PATHOPHYSIOLOGY AND DIAGNOSIS OF IMMUNOGLOBULIN A NEPHROPATHY

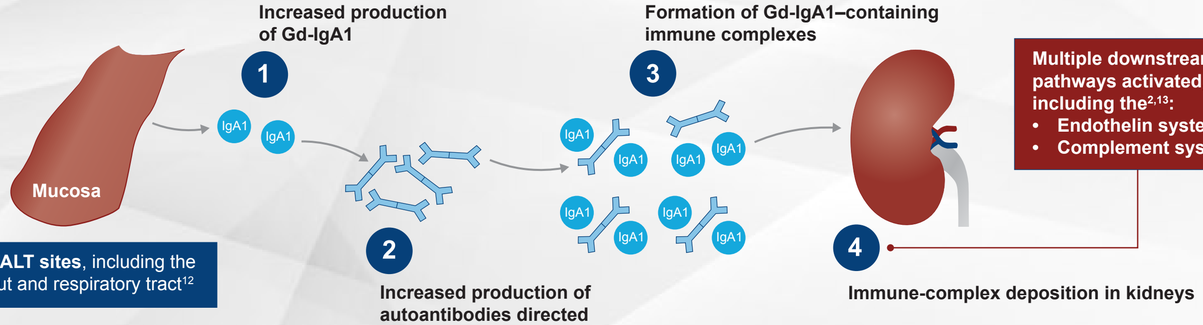
IgA NEPHROPATHY IS THE MOST COMMON PRIMARY GLOMERULONEPHRITIS GLOBALLY[1-7]

- Estimated annual US incidence: 13 cases per million[8]

Affects younger adults (aged 20-30 years) more than older adults (>65 years)[1]

2-3:1
Higher incidence in men in North America and Europe[9,10]

IgA NEPHROPATHY IS DRIVEN BY MULTIPLE "HITS" AND UNDERLYING MECHANISMS[2,11]



MALT sites, including the gut and respiratory tract[12]

Adapted with permission from Boyd et al.[11]

Multiple downstream pathways activated, including the[2,13]:
- **Endothelin system**
- **Complement system**

Immune-complex deposition in the mesangium can trigger a series of downstream pathways, including complement and endothelin, which may result in[2,11,13,14]:
- **Inflammation**
- **Glomerular injury**
- **Tubulointerstitial scarring**

IgA NEPHROPATHY HAS A HETEROGENEOUS CLINICAL PRESENTATION[2-4]

- Multiple clinical phenotypes with a variable risk of progression to kidney failure[5-7]:

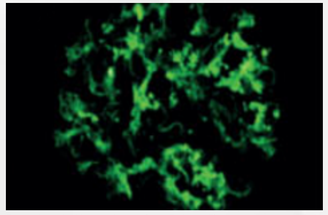
Glomerular inflammatory presentation may include:
- Persistent proteinuria
- eGFR decline[15]
- Hematuria[16]
- Mesangial or endocapillary proliferation or crescents[6]

Chronic progressive presentation may include:
- Persistent proteinuria

KIDNEY BIOPSY IS THE GOLD STANDARD FOR IgA NEPHROPATHY DIAGNOSIS[17]

- Many US patients go undiagnosed until they present with evidence of kidney disease[8,18-20,*]
- Kidney biopsy evaluation includes:
  - Light microscopy with MEST-C scoring[17]
  - IF staining
  - Electron microscopy

IgA deposits in the mesangium visualized by IF[21]



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UP TO 50% OF PATIENTS MAY PROGRESS TO KIDNEY FAILURE WITHIN 10 TO 20 YEARS OF DIAGNOSIS[3,19,22-25]

Patients with evidence of glomerular inflammation or persistent proteinuria are at a higher risk of progression to kidney failure.[6,22,23,26] Retrospective data† suggest that[22]:
- Patients with greater degree of proteinuria (ie, >0.88 g/g [100 mg/mmol‡]) are likely to progress more quickly to kidney failure than patients with proteinuria <0.88 g/g (100 mg/mmol)
  - Some patients with low-grade proteinuria (ie, <0.88 g/g [100 mg/mmol]) may also progress to kidney failure

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Gd, galactose-deficient; IF, immunofluorescence; IgA, immunoglobulin A; KDIGO, Kidney Disease: Improving Global Outcomes; MALT, mucosa-associated lymphoid tissue; MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental glomerulosclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]).

