circulatory immune complex disease
17	Takeuchi *et al*. (67)	2010	25 IgAVN adults with IgA deposition were recruited, clinical manifestations were compared	IgM deposition was associated with renal involvement
18	Hisano *et al*. (59)	2005	Renal tissues from 31 patients with IgAVN and 20 non-IgA glomerulonephritis controls were stained immune histologically with antibodies	Complement activation in IgAVN patients were triggered by alternative and lectin routes
19	Allen *et al*. (46)	1998	The binding of Vicia villosa lectin to serum IgA1 was studied in 24 IgAVN patients, 22 IgAV patients without nephritis, 7 patients with acute nephritic syndrome and 22 HC	IgA1 O-glycosylation played a role in the pathogenesis of IgAVN
20	Abou-Ragheb *et al*. (40)	1992	Plasma anaphylatoxins C3a and C4a were measured in46 patients with IgAN/IgAVN as markers of complement activation *in vivo*	C3a and C4a played roles in the pathogenesis of IgAVN
21	Conley *et al*. (122)	1980	Using monoclonal anti-IgA subclass reagents, anti-light chain reagents and anti-J chain reagents, patients with IgA deposited in glomeruli was assessed by immunofluorescence staining	IgA1 monomers predominated in the glomerular IgA deposits

diaPASEF, parallel accumulation-Sequence fragment combined Data Independent Acquisition; AZGP1, zinc-alpha-2-glycoprotein; IgAV, IgA vasculitis; IgAVN, IgA vasculitis nephritis; SLE, systemic lupus erythematosus; HC, healthy controls; ELISA, enzyme-linked immunosorbent assay; AIM, apoptosis inhibitor of macrophage; Gd-IgA1, galactose-deficient IgA1; s-Gd-IgA1, serum Gd-IgA1; KM55, anti-human Gd-IgA1 specific monoclonal antibody; g-Gd-IgA1, glomerulus Gd-IgA1; CTLs, cytotoxic T lymphocytes; NK cells, natural killer cells; TLRs, Toll-like receptors; IgAN, IgA nephritis; PBMCs, peripheral blood mononuclear cells; FDPs, fibrin degradation products; nanoLC-MS/MS, nanoscale ultra performance liquid chromatography-mass spectrometry; GFR, glomerular filtration rate.

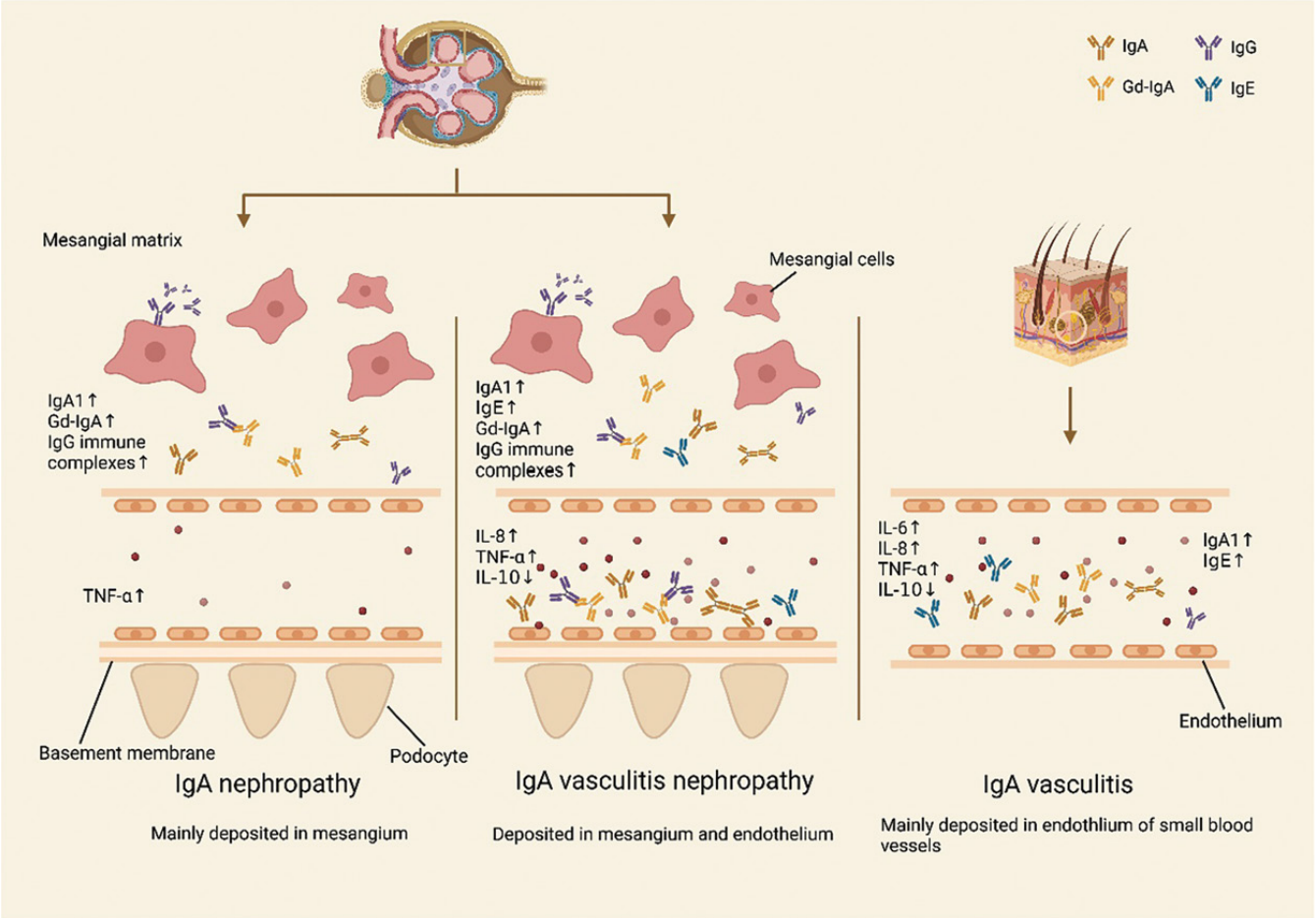

Fig. 1. Comparison of immune complexes deposition and main inflammatory factors in IgAN, IgAVN and IgAV. Immune complexes were found primarily in the mesangium of IgAN patients, as well as in the mesangium and endothelium of IgAVN patients and the endothelium of small vessels in IgAV patients. The level of IgA1 in all three diseases increased. There was no significant difference of immune complexes in IgAN and IgAVN in mesangium. Gd-IgA was discovered in IgAN and IgAVN patients, but not in IgAV patients without nephritis. The level of IgG immune complexes increased in IgAN and IgAVN patients and its level was higher in endothelium than in mesangium in IgAVN patients. Additionally, the level of IgE increased in IgAV and IgAVN. Inflammation in IgAN was less apparent than that in IgAV and IgAVN patients. The level of IL-8 and TNF-α significantly increased in IgAVN patients, compared with healthy individuals and IgAN patients. The figure was created with Biorender.com.

cerning the pathogenesis of IgAVN. We summarised the potential contributing factors to IgAVN, as described in Table III. Studies indicated that immune system played a vital role in the development and progression of IgAVN (36-41). Multi-hit pathogenesis model could explain some clinical manifestations of IgAVN (42, 43), and Gd-IgA1 was a crucial component in the pathogenesis of IgAVN (44-46). Coagulation-fibrinolysis system took an essential part, resulting in immune dysfunction, inflammatory response and kidney damage (47, 48). Additionally, zinc-alpha-2 glycoprotein (AZGP1) (49), angiotensinogen (50) and other factors were also involved in the development of IgAVN. The pathogenesis of IgAVN is described in Figure 2.

