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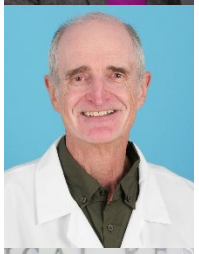

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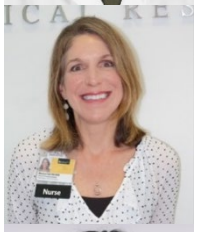

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C3 GLOMERULOPATHY

MORL
Molecular Otolaryngology & Renal Research Laboratories

University of Iowa
Stead Family
Children's Hospital

This pamphlet was made possible through the generous donations of rare disease family members.

C3 Glomerulopathy (C3G)

C3G is an ultra-rare kidney disease that most frequently affects children and young adults. It may present with few obvious symptoms. Many times, findings of blood and/or protein in the urine are identified during a routine doctor appointment or while being evaluated for high blood pressure. Others present with more aggressive symptoms such as swelling and acute kidney injury. Fatigue is a frequent patient complaint.

C3G is caused by excessive activity of the alternative pathway (AP) of complement, an important part of our immune system. This is why it frequently presents for the first time after an infection – after the immune system has been activated. Once activated, the immune system of the C3G patient fails to shut down properly, and the excess activity begins to create many byproducts of complement activity (protein complexes and breakdown products) that deposit on the kidney and produce disease. Excess complement activity is why many (but not all) patients with C3G present with a low complement C3 level in the blood; C3 is being consumed ("used up") due to dysregulation of the alternative pathway of complement.

The driver or cause of C3G is most often autoimmune (~65%), and less frequently genetic (~20%). Autoimmune proteins known as nephritic factors (C3, C5 and/or C4) are most commonly identified. They bind to and disrupt the normal function of key enzymes in the complement system. Other complement protein autoantibodies may also be present. We do not know why these proteins are made.

The diagnosis of C3G is made by finding predominantly C3 deposits (at least 2 times more than any other protein) on the immunofluorescence (IF) part of the kidney biopsy. Other diseases (i.e., post infectious glomerulonephritis) may mimic this exact biopsy pattern therefore it may be difficult to diagnose C3G when the disease first presents itself. There are two types of C3G: C3 Glomerulonephritis (C3GN) and Dense Deposit Disease (DDD).

Outcomes/Treatment

We here at **MORL** spend a lot of time studying the natural history of C3G, however there is a lot to learn still. What we know currently is that C3G often leads to chronic kidney disease. Up to 50% of patients will suffer end stage renal disease within 10 years of diagnosis. Recurrence of C3 deposition in a transplant kidney happens in up to 90%. 50% of transplant patients will develop clinical recurrence and lose their kidney within 5 years.

There are currently no *targeted* (complement specific) treatments for C3G available for your physician to prescribe. Treatment is supportive initially, with escalation in approach based primarily on urine protein and changes in creatinine: *

