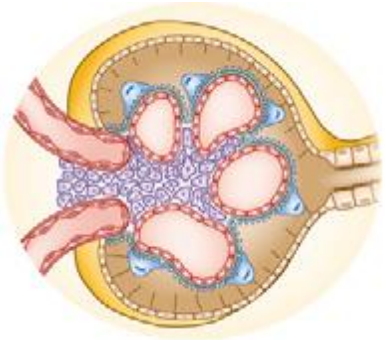

Minimal Change Disease in Adults

(Etiology, Symptoms, Diagnosis)

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Introduction

- MCD is the most common childhood nephrotic syndrome, also cause of 10–15% of adult-onset idiopathic nephrotic syndrome(3rd after MN & FSGS).
- Histologic picture of MCD is identical in adults and children.

- Other names:

lipoid nephrosis (1920s)

Nil syndrome

MCD in EM analysis (1950s)

Steroid-sensitive NS

Epidemiology

- Incidence of MCD in children varies between 2 and 7 new cases per 100,000 children
- Exact incidence in adults is less well documented
- Disease is slightly more common in Asia and has a male predominance (approximately 2:1) in young children that disappears in adolescents and adults

Etiology

- Primary (most common)
- Secondary :

  Allergens

  Malignancies

  Medications

  Infections

  Autoimmune disorders

Secondary causes of MCD

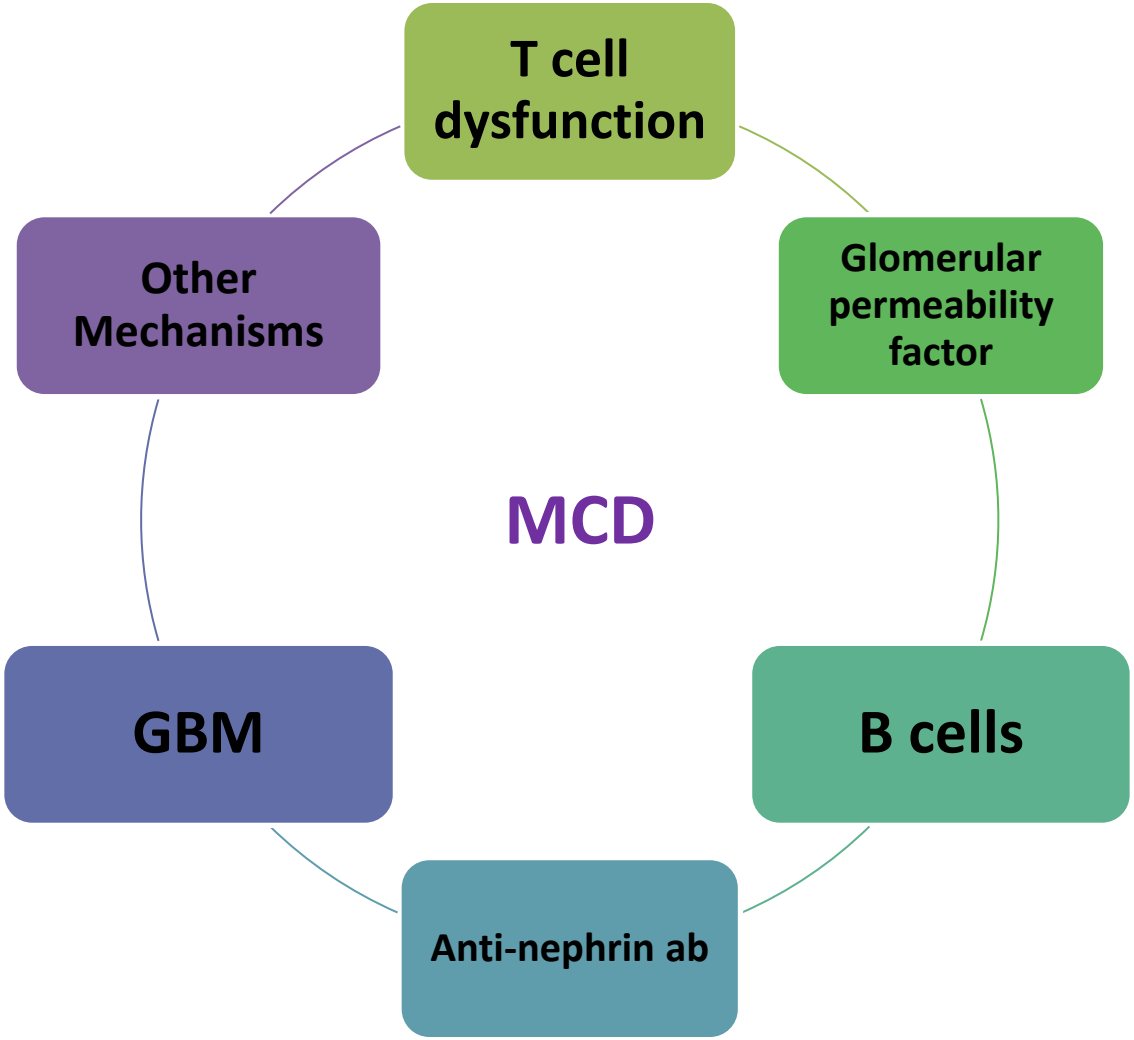
Allergy	Drugs
Pollen Dust Fungi Bee sting Cat fur Food allergens (cow's milk, egg)	Nonsteroidal anti-inflammatory drugs Salazopyrin D-penicillamine Mercury Gold Tiopronin Lithium Antimicrobial drugs Pamidronate Tyrosine-kinase inhibitors Gamma interferon
Malignancies	**Autoimmune disorders**
Hodgkin disease Non-Hodgkin lymphoma Leukemia Multiple myeloma Thymoma Bronchogenic cancer Colon cancer Eosinophilic lymphoid granuloma (Kimura disease)	SLE Diabetes mellitus Myasthenia gravis Autoimmune pancreatitis Celiac disease Allogeneic stem cell transplantation Immunizations
Infections	
Viral Parasitic Mycoplasma pneumonia TB Syphilis	

