
Letter to the editor

When to suspect Ig A nephropathy and Timing of Kidney Biopsy

Kubra Kaynar

Department of Nephrology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Dear Editor,

Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide [1]. It was first defined in 1968 by (two kidney pathologists) Jean Berger and Nicole Hinglais, in kidney biopsies with chronic mesangial proliferative glomerulonephritis associated with dominant or codominant IgA deposits observed by immunofluorescence [2]. Few cases (nearly 10%) are due to familial IgAN whereas more than 90% of IgAN cases are sporadic [3]. The four hit model was defined for pathogenesis. The first hit is the production of galactose-deficient (Gd) IgA1 by gut including the Peyer patches, and nasal mucosa, second hit is the production of autoantibodies (IgG, IgA, or IgM) against these Gd-IgA1 which were secreted into blood vessels, the third hit is the formation of immune complexes, and the fourth hit is the binding of these immune complexes to the kidney mesangial cells leading to activation of proliferative, fibrotic, and inflammatory pathways [4,5].

The prevalence of IgAN differs between the countries (11.8% in North America, 39.5% in Asia, 22.1% in Europe, and 6.1% in Latin America) [6]. These variations in prevalence of IgAN may reflect geographical differences in screening for kidney disease and kidney biopsy practices because the definitive diagnosis of IgAN can only be made by evaluation of a kidney biopsy [6]. This difference in prevalence may also be associated with genetic factors and environmental influences in addition to presence or absence of urinary screening programs and indications for kidney biopsy. The clinical presentation of IgAN also varies between the patients with a range of signs and symptoms from asymptomatic urine abnormality, macroscopic hematuria (20-25%), to nephrotic syndrome and chronic renal impairment [7]. In Japan, China, and Korea, it is mandatory to screen school students for early morning urinary hematuria [8]. Proteinuria accompanied by hematuria warrants a complete medical workup and kidney biopsy. So, exact prevalence is uncertain due to these differences in clinical presentations, screening programs for kidney diseases, and kidney biopsy indications to confirm the diagnosis.

The clinical presentations of IgAN range from asymptomatic hematuria to rapidly progressive glomerulonephritis. Brown, red, or cola colored urine, hypertension, acute kidney injury, frothy urine, synpharyngitic hematuria, hypervolemia (edema, basal lung crepitations), and recurrent episodes of macroscopic hematuria can be found in medical history and physical examination of patients with IgAN [3]. The diagnosis of IgAN should be suspected in any patient with one or more episodes of macroscopic hematuria, especially if accompanied by an upper respiratory or gastrointestinal infection, persistent microscopic hematuria (present in 93% of the patients) with or without proteinuria not otherwise explained, and slowly progressive kidney function impairment without any other reason [9]. Based on a study, patients with three or four markers (more than five red blood cells in urinary sediments; persistent proteinuria of more than 0.3 g/day; serum IgA levels of more than 315 mg/dL and serum IgA/C3 ratio of more than 3.01) have the 75% risk of IgA nephropathy [10]. Although an elevated IgA/C3 ratio is still biologically plausible, and can help initial triage, sensitivity and specificity are insufficient for clinical decision making. KDIGO 2021 does not endorse IgA/C3 ratio as a diagnostic criterion.

Although patients with three or four markers (more than five red blood cells in urinary sediments; persistent proteinuria of more than 0.3 g/day; serum IgA levels of more than 315 mg/dL and serum IgA/C3 ratio of more than 3.01) were reported to have the 75% risk of IgAN, IgAN can be diagnosed only by kidney biopsy by showing mesangioproliferative glomerulonephritis with dominant or codominant depositions of IgA [9,10]. Because there are no validated serum or urine biomarkers for the diagnosis of IgAN yet. In order to ensure early and prompt diagnosis and treatment of IgAN, kidney biopsy is indicated for all adults with proteinuria ≥ 0.5 g/d and a possible diagnosis of IgAN without any contraindication of kidney biopsy [11]. Before biopsy, serum complement levels (C3, C4, CH50), viral serologies (human immunodeficiency virus, hepatitis B, and C), autoantibodies (antinuclear, anti-double stranded DNA, antineutrophil cytoplasmic, extractable nuclear antigen, and antiphospholipid antibodies), glycated hemoglobin (HbA1c), protein elec-

Correspondence to:

Kubra Kaynar, Karadeniz Teknik Universitesi, Tıp Fakultesi, Nefroloji Bilim Dalı, 61080 Trabzon, Turkey; E-mail: kkaynar@yahoo.com

trophoresis (older than 50 years), anti-PLA2R auto-antibody should be evaluated if possible [12].

