**Archana Vajjala**

@ArchanaVajjala

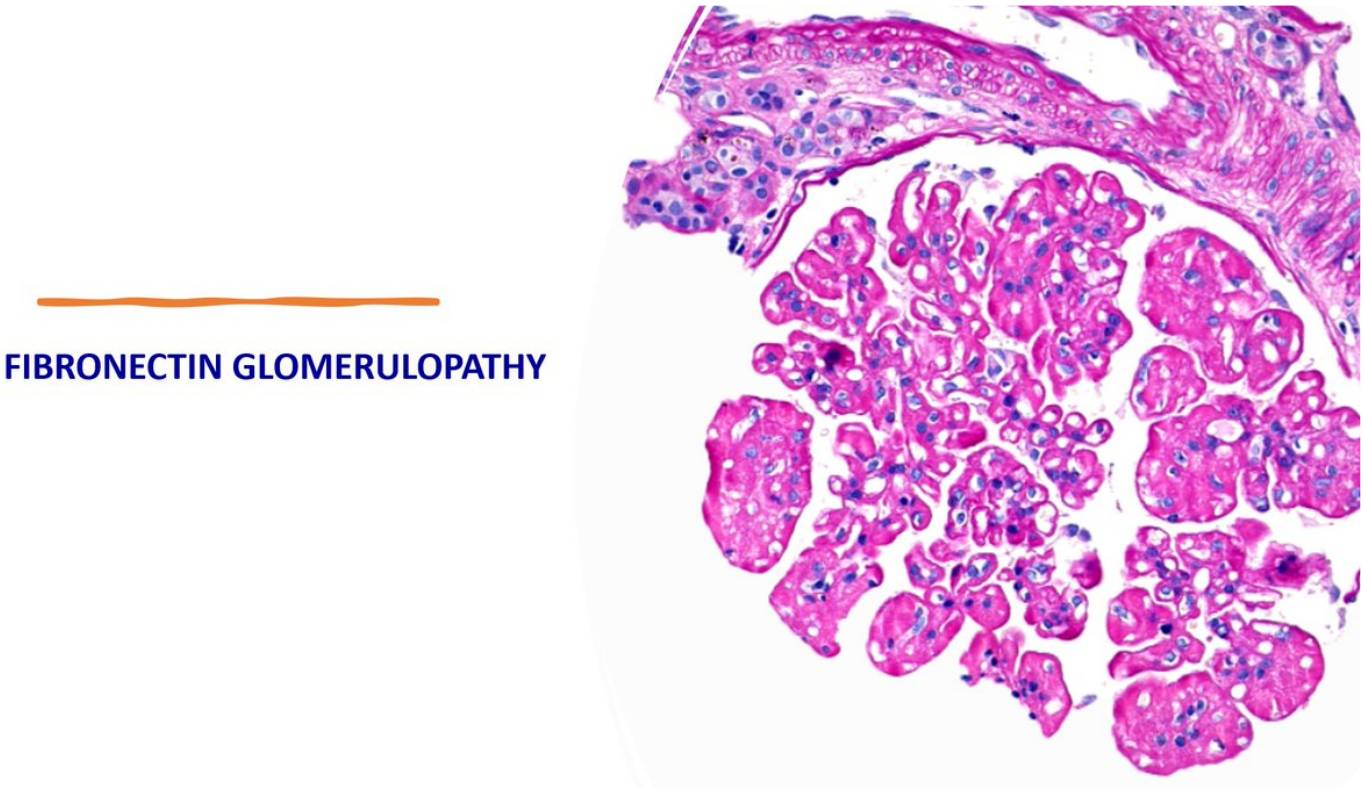


24 Tweets • 2021-12-08 20:11:15 UTC • See on Twitter

rattibha.com ♥


1/📢Hello #medtwitter
This November's @ASPNeph Renal Pathology webinar was on ⚡Fibronectin glomerulopathy (FNG)⚡ Here are some interesting points I learned!

#medtweetorial #NephTwitter #ASPNeph #pedneph #Renalpath #Nephpath



2/ Let's begin with a quick poll!

