UPDATES on JUVENILE NEPHRONOPHTHISIS(NPHP)

Ali Derakhshan MD

Shiraz University of Medical Sciences

Shiraz Nephro-Urology Research Center

Shiraz-Iran

TEHRAN 2023

Case presentation

3 cases in a family

1st one presented at 12 yr♂ in ESKD July 2011,Wt 30 kg,Bp130/80,SCr 6mg/dl,CAPD and DD waiting list Tx May 2012 . IS : CSA,Cellcept,Pred. 2023 wt 76kg,SCr 1.3+moderate COVID and recovery

- 2nd case His 9yr old sister upon screening 2011 ' Serum Cr1.7mg/dl and gradually →stage 5 CKD. 5yrs later. CAPD May 2016 ,Tx:April 2017, cr0.8 mg/dl, IS:TAC ,MMF,pred.

  Dec 2017 ↑ serum Cr1.8 and 2.7mg/dl.due to BK, Cipro.,IVIG ,D/C cellcept &TAC chaged to

  CSA .SCr gradually ↓ to1.4& also **BK --** Aug 2019 Rapamune added and 2mo later D/C due to Edema and proteinuria. Latest SCr NOV 2023 on pred.+CSA 1.17mg/dl

Their 4yr old♂ cousin referred for check up due to +F Hx, July 2012 + hx polyuria,polydipsia, cr0.7mg/dl,**urine SG 1.008**,gradual rise of SCr on supportive Rx, 7 Yrs. later2019 cr1.2mg/dl & his latest SCr is 4.1mg/dl ,OCT 2023 ,wt45kg,Ht157cm

AVF done and introduced to DD waiting list for KTX.

HISTORY of NEPHRONOPHTHISIS

Nephronophthisis (NPH), initially described

in 1945 by Smith & Graham

as medullary cystic disease

Fanconi in1951 described it as familial juvenile nephronophthisis

Nephronophthisis in Greek means disintegration of nephrons

Fanconi G, et al. Familial, juvenile nephronophthisis (idiopathic parenchymal contracted kidney) Helv Paediatr Acta. 1951;6:1–49

THE JUVENILE NEPHRONOPHTHISIS (JN)– MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX (MCKD)

Genetically determined cystic renal diseases

JN :Autosomal recessive

MCKD: Autosomal dominant

Common histologic finding in JN and MCKD is chronic TIN

Nephronophthisis-Related Ciliopathies (NPHP-RC)

- ✓ NPHP-RC are autosomal recessive disorders with corticomedullary renal cysts and extrarenal symptoms
- ✓ They are the most common **genetic** cause of ESKD in children and young adults
- ✓ NPHP-RC : presentation as isolated renal or syndromic

