

# **GDCN Study Updates**

*Saturday, April 18, 2009*

# Outline

## Recently Completed GDCN Studies

- Membranous Case-Control Study
  - Funded by the Halpin Foundation
- FSGS Case-Control Study
  - Supported by the NIH and UNC Kidney Center
- Outcomes in patients with vasculitis after ESRD
  - Supported by the NIH Program Project

## On the Horizon

- Rare Disease Registry

# Case-control Study in Membranous Glomerulopathy

- **Purpose:** To evaluate risk factors for the development of membranous glomerulopathy
  - Mailed questionnaire to assess a variety of risk factors
  - Focus on occupational exposures, infections and personal/family history of autoimmune diseases
- **113** GDCN membranous cases
- **184** controls (1.6:1)
  - GDCN patients with other glomerular diseases
  - 1<sup>st</sup> native kidney diagnosis
  - Frequency matched to cases by sex, race, age and date of biopsy (1999-2003, 2004-2007)
- Age 18 or older at the time of the questionnaire

## Comparison of Patients with Membranous to Controls

Percent or mean $\pm$ sd	Membranous Nephropathy (Cases) n=113	Other Glomerular Diseases (Controls) n=184	P-value
Male Gender	54%	51%	0.64
Caucasian Race	88%	78%	0.045
Age	55 $\pm$ 13	53 $\pm$ 17	0.66
Biopsy year 2004-2007 (vs. 1999-2003)	46%	50%	0.55
$\leq$ High School Education	24%	39%	0.008
History of Diabetes	5%	13%	0.046
Ever Smoked	57%	53%	0.63

## Occupational Exposure to Hydrocarbons, Solvents, Pesticides and Heavy Metals

	Membranous Nephropathy (Cases)	Other Glomerular Diseases (Controls)	Adjusted Odds Ratio (95% CI)	P- value
Hydrocarbons	43%	44%	1.0 (0.6, 1.7)	0.87
Solvents	64%	60%	1.2 (0.7, 1.9)	0.55
Pesticides	42%)	42%	0.9 (0.6, 1.6)	0.82
Heavy Metals (ever)	20%	9%	2.3 (1.1, 4.7)	0.029
Heavy Metal Exposure Duration:			1.0 (Reference)	NA
Never	80%	91%		
< 2 years	5%	4%	1.1 (0.4, 3.4)	0.86
≥ 2 years	15%	5%	3.8 (1.5, 9.6)	0.005

## Infections in the 12 Months Prior to Symptoms or Diagnosis

	Membranous Nephropathy (Cases)	Other Glomerular Diseases (Controls)	Adjusted Odds Ratio (95% CI)	P-value
<b>Any Infection</b> (excluding flu or colds):	50%	37%	1.60 (0.95, 2.71)	0.078
<b>Infection Type:</b>				
UTI	11%	10%	1.32 (0.57, 3.04)	0.52
Sinus	26%	25%	1.03 (0.58, 1.81)	0.92
Tooth/Gum	21%	11%	2.03 (1.04, 3.98)	0.039

# Patient and Family History of Autoimmune Diseases

	Membranous Nephropathy (Cases)	Other Glomerular Diseases (Controls)	Adjusted Odds Ratio (95% CI)	P-value
Patient:				
Any other autoimmune disease	38%	32%	1.4 (0.8, 2.4)	0.21
First Degree Relatives:				
Any with autoimmune disease	59%	58%	1.2 (0.7, 2.0)	0.45

# Case-control Study in Membranous

- Heavy metal exposure is associated with the onset of membranous, but the prevalence of high exposure is not common (15%)
- Membranous nephropathy can result from hepatitis B and C and syphilis
- More common infections may also be important, and potentially the gram negative bacteria found in periodontal disease
- No suggestion of an association with co-existence of other autoimmune diseases, but accurate evaluation by questionnaire/recall may be difficult

# Case-control Study in FSGS

- 140 GDCN FSGS cases
- 140 controls (~1:1)
  - GDCN patients with other glomerular diseases
  - 1<sup>st</sup> native kidney diagnosis
  - Frequency matched to cases by sex, race, age and date of biopsy (1999-2003, 2004+)
- Renal biopsy: 1999 or after
- Age 18 or older at the time of the questionnaire
- Focus on life course of weight (birth, adolescence, disease onset)

# Comparison of Patients with FSGS to Controls

Percent or mean $\pm$ sd	FSGS (Cases) n=140	Other Glomerular Diseases (Controls) n=140	P-value
Male Gender	53%	56%	0.63
Black Race	28%	21%	0.26
Age	50 $\pm$ 18	52 $\pm$ 15	0.63
Biopsy year 2004-2007 (vs. 1999-2003)	55%	49%	0.34
$\leq$ High School Education	39%	31%	0.17
History of Diabetes	15%	8%	0.09
Ever Smoked	57%	54%	0.63