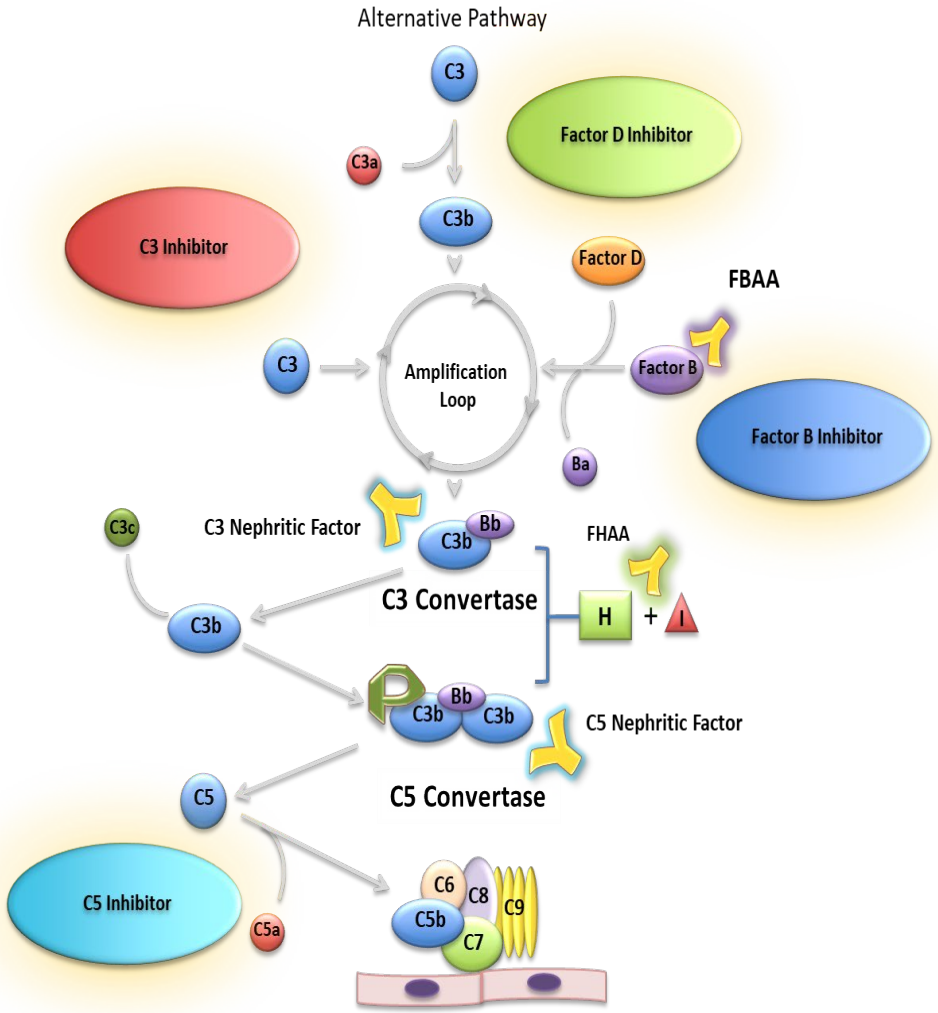
All patients	Supportive Cares: Blood pressure control, control of lipids, edema control, weight control and good diet
Urine protein up to 1g/24 hours	ACE inhibitors (i.e. Lisinopril, Enalapril), ARBs (i.e. Losartan, Valsartan), etc.
Urine protein between 1-2g despite above	Mycophenolate mofetil (i.e. Cellcept, Myfortic) and brief course of steroids (i.e. Prednisone)
Urine protein >2g of urine protein	Despite the above requires escalation in care. For most patients this means consideration of a clinical trial.

*KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

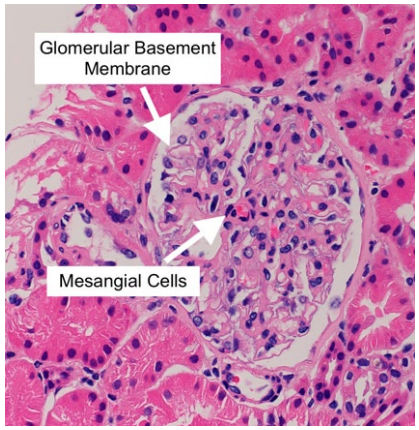
Notes:

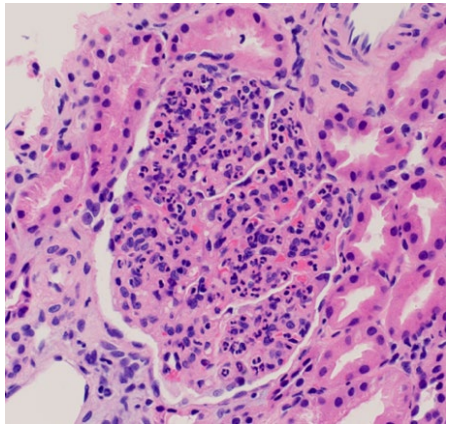
Complement Cascade

Abnormalities in the alternative pathway of complement in C3G patients may be detected in the laboratory. The figure below displays the relative location of these proteins. Included also in this figure for reference are the proteins that may be blocked by some of the emerging therapeutics.



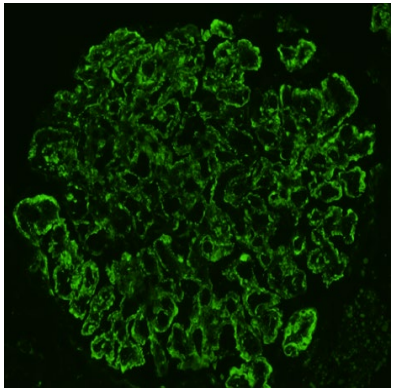
Pathology





Light Microscopy (LM) appearance of a glomerulus

Normal glomerulus (left): open, thin-walled blood vessels, no extra mesangial cells. C3G glomerulus (right): *proliferative* (hypercellular), blood vessel walls are thickened and often consumed by deposits, and contain many more cells (purple dots are cell nuclei).

