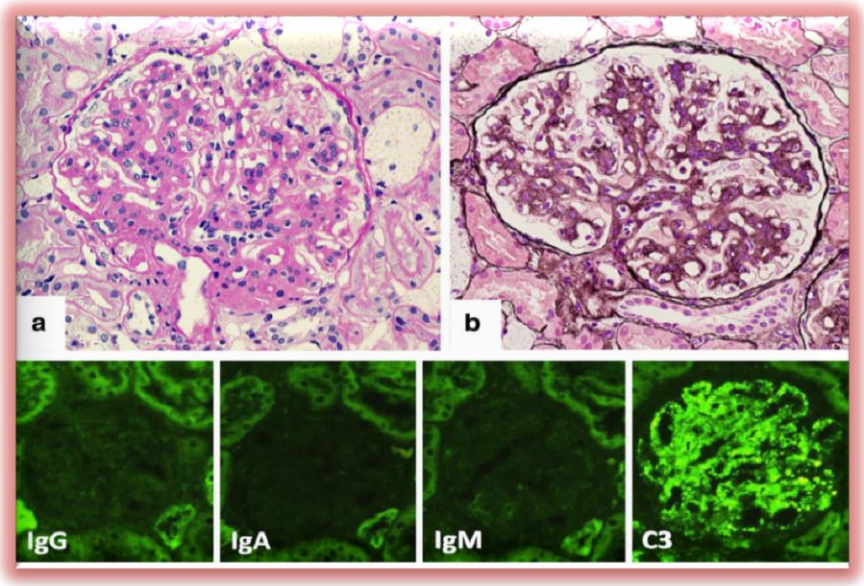
C3 Glomerulopathy



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OPEN

C3 glomerulopathy: consensus report

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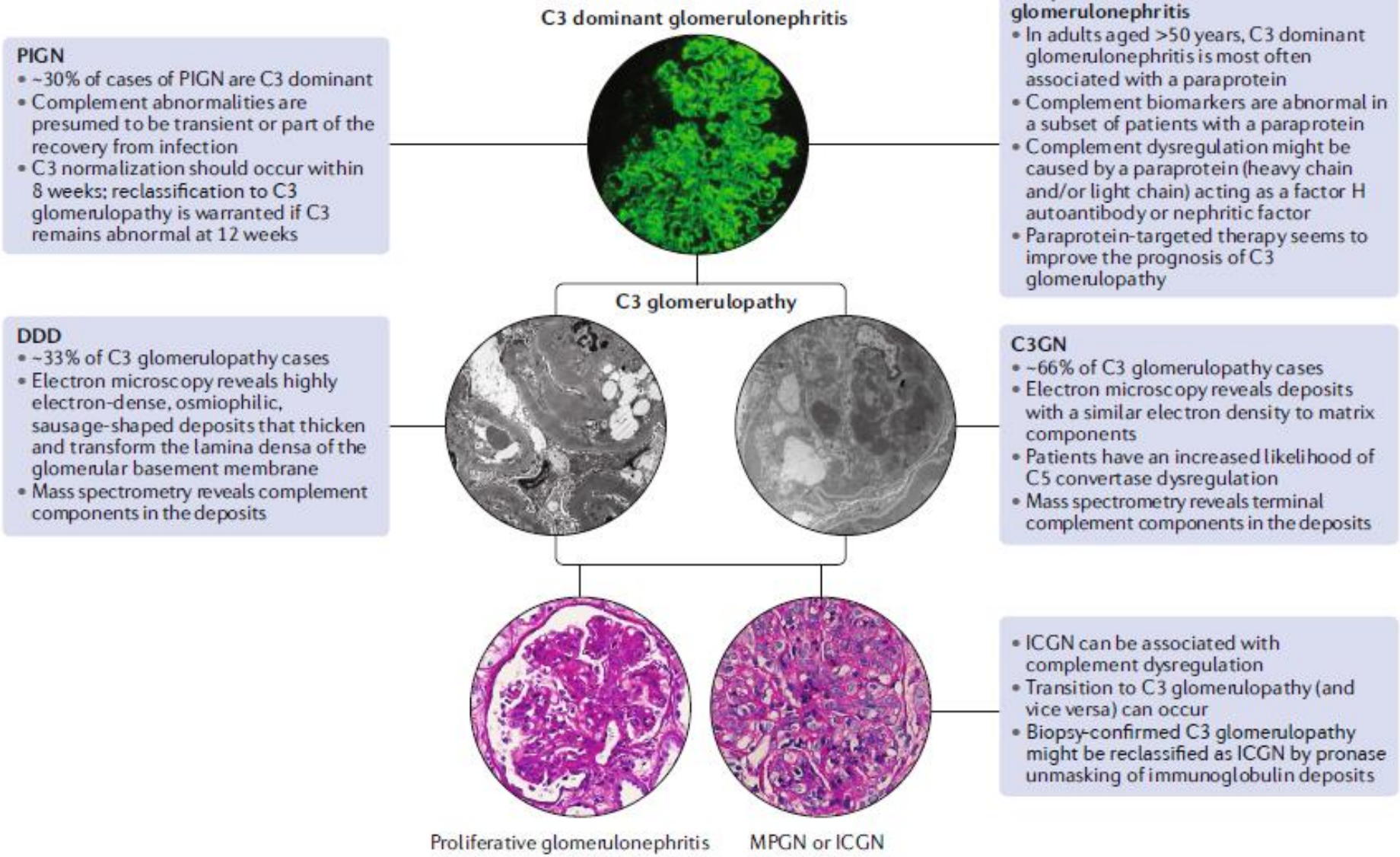
- The term C3 glomerulopathy was adopted by expert consensus in 2013
- A group of rare kidney diseases driven by dysregulation of the complement cascade

DEFINITION

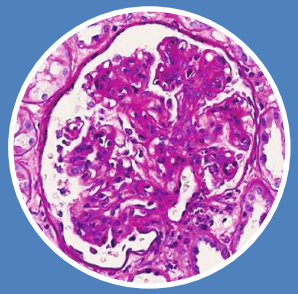
The disease is defined by the presence in renal biopsy sample of a glomerulonephritis with sole (or at least dominant glomerular immunofluorescence staining for C3 of at least two orders of magnitude greater intensity than for any other immunoreactant