- The role of immune system in the pathogenesis of IgAVN

In IgAVN patients, cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells were activated and produced glomerular granulysin and granzyme B (36), resulting in endothelial cells apoptosis and renal vascular damage (51). Notably, this phenomenon had not been discovered in IgAVN patients (36). Increased apoptosis inhibitor of macrophage (AIM) was observed in IgAVN patients (38). AIM had an impact on promoting the information of immune complexes in glomeruli (52), thus led to endothelial damage and aggravated inflammatory response (53). According to a study, the serum IL-10 in IgAVN patients decreased, and eGFR was positively correlated with serum IL-10 (37). IL-10 directly inhibited the infiltration and activation of glomerular macrophages (54). Therefore, we supposed that activated macrophage contributed to the inflammatory response and kidney damage. Studies demonstrated that IgAVN patients had higher levels of neutrophils (NE), neutrophil-to-lymphocyte ratio (NLR) and white blood cells (WBC) than IgAN patient, and the difference in NE was prominent (55), and the role of NE in leading to IgAVN was similar to IgAV. TNF-α was elevated in IgAVN patients, compared with IgAN patients (8) and healthy controls (56). TNF-α binding to tumour necrosis factor receptor 1 (TNFR1) would induce the inflammation and tissue damage (57). A study proved regulatory B cells was

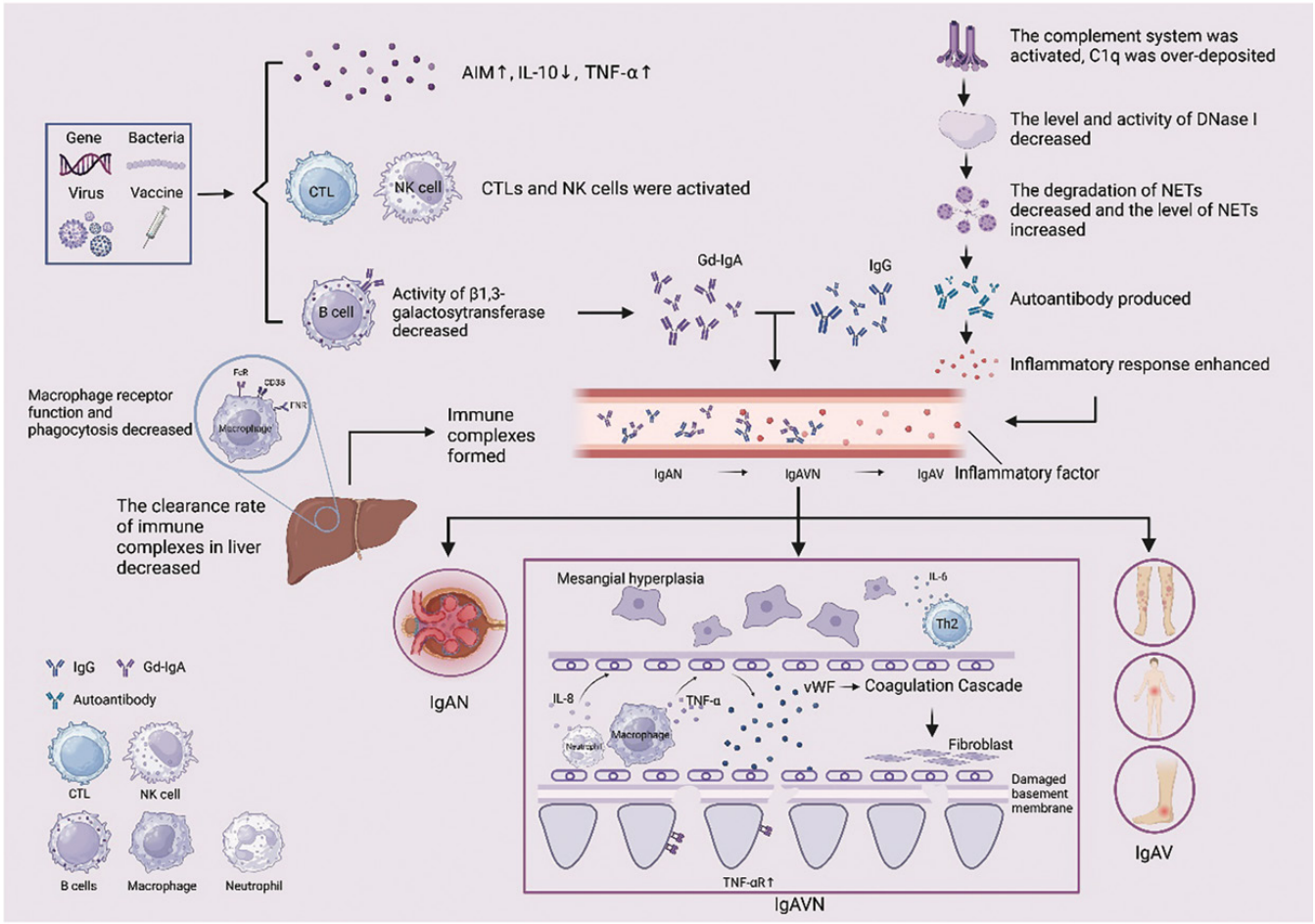

Fig. 2. The pathogenesis of IgAVN, compared with IgAN and IgAV. Similarities were found in the formation of Gd-IgA and immune complexes in IgAN and IgAVN, and strong inflammatory response were discovered in IgAV patients and IgAVN patients, but the progression of renal fibrosis and the development of crescents had specificity in IgAVN patients. Environmental and genetic factors contributed to the development of IgAVN, leading to the decreased IL-10, increased AIM and TNF-α, and activated CTLs and NK cells. Similar to IgAN, activity of β 1,3-galactosyltransferase in B cells decreased, resulting in the formation of Gd-IgA. Immune complexes formed when Gd-IgA combined with IgG. In IgAVN patients, the clearance rate of immune complexes in liver decreased because of the overproduction of immune complexes and the saturation of macrophage receptor. The immune complexes deposited in the kidneys, leading to mesangial hyperplasia and sclerosis of the glomeruli. In patients with IgAV and IgAVN, complements were over-activated, leading to the reduction of DNase I and activation of NETs. Thus, autoantibodies produced, contributing to strong inflammation. The immune complexes deposited in kidney and inflammatory triggered renal fibrosis and the formation of crescents. Additionally, IL-8 and TNF-α stimulated the formation of von Willebrand factor (vWF), thus triggered coagulation cascade reactions and the deposition of glomerular fibrin. The figure was created with Biorender.com.
Gd-IgA1: galactose-deficient IgA1; AIM: apoptosis inhibitor of macrophage; CTLs: cytotoxic T lymphocytes; NK cells: natural killer cells; DNase I: deoxyribonuclease I; NETs: neutrophil extracellular traps.

associated with the pathogenesis of IgAVN (37), and another study demonstrated B cell-depleting therapy was effective in treating with IgAVN patients (58), however, the mechanism of B cells remained unknown. Additionally, a study mentioned that the level of serum Gd-IgA (s-Gd-IgA) was positively correlated with IL-6, and glomerulus Gd-IgA (g-Gd-IgA) was positively correlated with IL-8 (8).