The most common extra-renal organs involved: liver, eye, bone and CNS

At least 25 genes associated with JN detected

New genes detection happens rapidly

Jianyi Li,et al. Pediatric Nephrology (2023) 38:1609–1620

CILIA

The cell organelles involved in renal cystic disease

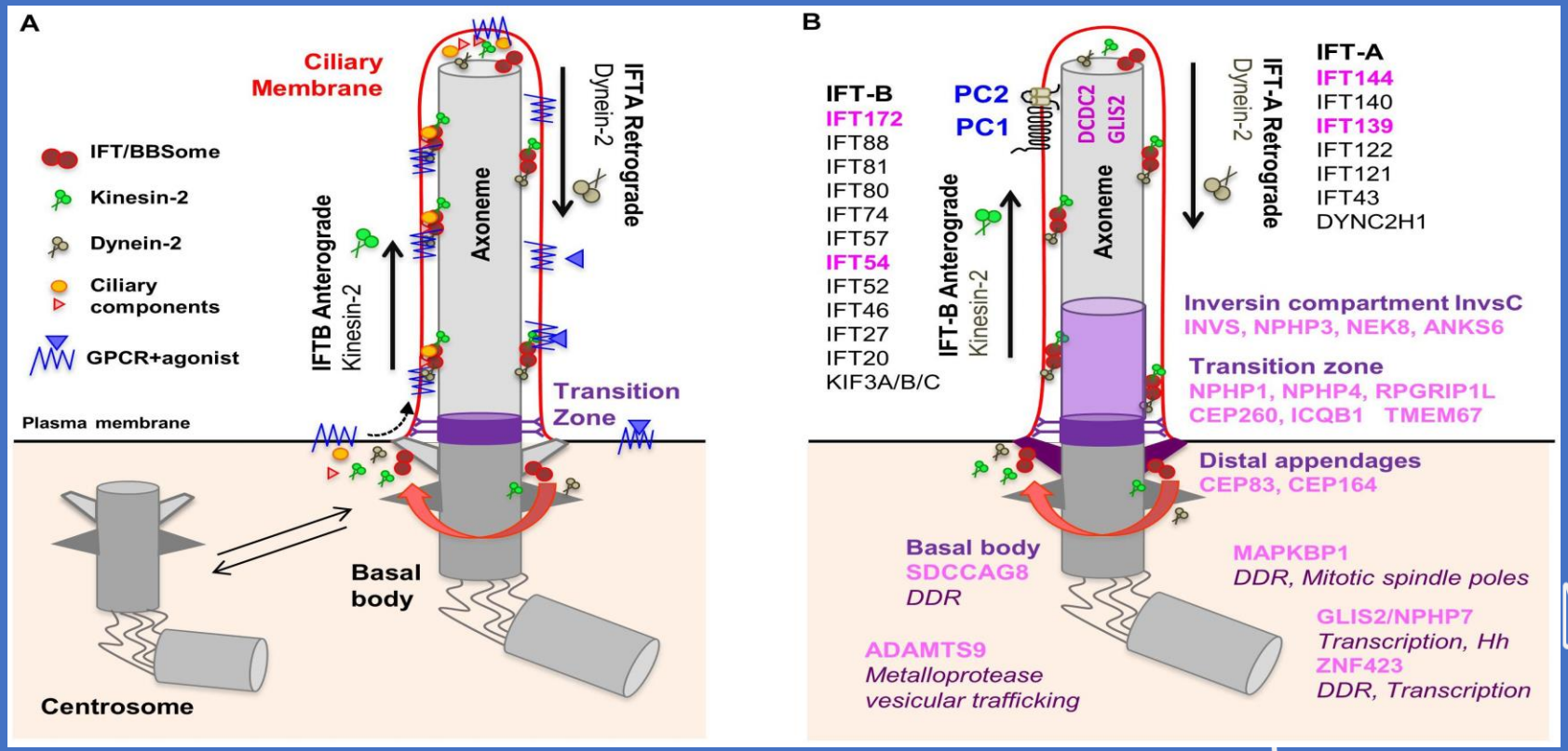
Two types of Cilia in the body

Motile (secondary cilia): sperm , bronchi , oviducts and ependymal cells of the brain vesicles

Non-motile(primary cilia): present in all cells

Non-motile cilia involved in cystic disease of the kidney

The STRUCTURE of CILIA



Cell Dev. Biol. 9:6531381

CILIA and The KIDNEY

- ✓ In 1993, the discovery of the intraflagellar transport system (IFT) (Kozminsky *et al*. 1993).
- ✓ IFT both builds and maintain cilia and flagella
- ✓ A branch of this discovery was one of the proteins involved in IFT function is the same as one involved in PKD in mice (Pazour *et al.* 2000)
- ✓ The cells that line the nephron have primary cilia and mice with PKD are unable to assemble cilia properly because of the defective protein
- ✓ PKD is the 1st of the disease group diagnosed as defective cilia function
- ✓ Later on other cystic disease of the kidney including **NPHP**

GENETICS and PATHOGENESIS of NEPHRONOPHTHISIS(NPHP)

- ✓ NPHP is caused by variants in a large number of genes that encode proteins involved in the function of primary cilia, basal bodies, and centrosomes

- ✓ They result in renal disease and extra-renal manifestations, including retinal degeneration, cerebellar ataxia, liver fibrosis and skeletal abn.