C3 dominant glomerulonephritis
PIGN
• ~30% of cases of PIGN are C3 dominant
• Complement abnormalities are presumed to be transient or part of the recovery from infection
• C3 normalization should occur within 8 weeks; reclassification to C3 glomerulopathy is warranted if C3 remains abnormal at 12 weeks
Paraprotein-associated glomerulonephritis
• In adults aged >50 years, C3 dominant glomerulonephritis is most often associated with a paraprotein
• Complement biomarkers are abnormal in a subset of patients with a paraprotein
• Complement dysregulation might be caused by a paraprotein (heavy chain and/or light chain) acting as a factor H autoantibody or nephritic factor
• Paraprotein-targeted therapy seems to improve the prognosis of C3 glomerulopathy
C3 glomerulopathy
DDD
• ~33% of C3 glomerulopathy cases
• Electron microscopy reveals highly electron-dense, osmiophilic, sausage-shaped deposits that thicken and transform the lamina densa of the glomerular basement membrane
• Mass spectrometry reveals complement components in the deposits
C3GN
• ~66% of C3 glomerulopathy cases
• Electron microscopy reveals deposits with a similar electron density to matrix components
• Patients have an increased likelihood of C5 convertase dysregulation
• Mass spectrometry reveals terminal complement components in the deposits
• ICGN can be associated with complement dysregulation
• Transition to C3 glomerulopathy (and vice versa) can occur
• Biopsy-confirmed C3 glomerulopathy might be reclassified as ICGN by pronase unmasking of immunoglobulin deposits
Proliferative glomerulonephritis
MPGN or ICGN

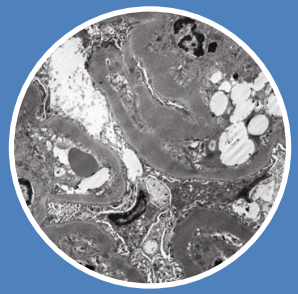
PATHOPHYSIOLOGY

C3 glomerulopathy is caused by excessive activation of the alternative complement pathway

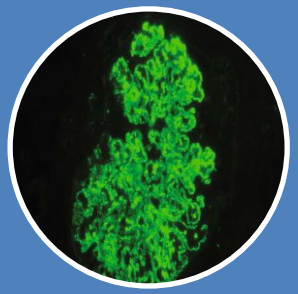
Defects in regulatory proteins, inhibitors or accelerators of alternative pathway



genetic mutations (abnormal genes for factors H, I, and MCP)



antibodies against inhibitory complement components (eg, antibodies to factor H)



Antibodies that accelerated this pathway (eg, C3 nephritic factor).

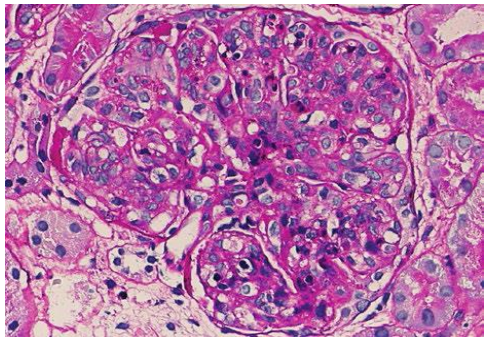
PATHOPHSIOLOGY

- A mutation or autoantibody alone is insufficient to cause C3 glomerulopathy.

- Multiple mutations, autoantibodies or additional genetic and environmental risk factors that activate complement factors – such as an infection – are thought to be required to elicit C3 glomerulopathy