Complements were activated, mainly by alternative pathway and lectin pathway, and the lectin pathway may be triggered by IgA2 (59). C3 was the core of the complement system. Various complement activation pathways produced C3 convertases, which cleaved C3 into C3a and C3b, and then the tissue injury was triggered by C3b-mediated phagocytosis, membrane attack complexes, and the generation of the anaphylatoxins C3a and C5a (60). A study indicated that there was a positive connection between the level of circling C3 and complement factor H (CFH), and the level of CFH was higher in IgAVN patients than in IgAN patients (61). Attaching to circling C3, CFH inhibited the activation of complements by alternative pathway (62). Plasma levels of C3a were correlated to plasma creatinine, and C4a was associated with creatinine and urea levels (40). Additionally, complement activation was critical in the progress of microangiopathy and would lead to the further progression of the disease (63). According to studies, urine complement C3, C4, C5 and C5a concentrations were all statistically higher in children with IgAVN than those without nephritis (39), and the level of C3 deposition was connected with severity (64), both of then implied that the level of C3 may indicate whether the kidneys were involved and the severity, and may help to the early detec-

Table IV. Summary of literature concerning the pathogenesis of IgAV.

No	Authors	Published year	Research method	Factors involved in the pathogenesis of IgAV
1	Chen *et al*. (86)	2023	24 IgAV rat models were established. dsDNA quantification kit was used to quantify cf-DNA. Serum immunoglobulins, C3 and MPO-DNA were analysed by ELISA. IgA, C3 and NETs were tested by immunofluorescences	NETs played roles in the pathogenesis of IgAV rats
2	Chen *et al*. (87)	2021	Blood samples from 193 IgAV patients and 192 HC were tested. Quant-iT PicoGreen DNA quantification kit were used to quantify cf-DNA. MPO-DNA, cit-H3, NE, DNase I were measured by ELISA. Immunofluorescence staining was used to identify the existence of NETs. The ability degrade NETs was tested *in vitro*	NETs played roles in the pathogenesis of IgAV
3	Prieto-Peña *et al*. (123)	2021	380 Caucasian IgAV patients and 845 matched healthy controls were genotyped	IL33-IL1R1 signalling pathway didn't contribute to IgAV
4	Prieto-Peña *et al*. (124)	2021	BAFF, APRIL and BAFFR were genotyped in 386 Caucasian IgAV patients and 806 matched healthy controls	BAFF, APRIL and BAFFR didn't contribute to IgAV
5	López-Mejías *et al*. (125)	2020	Five IL17A tag polymorphisms were genotyped in 360 Caucasian patients with IgAV and 1003 sex and ethnically matched healthy controls using TaqMan probes	IL17A didn't contribute to IgAV
6	Zhu *et al*. (126)	2019	200 children with IgAV were recruited. Chemoluminescence was used to measure the level of IL-6 and TNF-α. Thiobarbituric acid colorimetry, hydroxylamine technique, and chemical colorimetry were used to measure the MDA, SOD, and T-AOC levels	Inflammatory and oxidative damage were related to IgAV and the degree of renal involvement
7	López-Mejías *et al*. (104)	2016	338 patients and 635 controls were genotyped for IL1β rs16944 by TaqMan genotyping assay	IL1β rs16944 polymorphism was associated with the severity of IgAV
8	Matayoshi *et al*. (127)	2013	Plasma factor XIII activity in 44 adults with IgAV was assessed by the latex agglutination immunoturbidity technique	Decreased factor XIII activities were related to the severity of IgAV
9	Schmitt *et al*. (93)	2010	Deposits of streptococcal IgA-BR were evaluated by immunohistochemistry and electron microscopy. Mass spectrometry was used to examine the skin samples from IgAV patients	IgA-BR interacted with circulating IgA and formed complexes of IgA-Fc, which would deposit in tissues and lead to the pathophysiology of IgAV
10	Mahajan *et al*. (99)	2009	The levels serum and urine RNI and citrulline were assessed by spectrophotometry in 14 patients with IgAV	Nitric oxide played a role in pathogenesis of IgAV

IgAV: IgA vasculitis; cf-DNA: cell free DNA; MPO-DNA: myeloperoxidase-DNA; ELISA: enzyme-linked immunosorbent assay; cit-H3: citrullinated-histone H3; NE: neutrophil elastase; DNase I: deoxyribonuclease I; NETs: neutrophil extracellular traps; MDA: malondialdehyde; SOD: superoxide dismutase; T-AOC: total anti-oxidant capability; IgA-BR: IgA-binding-region; RNI: reactive nitrogen intermediates.

tion. Nevertheless, the role of activated complements in IgAVN required further research.

- Immune complexes deposited in IgAVN patients

IgAVN was an immune complexes disease (65). The comparison of immune complexes deposited in IgAN, IgAVN and IgAV is described in Figure 1. Immune complexes in IgAVN patients usually deposited in the mesangium and endothelium while complexes were only observed in mesangium in IgAN patients (8). Similar to IgAN, Gd-IgA1 was also essential in the pathogenesis of IgAVN (46). According to a study, the level of Gd-IgA1was comparable in IgAVN and IgAN patients, and in IgAVN patients there was less Gd-IgA1deposited in endothelium than that in mesangium (8). Notably, elevated level of IgA-IgG immune complex was discovered in IgAVN patients but not in IgAV patients without nephritis (66). Several studies discovered that serum level of Gd-IgA1 was associated with kidney involvement, but not correlated to severity (44), indicating that the level of Gd-IgA may be a threshold for IgAVN (42). Additionally, IgM may play a role in IgAVN, which is closely related to C3 (67), but its mechanism required further research.

There were three essential enzymes that involved in glycosylating the antibody in B cells (68). Reduced activity of β 1,3-galactosyltransferase and activated N-acetylgalactosamine-specific α2,6-sialytransferase contributed to the production of Gd-IgA (69, 70). Additionally, elevated Gd-IgA1-specific IgG antibodies were produced in IgAVN patients (71, 72). IgG autoantibodies were generated by mesangial cells and its production was intermittent (71). Gd-IgA combined with IgG, thus formed immune complexes. Normal IgA can be identified and eliminated by the liver in healthy humans (73). However, the clearance rate of Gd-IgA immune complexes decreased in IgAVN patients (74, 75), which may partly because the abnormal immune complexes were excessively produced and the macrophage receptors were saturated (74). Thus, the bulk formation and reduced clearance rate led to the deposition of immune complexes in IgAVN patients.

- The role of coagulation-fibrinolysis system in the pathogenesis of IgAVN

Fibrosis and crescents were also observed in IgAVN patients and studies indicated that greater severity of coagulation issues was related to IgAVN compared to IgAN (76). Crescents were associated with more severe clinical symptoms and worse prognosis (47, 77). Inflammation and epithelial damage were the main factors contributed to renal fibrosis (78). TNF-α was related to the progression of renal fibrosis (79, 80). IL-8 and TNF-α produced by neutrophils and macrophages acted on endothelial cells, leading to the production of von Willebrand factor (vWF)

(74, 81), which combined with procoagulant factor VIII and prevented it from prematurely eliminated (82), thus triggered the coagulation cascade and resulted in the deposition of glomerular fibrin. Fibrinogen, a clotting agent, was critical to the renal fibrosis and blood coagulation (47, 48). There was a correlation between fibrosis and the elevation of alpha-smooth muscle actin (α-SMA), and macrophages can differentiate into myofibroblasts and directly led to the interstitial fibrosis (83). Renal complement activation triggered the development and progression of crescents by lectin pathway (59, 84), but its role in the formation of crescents remained unclear.

