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C3 GLOMERULOPATHY

MORL

Molecular Otolaryngology & Renal Research Laboratories

IOWA HEALTH CARE

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. Many times, the first signs of C3G are blood and/or protein in the urine found during a routine doctor appointment or while being evaluated for high blood pressure. Other people have more intense symptoms, such as swelling, and abnormal lab values, including elevated creatinine and low albumin and C3 levels. Being very tired is a frequent patient complaint.

C3G is caused by uncontrolled activity of one of the immune pathways called the alternative pathway (AP). This is why C3G is often found for the first time after an infection – after the immune system has been activated. Once activated, the immune system of the C3G patient cannot shut down properly, and the extra activity begins to create many breakdown products of complement that land on the kidney and produce disease. Excess complement activity is why many patients with C3G have a low complement C3 level in the blood; C3 is being "used up" due to the extra activity. We call this extra activity "dysregulation" of the alternative pathway of complement.

Our goal is to find out what causes each person's C3G. We call this the "driver of disease". The driver of C3G is most often related to autoimmune reasons (~65%), and less often to genetic reasons (~20%). Autoimmune proteins called nephritic factors (C3 Nef, C5 Nef and/or C4 Nef) are most often found. Autoimmune proteins bind to complement proteins and change the normal function of the complement system. This change is called "dysregulation". Other complement protein autoantibodies may also be present. We do not know why these proteins are made.

The diagnosis of C3G is made by preforming a kidney biopsy. For C3G, the immunofluorescence (IF) part of the kidney biopsy will show extra cells called "proliferation" and more C3 proteins (at least 2 times more than any other protein). Other diseases, like post-infectious glomerulonephritis, may look exactly like the C3G biopsy pattern. Therefore, it may be difficult to diagnose C3G right away. Often, we need to watch a patient's labs (C3 and urine protein and blood) for 3 months to determine if they have C3G.

There are two types of C3G: C3 Glomerulonephritis (C3GN) and Dense Deposit Disease (DDD).

Outcomes/Treatment

While significant progress has been made in understanding the natural history of C3G, investigation is ongoing to further characterize the disease. 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. However, statistics may be changing for the better with the use of the new complement therapies that have just completed clinical trials.

C3G can show up again in a transplanted kidney biopsy in up to 90% of patients. We do not consider this C3G recurrence unless there is proliferation on biopsy, protein and blood in the urine, a rising creatinine or lowering C3. This definition of recurrence may change in the near future.

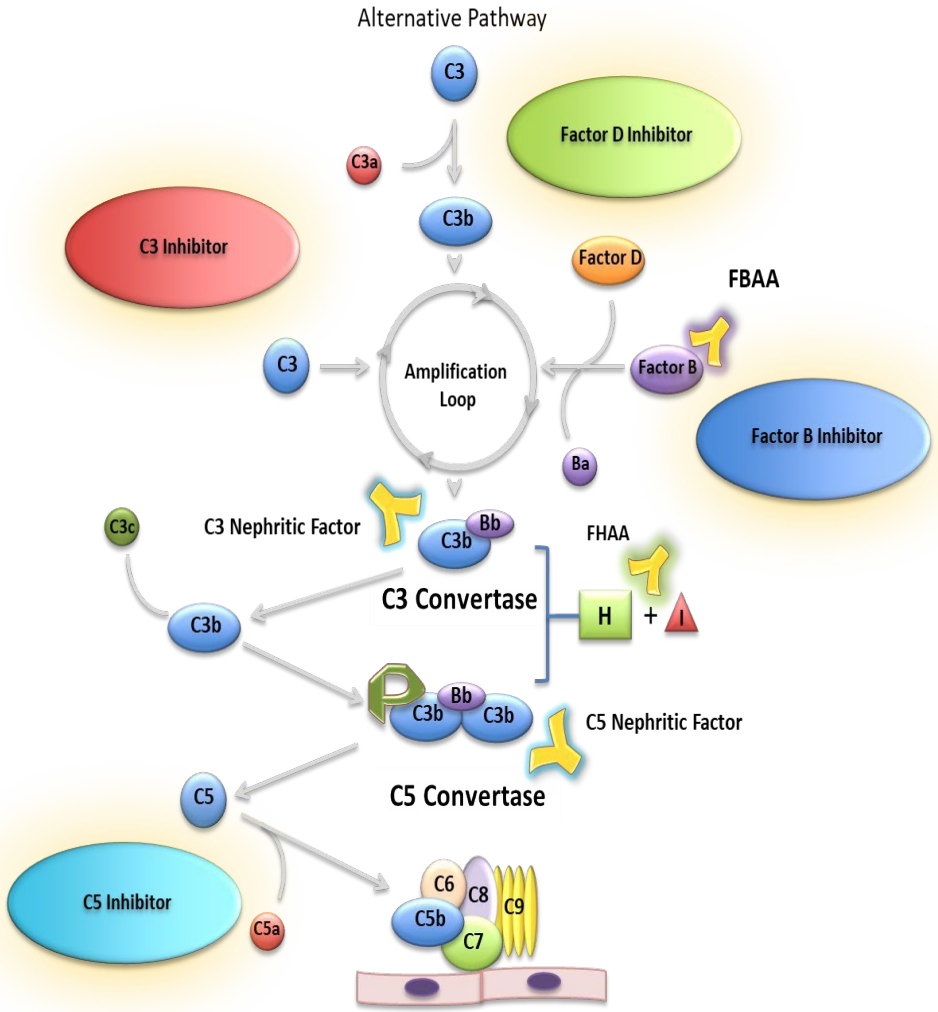
Until recently, treatment for C3G was primarily supportive, with an escalation approach based on the urine protein and changes in the creatinine. Now physicians have more choices. All patients require supportive care; however, the sequence of next steps is changing rapidly. Though the sequence for each patient will need to be individualized, below is the general approach.