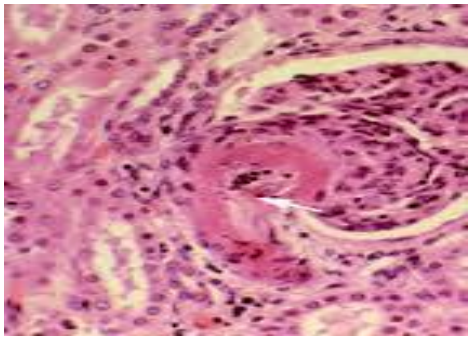
C3GN Vs HUS

C3GN

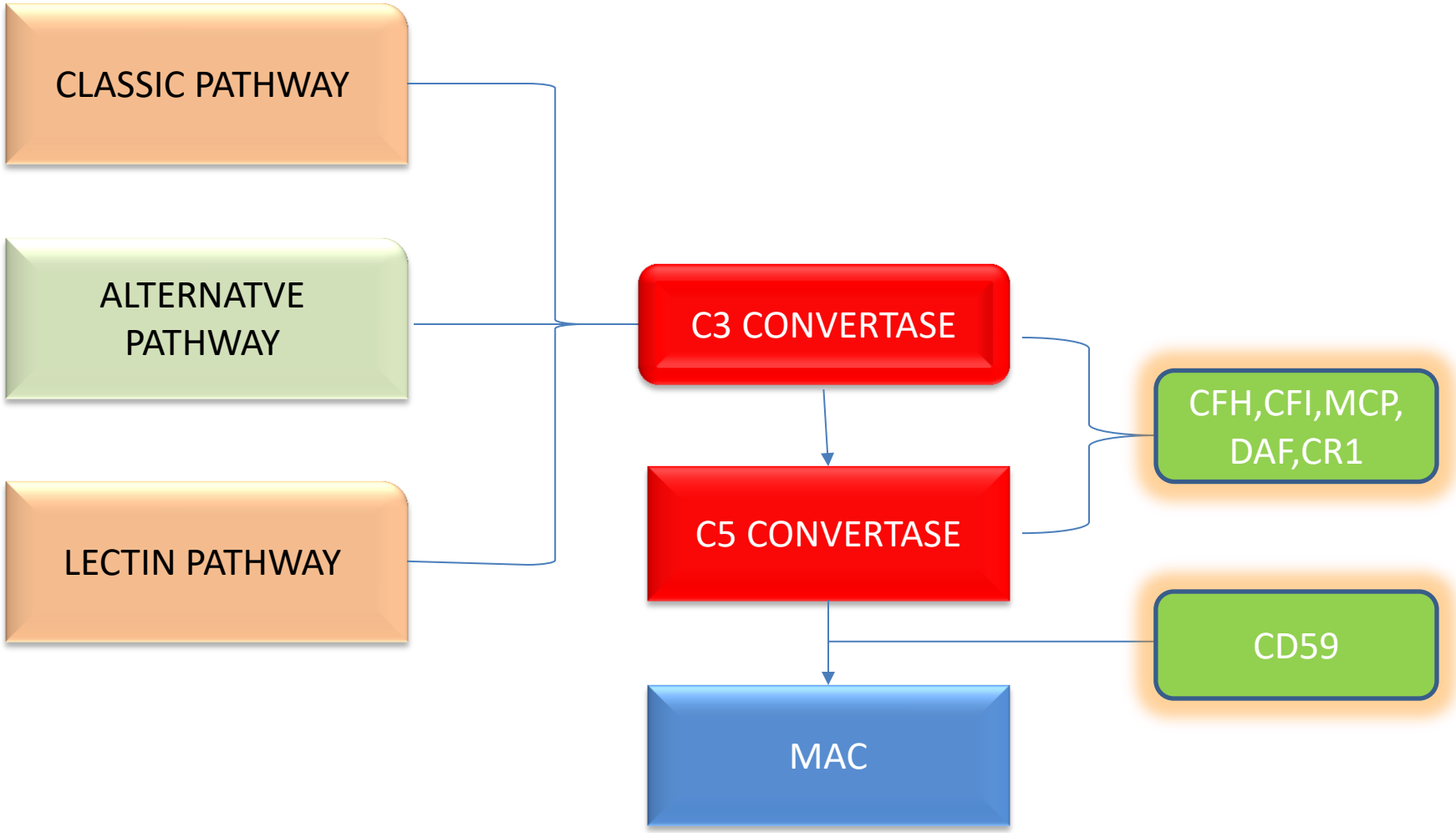


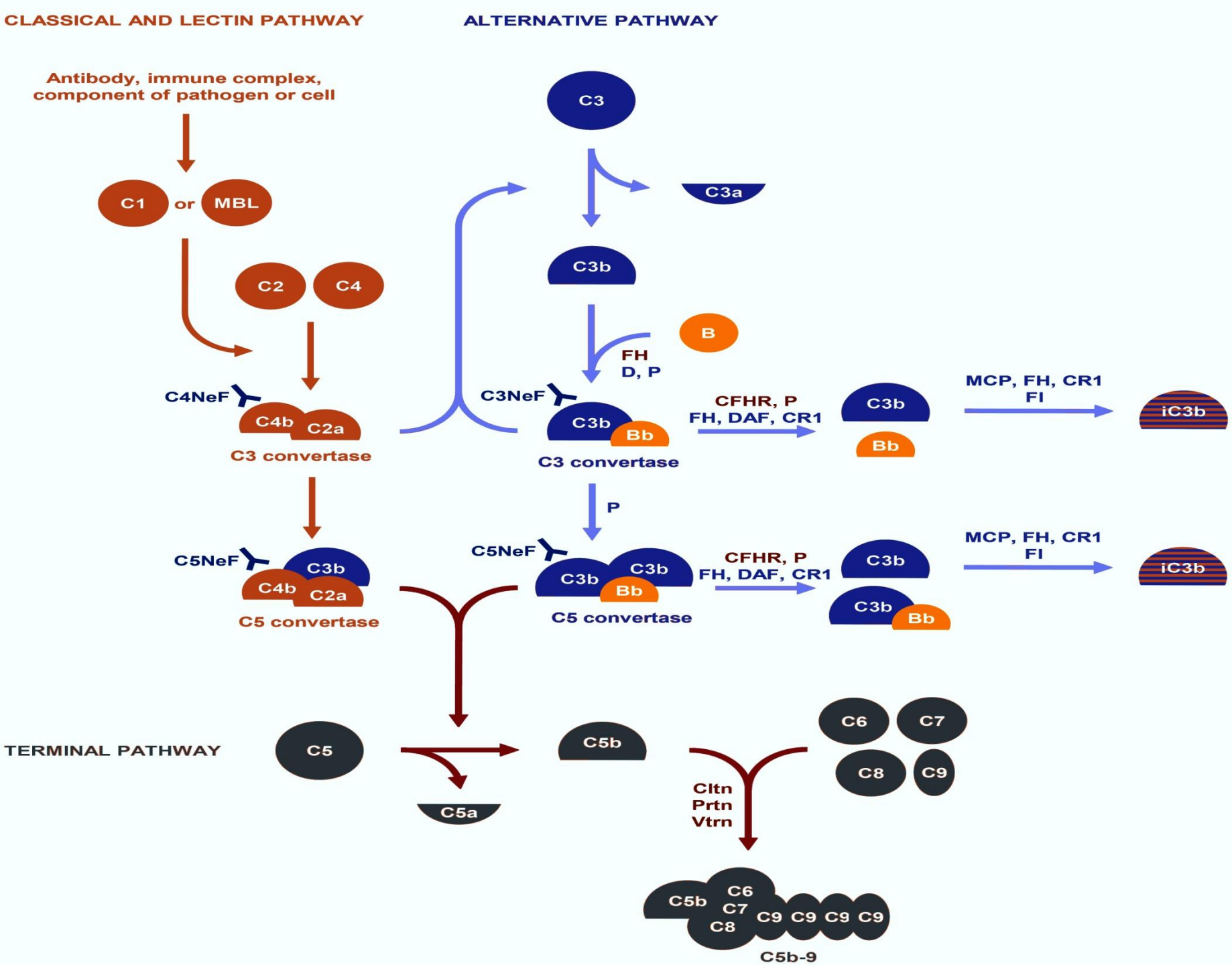
- mutations and autoantibodies predominantly affect fluid phase regulators
- Activation of the terminal pathway was detected in a subgroup of patients with C3G.