The pathogenesis of IgAV

Ten studies concerning the pathogenesis of IgAV were summarized in Table IV. Gd-IgA was essential in the progression of IgAN and IgAVN, but the level Gd-IgA IgAV patients was comparable to healthy individuals, and IgG was not observed in immune complexes of IgAV patients without nephritis (7), indicating Gd-IgA may be not involved in the pathogenesis of IgAV without nephritis. Inflammation was a key characteristic of IgAV. Neutrophil extracellular traps (NETs) played an important role in inflammation and the progression of IgAV (85, 86). Activated NETs were discovered in IgAV patients (87), raising the exposure of modified autoantigens and aggravating the inflammation (88). The deposition of the complexes may lower the threshold of NETs (89). The level of NETs may be used to evaluate the severity in children with IgAV (87). Decreased level of deoxyribonuclease I (DNase I) was observed in IgAV patients (87) and further studies demonstrated that dysfunctional DNase contributed to the decreased elimination of NETs (90), thus led to the increased level of NETs. Additionally, complements were also associated with NETs, and over-deposited C1q may directly inhibit the activity of DNase I (91).

IgAV occurred frequently in autumn and winter (92), and was associated with upper respiratory tract infections (7), streptococcal infections were prevalent (93). Recent studies indicated that Corona Virus Disease 2019 (COVID-19) may led to IgAV (94-96). Infections may directly lead to endothelial damage, triggering the clotting cascade and the release of inflammatory factors (97). Additionally, infections activated neutrophils, leading to the generation of NETs (98). Besides, studies discovered that nitric oxide took part in the pathogenesis of IgAV (99), which was crucial in maintaining endothelial homeostasis and regulating vasodilation (100).

Additionally, studies showed that there was a close connection between IgAV and genetics, especially the HLA region (101). There was a correlation between the susceptibility to IgAV and the HLA-A*03, HLA-B*37, and HLA-DRB1*12 alleles (102), and there may be a possible interplay of HMGB1, PCDH1, RAGE and Gd-IgA1 in the progression of IgAV (103). Moreover, IL1βrs16944 polymorphism may associated the severity of kidney damage (104).

The prognosis of IgAVN

IgAV without nephritis usually had a self-limiting course, especially in children (105). The higher level of IgM deposition in the skin of both children and adults with IgAV indicated potential renal involvement (67, 106). However, the involvement of kidney was closely associated with long-term morbidity and worse prognosis (107), and there was no clear evidence that IgAVN was self-limiting. Constant inflammation and activated immune system may result in chronic kidney damage (108), causing proteinuria, haematuria, hypertension and other symptoms, which needed treatments to relieve.

Children usually had better prognosis than adults (109-112). Renal damage, proteinuria more than 1.5 g/d and hypertension resulted in negative prognosis in adults, and interestingly, this connection had not been found in children (113). In active renal pathology, children and adults showed similar alteration (114). Mesangial hyperplasia was the predominant histological alteration observed in children, but adults were more likely to develop chronic renal pathological alteration with severe glomerulopathy, including tubular atrophy/interstitial fibrosis and global sclerosis (114), which suggested that the damage of adults' kidney were more severe and lasting. The biomarkers in children and adults were similar (115, 116). IgA and C3 were the main deposition in children and adults, but the degree of C3 deposition in adults was greater than in children (114), indicating the deposition of complexes, inflammatory responses and activation of complements in adults may be more complicated than in children. However, the differences between children and adults in detail necessitated further study.

Conclusion

In the present article, an analysis of clinical trials with different treatments was performed and their efficacy was compared. Immune system, immune complexes and coagulation-fibrinolysis system were involved in the pathogenesis of IgAVN. However, the exact pathogenesis of IgAVN remains elusive and required further research. The prognosis in children was better than adults, but the differences are still unclear.

References

1. GARDNER-MEDWIN JM, DOLEZALOVA P, CUMMINS C *et al*.: Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; 360: 1197-202. https://doi.org/10.1016/s0140-6736(02)11279-7
2. DAVIN JC, COPPO R: Henoch-Schönlein purpura nephritis in children. *Nat Rev Nephrol* 2014; 10: 563-73. https://doi.org/10.1038/nrneph.2014.126
3. PILLEBOUT E, THERVET E, HILL G *et al*.: Henoch-Schönlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; 13: 1271-8. https://doi.org/10.1097/01.asn.0000013883.99976.22
4. LEE M, SUZUKI H, NIHEI Y *et al*.: Ethnicity and IgA nephropathy: worldwide differences in epidemiology, timing of diagnosis, clinical manifestations, management and prognosis. *Clin Kidney J* 2023; 16: ii1-ii8. https://doi.org/10.1093/ckj/sfad199
5. RAVELLI A, CARNEVALE-MAFFE G, RUPERTO N *et al*.: IgA nephropathy and Henoch-Schönlein syndrome occurring in the same patient. *Nephron* 1996; 72: 111-12. https://doi.org/10.1159/000188822
6. MEADOW SR, SCOTT DG: Berger disease: Henoch-Schönlein syndrome without the rash. *J Pediatr* 1985; 106: 27-32. https://doi.org/10.1016/s0022-3476(85)80459-5
7. HEINEKE MH, BALLERING AV, JAMIN A *et al*.: New insights in the pathogenesis of im-