Timing of kidney biopsy for the early and prompt diagnosis of IgAN is very important. Because by the time IgAN diagnosis, unfortunately more than 50% (74.6%) of adult patients already have chronic kidney disease (CKD) stage 3 or greater [13]. The delay in diagnosis exposes kidneys to persistent injury resulting in progression to irreversible kidney failure [13]. The prognosis among patients with IgAN also is not similar, just like the differences in prevalence and clinical presentations of IgAN [14]. Outcomes in IgAN cohorts are generally worst in poor prognosis group with possibility of dialysis in 5 years [14]. The prognostic parameters are listed as age, race, proteinuria, systolic and diastolic blood pressure, medication used, estimated GFR, and histologic score (MEST) of kidney biopsy [15]. Urinary albumin creatinine ratio of more than 0.1 g/g was reported to be independently associated with greater risk of composite kidney events in patients with IgAN [16]. As more studies and data are received regarding the timing for kidney biopsy to achieve prompt diagnosis of IgAN, the indications for kidney biopsy may change accordingly. Until then, KDIGO 2025 clinical practice guideline should be followed for biopsy timing of patients with IgAN.

Once IgA nephropathy is confirmed by kidney biopsy, secondary causes-including systemic diseases, chronic infections, malignancies, and drug exposure-should be actively investigated to allow early diagnosis and appropriate treatment. Crohn's disease, ulcerative colitis, celiac disease, HIV infection, psoriasis, cirrhosis, Lyme disease, malaria, osteomyelitis, cat scratch disease, renal cell carcinoma, and use of dabigatran, warfarin, ustekinumab, should be searched in order to diagnose and treat early and appropriately [17].

In conclusion, it should be known that by the diagnosis of IgAN, unfortunately most of the patients already have severe and irreversible kidney injury. In order not to be late for prompt treatment of these patients, clinicians should be aware of the clues for the presence of IgAN in medical history, physical examination, urine and blood tests of the patients so that optimal timing of kidney biopsy is not missed.

Conflict of interest statement. None declared.

References

1. Pawluczyk I, Nicholson M, Barbour S, *et al.* A Pilot Study to Predict Risk of IgA Nephropathy Progression Based on miR-204 Expression. *Kidney Int Rep* 2021; 6(8): 2179-2188.
2. Berger J, Hinglais N. Les ddpôts intercapillaires d'IgA-IgG [Intercapillary deposits of IgA-IgG]. *J Urol Nephrol (Paris)* 1968; 74(9): 694-695.
3. Rout P, Afzal M. IgA Nephropathy (Berger Disease). 2024 Apr 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
4. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. *J Am Soc Nephrol* 2024; 35(1): 103-116.
5. Ramsawak S, Cohen S, Linares A, Cavanaugh C. IgA nephropathy: Update on pathogenesis and treatment. *Cleve Clin J Med* 2025; 92(6): 373-383.
6. O'Shaughnessy MM, Hogan SL, Thompson BD, *et al.* Glomerular disease frequencies by race, sex and region: results from the International Kidney Biopsy Survey. *Nephrol Dial Transplant* 2018; 33(4): 661-669.
7. Lai KN, Tang SC, Schena FP, *et al.* IgA nephropathy. *Nat Rev Dis Primers* 2016; 2: 16001.
8. Honda K, Akune Y, Goto R. Cost-Effectiveness of School Urinary Screening for Early Detection of IgA Nephropathy in Japan. *JAMA Netw Open* 2024; 7(2): e2356412.
9. Cheung CK, Barrat J. IgA nephropathy: Clinical features and diagnosis. 2025 Nov. UpToDate.com. Available at <https://www.uptodate.com/contents/iga-nephropathy-clinical-features-and-diagnosis> date accessed: 10/12/2025.
10. Nakayama K, Ohsawa I, Maeda-Ohtani A, *et al.* Prediction of diagnosis of immunoglobulin A nephropathy prior to renal biopsy and correlation with urinary sediment findings and prognostic grading. *J Clin Lab Anal* 2008; 22(2): 114-118.
11. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group; Rovin BH, Barratt J, Cook HT, Noronha IL, Reich HN, Suzuki Y, Tang SCW, Trimarch H, Floege J. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int* 2025; 108(4S): S1-S71.
12. Radhakrishnan J. Glomerular disease: Evaluation and differential diagnosis in adults. 2025 Nov. UpToDate.com. Available at <https://www.uptodate.com/contents/glomerular-disease-evaluation-and-differential-diagnosis-in-adults?> date accessed: 10/12/2025.
13. Caster DJ, Abner CW, Walker PD, *et al.* Clinicopathological Characteristics of Adult IgA Nephropathy in the United States. *Kidney Int Rep* 2023; 8(9): 1792-1800.
14. Tomino Y. Immunoglobulin A nephropathy and chronic kidney disease. *Nephrology (Carlton)* 2010; 15(Suppl 2): 23-26.
15. Barbour SJ, Coppo R, Zhang H, *et al.* Evaluating a New International Risk-Prediction Tool in IgA Nephropathy. *JAMA Intern Med* 2019; 179(7): 942-952.
16. Stamellou E, Nadal J, Hendry B, *et al.* GCKD study investigators. Long-term outcomes of patients with IgA nephropathy in the German CKD cohort. *Clin Kidney J* 2024; 17(8): sfac230.
17. Tota M, Baron V, Musial K, *et al.* Secondary IgA Nephropathy and IgA-Associated Nephropathy: A Systematic Review of Case Reports. *J Clin Med* 2023; 12(7): 2726.