Two FDA-approved treatments are now available. Iptacopan, approved for individuals 18 years old and older, works by binding to Factor B of the AP. This regulates the cleavage of C3, the accumulation of downstream effectors, and amplification of the pathway. Pegcetacoplan, approved for individuals 12 years old and older, is a C3 and C3b inhibitor that blocks the cleavage of C3, reducing C3 fragment deposition and the impact of downstream effectors.

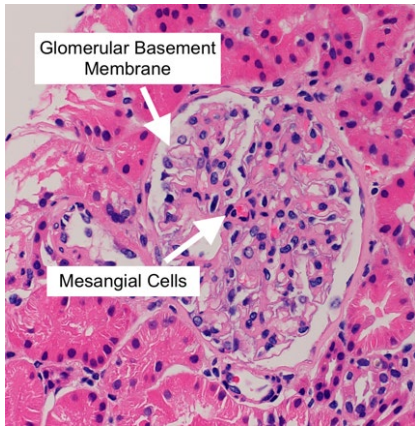
All patients	Supportive Care: Blood pressure control, control of lipids, edema control, weight control and good diet
Urine protein up to 1 g/24 hours (urine protein/creatinine ratio </= 1)	ACE inhibitors (i.e. Lisinopril, Enalapril), ARBs (i.e. Losartan, Valsartan) AND consider alternative pathway blockade based on combined features.
Urine protein 1-2 g/24 hours (urine protein/creatinine ratio = 1-2)	Mycophenolate mofetil (i.e. Cellcept, Myfortic) and brief course of steroids (i.e. prednisone) OR consider alternative pathway of complement blockade based on combined features.
Urine protein >2 g/24 hours (urine protein/creatinine ratio >/= 2)	If traditional immune suppression has been used and has proven ineffective, consider alternative pathway of complement blockade. Consider a clinical trial.

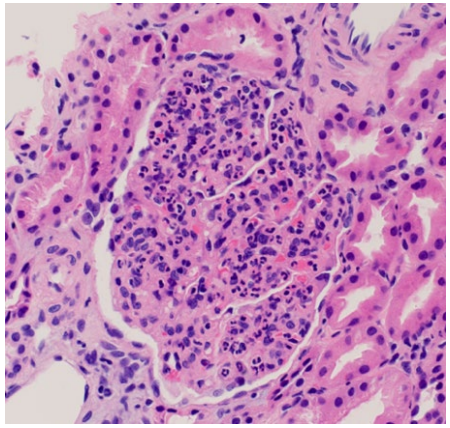
Complement Cascade

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.