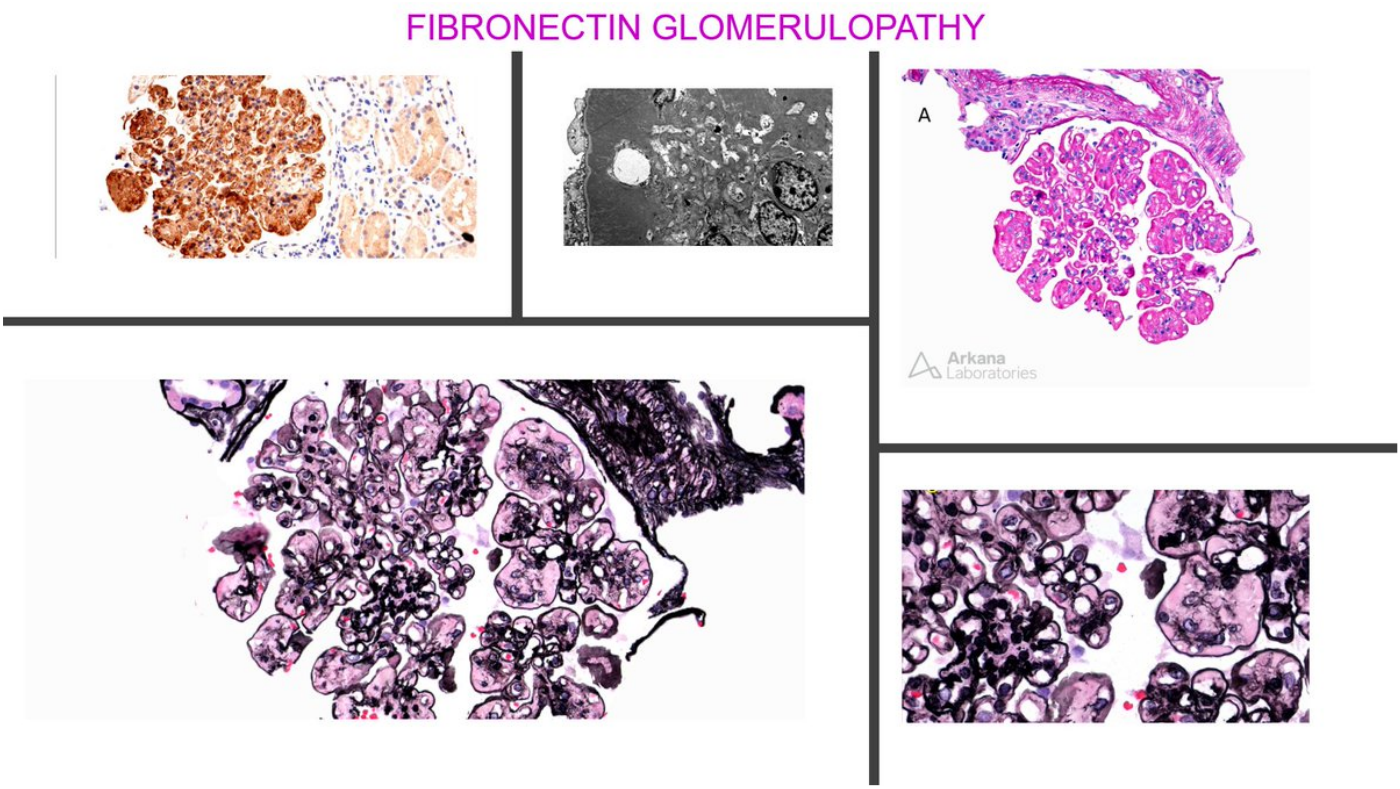
Fibronectin glomerulopathy is

3/ Ans: D - All the above

Fibronectin glomerulopathy (FGN) is a rare genetic glomerular disease caused by deposition of fibronectin protein in the glomeruli

PMID: 26064516

Image @arkanalabs



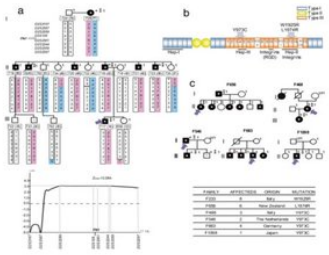
4/ 🧬Genetics 🧬

🔸40% of pts have fibronectin gene (FN1) mutations

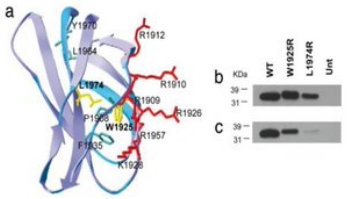
🔸Most of the cases are familial inherited as autosomal-dominant (AD) glomerulopathy

