IgA Nephropathy (IgAN) et IgA Vasculitis (HSP- IgAV): same disease?

E PILLEBOUT
Nephrology Unit - St Louis Hospital,
Center of Research on Inflammation INSERM U1149 – Bichat University
Paris - France
IgAV is considered to be a systemic form of IgAN, and it has been suggested that the two conditions are different manifestations of a single disease process.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
</table>
Some reviews

**Berger disease: Henoch-Schönlein syndrome without the rash**

Identical 7-year-old twin boys each had a proved adenovirus infection at the same time. A few days later one developed florid Henoch-Schönlein purpura, severe alimentary tract symptoms, and transient joint symptoms. He had an acute nephritic syndrome, which progressed to nephrotic syndrome and renal insufficiency. Biopsy showed severe proliferative glomerulonephritis with crescents and marked deposition of IgA, IgG, C3, and fibrin. The second twin had hematuria and abdominal pain but no rash. Biopsy showed mesangial proliferative glomerulonephritis with mesangial deposits of IgA and, to a lesser extent, IgG and C3. The appearance was characteristic of Berger disease, and the subsequent clinical course has been that of symptomless microscopic hematuria and recurrent macroscopic hematuria with normal renal function. Immunologic studies have not revealed why these identical twins responded differently to the same provocation. Perhaps Berger disease may be considered a variant of Henoch-Schönlein nephritis. (J Pediatr 106:27, 1985)


**IgA nephropathy and Henoch–Schönlein purpura nephritis**

Sandos, John T. Wyatt, Robert J

doi: 10.1097/MOP.0b013e32824308b
Nephrology. Edited by Michel Baum

**What is the difference between IgA nephropathy and Henoch-Schönlein purpura nephritis?**

JEAN-CLAUDE DAVIN, INEKE J. TEN BERGE, and JAN J. WERING

Departments of Pediatrics, Internal Medicine, and Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
IgAN $\approx$ IgAV?

Differences and similarities in terms of
• Epidemiology
• Presentation/outcome
• Treatment
• Physiopathology/biomarkers
• Genetic

My point of view
What is the next stage?
Epidemiology

**Fig. 1** Age distribution of IgA nephropathy (*n* = 5679) and Henoch–Schönlein purpura nephritis (*n* = 513). Each histogram shows 10-year intervals. Frequency of HSPN diagnosis is bimodal with peaks at 1–19 and 60–69 years; frequency of IgAN diagnosis peaks at 30–39 years.
Clinical Presentations of IgA Nephropathy and Henoch-Schönlein Purpura in Relation to Age
Outcome

Children: 31 IgA N - 120 IgAV (32 renal biopsies)
IgAV younger
RB: Sclerotic lesions > IgAN, but endothelial proliferation > IgAV
34 months follow-up: CR 72.5% IgAV, 19.4% IgAN
Outcome

61 IgA N - 142 IgAV
IgAV younger
Clinical presentation was less severe in IgAV than IgAN:
renal insufficiency 25 vs 63.4%; nephrotic syndrome 12.5 vs 43.7%
After 121 and 139 months of follow-up: prognosis is less severe in IgAV than IgAN:
dialysis 2.9 vs 43.5%, transplantation 0 vs 36%, chronic renal insufficiency 4.9 vs 63.8%
Clinical outcomes, when matched at presentation, do not vary between adult-onset Henoch-Schönlein purpura nephritis and IgA nephropathy

Hyung Jung Oh¹, Song Vogue Ahn², Dong Eun Yoo¹, Seung Jun Kim¹, Dong Ho Shin¹, Mi Jung Lee¹, Hyoung Rae Kim¹, Jung Tak Park¹, Tae-Hyun Yoo¹, Shin-Wook Kang¹,³, Kyu Hun Choi¹ and Seung Hyeok Han¹

*Kidney International (2012) 82, 1304–1312; doi:10.1038/ki.2012.302; published online 15 August 2012*

1011 IgA N - 92 IgAV; matching pairs 178 IgAN 89 IgAV
IgAV younger
Clinical presentation was less severe in IgAV/IgAN
Renal insufficiency 7.6 vs 14.4%.
After 60 months of follow-up:
The outcome was better in the IgAV group but there were no significant differences in the individual renal outcome between the 2 groups in the match cohort. In a multivariate Cox analysis adjusted for clinical factors, steroid use and pathological findings, the risk of bad outcome was comparable in patients with IgAV and with IgAN.
Children