# Life Course of Weight and Risk of FSGS

	FSGS Cases	Controls	AdjOR (95% CI)	p-value
Low Birth Wt	11%	8%	1.2 (0.5, 2.8)	0.70
Adolescent Body Size:				
Normal	45%	51%	1.0 (reference)	NA
Heavy	25%	16%	2.0 (1.1, 3.7)	0.0285
Thin	35%	33%	1.0 (0.6, 1.7)	0.98
Onset Adult BMI Group:				
Normal (<25)	38%	43%	1.0 (reference)	NA
Overweight (25≤30)	33%	26%	1.6 (0.9, 2.9)	0.13
Obese (>30)	29%	31%	1.1 (0.6, 2.0)	0.58

# Life Course of Weight and Risk of FSGS

- There was no interaction between LBW and adolescent or adult heaviness ( $p > 0.2$ ).
- Heavy adolescents were more often overweight or obese (75%) as adults, compared to normal (59%) or thin (50%) adolescents.
- Increased risk of FSGS among heavy adolescents likely represents long-standing obesity

# The Clinical Course of ANCA Small Vessel Vasculitis on Chronic Dialysis

## ■ Purpose:

- To describe rates of relapse, malignancy and death before and after ESKD and compared to patients with preserved renal function
- To evaluate infection rates after ESKD with and without immunosuppressive therapy
- Of 523 patients in the cohort, 136 (26%) reached ESKD and 387 had preserved renal function over a median follow up time of 40 months

# Summary of Cause of, and Disease Activity among ANCA SVV Patients Reaching ESKD

ESKD Sub-group	N (%)	% with active disease	BVAS (mean $\pm$ SD)
ESKD group	136	51.5	7.8 $\pm$ 8.0
New-onset GN	51%	100	13.8 $\pm$ 6.0
Relapsing GN	6%	100	7.5 $\pm$ 5.9
Progressive CKD without active vasculitis	43%	0	0

# ANCA-SVV: Patients with ESKD compared to Patients with Preserved Renal Function

		ESKD	Non-ESKD	
ANCA-SVV Relapse Rate, episodes per person-year (95% CI)	<b>Pre- ESKD</b>	0.20 (0.13-0.26)	0.16 (0.13-0.17)	0.20
	<b>Post- ESKD</b>	0.08 (0.04-0.11) <b>p-value vs. Pre-ESKD= 0.0012</b>	NA	
Malignancy Rate, episodes per person-year (95% CI)		0.04 (0.01-0.07)	0.01 (0.007-0.02)	0.046
Malignancies in # patients		8 in 5	15 in 15	
Mortality Rate, (deaths/person- year)		0.31 (0.26-0.36)	0.07 (0.05-0.08)	<0.0001

# Infections in ANCA-SVV ESKD

- 354 episodes of infections occurred in 61 patients on dialysis:
- Incidence rate = 1.92 episodes per person year
- Higher infection rate among those on immunosuppressive therapy than those not ( $p < 0.001$ ):
  - 1.94 episodes/person-year, 95% CI: 1.61-2.26
  - 1.03 episodes/person-year, 95% CI 0.87-1.19

# Summary of ESKD in ANCA SVV

- >25% of patients with ANCA-SVV reach ESKD
- ESKD is largely from new onset disease, rather than persistent or relapsing vasculitis, underscoring the need for prompt diagnosis and therapy
- Patients with ANCA-SVV and ESKD experience a low rate of relapses
- There is a high risk of infectious complications, especially with use of immunosuppressive therapy
- Judicious use of immunosuppression in patients with ANCA-SVV ESKD is recommended, with restriction to use only in the setting of active vasculitis.

# Proposal: A Nephrotic Syndrome Rare Disease Consortium (NSRDC)

## Goal:

- Multidisciplinary research and education platform
- Consortium of:
  - clinical and translational scientists
  - lay research and patient education foundations
- Aim is to develop an infrastructure and establish cohorts to better study FSGS, MCD, and MN

Projected to start: Late summer/Fall 2009

# NSRDC: Primary Participating Centers

	<b>PI</b>	<b>Co-PI</b>
Albert Einstein College, Montefiore, Bronx	R. Kaskel	
Mayo Clinic, Rochester	F. Fervenza	
University of Michigan, Ann Arbor	M.Kretzler	A.Ojo
Glomerular Disease Collaborative Network	P. Nachman	S. Hogan
University of Toronto, Toronto	D. Cattran	H. Reich

# NSRDC: Research Aims

- Establish investigational infrastructure
  - Cohorts of newly diagnosed patients
  - Shared repository of clinical data and biospecimens
  - Web based information collection and distribution
- Identify and characterize novel biomarkers
  - transcriptional signatures, podocyte shedding, metabolomics, etc
- Perform prospective cohort studies of NS
  - Adult FSGS & MCD
  - Pediatric FSGS & MCD } n=250
  - Membranous Nephropathy: n=200
  - Study visits at biopsy then every 4 months for a year, then every 6 months
- Conduct two pilot clinical studies in NS

# NSRDC: Research Aims

- Provide post-doctoral training program in related clinical studies
- Develop and disseminate multimedia lay and physician educational resources on NS in collaboration with disease-specific foundations
  - Nephcure Foundation (FSGS)
  - Halpin Foundation (Membranous)