munoglobulin A vasculitis (Henoch-Schönlein purpura). *Autoimmun Rev* 2017; 16: 1246-53. https://doi.org/10.1016/j.autrev.2017.10.009
8. SUGIYAMA M, WADA Y, KANAZAWA N *et al*.: A cross-sectional analysis of clinicopathologic similarities and differences between Henoch-Schönlein purpura nephritis and IgA nephropathy. *PLoS One* 2020; 15: e0232194. https://doi.org/10.1371/journal.pone.0232194
9. BUTZER S, HENNIES I, GIMPEL C *et al*.: Early clinical course of biopsy-proven IgA vasculitis nephritis. *BMC Pediatr* 2022; 22: 570. https://doi.org/10.1186/s12887-022-03611-9
10. GENG HY, CHEN CY, LI HR *et al*.: [Efficacy and safety of mycophenolate mofetil versus cyclophosphamide in the treatment of Henoch-Schönlein purpura nephritis with nephrotic-range proteinuria in children: a prospective randomized controlled trial]. *Zhongguo Dang Dai Er Ke Za Zhi* 2021; 23: 338-42. https://doi.org/10.7499/j.issn.1008-8830.2012145
11. PILLEBOUT E, ALBERTI C, GUILLEVIN L *et al*.: Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura. *Kidney Int* 2010; 78: 495-502. https://doi.org/10.1038/ki.2010.150
12. TARSHISH P, BERNSTEIN J, EDELMANN CM, JR: Henoch-Schönlein purpura nephritis: course of disease and efficacy of cyclophosphamide. *Pediatr Nephrol* 2004; 19: 51-56. https://doi.org/10.1007/s00467-003-1315-x
13. KAWASAKI Y, SUZUKI J, SUZUKI H: Efficacy of methylprednisolone and urokinase pulse therapy combined with or without cyclophosphamide in severe Henoch-Schönlein nephritis: a clinical and histopathological study. *Nephrol Dial Transplant* 2004; 19: 858-64. https://doi.org/10.1093/ndt/gfg617
14. LI VOLTI S, LI VOLTI G: Early treatment with oral immunosuppressants in severe proteinuric purpura nephritis. *Pediatr Nephrol* 2003; 18: 1197-98. https://doi.org/10.1007/s00467-003-1272-4
15. FLYNN JT, SMOYER WE, BUNCHMAN TE *et al*.: Treatment of Henoch-Schönlein Purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001; 21: 128-33. https://doi.org/10.1159/000046235
16. UMEDA C, FUJINAGA S, ENDO A *et al*.: Preventive effect of tonsillectomy on recurrence of Henoch-Schönlein purpura nephritis after intravenous methylprednisolone pulse therapy. *tohoku j exp med* 2020; 250: 61-69. https://doi.org/10.1620/tjem.250.61
17. YANG D, HE L, PENG X *et al*.: The efficacy of tonsillectomy on clinical remission and relapse in patients with IgA nephropathy: a randomized controlled trial. *Ren Fail* 2016; 38: 242-48. https://doi.org/10.3109/0886022x.2015.1128251
18. MAEDA I, HAYASHI T, SATO KK *et al*.: Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy. *Nephrol Dial Transplant* 2012; 27: 2806-13. https://doi.org/10.1093/ndt/gfs053
19. KAWAMURA T, YOSHIMURA M, MIYAZAKI Y *et al*.: A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. *Nephrol Dial Transplant* 2014; 29: 1546-53. https://doi.org/10.1093/ndt/gfu020
20. MORONI G, GALLELLI B, DIANA A *et al*.: Renal transplantation in adults with Henoch-Schönlein purpura: long-term outcome. *Nephrol Dial Transplant* 2008; 23: 3010-16. https://doi.org/10.1093/ndt/gfn209
21. JAUHOLA O, RONKAINEN J, AUTIO-HARMAINEN H *et al*.: Cyclosporine A vs. methylprednisolone for Henoch-Schönlein nephritis: a randomized trial. *Pediatr Nephrol* 2011; 26: 2159-66. https://doi.org/10.1007/s00467-011-1919-5
22. RONKAINEN J, AUTIO-HARMAINEN H, NUUTINEN M: Cyclosporin A for the treatment of severe Henoch-Schönlein glomerulonephritis. *Pediatr Nephrol* 2003; 18: 1138-42. https://doi.org/10.1007/s00467-003-1245-7
23. NIAUDET P, HABIB R: Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein-Henoch purpura nephritis. *Pediatr Nephrol* 1998; 12: 238-43. https://doi.org/10.1007/s004670050446
24. OZEN S, MARKS SD, BROGAN P *et al*.: European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. *Rheumatology* (Oxford) 2019; 58: 1607-16. https://doi.org/10.1093/rheumatology/kez041
25. FUJINAGA S, SAITO K: Initial treatment with tonsillectomy combined with intravenous methylprednisolone pulse - another option for Japanese children with severe nephrotic IgA vasculitis with nephritis. *Pediatr Nephrol* 2024; 39: 1671-72. https://doi.org/10.1007/s00467-023-06203-6
26. WILLIAMS CEC, LAMOND M, MARRO J *et al*.: A narrative review of potential drug treatments for nephritis in children with IgA vasculitis (HSP). *Clin Rheumatol* 2023; 42: 3189-200. https://doi.org/10.1007/s10067-023-06781-8
27. JAUHOLA O, RONKAINEN J, KOSKIMIES O *et al*.: Clinical course of extrarenal symptoms in Henoch-Schönlein purpura: a 6-month prospective study. *Arch Dis Child* 2010; 95: 871-76. https://doi.org/10.1136/adc.2009.167874
28. TAN J, TANG Y, XU Y *et al*.: The Clinicopathological Characteristics of Henoch-Schönlein Purpura Nephritis with Presentation of Nephrotic Syndrome. *Kidney Blood Press Res* 2019; 44: 754-64. https://doi.org/10.1159/000501459
29. PILLEBOUT E, ROCHA F, FARDET L *et al*.: Successful outcome using rituximab as the only immunomodulation in Henoch-Schönlein purpura: case report. *Nephrol Dial Transplant* 2011; 26: 2044-46. https://doi.org/10.1093/ndt/gfr137
30. YAMAKAWA T, YAMAMOTO I, KOMATSUZAKI Y *et al*.: Successful treatment of recurrent Henoch-Schönlein purpura nephritis in a renal allograft with tonsillectomy and steroid pulse therapy. *Nephrology* (Carlton) 2016; 21 Suppl 1: 53-56. https://doi.org/10.1111/nep.12770
31. SUGIYAMA H, WATANABE N, ONODA T *et al*.: Successful treatment of progressive Henoch-Schönlein purpura nephritis with tonsillectomy and steroid pulse therapy. *Intern Med* 2005; 44: 611-15. https://doi.org/10.2169/internalmedicine.44.611
32. TANAKA Y, NAKASHIMA Y, MIMA T *et al*.: Effects of cyclophosphamide pulse therapy on the clinical and histopathological findings, particularly crescent formation, in a patient with adult-onset steroid-refractory Henoch-Schönlein purpura nephritis. *Intern Med* 2015; 54: 2207-11. https://doi.org/10.2169/internalmedicine.54.4330
33. KUSUDA A, MIGITA K, TSUBOI M *et al*.: Successful treatment of adult-onset Henoch-Schönlein purpura nephritis with high-dose immunoglobulins. *Intern Med* 1999; 38: 376-79. https://doi.org/10.2169/internalmedicine.38.376
34. ISHIGURO H, HASHIMOTO T, AKATA M *et al*.: Rituximab treatment for adult purpura nephritis with nephrotic syndrome. *Intern Med* 2013; 52: 1079-83. https://doi.org/10.2169/internalmedicine.52.9325
35. SCHMALDIENST S, WINKLER S, BREITENEDER S *et al*.: Severe nephrotic syndrome in a patient with Schönlein-Henoch purpura: complete remission after cyclosporin A. *Nephrol Dial Transplant* 1997; 12: 790-92. https://doi.org/10.1093/ndt/12.4.790
36. IMAI T, NISHIYAMA K, UEKI K *et al*.: Involvement of activated cytotoxic T lymphocytes and natural killer cells in Henoch-Schönlein purpura nephritis. *Clin Transl Immunology* 2020; 9: e1212. https://doi.org/10.1002/cti2.1212
37. HU X, TAI J, QU Z *et al*.: A lower proportion of regulatory B cells in patients with Henoch-Schönlein purpura nephritis. *PLoS One* 2016; 11: e0152368. https://doi.org/10.1371/journal.pone.0152368
38. IRABU H, SHIMIZU M, KANEKO S *et al*.: Apoptosis inhibitor of macrophage as a biomarker for disease activity in Japanese children with IgA nephropathy and Henoch-Schönlein purpura nephritis. *Pediatr Res* 2021; 89: 667-72. https://doi.org/10.1038/s41390-020-0951-1
39. WRIGHT RD, MARRO J, NORTHEY SJ *et al*.: Urinary complement proteins are increased in children with IgA vasculitis (Henoch-Schönlein purpura) nephritis. *Pediatr Nephrol* 2023; 38: 1491-98. https://doi.org/10.1007/s00467-022-05747-3
40. ABOU-RAGHEB HH, WILLIAMS AJ, BROWN CB *et al*.: Plasma levels of the anaphylatoxins C3a and C4a in patients with IgA nephropathy/Henoch-Schönlein nephritis. *Nephron* 1992; 62: 22-26. https://doi.org/10.1159/000186989
41. SAITO A, KOMATSUDA A, KAGA H *et al*.: Different expression patterns of toll-like receptor mRNAs in blood mononuclear Cells of IgA nephropathy and IgA vasculitis with nephritis. *Tohoku J Exp Med* 2016; 240: 199-208. https://doi.org/10.1620/tjem.240.199

