PATHOPHYSIOLOGY AND DIAGNOSIS OF IMMUNOGLOBULIN A NEPHROPATHY

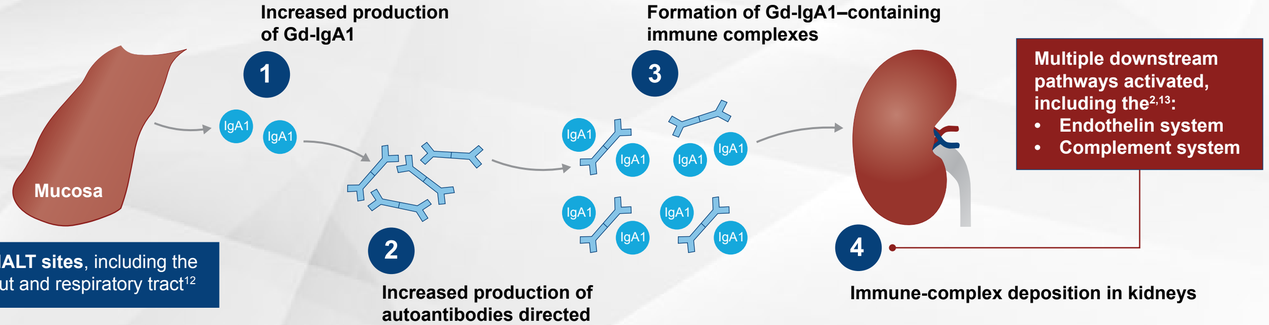
IgA NEPHROPATHY IS THE MOST COMMON PRIMARY GLOMERULONEPHRITIS GLOBALLY[1-7]

- 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]:

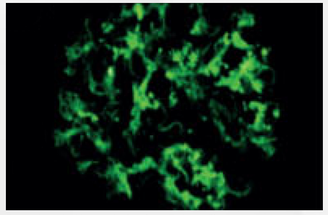
Glomerular inflammatory presentation may include:
- Persistent proteinuria
- eGFR decline[15]
- Hematuria[16]
- Mesangial or endocapillary proliferation or crescents[6]

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]



Reproduced with permission from Roberts.[21]

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 m². 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.

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