Pathogenesis

- main histologic feature is foot process effacement, visible by EM , studies have concentrated on finding what disrupts the integrity of the glomerular filtration barrier.
- lack of inflammatory changes or IC deposits in the kidney tissue, MCD has been traditionally thought to be mediated by an unknown circulating factor(s)

- existence of one or more circulating factors by abnormal T cells capable of increasing its permeability, thus resulting in foot process effacement and proteinuria

Pathogenesis



T cell dysfunction

1) remission may follow measles infection, which causes cell-mediated immunosuppression;
2) MCD may occur in Hodgkin disease, a lymphoid neoplasia
3) MCD responds to drugs that suppress cell-mediated immunity.
4) in children with glucocorticoid-sensitive nephrotic syndrome, relapses were associated with a decrease in T regulatory cells
5) Atopic individuals are at higher risk for the development of MCD
6) unlike other glomerular disorders, there is an absence of humoral (Ig and complement) deposition in glomeruli

Glomerular permeability factor

- A T cell hybridoma made from a patient with MCD released a substance that, when injected into rats, induced proteinuria and foot process effacement
- identity of the glomerular permeability factor in MCD has not been determined in humans

- Th2-derived cytokines, particularly IL 13
- Hemopexin

(activated as a serine protease, leading to nephrin-dependent cytoskeletal rearrangement in podocytes and changes in permeability of the glomerular filtration barrier by a reduction in glycocalyx)

Role of B cells

- Role of B cells in the pathophysiology of MCD was, for many years, considered negligible.

- However, studies on the favorable effect on MCD of Rituximab, suggest that a glomerular permeability factor could be produced by B cells or T cells through pathways regulated or stimulated by B cells .