42. XU L, LI Y, WU X: IgA vasculitis update: epidemiology, pathogenesis, and biomarkers. *Front Immunol* 2022; 13: 921864. https://doi.org/10.3389/fimmu.2022.921864
43. HASTINGS MC, RIZK DV, KIRYLUK K *et al*.: IgA vasculitis with nephritis: update of pathogenesis with clinical implications. *Pediatr Nephrol* 2022; 37: 719-33. https://doi.org/10.1007/s00467-021-04950-y
44. TANG M, ZHANG X, LI X *et al*.: Serum levels of galactose-deficient IgA1 in Chinese children with IgA nephropathy, IgA vasculitis with nephritis, and IgA vasculitis. *Clin Exp Nephrol* 2021; 25: 37-43. https://doi.org/10.1007/s10157-020-01968-8
45. ZHANG X, XIE X, SHI S *et al*.: Plasma galactose-deficient immunoglobulin A1 and loss of kidney function in patients with immunoglobulin A vasculitis nephritis. *Nephrol Dial Transplant* 2020; 35: 2117-23. https://doi.org/10.1093/ndt/gfz151
46. ALLEN AC, WILLIS FR, BEATTIE TJ *et al*.: Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. *Nephrol Dial Transplant* 1998; 13: 930-34. https://doi.org/10.1093/ndt/13.4.930
47. WANG F, HUANG L, TANG H *et al*.: Significance of glomerular fibrinogen deposition in children with Henoch-Schönlein purpura nephritis. *Ital J Pediatr* 2018; 44: 97. https://doi.org/10.1186/s13052-018-0538-1
48. TIAN M, LIU C: Heparin calcium treated Henoch-Schönlein purpura nephritis in children through inhibiting hyperfibrinolysis. *Ren Fail* 2015; 37: 1100-4. https://doi.org/10.3109/0886022x.2015.1061668
49. ZHU ZQ, ZHANG T, CHANG S *et al*.: AZGP1 as a potential biomarker of IgA vasculitis with nephritis in a children-based urinary proteomics study by diaPASEF. *Mol Med Rep* 2023; 28. https://doi.org/10.3892/mmr.2023.13044
50. HE X, YIN W, DING Y *et al*.: Higher serum angiotensinogen is an indicator of IgA vasculitis with nephritis revealed by comparative proteomes analysis. *PLoS One* 2015; 10: e0130536. https://doi.org/10.1371/journal.pone.0130536
51. CHOY JC, CRUZ RP, KERJNER A *et al*.: Granzyme B induces endothelial cell apoptosis and contributes to the development of transplant vascular disease. *Am J Transplant* 2005; 5: 494-99. https://doi.org/10.1111/j.1600-6143.2004.00710.x
52. TAKAHATA A, ARAI S, HIRAMOTO E *et al*.: Crucial role of AIM/CD5L in the development of glomerular inflammation in IgA nephropathy. *J Am Soc Nephrol* 2020; 31: 2013-24. https://doi.org/10.1681/asn.2019100987
53. MAKITA Y, SUZUKI H, NAKANO D *et al*.: Glomerular deposition of galactose-deficient IgA1-containing immune complexes via glomerular endothelial cell injuries. *Nephrol Dial Transplant* 2022; 37: 1629-36. https://doi.org/10.1093/ndt/gfac204
54. HUANG XR, KITCHING AR, TIPPING PG *et al*.: Interleukin-10 inhibits macrophage-induced glomerular injury. *J Am Soc Nephrol* 2000; 11: 262-69. https://doi.org/10.1681/asn.v112262
55. LI Q, SHI S, LIU L *et al*.: Neutrophil-to-lymphocyte ratio as an independent inflammatory indicator for poor renal prognosis in adult IgA vasculitis with nephritis. *Int Immunopharmacol* 2022; 111: 109178. https://doi.org/10.1016/j.intimp.2022.109178
56. WU H, WEN Y, YUE C *et al*.: Serum TNF-α level is associated with disease severity in adult patients with immunoglobulin A vasculitis nephritis. *Dis Markers* 2020; 2020: 5514145. https://doi.org/10.1155/2020/5514145
57. LOUSA I, REIS F, SANTOS-SILVA A *et al*.: The signaling pathway of TNF receptors: linking animal models of renal disease to human CKD. *Int J Mol Sci* 2022; 23. https://doi.org/10.3390/ijms23063284
58. LUNDBERG S, WESTERGREN E, SMOLANDER J *et al*.: B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis. *Clin Kidney J* 2017; 10: 20-26. https://doi.org/10.1093/ckj/sfw106
59. HISANO S, MATSUSHITA M, FUJITA T *et al*.: Activation of the lectin complement pathway in Henoch-Schönlein purpura nephritis. *Am J Kidney Dis* 2005; 45: 295-302. https://doi.org/10.1053/j.ajkd.2004.10.020
60. GENEST DS, BONNEFOY A, KHALILI M *et al*.: Comparison of complement pathway activation in autoimmune glomerulonephritis. *Kidney Int Rep* 2022; 7: 1027-36. https://doi.org/10.1016/j.ekir.2022.02.002
61. JIA M, ZHU L, ZHAI YL *et al*.: Variation in complement factor H affects complement activation in immunoglobulin A vasculitis with nephritis. *Nephrology* (Carlton) 2020; 25: 40-47. https://doi.org/10.1111/nep.13580
62. MOORE SR, MENON SS, CORTES C *et al*.: Hijacking factor H for complement immune evasion. *Front Immunol* 2021; 12: 602277. https://doi.org/10.3389/fimmu.2021.602277
63. CHUA JS, ZANDBERGEN M, WOLTERBEEK R *et al*.: Complement-mediated microangiopathy in IgA nephropathy and IgA vasculitis with nephritis. *Mod Pathol* 2019; 32: 1147-57. https://doi.org/10.1038/s41379-019-0259-z
64. LV Y, FU R, PENG XJ *et al*.: Comparative study on clinicopathological features and prognosis of IgA vasculitis nephritis and IgA nephropathy in children. *BMC Pediatr* 2023; 23: 423. https://doi.org/10.1186/s12887-023-04243-3
65. HILHORST M, VAN PAASSEN P, VAN BREDA VRIESMAN P *et al*.: Immune complexes in acute adult-onset Henoch-Schönlein nephritis. *Nephrol Dial Transplant* 2011; 26: 3960-67. https://doi.org/10.1093/ndt/gfr149
66. LEVINSKY RJ, BARRATT TM: IgA immune complexes in Henoch-Schönlein purpura. *Lancet* 1979; 2: 1100-3. https://doi.org/10.1016/s0140-6736(79)92505-4
67. TAKEUCHI S, SOMA Y, KAWAKAMI T: IgM in lesional skin of adults with Henoch-Schönlein purpura is an indication of renal involvement. *J Am Acad Dermatol* 2010; 63: 1026-29. https://doi.org/10.1016/j.jaad.2009.11.690
68. SONG Y, HUANG X, YU G *et al*.: Pathogenesis of IgA vasculitis: an up-to-date review. *Front Immunol* 2021; 12: 771619. https://doi.org/10.3389/fimmu.2021.771619
69. ALLEN AC, TOPHAM PS, HARPER SJ *et al*.: Leucocyte beta 1,3 galactosyltransferase activity in IgA nephropathy. *Nephrol Dial Transplant* 1997; 12: 701-6. https://doi.org/10.1093/ndt/12.4.701
70. SUZUKI H, MOLDOVEANU Z, HALL S *et al*.: IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. *J Clin Invest* 2008; 118: 629-39. https://doi.org/10.1172/jci33189
71. O'DONOGHUE DJ, DARVILL A, BALLARDIE FW: Mesangial cell autoantigens in immunoglobulin A nephropathy and Henoch-Schönlein purpura. *J Clin Invest* 1991; 88: 1522-30. https://doi.org/10.1172/jci115462
72. SUZUKI H, MOLDOVEANU Z, JULIAN BA *et al*.: Autoantibodies specific for galactose-deficient IgA1 in IgA vasculitis with nephritis. *Kidney Int Rep* 2019; 4: 1717-24. https://doi.org/10.1016/j.ekir.2019.08.015
73. STOCKERT RJ, KRESSNER MS, COLLINS JC *et al*.: IgA interaction with the asialoglycoprotein receptor. *Proc Natl Acad Sci USA* 1982; 79: 6229-31. https://doi.org/10.1073/pnas.79.20.6229
74. DAVIN JC, TEN BERGE IJ, WEENING JJ: What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis? *Kidney Int* 2001; 59: 823-34. https://doi.org/10.1046/j.1523-1755.2001.059003823.x
75. ROCCATELLO D, PICCIOTTO G, COPPO R *et al*.: The fate of aggregated immunoglobulin A injected in IgA nephropathy patients and healthy controls. *Am J Kidney Dis* 1991; 18: 20-25. https://doi.org/10.1016/s0272-6386(12)80285-x
76. WANG Y, WANG H, MA X *et al*.: Characteristics of renal pathology and coagulation function in IgA nephropathy and IgA vasculitis associated nephritis. *BMC Nephrol* 2024; 25: 35. https://doi.org/10.1186/s12882-024-03465-6
77. HUANG X, WU J, WU XM *et al*.: Significance of histological crescent formation in patients with IgA vasculitis (Henoch-Schönlein purpura)-related nephritis: a cohort in the adult Chinese population. *BMC Nephrol* 2018; 19: 334. https://doi.org/10.1186/s12882-018-1117-9
78. EDELING M, RAGI G, HUANG S *et al*.: Developmental signalling pathways in renal fibrosis: the roles of Notch, Wnt and Hedgehog. *Nat Rev Nephrol* 2016; 12: 426-39. https://doi.org/10.1038/nrneph.2016.54
79. TAGUCHI S, AZUSHIMA K, YAMAJI T *et al*.: Effects of tumor necrosis factor-α inhibition on kidney fibrosis and inflammation in a mouse model of aristolochic acid nephropathy. *Sci Rep* 2021; 11: 23587. https://doi.org/10.1038/s41598-021-02864-1
80. KARKAR AM, SMITH J, PUSEY CD: Prevention and treatment of experimental crescentic glomerulonephritis by blocking tumour necrosis factor alpha. *Nephrol Dial Transplant* 2001; 16: 518-24. https://doi.org/10.1093/ndt/16.3.518
81. DAVIN JC: Henoch-Schönlein purpura nephritis: pathophysiology, treatment, and future strategy. *Clin J Am Soc Nephrol* 2011; 6: 679-89.