HUS

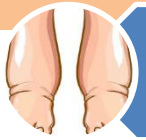


- mutations and antibodies impair complement control on the endothelial surface resulting in terminal pathway activation, endothelial cell injury and thrombus formation


CLASSIC PATHWAY
ALTERNATVE PATHWAY
LECTIN PATHWAY
C3 CONVERTASE
C5 CONVERTASE
MAC
CFH,CFI,MCP, DAF,CR1
CD59


CLASSICAL AND LECTIN PATHWAY
ALTERNATIVE PATHWAY
Antibody, immune complex, component of pathogen or cell
C1
or
MBL
C2
C4
C4NeF
C4b
C2a
C3 convertase
C5NeF
C3b
C4b
C2a
C5 convertase
TERMINAL PATHWAY
C5
C5a
C5b
C3
C3a
C3b
B
FH
D, P
C3NeF
C3b
Bb
C3 convertase
CFHR, P
FH, DAF, CR1
C3b
Bb
MCP, FH, CR1
FI
iC3b
P
C5NeF
C3b
C3b
Bb
C5 convertase
CFHR, P
FH, DAF, CR1
C3b
C3b
Bb
MCP, FH, CR1
FI
iC3b
C6
C7
C8
C9
Cltn
Prtn
Vtrn
C5b
C6
C7
C8
C9
C9
C9
C9
C5b-9

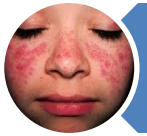
Clinical presentation



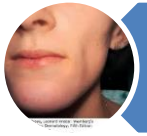
Nephrotic(27-55%) and nephritic sx(90-95%)

Microscopic hematuria(64-88%) macroscopic hematuria(16-38%)

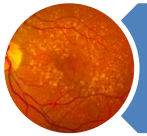
Hypertension(21-46%)



Symptmos of systemic autoimmune dx

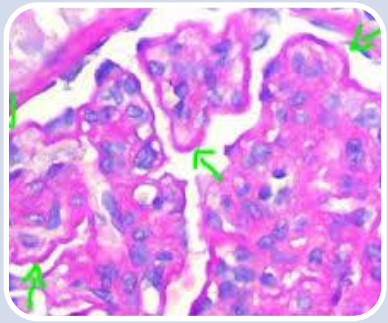


Partial lipodystrophy



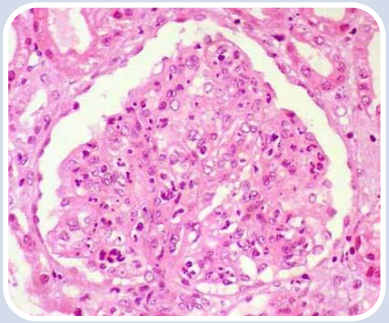
Visual disturbance (ocular drusen)