- ✓ *NPHP1* gene is the most common and accounting for 20% of cases
- ✓ Each of the other genes <3%
- ✓ In 30% of NPHP cases the gene is still unknown

TEHRAN 2023

PATHOGENESIS

- ✓ The proposed common mechanism is ciliary dysfunction
- ✓ Most of the contributory proteins to renal cystic disease including nephrocystins are localized on primary cilia, basal bodies, and centrosomes
- ✓ Nephrocystins interact with one another and with other proteins (such as tensin , filamins, and tubulins) that are involved with cell-cell and cell-matrix signaling

TEHRAN 2023

PATHOGENESIS

Mutations in the NPHP genes alter cilia function→

defect in signaling pathways→ dysregulated tissue growth and subsequent renal cysts

The NPHP genes are found in the cilia of other organs

Variants of these genes results in the non-renal manifestations of NPHP (Retinitis pigmentosa in 20 percent of all cases of NPHP)

Attanasio M,et al. Nat Genet 2007; 39:1018

Sayer JA, et al. Nat Genet 2006; 38:674

BARDET-BIEDL SYNDROME (BBS)

BBS a disease that is characterized by a combination of

renal disease, vision loss, obesity, hypogonadism

polydactyly and mental defects

Why so many apparently unrelated dysfunctions in BBS?

All the affected functions depends on disruption of primary cilia

HISTOLOGICAL FINDINGS IN NPHP

Juvenile and adolscent variant

Kidney size normal or small size

Small corticomedullary cysts up to 1.5 cm in size

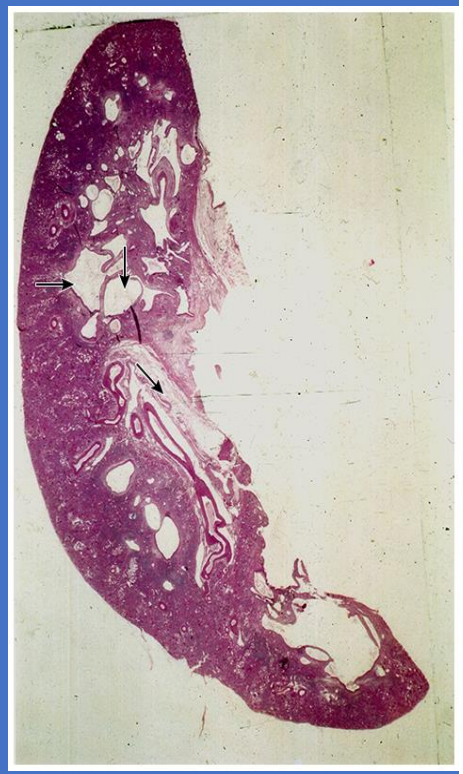
Initial interstitial fibrosis and limited signs of inflammation

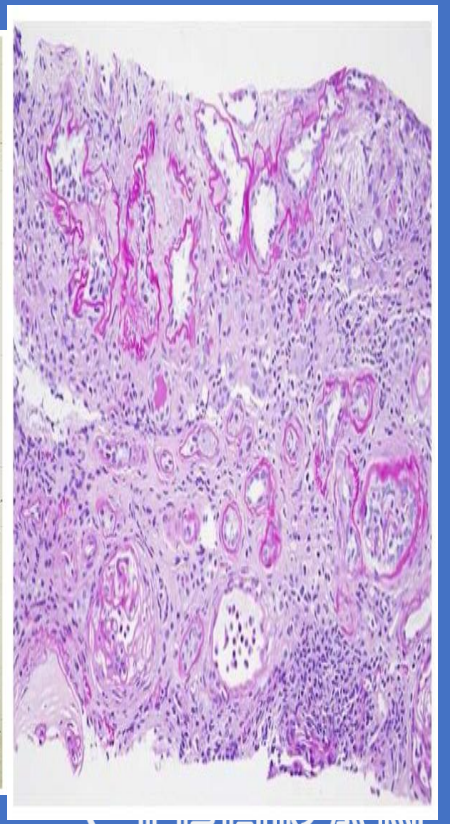
Atrophic tubules with thickened and multilayered basement membranes