🔸Sporadic cases have also been reported

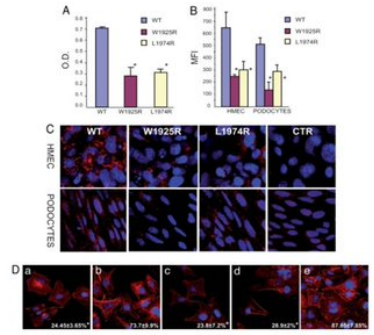
PMID: 18268355



*FN1* mutations in GFND. (*a*) (*Upper*) Haplotype analysis at *FN1* locus in pedigree F233. Microsatellite loci are on the left. (*Lower*) Multipoint linkage analysis by GENEHUNTER (model: autosomal dominant transmission with age-related penetrance, analysis with liability classes). For markers *D1S128* and *D1S2361*, the maximum lod score was $Z_{max} = 3.084$, as indicated. *, subjects previously published. ‡, biopsy-proven GFND. Solid symbols, affected individuals; crossed symbols, deceased; violet arrow, proband: the whole *FN1* was sequenced; red dots, *FN1* mutation carriers. ¶, subjects screened for the *FN1* mutation and for SNP segregation; un, unavailable. (*b*) Schematic diagram of fibronectin. Fibronectin monomer consists of type I (blue), II (green), and III (orange) repeats and the alternatively spliced sites EDI, EDII, and IIICS. The three main heparin-binding domains and the binding sites for integrins are shown. Positions of the GFND-associated mutations are indicated by arrows. (*c Upper*) Pedigrees of the other five families with *FN1* mutations. (*Lower*) The number of affected subjects, the mutation, and the origin of all of the six mutated families, are reported.




Expression of recombinant wild-type and mutant Hep-II domains of fibronectin. (*a*) Structure of FN $III_{13}$. Amino acid residues are color marked for positively charged (red), hydrophobic core (green), and residues W1925 and L1974 (yellow). (*b* and *c*) WT and mutant purified recombinant proteins were analyzed by SDS/PAGE on 12% gels and visualized by Western blotting with either an antibody anti-His (C-term) (*b*) or an antifibronectin mAb against the Hep-II domain. (*c*) Position of standards (kDa) are shown. Equal amounts (5 μg each) of WT and mutant proteins were loaded. Separate lanes were labeled with Coomassie blue as control for loading. Unt, untransfected.




Mutations in FN Hep-II domain cause reduced binding to heparin, endothelial cells, and podocytes and impair stress fiber formation. (*A*) Binding of $III_{12-14}^{wt}$, $III_{12-14}^{W1925R}$, and $III_{12-14}^{L1974R}$ to heparin by ELISA. O.D., optical density. (*B* and *C*) Binding of WT and mutant poli-His-tagged $III_{12-14}^{W1925R}$ and $III_{12-14}^{L1974R}$ recombinants added to human endothelial cells (HMEC) and mouse podocytes (*b*) FACS analysis. (*C*) Confocal microscopy; original magnification, ×600). Staining was done with an anti-His antibody plus FITC-conjugated (FACS) or Cy3-conjugated (confocal, red) secondary antibodies. MFI, median fluorescence intensity. (*D*) HMEC were plated on a 120-kDa N-terminal FN fragment in the absence (*a*) or presence of $III_{12-14}^{wt}$ (*b*), $III_{12-14}^{W1925R}$ (*c*), $III_{12-14}^{1974R}$ (*d*), or full length FN (*e*), in serum-free medium for 3 h and then labeled with rhodamine-phalloidin to visualize stress fibers. The percent of stress-positive cells (mean ± SD) is shown in the bottom (white numbers). Data are mean ± SD of three independent experiments. *, $P < 0.01$ vs. WT. O.D. and MFI values were calculated after subtracting values recorded with addition of buffer alone (blanks).

5/ FNG one entity: Many names!