https://doi.org/10.2215/cjn.06710810
82. McGRATH RT, McRAE E, SMITH OP *et al*.: Platelet von Willebrand factor--structure, function and biological importance. *Br J Haematol* 2010; 148: 834-43. https://doi.org/10.1111/j.1365-2141.2009.08052.x
83. WANG YY, JIANG H, PAN J *et al*.: Macrophage-to-myofibroblast transition contributes to interstitial fibrosis in chronic renal allograft injury. *J Am Soc Nephrol* 2017; 28: 2053-67. https://doi.org/10.1681/asn.2016050573
84. WANG Z, XIE X, LI J *et al*.: Complement activation is associated with crescents in IgA nephropathy. *Front Immunol* 2021; 12: 676919. https://doi.org/10.3389/fimmu.2021.676919
85. CHEN XQ, TU L, TANG Q *et al*.: An emerging role for neutrophil extracellular traps in IgA vasculitis: a mini-review. *Front Immunol* 2022; 13: 912929. https://doi.org/10.3389/fimmu.2022.912929
86. CHEN XQ, ZOU JS, TU L *et al*.: Neutrophil extracellular traps involved in the pathogenesis of IgA vasculitis: Confirmed in two IgAV rat models. *PLoS One* 2023; 18: e0288538. https://doi.org/10.1371/journal.pone.0288538
87. CHEN XQ, TU L, ZOU JS *et al*.: The involvement of neutrophil extracellular traps in disease activity associated with IgA vasculitis. *Front Immunol* 2021; 12: 668974. https://doi.org/10.3389/fimmu.2021.668974
88. WIGERBLAD G, KAPLAN MJ: Neutrophil extracellular traps in systemic autoimmune and autoinflammatory diseases. *Nat Rev Immunol* 2023; 23: 274-88. https://doi.org/10.1038/s41577-022-00787-0
89. MAYER-HAIN S, GEBHARDT K, NEUFELD M *et al*.: Systemic activation of neutrophils by immune complexes is critical to IgA vasculitis. *J Immunol* 2022; 209: 1048-58. https://doi.org/10.4049/jimmunol.2100924
90. ANGELETTI A, VOLPI S, BRUSCHI M *et al*.: Neutrophil Extracellular Traps-DNase Balance and Autoimmunity. *Cells* 2021; 10. https://doi.org/10.3390/cells10102667
91. LEFFLER J, MARTIN M, GULLSTRAND B *et al*.: Neutrophil extracellular traps that are not degraded in systemic lupus erythematosus activate complement exacerbating the disease. *J Immunol* 2012; 188: 3522-31. https://doi.org/10.4049/jimmunol.1102404
92. YANG YH, HUNG CF, HSU CR *et al*.: A nationwide survey on epidemiological characteristics of childhood Henoch-Schönlein purpura in Taiwan. *Rheumatology* (Oxford) 2005; 44: 618-22. https://doi.org/10.1093/rheumatology/keh544
93. SCHMITT R, CARLSSON F, MÖRGELIN M *et al*.: Tissue deposits of IgA-binding streptococcal M proteins in IgA nephropathy and Henoch-Schönlein purpura. *Am J Pathol* 2010; 176: 608-18. https://doi.org/10.2353/ajpath.2010.090428
94. ALLEZ M, DENIS B, BOUAZIZ JD *et al*.: COVID-19-related IgA vasculitis. *Arthritis Rheumatol* 2020; 72: 1952-3. https://doi.org/10.1002/art.41428
95. MACHURA E, KRAKOWCZYK H, BĄKDRABIK K *et al*.: SARS-CoV-2 infection as a possible trigger for IgA-associated vasculitis: a case report. *Children* (Basel) 2023; 10. https://doi.org/10.3390/children10020344
96. JEDLOWSKI PM, JEDLOWSKI MF: Coronavirus disease 2019-associated immunoglobulin A vasculitis/Henoch-Schönlein purpura: a case report and review. *J Dermatol* 2022; 49: 190-96. https://doi.org/10.1111/1346-8138.16211
97. BATU ED, SENER S, OZEN S: COVID-19 associated pediatric vasculitis: A systematic review and detailed analysis of the pathogenesis. *Semin Arthritis Rheum* 2022; 55: 152047. https://doi.org/10.1016/j.semarthrit.2022.152047
98. ZHU Y, CHEN X, LIU X: NETosis and neutrophil extracellular traps in COVID-19: immunothrombosis and beyond. *Front Immunol* 2022; 13. https://doi.org/10.3389/fimmu.2022.838011
99. MAHAJAN V, SINGH S, KHULLAR M *et al*.: Serum and urine nitric oxide levels in children with Henoch-Schönlein purpura during activity and remission: a study from North India. *Rheumatol Int* 2009; 29: 1069-72. https://doi.org/10.1007/s00296-008-0800-8
100. TOUSOULIS D, KAMPOLI AM, TENTOLOURIS C *et al*.: The role of nitric oxide on endothelial function. *Curr Vasc Pharmacol* 2012; 10: 4-18. https://doi.org/10.2174/157016112798829760
101. GONZÁLEZ-GAY M, HERAS-RECUERO E, BLÁZQUEZ-SÁNCHEZ T *et al*.: Genetics of vasculitis. *Best Pract Res Clin Rheumatol* 2024; 101969. https://doi.org/10.1016/j.berh.2024.101969
102. GONZÁLEZ-GAY MA, LÓPEZ-MEJÍAS R, PINA T *et al*.: IgA vasculitis: genetics and clinical and therapeutic management. *Curr Rheumatol Rep* 2018; 20: 24. https://doi.org/10.1007/s11926-018-0735-3
103. HELD M, KOZMAR A, SESTAN M *et al*.: Insight into the interplay of Gd-IgA1, HMGB1, RAGE and PCDH1 in IgA vasculitis (IgAV). *Int J Mol Sci* 2024; 25. https://doi.org/10.3390/ijms25084383
104. LÓPEZ-MEJÍAS R, GENRE F, REMUZGO-MARTÍNEZ S *et al*.: Interleukin 1 beta (IL1ß) rs16944 genetic variant as a genetic marker of severe renal manifestations and renal sequelae in Henoch-Schönlein purpura. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S84-88.
105. BATU ED, SARI A, ERDEN A *et al*.: Comparing immunoglobulin A vasculitis (Henoch-Schönlein purpura) in children and adults: a single-centre study from Turkey. *Scand J Rheumatol* 2018; 47: 481-86. https://doi.org/10.1080/03009742.2018.1448111
106. YÜKSEL S, ÇAĞLAR M, EVRENGÜL H *et al*.: Could serum pentraxin 3 levels and IgM deposition in skin biopsies predict subsequent renal involvement in children with Henoch-Schönlein purpura? *Pediatr Nephrol* 2015; 30: 969-74. https://doi.org/10.1007/s00467-014-3026-x
107. DYGA K, SZCZEPAŃSKA M: IgA vasculitis with nephritis in children. Adv *Clin Exp Med* 2020; 29: 513-19. https://doi.org/10.17219/acem/112566
108. ZHANG C, PENG J, LIU Z *et al*.: Kidney involvement in autoinflammatory diseases. *Kidney Dis* (Basel) 2023; 9: 157-72. https://doi.org/10.1159/000529917
109. TRACY A, SUBRAMANIAN A, ADDERLEY NJ *et al*.: Cardiovascular, thromboembolic and renal outcomes in IgA vasculitis (Henoch-Schönlein purpura): a retrospective cohort study using routinely collected primary care data. *Ann Rheum Dis* 2019; 78: 261-69. https://doi.org/10.1136/annrheumdis-2018-214142
110. NOSSENT J, RAYMOND W, KEEN H *et al*.: Hospitalisation rates and characteristics for adult and childhood immunoglobulin A vasculitis in Western Australia. *Intern Med J* 2019; 49: 475-81. https://doi.org/10.1111/imj.14065
111. VILLATORO-VILLAR M, CROWSON CS, WARRINGTON KJ *et al*.: Clinical characteristics of biopsy-proven IgA vasculitis in children and adults: a retrospective cohort study. *Mayo Clin Proc* 2019; 94: 1769-80. https://doi.org/10.1016/j.mayocp.2019.04.034
112. UPPAL SS, HUSSAIN MA, AL-RAQUM HA *et al*.: Henoch-Schönlein's purpura in adults versus children/adolescents: A comparative study. *Clin Exp Rheumatol* 2006; 24 (Suppl. 41): S26-30.
113. COPPO R, MAZZUCCO G, CAGNOLI L *et al*.: Long-term prognosis of Henoch-Schönlein nephritis in adults and children. Italian Group of Renal Immunopathology Collaborative Study on Henoch-Schönlein purpura. *Nephrol Dial Transplant* 1997; 12: 2277-83. https://doi.org/10.1093/ndt/12.11.2277
114. XU JJ, CAI J, HU B: Renal histopathological manifestations of IgA vasculitis nephritis in children and adults. *Int Immunopharmacol* 2023; 116: 109760. https://doi.org/10.1016/j.intimp.2023.109760
115. PILLEBOUT E, JAMIN A, AYARI H *et al*.: Biomarkers of IgA vasculitis nephritis in children. *PLoS One* 2017; 12: e0188718. https://doi.org/10.1371/journal.pone.0188718
116. BERTHELOT L, JAMIN A, VIGLIETTI D *et al*.: Value of biomarkers for predicting immunoglobulin A vasculitis nephritis outcome in an adult prospective cohort. *Nephrol Dial Transplant* 2018; 33: 1579-90. https://doi.org/10.1093/ndt/gfx300
117. KHOR SY, OSMAN AF, HADDAD I *et al*.: Adult-onset immunoglobulin A vasculitis with renal involvement. *Cureus* 2022; 14: e23649. https://doi.org/10.7759/cureus.23649
118. MIZERSKA-WASIAK M, WINIARSKA M, NOGAL K *et al*.: IgA vasculitis complicated by both CMV reactivation and tuberculosis. *Pediatr Rep* 2021; 13: 416-20. https://doi.org/10.3390/pediatric13030048
119. HOU L, ZHANG Z, DU Y: Leflunomide therapy for IgA vasculitis with nephritis in children. *BMC Pediatr* 2021; 21: 391. https://doi.org/10.1186/s12887-021-02866-y
120. MARRO J, CHETWYND AJ, EDWARDS S *et al*.: Increased urinary IgA in paediatric IgA vasculitis nephritis. *Int J Mol Sci* 2022; 23. https://doi.org/10.3390/ijms232314548
121. MIZERSKA-WASIAK M, GAJEWSKI Ł, CICHOŃ-KAWA K *et al*.: Relationship between Gd-IgA1 and TNFR1 in IgA nephropathy and IgA vasculitis nephritis in children - multicenter study. *Cent Eur J Immunol*