Dilated or collapsed tubules alternate with the atrophied damaged tubules

The glomeruli are often normal initially , then preglomerular fibrosis and segmental and global sclerosis

EM : multilayered thickening of tubular basement membranes





CLINICAL CORRELATION AND GENE VARIANT

The clinical findings vary with the involved gene

- ✓ **Juvenile** NPHP is associated with variants in all the NPHP genes except *NPHP2*
- ✓ *NPHP1*,the most commonly affected gene
- ✓ Variants in *NPHP2* result in infantile and *NPHP3* in adolescent NPHP
- ✓ Variants in *NPHP5* are associated with retinitis pigmentosa (also referred to as tapetoretinal degeneration) and the Senior-Loken syndrome.
- ✓ Variants in *NPHP6* and *NPHP8* are associated with retinal degeneration and cerebellar vermis aplasia in the Joubert syndrome or Meckel-Gruber syndrome
- ✓ Variants in *NPHP7* and *NPHP9* are rare causes of NPHP

NPHP1 GENE

- ✓ *NPHP1* gene deletions or variants have also been described in association with moderate retinitis pigmentosa, Cogan syndrome with oculomotor apraxia and a subset of individuals with Joubert syndrome
- ✓ In most patients with *NPHP1* gene variants presentation is in childhood and ESKD <20 years
- ✓ Adult cases with homozygous *NPHP1* deletions has been reported

TEHRAN 2023

EPIDEMIOLOGY of NPHP

- ✓Males and females equally affected
- ✓Juvenile form the most common type
- ✓Worldwide distribution
- ✓The most frequent genetic cause of ESKD in 1st 3 decades of life
- ✓In United States* 2.4% and in Europe**15% of childhood ESKD
- ✓ About 6%percent of ESKD cases in a single center in IRAN+

Kidney Int Suppl 1993; 43:S104

**J Am Soc Nephro2007; 18:1855

+Medical Journal of Islamic R of Iran2001vol15 ,NO1,Ali Derakhshan

TEHRAN 2023

CLINICAL VARIANTS OF NPHP

Three clinical variants on the basis of median age of ESKD

Infantile – one year of age

Juvenile – 13 years of age

Adolescent – 19 years of age

These variants are associated with specific gene defects also the extrarenal findings

CLINICAL MANIFESTATIONS (RENAL DISEASE)

- ✓ NPHP almost always progresses to ESKD before the age of 20
- ✓ Rare case reports of ESKD at 27 and 56years
- ✓ Also cases of retinal dystrophy before renal findings
- ✓ **Initial presentation** : polyuria , polydipsia , nocturia, enuresis

  growth retardation and With progression of CKD

  Anemia, metabolic acidosis & early uremic symptoms

  Usually normotensive

  Usually delayed diagnosis
- ✓ Early stages: no proteinuria or mild tubular proteinuria ,no hematuria
- ✓ **Late stages glomerular proteinuria due to glomerulosclerosis**

RATE OF PROGRESSION TO ESKD

- ✓ Determined in part by the type and severity of the genetic defect
- ✓ Among NPHP genes, four of them account for 75% of identified disease (NPHP1, NPHP3, NPHP4 and NPHP11/TMEM67)
- ✓ Kidney survival was analyzed in 383 pt. with NPHP

Median age at onset of ESKD was as follows:

NPHP3, 4 years

NPHP1, 13.5 years

NPHP4, 16 years

NPHP11/TMEM67, 19 years

- ✓ Significant association of Kidney survival with the NPHP1, NPHP3, and NPHP4

König JC, et al.Kidney Int Rep 2022; 7:2016

TYPES OF NPHP

Infantile

Rare but more severe form of NPHP

Hx of prenatal oligohydramnios

Hypertension is common

Prenatal DX at 22weeks of gestation

ESKD from birth to 3yrs of age

US: hyperechoic kidneys, size: normal ,small or large

Extra renal findings more common

hepatic 50%,cardiac 20%,bronchial 18%

Typically caused by variants in NPHP2 and NPHP3genes

Variants of NPHP2 genes which encodes inversin (nephrocystin-2) associated with situs inversus

TYPES OF NPHP…

Juvenile the most common type

clinical symptoms: polyuria, polydipsia, and secondary enuresis

Age of onset: 4-6 years

Tubular dysfunction→ impaired concentrating ability and Na reabsorption

BP usually normal

ESKD median age 13 years

Urine osmolality<400mosmol and not responding to vasopressin

Poor growth 1st due to hypovolemia and then CKD

Anemia preceding to a significant decline in GFR due to EPO deficiency

The most common gene NPHP1 then others except NPHP2

US decreased to normal size kidneys with ↑echogenicity

TYPES OF NPH…

Adolescent onset

Mostly with *NPHP3* gene variants

ESKD: late adolescence and young adulthood

Median age of ESKD 19yeas (4-37 years)

Onset of polyuria, nocturia ,polydipsia at a later age than JN

Ultrasonography

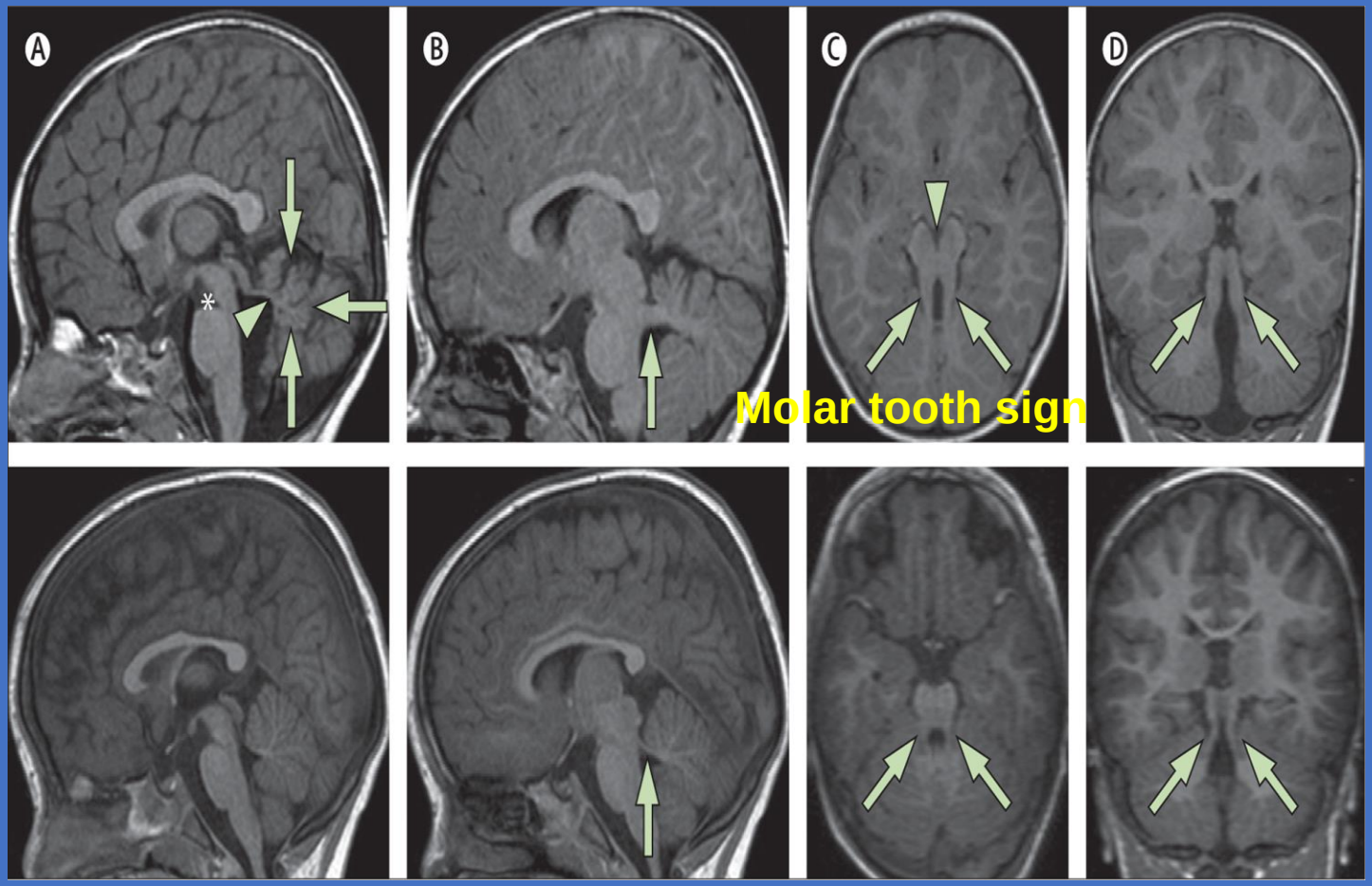
- ✓Loss of corticomedullary differentiation
- ✓Increased echogenicity of kidneys
- ✓Size of kidneys smaller than normal to normal
- ✓Variable number of **cysts** in the medulla and corticomedullary junction