🔹Familial glomerulonephritis with fibronectin deposits

🔹Familial lobular glomerulopathy

🔹Glomerular Nephritis with fibronectin deposits (GNFD)

🔹Glomerulopathy with fibronectin deposits

🔹Glomerulopathy with giant fibrillar deposits

6/ History of FNG

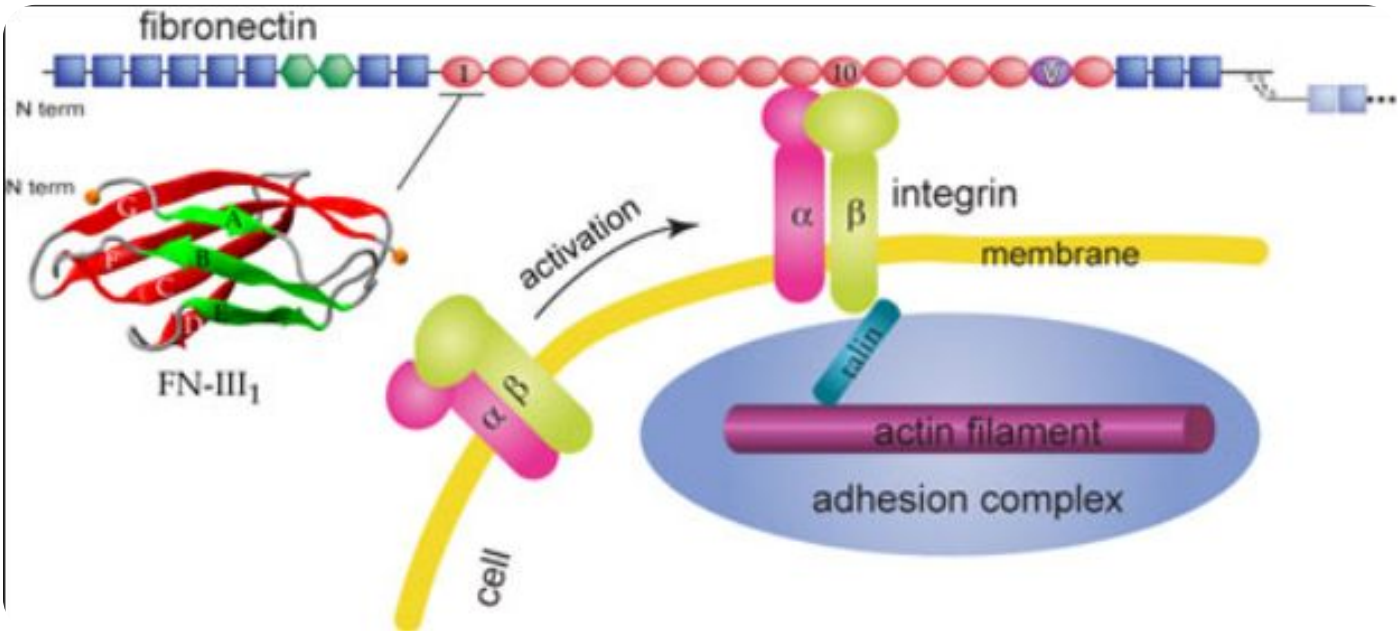
➡️Burgin first reported the disease in 1980

➡️Strom recognized it as autosomal dominant (AD) kidney disease with glomerular fibrillary deposits showing strong immune reactivity to fibronectin