41 IgA N – 137 IgAV
No significant difference in term of clinical or histological renal presentation

5679 IgAN, 513 IgAV
Clinical and histological presentation was more severe in IgAV / IgAN
Renal insufficiency 45.5 vs 37.5%; nephrotic syndrome 10.5 vs 3%
RB : endothelial proliferation (6.4 vs 0.9%) and crescentic glomerulonephritis (6.6 vs 0.8%)
After 121 and 139 months of follow-up: prognosis is less severe in IgAv than IgAN: dialysis 3 vs 43%, transplantation 0 vs 36%, chronic renal insufficiency 5 vs 64%
Absolute renal risk score

Validation of the absolute renal risk of dialysis/death in adults with IgA nephropathy secondary to Henoch-Schönlein purpura: a monocentric cohort study

Hesham Mohey¹, Blandine Laurent¹, Christophe Mariat¹ and Francois Berthoux¹,²*

74 IgAV - 993 IgAN
8.2 years of follow-up

The absolute renal risk (ARR) of dialysis/death (D/D) is validated in IgAV as well as IgAN
- Hypertension
- Proteinuria > 1gramme/day
- Severe pathological lesions (local classification score ≥ 8)
Treatment

- Rauen T, N Engl J Med. 2015 Intensive Supportive Care plus Immunosuppression in the STOP-IgAN study.
- Jicheng Lv JAMA. 2017 Effect of Oral Methylprednisolone in The TESTING Randomized Clinical Trial.
Physiopathology: multi-hit hypothesis

Heineke and al, Autoimmunity Reviews 16 (2017) 1246–1253
## Physiopathology - biomarkers

<table>
<thead>
<tr>
<th></th>
<th>IgA N</th>
<th>IgA V</th>
<th>IgA N + V</th>
</tr>
</thead>
<tbody>
<tr>
<td>GdIgA1</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>GdIgA1/CD89</td>
<td>x</td>
<td>x</td>
<td>NE</td>
</tr>
<tr>
<td>GdIgA1/IgG</td>
<td>x</td>
<td>x</td>
<td>NE</td>
</tr>
<tr>
<td>sCD89</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Transglutaminase2</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CD71 (TfR)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>TLR9</td>
<td>x</td>
<td>NE</td>
<td>x</td>
</tr>
<tr>
<td>TLR4</td>
<td>x</td>
<td>NE</td>
<td>x</td>
</tr>
<tr>
<td>TGFβ-1 MCP-1</td>
<td>x</td>
<td>NE</td>
<td>x</td>
</tr>
</tbody>
</table>

NE : Not evaluated

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Int (2011)</td>
<td>80: 79-87</td>
</tr>
<tr>
<td>BBA Clinical (2016)</td>
<td>5: 79-84</td>
</tr>
<tr>
<td>Clinics (2017)</td>
<td>72: 95-102</td>
</tr>
</tbody>
</table>
Galactose deficiency of O-linked glycans in the hinge region of IgA1

Quantify by:

Mass spectrometry-based analyses
Lectin assay using the lectin Helix aspersa agglutinin (HAA)
Lectin-independent method (ELISA) with monoclonal antibody (KM55 mAb)
In all glomeruli of the 48 patients with IgAN and 14 patients with IgAV, Gd-IgA1, detected by KM55 mAb, was clearly localized to a similar pattern as IgA glomerular. Gd-IgA1 was negative in other types of glomerular, including lupus nephritis, membranous nephropathy HCV-RN, hepatic glomerulosclerosis, MPGN
Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch–Schönlein purpura nephritis

Krzysztof Kiryluk¹, Zina Moldoveanu², John T. Sanders³,⁴, T. Matthew Eison³,⁴, Hitoshi Suzuki²,⁵, Bruce A. Julian², Jan Novak², Ali G. Gharavi¹ and Robert J. Wyatt³,⁴

http://www.kidney-international.org
© 2011 International Society of Nephrology
HLA-DRB1 positions 13 and 11
My point of view

IgA-V and IgA-N:
Different ends of a continuous spectrum of disease

Because of the rash, patients with IgA-V are diagnosed at the beginning of the disease.

In the absence of any clinical finding however, renal biopsy to confirm nephritis in IgA-N patients is done at any time during the history of the disease, which can explain the frequent chronic lesions upon diagnosis.
My point of view

IgA-V and IgA-N:
Different ends of a continuous spectrum of disease

THE questions:

Why do some patients with IgA-N not have skin lesions and some patients with IgA-V do not have nephritis?

Which patients will recover spontaneously and which ones will not and need to be treated?
What is the next stage?

Larger clinical studies are required
→ including the two diseases
→ stratified on age and genetic background
to evaluate their outcome and the therapeutic strategies.