Associated Syndromes with JN

- Senior-Løken syndrome (retinitis pigmentosa)
- Joubert syndrome (cerebellar vermis hypoplasia,22 subtypes),
- Bardet-Biedl syndrome (intellectual disability, obesity; 17 subtypes),
- Jeune asphyxiating thoracic dystrophy (shortening of the long bones, narrow rib cage; 11 subtypes)

Joubert syndrome AR neurologic disorder with cerebellar vermis hypoplasia resulting in ataxia ,polydactyly, hypotonia, developmental delay,neonatal respiratory dysregulation, abn. eye movements

Figure 1



TEHRAN 2023

DIAGNOSIS and DIFF.DIAGNOSIS

- Clinical findings
- Extrarenal manifestations
- Genetic study
- Ultra sonography
- Kidney biopsy
- Diff.Dx: **Renal hypo-dysplasia , urinary tract obstruction**

  ADPKD and ARPKD

MANAGEMENT

There is no specific treatment for NPHP

Management in early stages with acceptable renal function :

Maintaining fluid and electrolyte balance

Treatment **of anemia** ,**acidosis** and growth promotion

✓ For patients with CKD: Treatment of anemia ,Acidosis,

growth promotion and Ca-P hemostasis **,----------more frequent**

check of GFR as kidney function declines,……

✓In patient with ESKD, the recommend Rx is KTX

✓The outcome of KTX is excellent due to lack of recurrence

SUMMARY

- Nephronophthisis-Related Ciliopathies (NPHP-RC)

  AR renal cystic disease
- Insidious onset of ESKD in children usually before the age of 20
- More than 25 genotypes
- The common signs at the onset is polyuria,polydipsia,2nd Enuresis, disproportionate anemia to the GFR,
- Association with retinitis pigmentosa and other syndromes
- **Often delayed diagnosis**
- Family survey
- Avoiding consanguineous marriage ----
- Rx of choice for ESKD KTX