➡️Sato (1998) reported the first Asian case in a 23Y old Japanese man

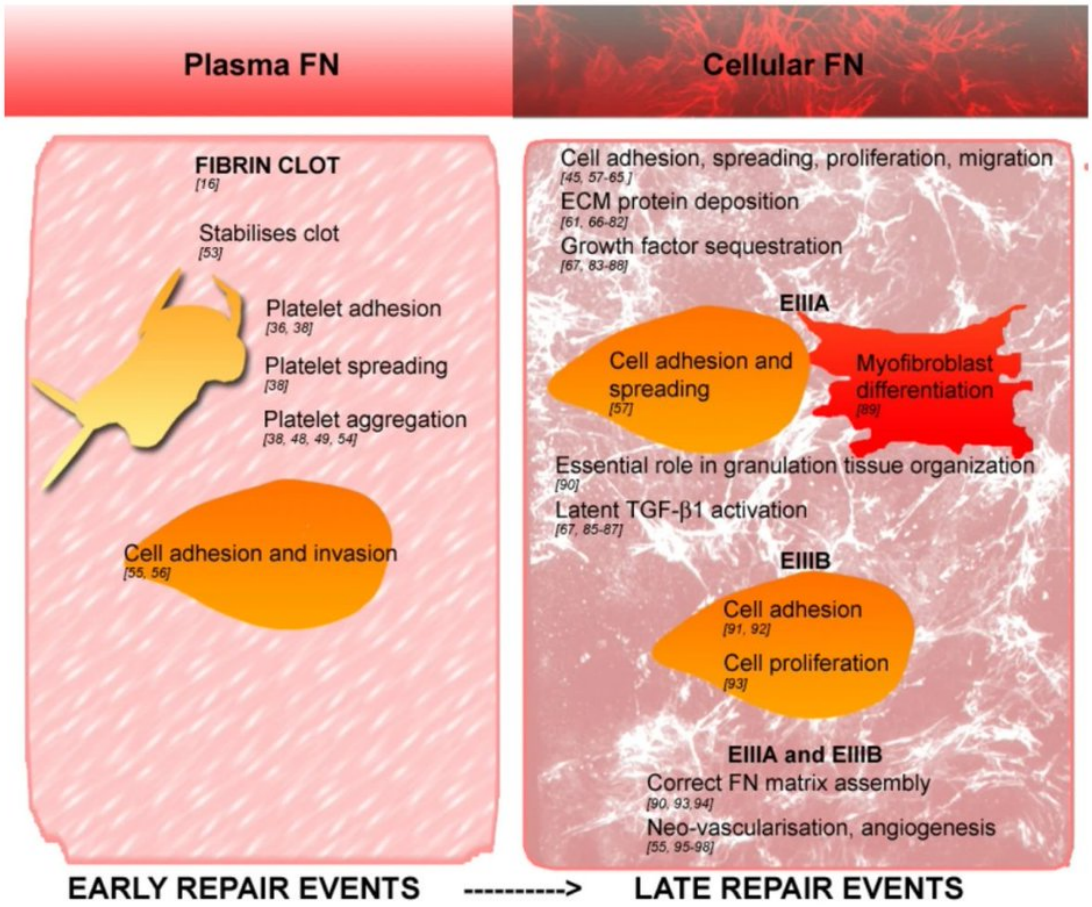
7A/So, what is this fibronectin ?

- Large, dimeric glycoprotein with two similar subunits
- Exists in 2 forms
- Soluble/plasma form is produced in liver & circulates in blood. Insoluble/cellular form is secreted by fibroblasts found in basement membranes & extracellular matrix




7B/ What does fibronectin do ?

It is important for cell adhesion, growth, migration and differentiation thus playing a major role in wound healing & embryonic development




**Functions of plasma and cellular fibronectin (FN) during wound healing.** The different forms of FN play distinct roles during the different stages of wound healing.

PMID: 21923916

## 8/ Fibronectin Deposition

Usually found in normal glomerular mesangial matrix

Enhanced accumulation is seen in different glomerulopathies (Eg: diabetic nephropathy)

Increased expression is secondary to locally stimulated mesangial & epithelial cell production of cellular form

9/ Typical presents between the age of 20-40y
Slight male predominance in White and Asian individuals
Proteinuria (Mild to Nephrotic range)
Microscopic hematuria
Hypertension
Hemolytic anemia
Slow progression of CKD to ESKD
May recur after kidney transplant
PMID: 33551409

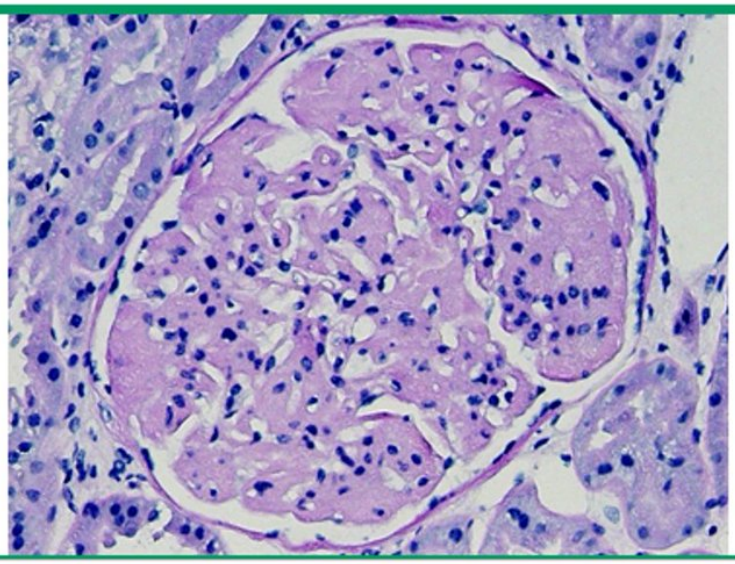
10/ Diagnosis is made only by kidney biopsy
It is suggested by the presence of large, finely granular, electron-dense deposits AND confirmed by the demonstration of fibronectin staining by immunohistochemistry or glomerular proteomics.
No clinical/lab findings are characteristic