Histopathology



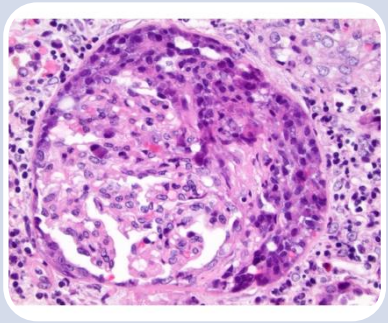
MPGN

44-76%



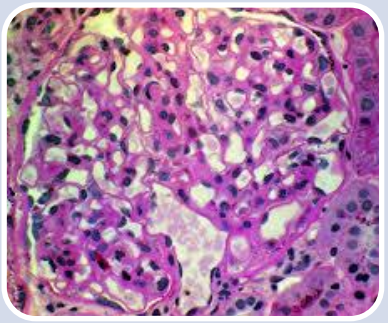
Diffuse endocapillary PGN

8-19%



Crescentic GN

9%



Mes PGN

21-28%

Diagnostic dilemmas in C3 glomerulopathy

C3G versus PIGN

DDD versus C3GN

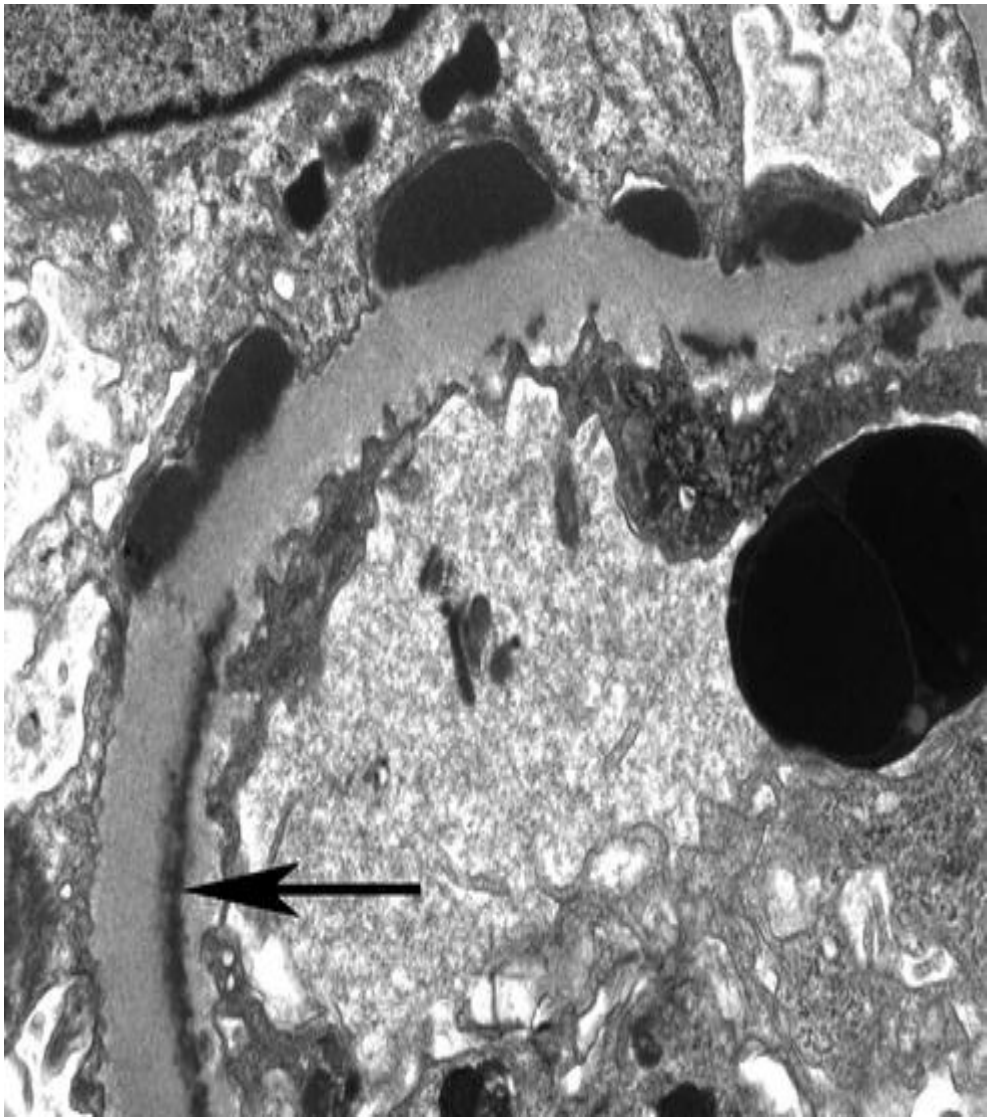
PIGN

PIGN is an IC mediated GN but it sometimes shows isolated C3 deposition without immunoglobulins, particularly during the post acute phase

Hump is not specific for PIGN

C3G occasionally show endocapillary proliferative glomerulonephritis similar to PIGN and vice versa

The IF pattern alone is insufficient to discriminate whether a faint deposit of IgG is an immune complex or not, and c4d may be useful

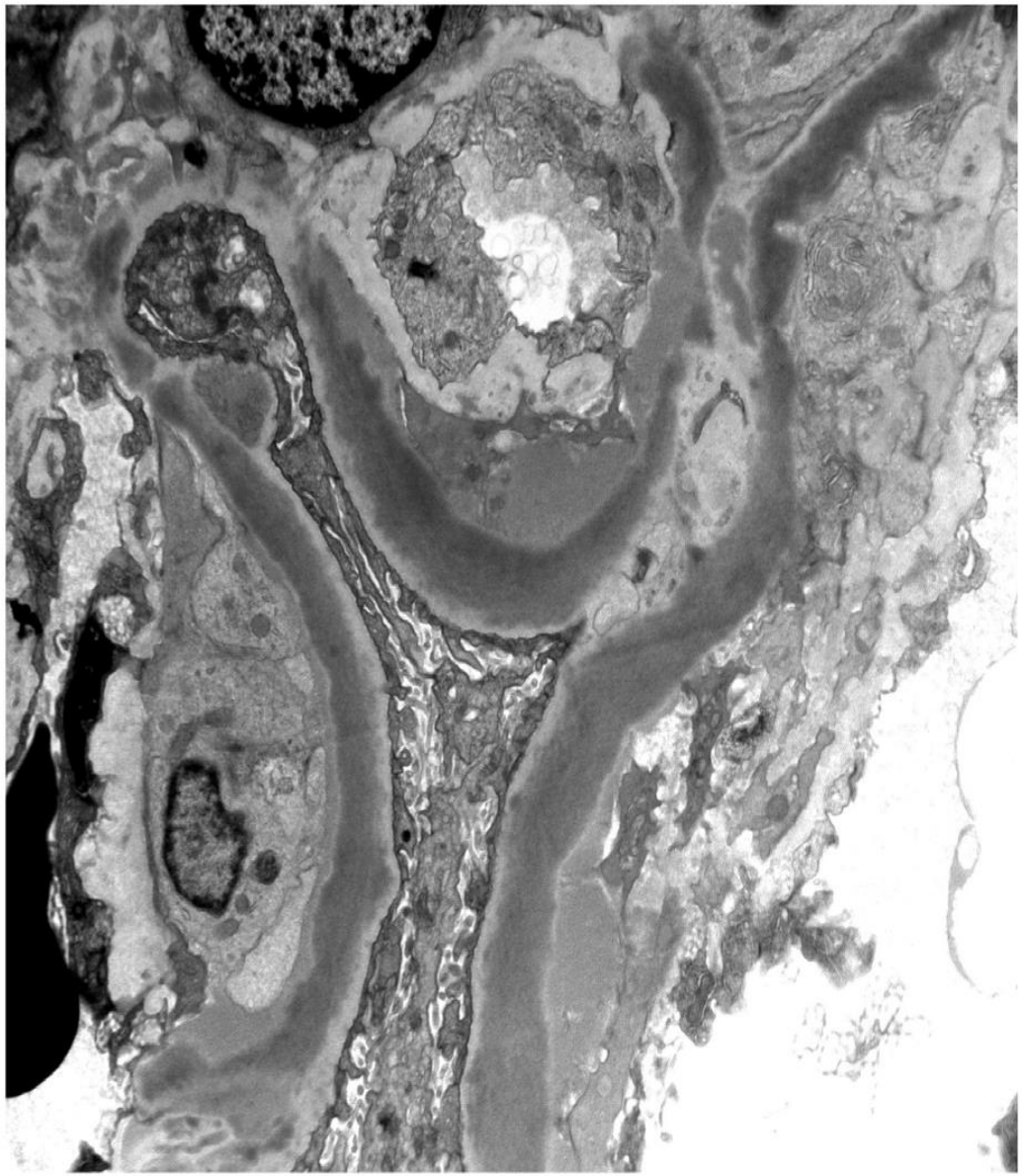


DDD

Electron microscopy is necessary to distinguish the two major subtypes of C3 glomerulopathy

In DDD, electron microscopy reveals highly electrondense, osmiophilic deposits with appearance that thicken and transform the lamina densa of the glomerular basement membrane (GBM)

Similar extremely electron- dense deposits can also be identified in Bowman's capsules and some tubular basement membranes.