B cell role

1)total IgG alterations in nephrotic patients during remission

2)MCD has been observed in diseases(monoclonal light chains)

3)plasma CD23, is increased during relapse

4)Measles virus also has an inhibitory effect on Ig synthesis

5)immunosuppressors in treatment of MCD have an antiproliferative effect on B cells, as well as on T cells

1)there is little or no Ig deposition

2)Rituximab binds directly to podocyte SMPDL3b and suggested that its antiproteinuric effect may be independent of B cell depletion

3) after Rituximab infusion, some patients maintain prolonged remission despite reconstitution

of B cells

Clinical Journal of the American Society of Nephrology12(2):332-345, 2017.

Role of B cells

Conclusion:

- Targeting B cells may affect costimulatory pathways involved in T cell activation, and this may well be one of the mechanisms involved in the effectiveness of CD20-depleting agents, such as Rituximab and the newer humanized anti-CD20 monoclonal antibody, Ofatumumab

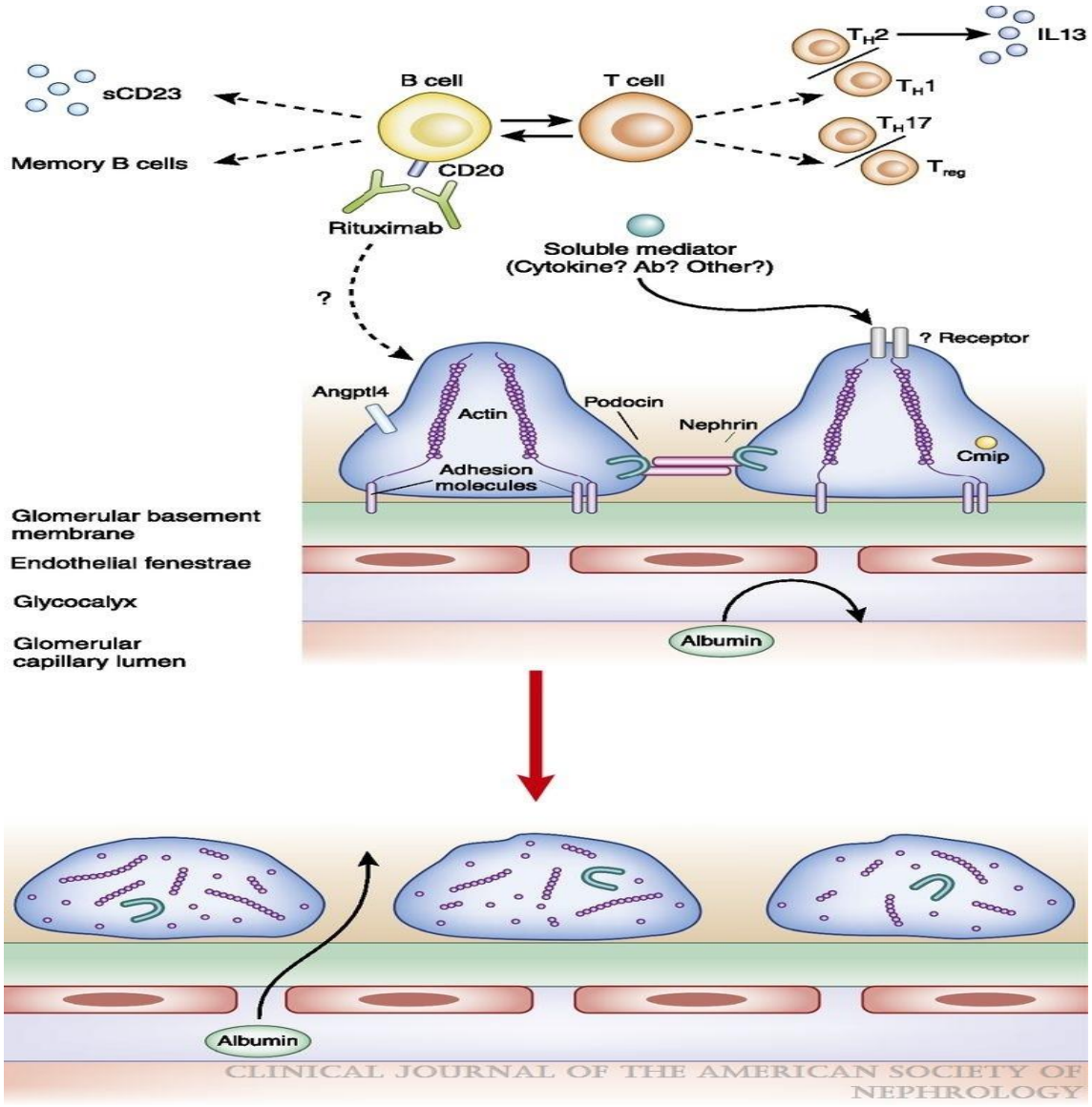
Anti-nephrin autoantibodies

- Nephrin is an essential structural component of the slit diaphragm, genetic mutations in NPHS1 that cause complete lack of nephrin cell surface localization, underlying congenital nephrotic syndrome of the Finnish type.

- Antibodies targeting nephrin have been shown to cause massive proteinuria when administered in animal models.

- these findings suggest that an autoimmune etiology may be responsible in a subset of patients with MCD.

Role of the GBM



Minimal Change Disease

Vivarelli, Marina; Massella, Laura; Ruggiero, Barbara; Emma, Francesco

Clinical Journal of the American Society of Nephrology12(2):332-345, February 2017.

doi: 10.2215/CJN.05000516

Pathogenesis of minimal change disease: hypotheses. In the presence of a normal glomerular basement membrane (shown at the center), with healthy podocyte foot processes (light blue), serum proteins, mainly albumin, remain within the glomerular capillary lumen. Mechanisms, that are as yet not fully elucidated but are partly intrinsic to the podocyte and partly due to the presence of soluble mediators released by a disregulated immune system (see top of the figure and text), modify this integrity. Therefore (red arrow), the actin cytoskeleton of the podocyte and the glomerular basement membrane are disrupted, and albumin and other serum proteins filter out of the bloodstream and into the urinary space. This leads to the intense proteinuria seen in nephrotic syndrome.