11/ Histopathologic Findings

11A/ Light Microscopy:

There is no consistent specific tubulointerstitial compartment abnormality. However, interstitial fibrosis and tubular atrophy become more prominent over time, a common finding in progressive kidney disease

**Light micrograph showing fibronectin glomerulopathy**

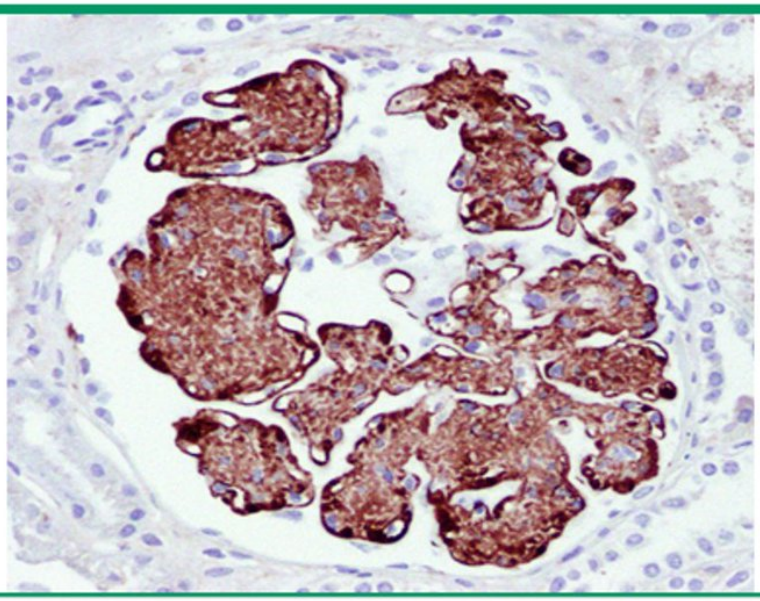


Light micrograph (400x) of a glomerulus in a patient with fibronectin glomerulopathy. There is glomerular enlargement and minimal cellular proliferation, producing a lobular or clover-like appearance.

UpToDate®

11B/ Immunofluorescence:
Immunoglobulin and complement component staining is absent or weak in GFND
Immunohistochemistry showing staining for fibronectin in the mesangium and along the capillary walls confirms the diagnosis

**Immunohistochemistry showing fibronectin staining in the glomerulus**



Immunohistochemical staining of a glomerulus for fibronectin in a patient with fibronectin glomerulopathy. Fibronectin is deposited in the mesangium and along the capillary walls.

UpToDate®



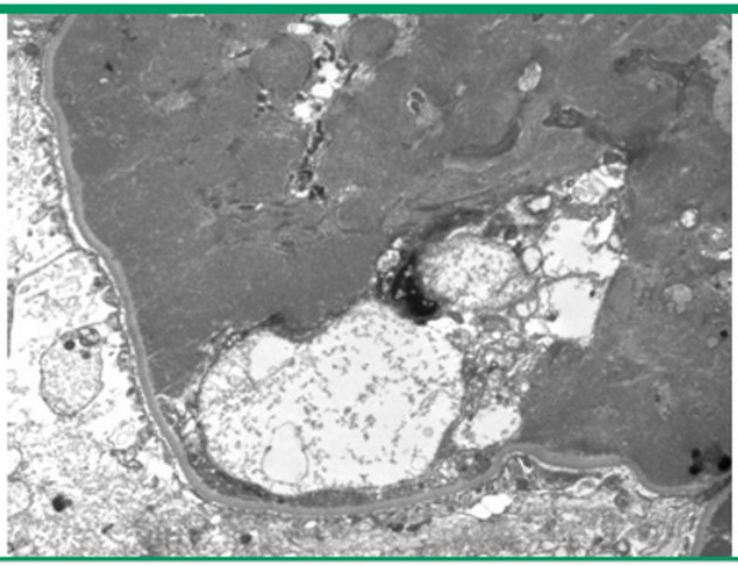
11C/ Let's do another poll with numbers!
Fibronectin glomerulopathy fibrils are typically