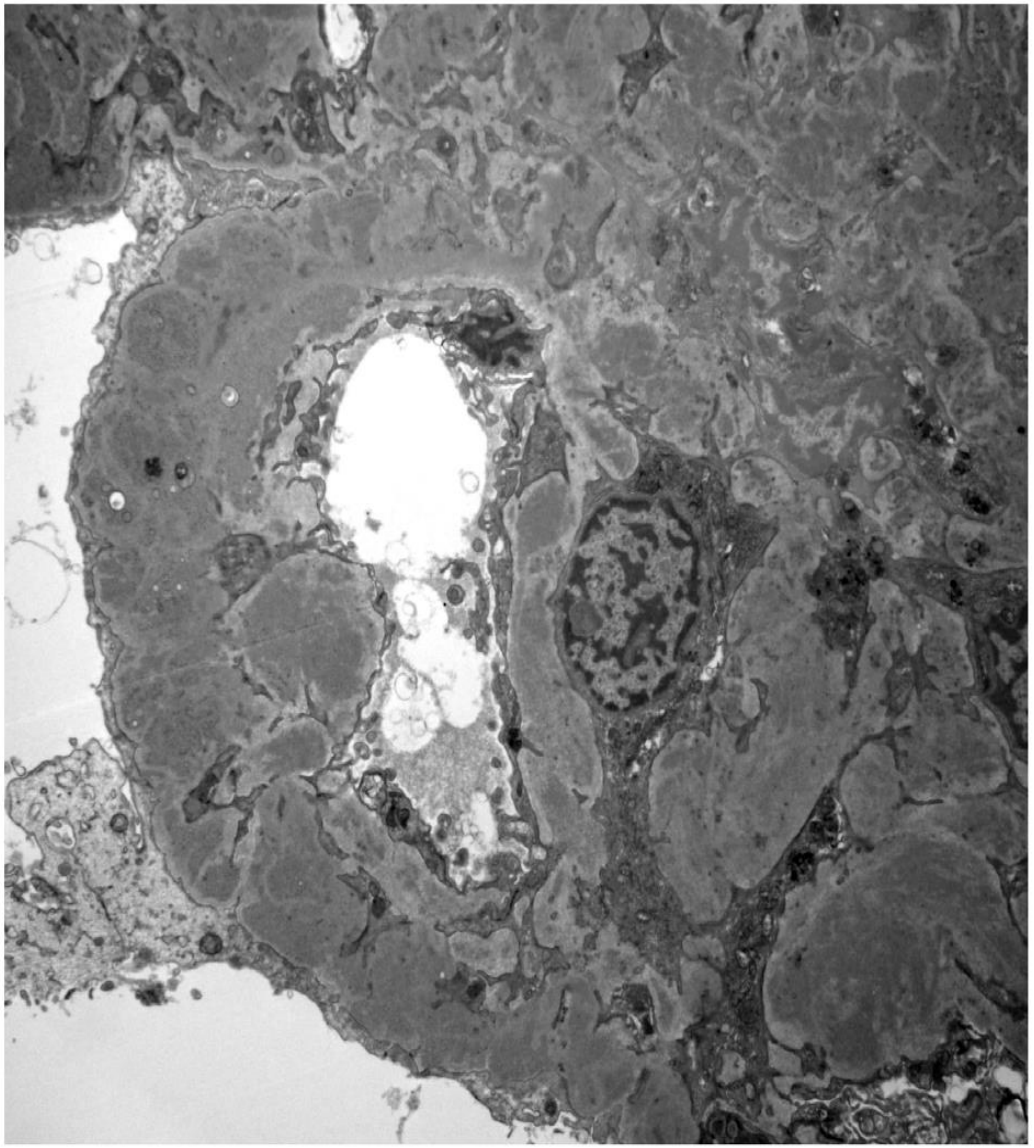


C3GN

the electron density of deposits approaches that of the glomerular matrix components

These deposit often have an amorphous cloudy appearance within the mesangium and can appear as ill- defined, subendotheliaL (intramembranous and/or subepithelial) inclusions

Subepithelial humps can occur in both subtypes



Evaluation of C3G

Assessment of overall complement activity

Measurement of serum level of complement proteins and split products

Screening for autoantibodies

Genetic tests

Biochemical tests

General tests	Peripheral blood smear, liver enzymes, glucose, lipid spectrum, prothrombin time, activated partial prothrombin time
Renal function	Creatinine, estimated glomerular filtration rate, urea, electrolytes
Urinalysis	Urine sediment, 24-hour urine with quantification of creatinine, total protein and sodium
Presence of infection or inflammation	Erythrocyte sedimentation rate, C-reactive protein, cultures of blood, urine or other body liquids
Presence of monoclonal gammopathy	Protein electrophoresis for monoclonal light chains and monoclonal immunoglobulins in serum and urine

Immunological tests

Function of the complement pathways	Serum levels of C1q, C3, C3d, C4, soluble C5b-9, CH50, AH50, factor H and factor I
Immunological cause of C3 glomerulopathy	Serum levels of C3 nephritic factor and autoantibodies against factor H
Preceding streptococcal infection as cause of C3 glomerulopathy or postinfectious glomerulonephritis	Serum levels of antistreptolysin O antibodies and anti-DNase B antibodies
Presence of infection or autoimmune disease as cause of C3 glomerulopathy or alternative diagnosis	Serology of hepatitis B and hepatitis C, serum levels of cryoglobulins, antinuclear antibodies, antibodies against extractable nuclear antigens, anti-double stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies