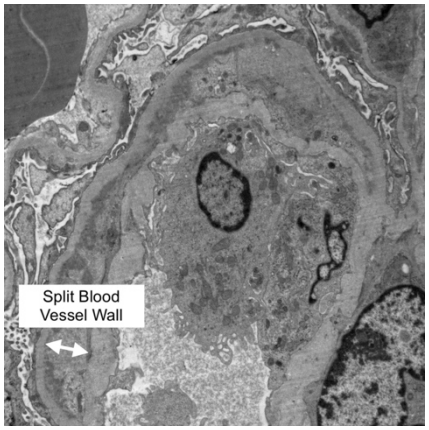


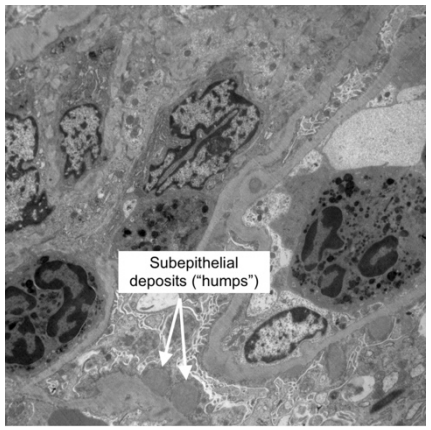
Immunofluorescence (IF)

Left: Typical appearance of bright green C3 deposits on a C3G biopsy specimen.

Electron Microscopy

Below Left: Split blood vessel wall basement membrane (MPGN pattern)
Below Right: Subepithelial humps – seen in C3G and post infectious glomerulonephritis





Interpreting the Biomarker/Genetic Panels

GENETIC TESTING		
Gene	***Chromosomal Location***	***Interpretation***
Complement gene that have been reported to be associated with C3G	The location on the gene where the abnormality is	**Pathogenic known**: a variant that has been proven to be disease-causing **Likely pathogenic**: a variant that is likely to be disease causing based on all of our current data **Unknown significance:** a variant for which further interpretation is not possible based on available data **Likely benign:** a variant not currently known to cause disease

PATHWAYS			AUTOANTIBODIES					
CH50 *(41-95 Units/mL)*	***APFA*** *(50-103%)*	***C3b Deposition Assay*** *(normal)*	***FH Autoantibody*** *(<200 AU)*	***FB Autoantibody*** *(<200 AU)*	***Fluid Phase Activity -IFE*** *(<7.5%)*	***C3Nef - C3CSA*** *(<20%)*	***C5Nef- C3CSAP*** *(<20%)*	***C4Nef*** *(<20%)*
Determines whether the CP is overactive or whether a CP protein has been abnormally consumed	Determines whether the AP is overactive or whether an AP protein has been abnormally consumed	Identifies whether abnormal C3 activation is occurring	An antibody that interferes with the function of FH; interferes with the regulation of the AP	Antibody that interferes with C3 convertase regulation	Determines if a protein in the blood is causing complement dysregulation/activation	Nephritic factors stabilize the convertases, preventing them from naturally falling apart.		Similar to C3 or C5 Nef, however, they stabilize the classical pathway convertase

BIOMARKERS												
	C3c Level *(<1.5 mg/L)*	***C3c Level*** *(<1.5 mg/L)*	***C4 Level*** *(15-47 mg/dL)*	***FB Level*** *(22-50 mg/dL)*	***Ba Level*** *(<1.2 mg/L)*	***Bb Level*** *(<2.2 mg/L)*	***FD Level*** *(0.78-1.59 mg/L)*	***C5 Level*** *(13.5-27 mg/L)*	***Properdin Level*** *(10-33 mg/L)*	***Soluble C5b-9*** *(<0.3 mg/L)*	***FI Level*** *(18-44 mg/L)*	***FH Level*** *(180-420 mg/L)*
High Result	Represents inflammation or obesity	A breakdown product of C3, suggests overactivity of the AP	Represents inflammation	Represents inflammation	The two main cleavage products of FB. High levels mean that FB is being broken down excessively. High Ba only is seen in ESKD		Excess FD levels suggest worsening kidney function irrespective of complement activity	Elevated in terminal complement pathway inhibitor patients or Represents inflammation		Increased activity of the terminal complement pathway	Represents inflammation	Represents inflammation
Low Result	C3 is either deficient because of a gene abnormality or C3 is being inappropriately consumed		C4 is either deficient because of a gene abnormality or C4 is being inappropriately consumed	FB is either deficient because of a gene abnormality or consumption due to overactive AP				Suggests terminal pathway hyperactivity	Suggests a hyperactive complement pathway, and that properdin is being consumed	Will be low if on terminal complement blockade	FI is either deficient because of a gene abnormality	FH is either deficient because of a gene abnormality or FH is being inappropriately consumed

*All lab results may be significantly altered by inappropriate specimen handling

AP = Alternate Pathway; CP = Classical Pathway; Nef = Nephritic Factor