*Often not until >30 years of age and CKD stage 3+. †Data from retrospective cohort of 2299 adults and 140 children with IgA nephropathy from the UK National Registry of Rare Kidney Diseases. Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m^2. Analyses of kidney survival were conducted using Kaplan-Meier and Cox regression. Availability of patient medication and blood pressure data was a limiting factor in this study. ‡0.88 g/g is approximately equivalent to 1 g/day.

1. Lai KN et al. *Nat Rev Dis Primers*. 2016;2:16001. doi:10.1038/nrdp.2016.1 2. Rizk DV et al. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504 3. Xie J et al. *PLoS One*. 2012;7(6):e38904 4. Penfold RS et al. *Int J Nephrol Renovasc Dis*. 2018;11:137-148. doi:10.2147/IJNRD.S129227 5. Zand L et al. *Clin Kidney J*. 2023;16(suppl 2):ii19-ii27. doi:10.1093/ckj/sfad232 6. Karoui KE et al. *J Am Soc Nephrol*. 2024;35(1):103-116. doi:10.1681/ASN.0000000000000242
7. Trimarchi H et al. *J Nephrol*. Published online January 18, 2024. doi:10.1007/s40620-023-01833-3 8. Kwon CS et al. *J Health Econ Outcomes Res*. 2021;8(2):36-45. doi:10.36469/001c.26129 9. Magistroni R et al. *Kidney Int*. 2015;88(5):974-989. doi:10.1038/ki.2015.252 10. Kiryluk K et al. *Kidney360*. 2023;4(8):1112-1122. doi: 10.34067/KID.0000000000000165 11. Boyd JK et al. *Kidney Int*. 2012;81(9):833-843. doi:10.1038/ki.2011.501 12. Gesualdo L et al. *Semin Immunopathol*. 2021;43(5):657-668. doi:10.1007/s00281-021-00871-y 13. Kohan DE et al. *Kidney Int Rep*. 2023;8(11):2198-2210. doi:10.1016/j.ekir.2023.07.023 14. Tecklenborg J et al. *Clin Exp Immunol*. 2018;192(2):142-150. doi:10.1111/cei.13119 15. Ştefan G et al. *Kidney Int Rep*. 2023;9(2):356-369. doi:10.1016/j.ekir.2023.11.005 16. Bobart SA et al. *Nephrol Dial Transplant*. 2021;36(5):840-847. doi:10.1093/ndt/gfz267 17. KDIGO Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021 18. Lafayette RA, Kelepouris E. *Am J Nephrol*. 2018;47(suppl 1):43-52. doi:10.1159/000481636 19. Hastings MC et al. *Kidney Int Rep*. 2018;3(1):99-104. doi:10.1016/j.ekir.2017.08.008 20. Jarrick S et al. *J Am Soc Nephrol*. 2019;30(5):866-876. doi:10.1681/ASN.2018101017 21. Roberts ISD. *Nat Rev Nephrol*. 2014;10(8):445-454. doi:10.1038/nrneph.2014.92 22. Pitcher D et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135 23. Reich HN et al. *J Am Soc Nephrol*. 2007;18(12):3177-3183. doi:10.1681/ASN.2007050526 24. Moriyama T et al. *PLoS One*. 2014;9(3):e91756. doi:10.1371/journal.pone.0091756 25. Rauen T et al. *Kidney Int*. 2020;98(4):1044-1052. doi: 10.1016/j.kint.2020.04.046 26. Cattran DC et al. *Kidney Int Rep*. 2023;8(12):2515-2528. doi:10.1016/j.ekir.2023.09.020

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