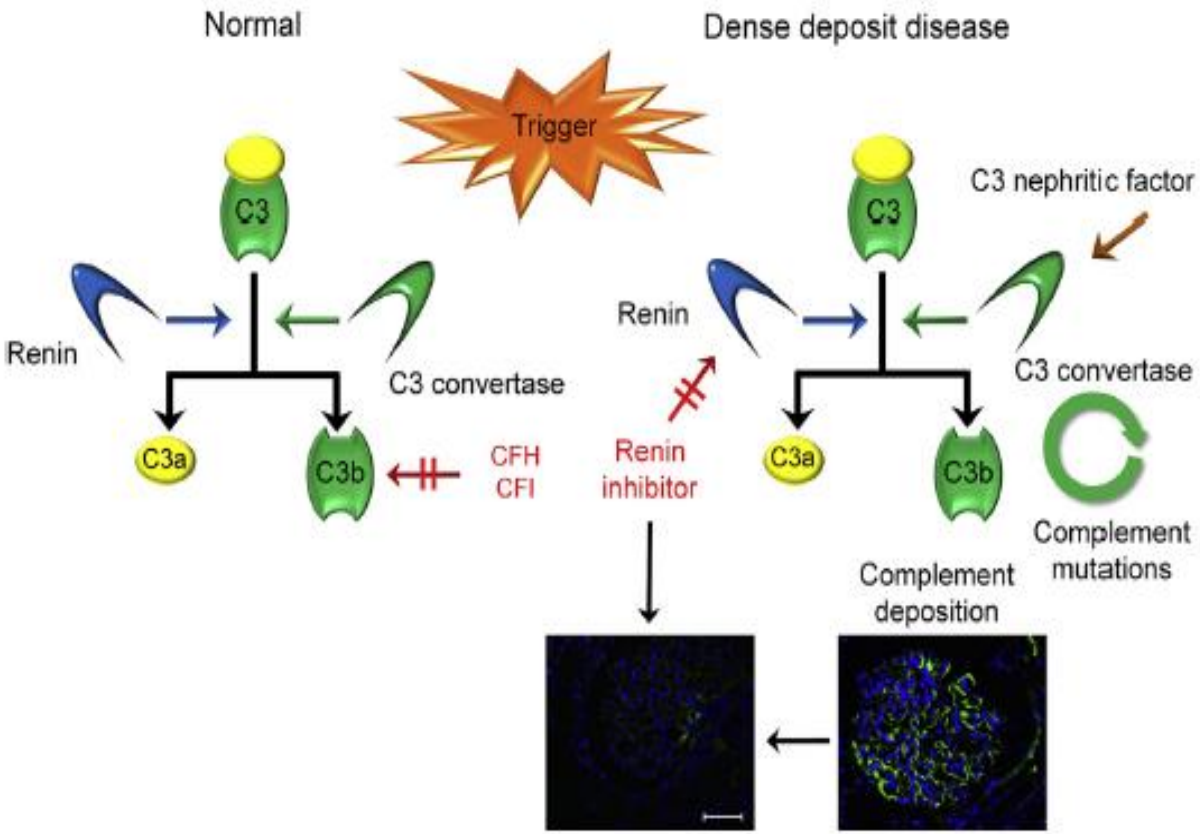
Genetic tests

Genetic cause of C3 glomerulopathy	Detection of mutations of C3, factor H, factor I, factor B, membrane cofactor protein and CFHR1-5; MLPA analysis of factor H operon

Treatment according to disease activity

Normal renal function and proteinuria less than 0.5 gr/day	• BP control • ACE,ARB • Lipid control
Proteinuria 0.5-2gr/day, moderate inflammation on BX, rise in Scr	• MMF and prednisolone • Not uniformly successful
Proteinuria>2gr/day, severe inflammation on BX , and progressive renal insufficiency on MMF	• Pulse methyl prednisolone • Anti complement treatment

Renin-mediated C3 cleavage and its inhibition by aliskiren



Aliskiren inhibits renin-mediated complement activation

see commentary on page 650

Zivile D. Békássy[1], Ann-Charlotte Kristoffersson[1], Johan Rebetz[1], Ramesh Tati[1], Anders I. Olin[1] and Diana Karpman[1]

[1]Department of Pediatrics, Clinical Sciences Lund, Lund University, Lund, Sweden

- Renin, a kidney specific enzyme, cleaves C3 into C3b and C3a, in a manner identical to the C3 convertase.
- The effect of aliskiren was studied in three patients with dense deposit disease and this demonstrated decreased systemic and renal complement activation over a follow-up period of four to seven years.