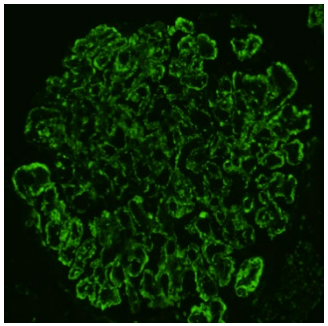
Pathology





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).



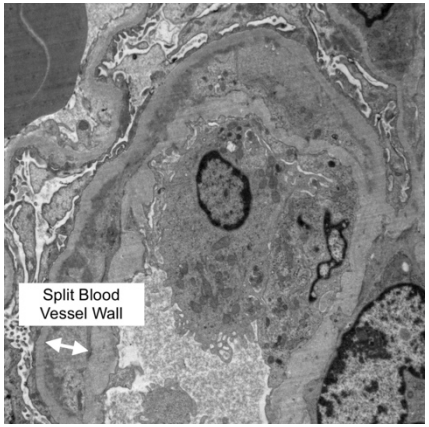
Immunofluorescence (IF)

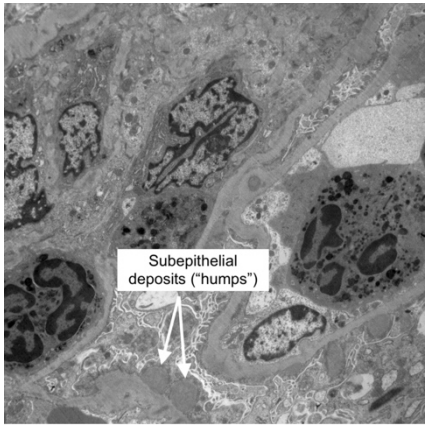
Left: Typical appearance of bright green C3 deposits on a C3G biopsy specimen.

Electron Microscopy

Below Left: Split blood vessel wall basement membrane (MPGN pattern)

Below Right: Subepithelial humps – seen in C3G and post infectious glomerulonephritis





Interpreting MORL Complement-Mediated Kidney Disease Genetic and Functional Results

GENETIC TESTING		
Gene	**Chromosomal Location**	**Interpretation**
Complement gene that has been reported to be associated with TMAs/C3G	The specific location on a chromosome of a given gene	**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 current data **Unknown significance:** a variant for which further interpretation is not possible based on available data **Likely benign:** a variant not known to cause disease

PATHWAYS			AUTOANTIBODIES					
CH50 (41-95 Units/mL	**APFA** (50-130%)	**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 binds to Factor H (FH); can interfere with FH function and compromise AP regulation	An antibody that binds to Factor B (FB); can interfere with C3 convertase regulation; often seen in PIGN	Determines if a protein in the blood is causing complement dysregulation/activation	Antibodies to C3- or C5-convertase, preventing them from naturally falling apart		Similar to C3- or C5-nephritic factors, however they stabilize the classical pathway convertase

BIOMARKERS												
	C3 level (90-180 mg/dL)	**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	A breakdown product of C3, suggests overactivity of the AP	Represents inflammation	Represents inflammation	Cleavage products of FB; high levels mean that FB is being consumed excessively; high levels of Ba are also seen with ESKD		High levels of Factor D (FD) suggest declining kidney function irrespective of complement activity	Elevated with terminal complement pathway inhibitor		Increased activity of the terminal complement pathway	Represents inflammation	Represents inflammation
Low Result	Deficient because of a gene abnormality or inappropriately consumed		Deficient because of a gene abnormality or inappropriately consumed	Deficient because of a gene abnormality or consumed due to overactive AP				Suggests terminal pathway hyperactivity	Suggests terminal pathway hyperactivity	Low if on terminal complement blockade	Deficiency typically reflects a gene abnormality	Deficiency typically reflects a gene abnormality or inappropriate consumption

* AP = Alternate Pathway; CP = Classical Pathway; Nef = Nephritic Factor, ESKD= End Stage Kidney Disease; laboratory results may be significantly altered by inappropriate specimen handling; due to the extreme complexity of the complement cascade, assessing complement activity and regulation is best performed by pathway analysis, together with autoantibody testing and biomarker profiling as opposed to doing tests in isolation