11D/ Ans: C

Electron microscopy:

Large to massive, electron-dense sub-endothelial and mesangial deposits, finely granular or fibrillar in some cases

**Electron micrograph showing fibronectin glomerulopathy**



Electron microscopy of a glomerulus in a patient with fibronectin glomerulopathy. There is mesangial expansion with nondescript, electron-dense material.

UpToDate®

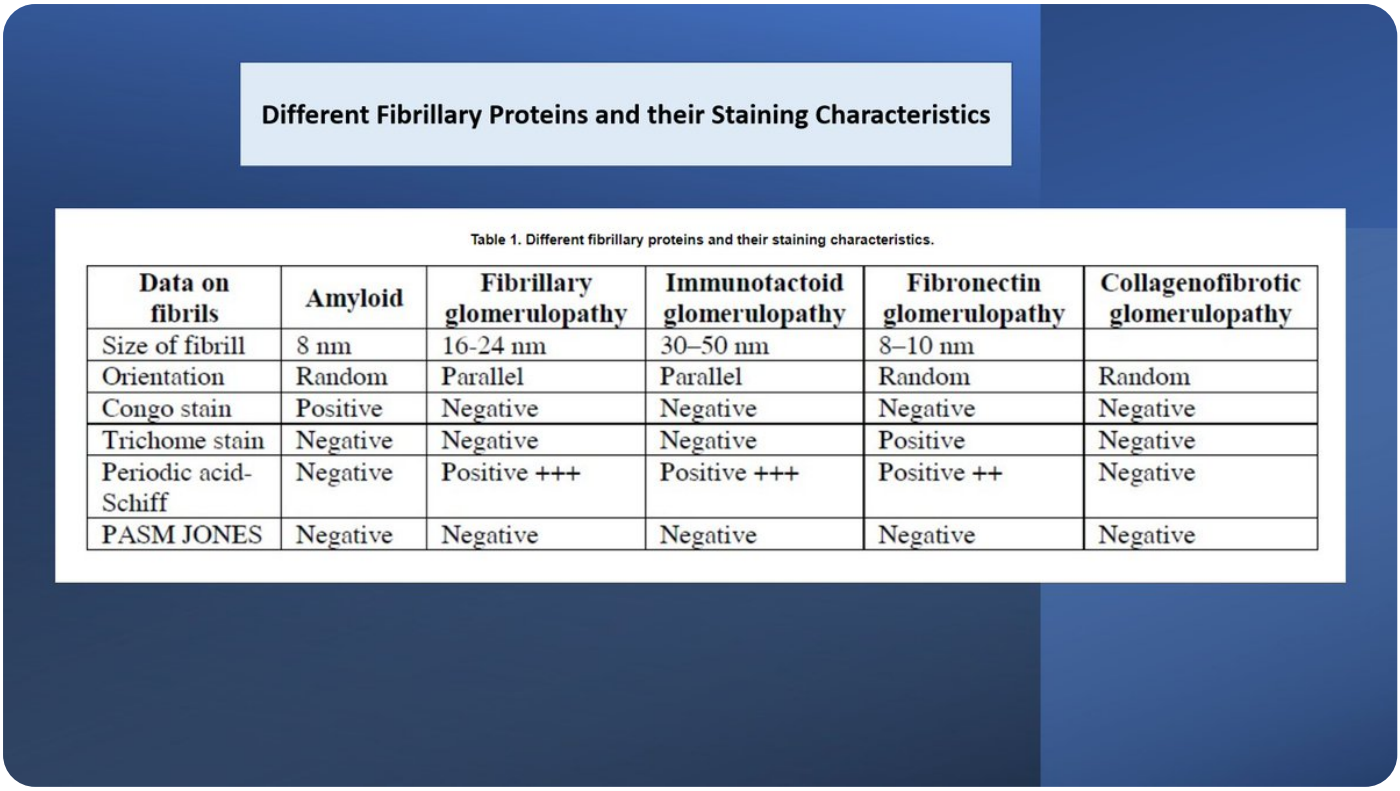



Table 1. Different fibrillary proteins and their staining characteristics.