2021; 46: 199-209. https://doi.org/10.5114/ceji.2021.108177
122. CONLEY ME, COOPER MD, MICHAEL AF: Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. *J Clin Invest* 1980; 66: 1432-36. https://doi.org/10.1172/jci109998
123. PRIETO-PEÑA D, REMUZGO-MARTÍNEZ S, GENRE F *et al*.: Role of the IL33 and IL-1RL1 pathway in the pathogenesis of immunoglobulin A vasculitis. *Sci Rep* 2021; 11: 16163. https://doi.org/10.1038/s41598-021-95762-5
124. PRIETO-PEÑA D, GENRE F, REMUZGO-MARTíNEZ S *et al*.: BAFF, APRIL and BAFFR on the pathogenesis of immunoglobulin-A vasculitis. *Sci Rep* 2021; 11: 11510. https://doi.org/10.1038/s41598-021-91055-z
125. LÓPEZ-MEJÍAS R, GENRE F, REMUZGO-MARTÍNEZ S *et al*.: Influence of IL17A gene on the pathogenesis of immunoglobulin-A vasculitis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S166-70.
126. ZHU Y, DONG Y, WU L *et al*.: Changes of inflammatory mediators and oxidative stress indicators in children with Henoch-Schönlein purpura and clinical effects of hemoperfusion in the treatment of severe Henoch-Schönlein purpura with gastrointestinal involvement in children. *BMC Pediatr* 2019; 19: 409. https://doi.org/10.1186/s12887-019-1802-2
127. MATAYOSHI T, OMI T, SAKAI N *et al*.: Clinical significance of blood coagulation factor XIII activity in adult Henoch-Schönlein purpura. *J Nippon Med Sch* 2013; 80: 268-78. https://doi.org/10.1272/jnms.80.268