Other Mechanisms

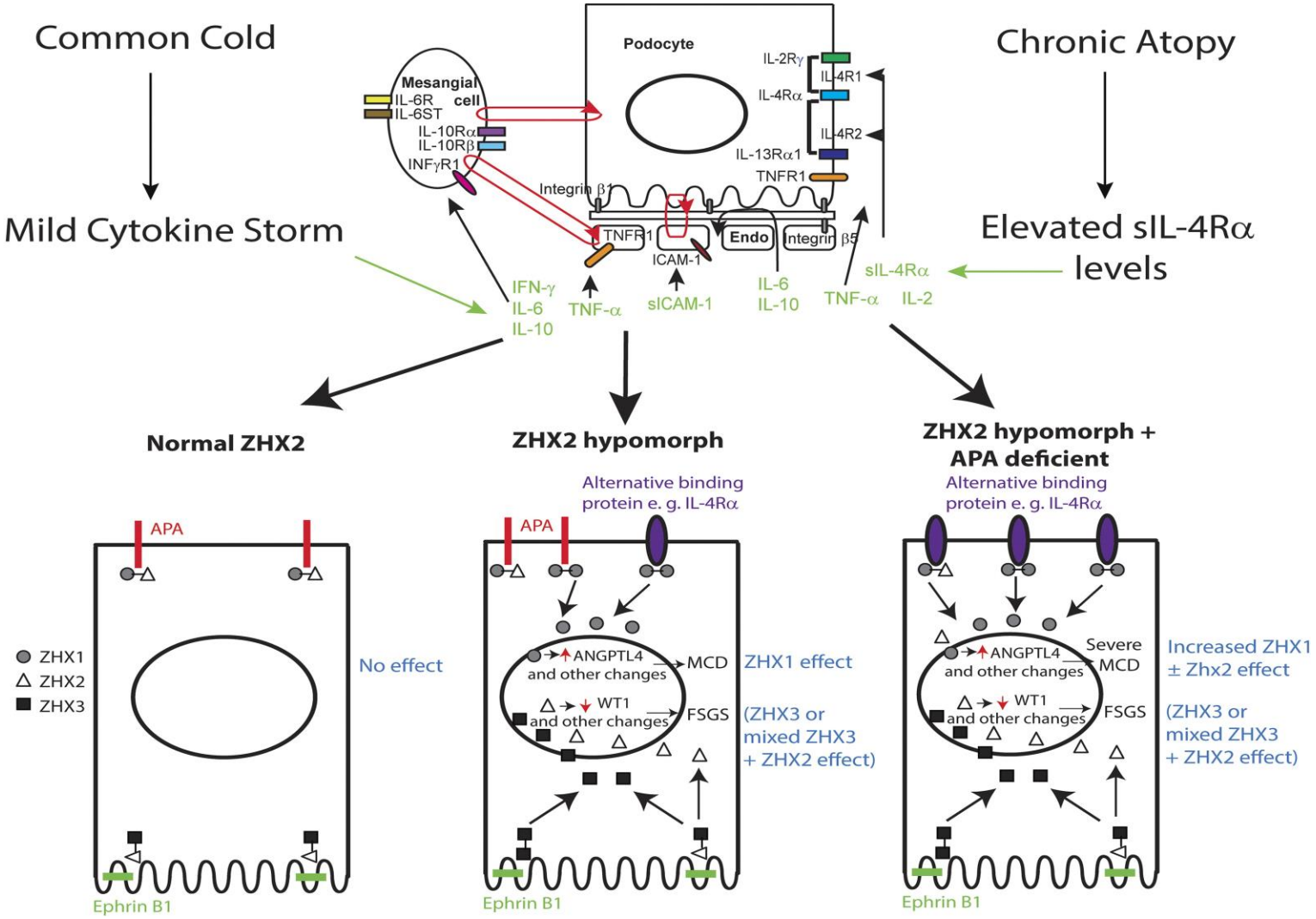
Podocyte:

- CD80(B7-1): One potential target of T cells on the podocyte, a T cell costimulatory molecule which has been found in the urine of patients with MCD during disease relapse
- Hemopexin: a plasma protein that binds sialoglycoproteins in podocytes, leading to proteinuria and foot process effacement in rats and cytoskeletal rearrangement in human cultured podocytes
- c-mip: interferes with podocyte signaling, leading to cytoskeletal disorganization and foot processes effacement

Other Mechanisms

- **ZHX-Angiopoietin-Like 4 pathway**
- zinc fingers and homeoboxes (ZHX) transcriptional factors and the upregulation of hyposialylated angiopoietin-like 4 (ANGPTL4) in podocytes have been crucial in explaining the cardinal manifestations of human minimal change nephrotic syndrome (MCNS).

- Administration of glucocorticoids reduces ANGPTL4 upregulation, which reduces hyposialylation injury to improve the clinical phenotype.



DOI: (10.1152/ajprenal.00219.2023)

Clinical presentation

- sudden onset over days to a week ,signs and symptoms of the nephrotic syndrome, often following an upper respiratory or systemic infection
- Nephrotic syndrome:

  proteinuria, mostly albuminuria (3.5 to 4.0 g/day and occasionally > 15 to 20 g/day)

  increased a2-globulin & reduced g-globulin fraction

  weight gain & edema (ascitis, Pl E, Pr E)

  hypoalbuminemia (albumin < 1.5 to 2.0 g/dL)

  hyperlipidemia.
- Microscopic hematuria (20-25%)

