Updates on the Pathogenesis IgA Nephropathy and IgA Vasculitis (HSP)

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IgA NEPHROPATHY

IgA nephropathy is glomerular disease with IgA dominant or codominant mesangial immunoglobulin

(Predominantly IgA1)
Frequency of Renal Biopsy Diagnoses vs Age at UNC from 1985-2007

Causes of Nephritis

- Lupus
- IgA Nep
- ANCA GN
- TBM Lesion
- Fibrillary GN
- Post Infect GN
- Anti-GBM GN
- Hereditary Nep

Jennette JC, Falk RJ. NKF Primer on Kidney Disease, 6th Ed, 2014, Chapter 16:152-163
IgA Nephropathy

mesangial immune complex deposits
Focal thinning of the GBM

Mesangial dense deposits

Focal thinning of the GBM
RBC penetrating the glomerular capillary wall in thin basement membrane lesion

Collar et al. Kid Intern 59:2069-2072, 2001
IgA Nephropathy

Frequency in Biopsy Specimens

Histologically
Normal Glomeruli

Focal or Diffuse Mesangioproliferative Glomerulonephritis

Focal or Diffuse Proliferative or Necrotizing Glomerulonephritis

Focal or Diffuse Sclerosing Glomerulonephritis

Crescentic Glomerulonephritis
IgA Nephropathy

Histologically Normal Glomeruli → Focal or Diffuse Mesangial Proliferative Glomerulonephritis → Focal or Diffuse Proliferative or Necrotizing Glomerulonephritis → Focal or Diffuse Sclerosing Glomerulonephritis → Crescentic Glomerulonephritis

Mild to Moderate Nephritis
Asymptomatic Hem / Proteinuria
Severe to Rapidly Progressive Nephritis
Chronic Nephritis
Analysis of the Oxford Data Using the ISN/RPS Classification Approach

J C Jennette, Y Hu, SL Hogan, S Troyanov, M Haas. Unpublished data
IgA NEPHROPATHY

Mesangial IgA

Mesangial and Capillary Wall IgA
% IgA Nephropathy Specimens with Capillary Wall Electron Dense Deposits Relative to Histologic Phenotype

- no lesion
- mesangio-proliferative
- focal proliferative
- diffuse proliferative
- crescentic
- chronic

n=447
• The presence of capillary wall IgA deposits was associated with a higher mesangial cellularity score and endocapillary proliferation.
• The presence of IgG was associated with a higher mesangial cellularity score and endocapillary proliferation.
• There was no significant association between the location of IgA or the presence of IgG and rate of loss of renal function.
• There was a trend towards poorer renal survival in those patients with glomerular IgG.

IgA nephropathy probably can be caused by multiple different etiologies and pathogenic processes:

1) abnormally glycosylated IgA

2) antibodies against abnormally glycosylated IgA

3) reduced clearance of circulating IgA complexes

4) increased affinity for or reduced clearance of IgA deposits from the glomerular mesangium

5) excessive IgA antibody production in response to mucosal antigen exposure

6) increased permeability of mucosa to antigen

7) combinations of these factors

Aberrant glycosylation of IgA1 may be caused by genetically determined aberrant mucosal immune responses to infections.
IgA1 but not IgA2 has a hinge region with 0-linked glycan chains. Each O-glycan chain is based on a core N-acetyl galactosamine unit (GalNAc) O-linked to serine or threonine. This can exist alone but usually carries galactose and sialic acid. Each IgA1 molecule can carry a mixture of chain types.

In IgA nephropathy and IgA vasculitis, serum IgA1 has reduced terminal sialation and galactosylation (X), resulting in increased exposure of terminal GalNAc.

A lectin that recognizes N-acetylgalactosamine was used in an ELISA to measure serum galactose-deficient IgA1. The diagnostic sensitivity 76.5%, with specificity 94%; the positive predictive value was 88.6% and the negative predictive value was 78.9%.

Children with HSP nephritis showed significantly higher IgA1-VV binding than children with HSP lacking renal involvement ($P=0.004$), children with post-streptococcal GN ($P=0.002$), or control children ($P=0.005$).

Adults with IgAN showed significantly higher IgA1-VV binding than adults with non-IgA glomerulonephritis or adult controls. There was no difference in IgA1-VV binding between adults with HSPN and IgAN.
Aberrant sialylation of serum IgA1 was associated with prognosis of patients with IgA nephropathy

IgA1 hinge glycopeptide characterization by quadrupole orthogonal acceleration time-of-flight MS & MS/MS tandem mass spectroscopy (Q-TOF LC-MS/MS)

Glycopeptides in higher mass range contain more sialic acids

1-2 sialic acids per glycopeptide
3-4 sialic acids per glycopeptide

Provided by Olivier Lardinois, PhD, UNC Kidney Center
Quadrupole orthogonal acceleration time-of-flight tandem mass spectroscopy in MS & MS/MS modes (Q-TOF LC-MS/MS)

Healthy Control

Active IgAN

Healthy Control treated with neuraminidase (=sialidase)

Provided by Olivier Lardinois, PhD, UNC Kidney Center
Comparison of glycosylation profiles between healthy controls and active IgAN

Conclusion: Sialylation is lower in IgAN

Profiles with 2 or more sialic acids are decreased

NeuAc = Sialic acid;  Gal = Galactose;  GalNAc = N-Acetylglactosamine

Average of:  
- 5 Healthy Controls (n = 5)
- 6 Active IgAN (n = 6)

Provided by Olivier Lardinois, PhD, UNC Kidney Center
Glycan-specific IgG antibodies may form immune complexes with aberrantly glycosylated IgA1
Glycan-specific IgG antibodies have 88% specificity and 95% sensitivity for IgA nephropathy.

Correlation between severity of hematuria/proteinuria and serum Gd-IgA1 or IgA/IgG-IC

Abnormally glycosylated IgA1 molecules (←), even in the absence of antigen, self aggregate or bind to antibodies directed against the abnormal glycosylation (→) and localize in the glomerular mesangium where they activate complement by the lectin and alternative pathways.

Hypothesis: Glycan-specific IgG antibodies binding to abnormally glycosylated IgA cause IgA nephropathy
Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens.


• Genome-wide association study (GWAS) of IgA nephropathy in 20,612 individuals of European and East Asian ancestry.

• Multiple risk alleles, most associated with maintenance of the intestinal epithelial barrier and response to mucosal pathogens, including risk of inflammatory bowel disease.

• The risk alleles suggest host-intestinal pathogen interactions in establishing genetic susceptibility to IgAN.
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