| Data on fibrils | Amyloid | Fibrillary glomerulopathy | Immunotactoid glomerulopathy | Fibronectin glomerulopathy | Collagenofibrotic glomerulopathy |
|---|---|---|---|---|---|
| Size of fibrill | 8 nm | 16-24 nm | 30–50 nm | 8–10 nm | |
| Orientation | Random | Parallel | Parallel | Random | Random |
| Congo stain | Positive | Negative | Negative | Negative | Negative |
| Trichome stain | Negative | Negative | Negative | Positive | Negative |
| Periodic acid-Schiff | Negative | Positive +++ | Positive +++ | Positive ++ | Negative |
| PASM JONES | Negative | Negative | Negative | Negative | Negative |

12/ Treatment

Optimal treatment for GNFD is uncertain

No high-quality data regarding the use of immunomodulating agents, plasmapheresis, or any other specific therapy

Nonspecific therapies like strict BP control & use of ACEI and ARBs for proteinuria may prolong kidney function

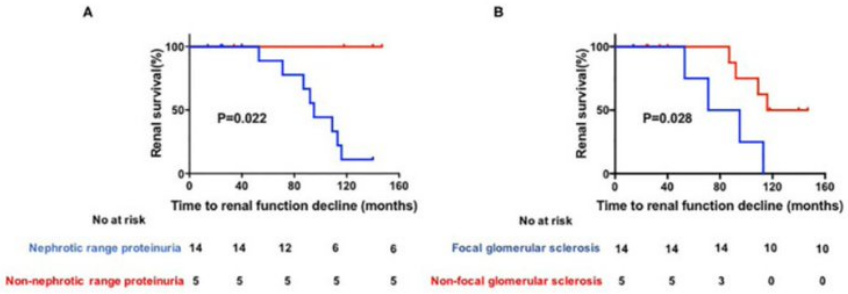
13/ Prognosis

♦Factors associated with kidney function decline in FNG include - Nephrotic range proteinuria & Focal glomerular sclerosis.

♦These can help clinicians to identify pts at risk of progressive kidney disease

PMID: 32923447

Factors associated with renal function decline in FNG




**(A,B)** Kaplan–Meier estimates of significant loss of renal function. Renal function was defined as impaired if serun creatinine (Scr) increased by 2-fold after biopsy, initiation of dialysis, transplantation or death.

14/ FNG & ESKD

Mgmt of ESKD in pts with FNG is similar to other types of Kidney diseases & these pts are candidates for all forms of kidney replacement therapy including transplantation

Disease recurrence is seen in some transplanted pts but the true risk isn't clearly understood

15A/ Recurrent Disease

🔹Seen in pts with kidney allografts transplanted for ESKD due to  GFND

🔹The mechanism behind this is unclear

🔹Possible hypothesis ➡️ renal accumulation of abnormal circulating plasma fibronectin

15B/ Fibronectin may be complexed with proteins like (matrix proteins fibulin-1 & fibulin-5 ) disrupting normal, fibronectin-dependent mesangial and/or podocyte motility, adhesion & spreading resulting in characteristic clinical features

🌟unique finding to the deposits of GFND🌟

16A/ Genetic Counselling
Disease appearance in successive generations is consistent with an AD pattern of inheritance with age-related penetrance. However, there is a poor genotype to phenotype correlation

16B/ Genetic counseling should be proposed to all individuals having the disease-causing mutation informing them that the risk of passing the mutation to offspring is 50%

17/ FNG - 🗝Key Points
⚡Autosomal dominant disease
⚡Mutations in the FN1 locus at 2q32
⚡Massive glomerular deposits of glycoprotein fibronectin (soluble plasma FN) ➡️ ESKD
⚡Globulin-negative results in immunostaining
⚡No standard treatment has been established for FNG

18/ That's all folks
For a case-based clinical discussion with a pathology expert login to @ASPNeph website, November webinar #Membereducation #ASPNFOAM group

Special thanks to @drM_sudha @SwastiThinks and #ASPNFOAM group

Until next time...