Clinical presentation

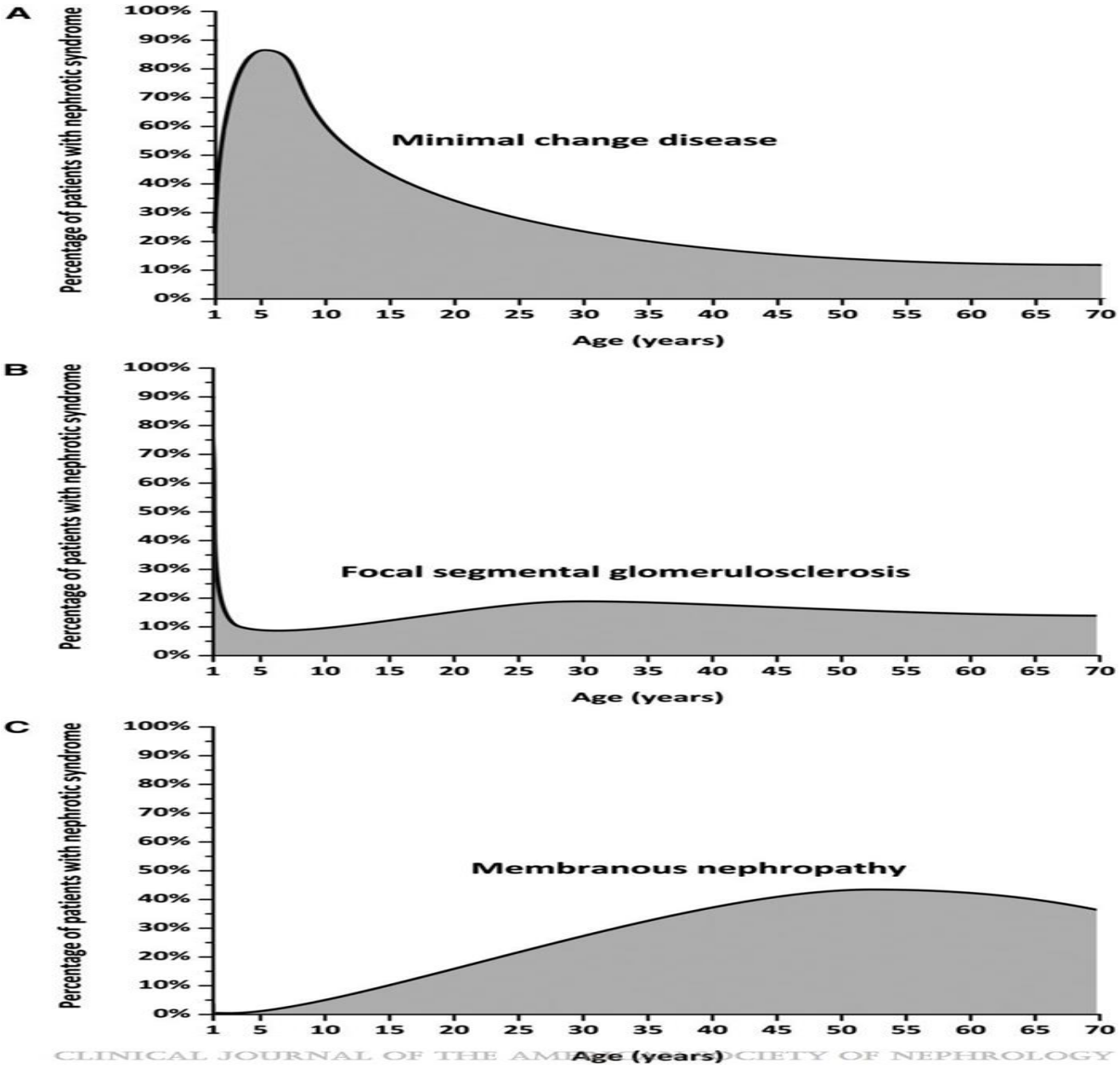
- AKI (30-40 %) adult> children

  Intravascular volume depletion

  sepsis,

  diarrhea,

  diuretics
- Hypertension (43%)
- Increased risk of thromboembolism
- Increased risk of infection
- IgG : ↓↓ IgA: ↓ IgM: ↑ IgE : → or ↑