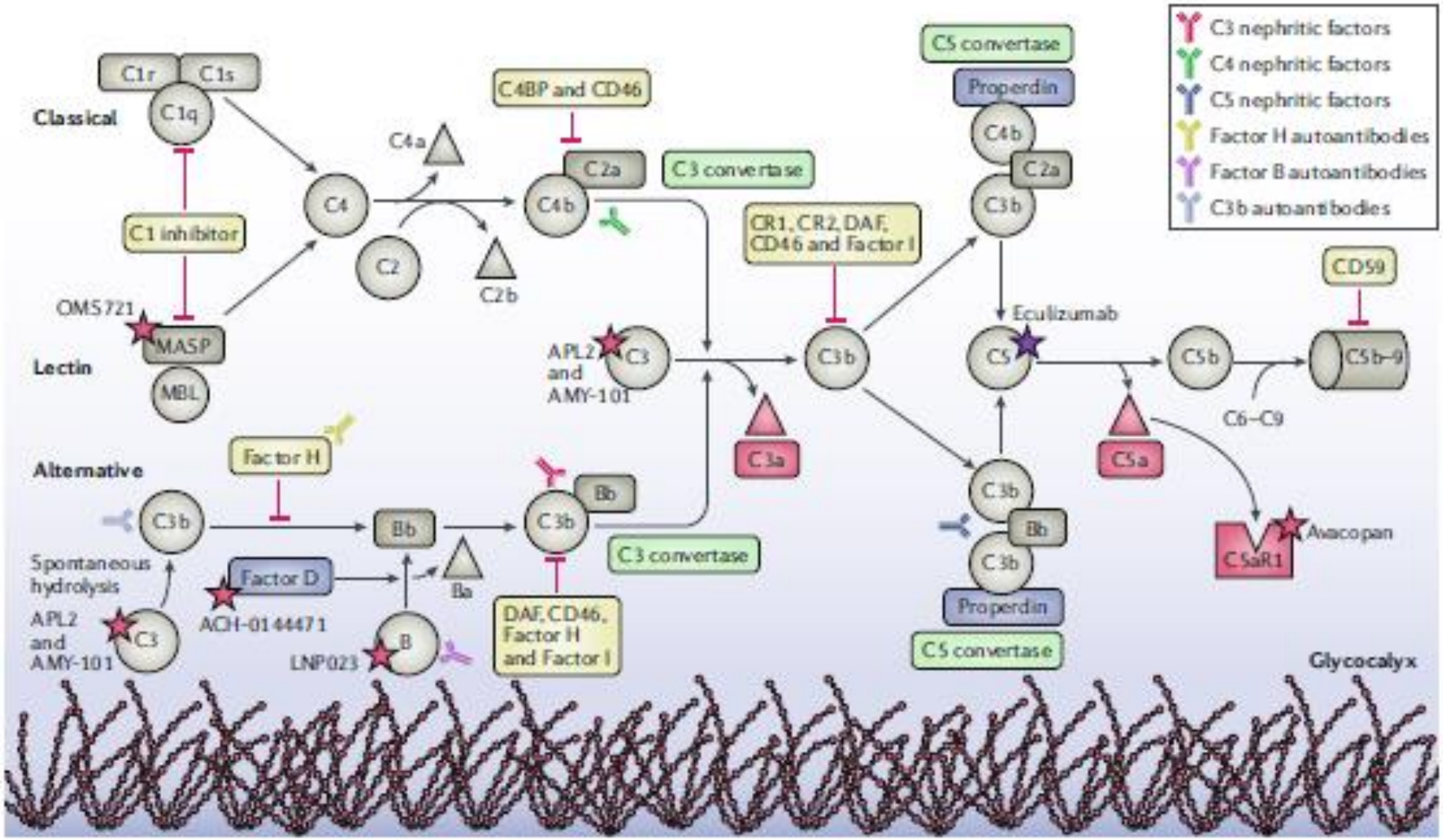
Plasma therapy and exchange

- The precise role for plasma therapy in C3 glomerulopathy patients remains to be defined.
- Favourable outcomes for such therapy when a mutated protein has been identified and is causally implicated in the disease
- Unsuccessful in patients with C3 nephritic factors, presumably because production of these autoantibodies continues after they are removed.

Novel complement targeted therapy

Drug	Target	Mechanism	Clinical trial number
ACH0144471	Factor D	Prevents formation of C3 and C5 convertases	NCT03369236, NCT03459443 and NCT03124368
LNP023	Factor B	Prevents formation of C3 and C5 convertases	Not yet registered
APL2	C3	Prevents formation of C3 and C5 convertases	NCT03453619
AMY101	C3	Prevents formation of C3 and C5 convertases	NCT03316521
OMS721	MASP2	Blocks initiation of lectin pathway	NCT02682407
Eculizumab	C5	Blocks progression of terminal pathway	Off-label use
Avacopan	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT03301467

Drug	Target	Mechanism
Danicopan (ACH4471)	Factor D	Prevents formation of C3 and C5 convertase
LNP023	Factor B	Prevents formation of C3 and C5 convertase
Pegcetacoplan (APL2)	C3	Prevents formation of C3 and C5 convertase
Compstatin (AMY101)	C3	Prevents formation of C3 and C5 convertase
Narsoplimab (OMS721)	MASP2	Blocks lectin pathway
Avacopan (CCX168)	C5aR1	Blocks anaphylatoxin formation(C3a, C4a, C5a)


C3 nephritic factors
C4 nephritic factors
C5 nephritic factors
Factor H autoantibodies
Factor B autoantibodies
C3b autoantibodies
Classical
C1r
C1s
C1q
C1 inhibitor
OMS721
MASP
MBL
Lectin
C4
C4a
C2
C2b
C4BP and CD46
C2a
C4b
C3 convertase
CR1, CR2, DAF, CD46 and Factor I
C5 convertase
Properdin
C4b
C2a
C3b
CD59
Eculizumab
C5
C5b
C5b-9
C6–C9
C5a
C5aR1
Avacopan
APL2 and AMY-101
C3
C3a
C3b
Alternative
Factor H
Bb
C3b
Spontaneous hydrolysis
APL2 and AMY-101
C3
Factor D
ACH-0144471
Bb
Ba
B
LNP023
DAF, CD46, Factor H and Factor I
C3 convertase
C3b
Bb
C3b
Properdin
C5 convertase
Glycocalyx

Eculizumab for Dense Deposit Disease and C3 Glomerulonephritis

Andrew S. Bomback, Richard J. Smith,† Gaetano R. Barile,‡ Yuzhou Zhang,† Eliot C. Heher,§ Leal Herlitz,‖ M. Barry Stokes,‖ Glen S. Markowitz,‖ Vivette D. D'Agati,‖ Pietro A. Canetta,* Jai Radhakrishnan,* and Gerald B. Appel**

- efficacy and safety study that involved three patients with DDD
- The authors concluded that some but not all patients respond to eculizumab
- an elevated soluble C5b-9 level is a potentially useful marker of response to this agent

Am J Kidney Dis. 2018 Jul;72(1):84-92. doi: 10.1053/j.ajkd.2017.11.019. Epub 2018 Feb 9.

Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy.

Le Quintrec M[1], e al.[6]

- Eculizumab in 26 patients (including 13 children or adolescents) with C3 glomerulopathy who were treated for a median duration of 14 months

- eculizumab mainly targets a single aspect of C3 glomerulopathy — namely, glomerular inflammation — and has no effect, or only a limited effect, on the C3 complement dysregulation that is the main driver of the disease

CONCLUSION

- C3 glomerulopathy is a rare and complex renal disease driven by complement dysregulation
- Renal biopsy is required to establish the diagnosis, and samples must show dominant glomerular C3 staining
- Clinical evaluation include genetic testing, assays of complement function, measurement of complement protein levels and screening for autoantibodies

CONCLUSION

- Collaboration between the clinician, renal pathologist and biochemical or genetic laboratory is required to elucidate both the underlying pathogenesis and the optimal therapeutic approach
- An optimal treatment for C3 glomerulopathy has not yet been established
- For the majority of patients, however, new therapies will be required