Wolters Kluwer

Minimal Change Disease

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Definitions on the basis of references and on the authors' clinical experience

Nephrotic Syndrome

Edema
Massive proteinuria (> 3.5 g/d in adults)
Hypoalbuminemia (< 2.5 g/dl)

Remission

Resolution of edema
Normalization of serum albumin (> 3.5 g/dl)
Marked reduction in proteinuria
Complete remission (< 0.3 g/d in adults)
Partial remission (< 3.5 g/d and decreased by 50% in adults)

Relapse

Recurrence of massive proteinuria (> 3.5 g/d in adults)
± Edema

Steroid-Sensitive Nephrotic Syndrome

Response to PDN 1 mg/kg per d or 2 mg/kg every other d, within 16 wk in adults

Nonrelapsing Nephrotic Syndrome

No relapses for >2 yr after the end of therapy for the first episode of nephrotic syndrome (applicable to children, not yet defined in adults)

Frequently Relapsing Nephrotic Syndrome

≥2 relapses per 6 mo (or ≥4 relapses per 12 mo)

Steroid-Dependent Nephrotic Syndrome

Relapse during steroid therapy or within 15 d of discontinuation

Steroid-Resistant Nephrotic Syndrome

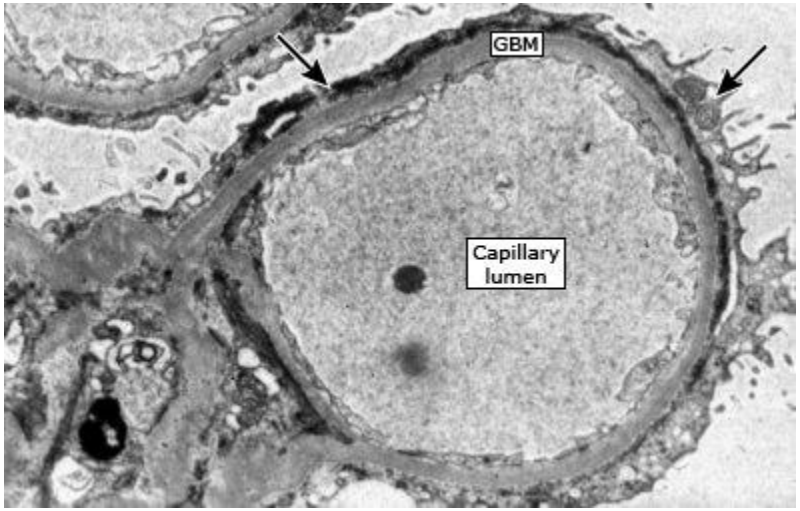
No response to PDN 1 mg/kg per d or 2 mg/kg every other d, within 16 wk in adults

Diagnosis

- A kidney biopsy is required to establish the diagnosis of MCD in adults and to exclude other causes of the nephrotic syndrome.
- There are no specific laboratory findings that can be used to distinguish MCD from other forms of nephrotic syndrome
- Adults with MCD on kidney biopsy should be evaluated for potential underlying secondary causes
- MCD is characterized pathologically by normal-appearing glomeruli on light microscopy and absence of complement or IG deposits on IF microscopy.
- Glomerular size is usually normal

Diagnosis

- characteristic histologic lesion is diffuse effacement of the epithelial foot processes on electron microscopy. (>80 %)
- degree of effacement does not correlate with the degree of proteinuria
- diffuse foot process effacement is also seen in other causes of the nephrotic syndrome (FSGS,MN,DN, amyloidosis)

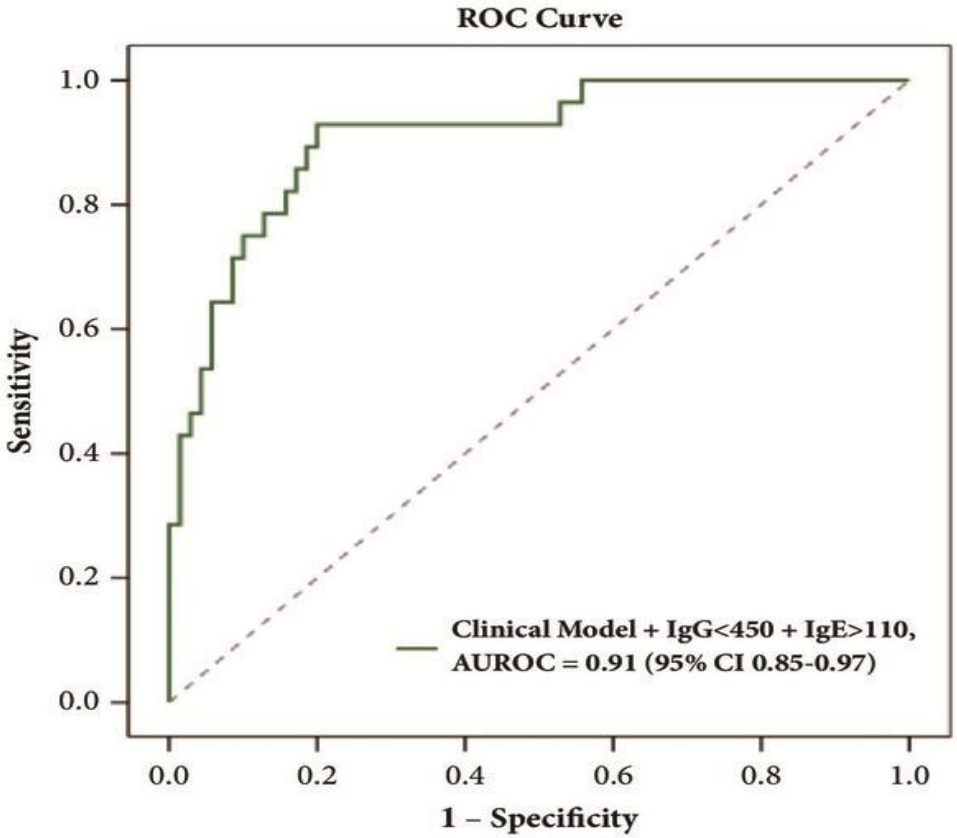


retraction, widening, and shortening of the foot processes

Research Article | Open Access

Immunoglobulin E and G Levels in Predicting Minimal Change Disease before Renal Biopsy

Ching-Chung Hsiao, Kun-Hua Tu, Chun-Yih Hsieh, Cheng-Chia Lee, Chih-Hsiang Chang, Pei-Chun Fan, Ya-Chung Tian, Ji-Tseng Fang



- 142 patients with nephrotic syndrome (biopsy)
- MCD was 26.8%.

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Distinguishing MCD from primary FSGS

MCD

- full nephrotic syndrome
- complete FPE on EM
- complete response to IS
- AKI, they usually recover, and ESKD is rare.
- Specific biomarkers:

  dystroglycan,

  Angptl4, urinary CD80,…

FSGS

- a descriptive term for sclerotic glomerular lesions
- several pathogenic mechanisms
- response to IS is seen only in approximately 50% of patients
- ESKD is common
- Specific biomarkers:CLCF1,suPAR,…
- sclerotic lesions are focal & first in juxtamedullary glomeruli
- may not be present in superficial biopsies
- differential gene expression

Take home massage

- MCD accounts for approximately 15% of idiopathic NS in adults

- Pathologic hallmark of disease is effacement of foot processes by EM
- Adult-onset MCD is associated with kidney failure in 33%, HTN in 35% and microscopic haematuria in 47%

- Discovering newer mechanism like ANGPTL4 has started new obsevation

Thank you