מקרה קליני: קומה נמוכה ו-DI

ד"ר נעמה פיש שוולב

מומחית באנדוקרינולוגיית ילדים

מ"ר שניידר

מרץ 2025

ק.מ תלונה עיקרית

- בן 6.5 שנים
- פנו בגלל שתיה מרובה והשתנה מרובה מזה כשנה וחצי
- אנורזיס שניוני
- מתעורר לשתות גם בלילה
- מגיע ל-6 ליטר ביום
- אם אין מים בוכה ודורש, מסוגל לשתות מי אסלה

ק.מ תיאור מקרה

- בנוסף כאבי ראש מזה שנה וחצי
- גדילה – בגיל שנתיים אחוזון 50 ומאז ירידה הדרגתית לאחוזון 3 עם BMI באחוזון 20
- ברקע הריון ולידה תקינים שבוע 40 מ.ל 3300ג
- התפתחות תקינה
- תרופות – לא אשפוזים /ניתוחים – לא
- אמא 160 ס"מ ו.ר 12-13 מוצא תימן
- אבא 183 ס"מ ג.ר לא ידוע מוצא סוריה
- 3 אחאים בריאים
- בן דוד עם קרוהן. אימה של האם עם סוכרת טייפ 1

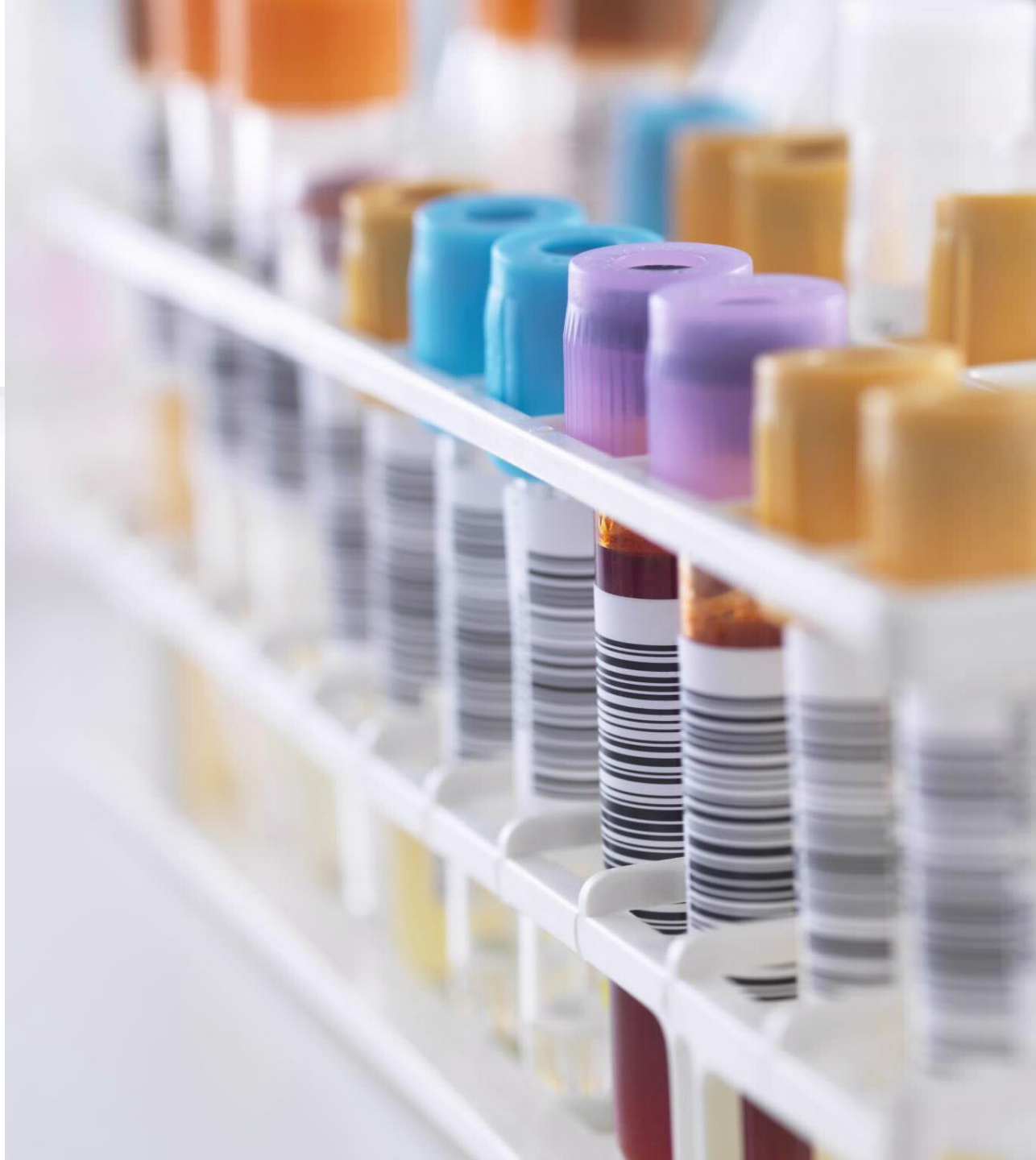
בדיקה גופנית

- בדיקה גופנית תקינה, ללא דיסמורפיזם
- התבגרות טאנר 1 אשכים 2 מל בשק

בדיקות עזר

- מעבדה חצי שנה טרם קבלתו – ס"ד תקינה שתן תקין אך SG 1.004
- ביוכימיה תקינה אך לא נלקחו אלקטרוליטים!
- תפקודי תריס תקינים
- רמת IGF1 בצד הנמוך של הנורמה
- קורטיזול בוקר תקין

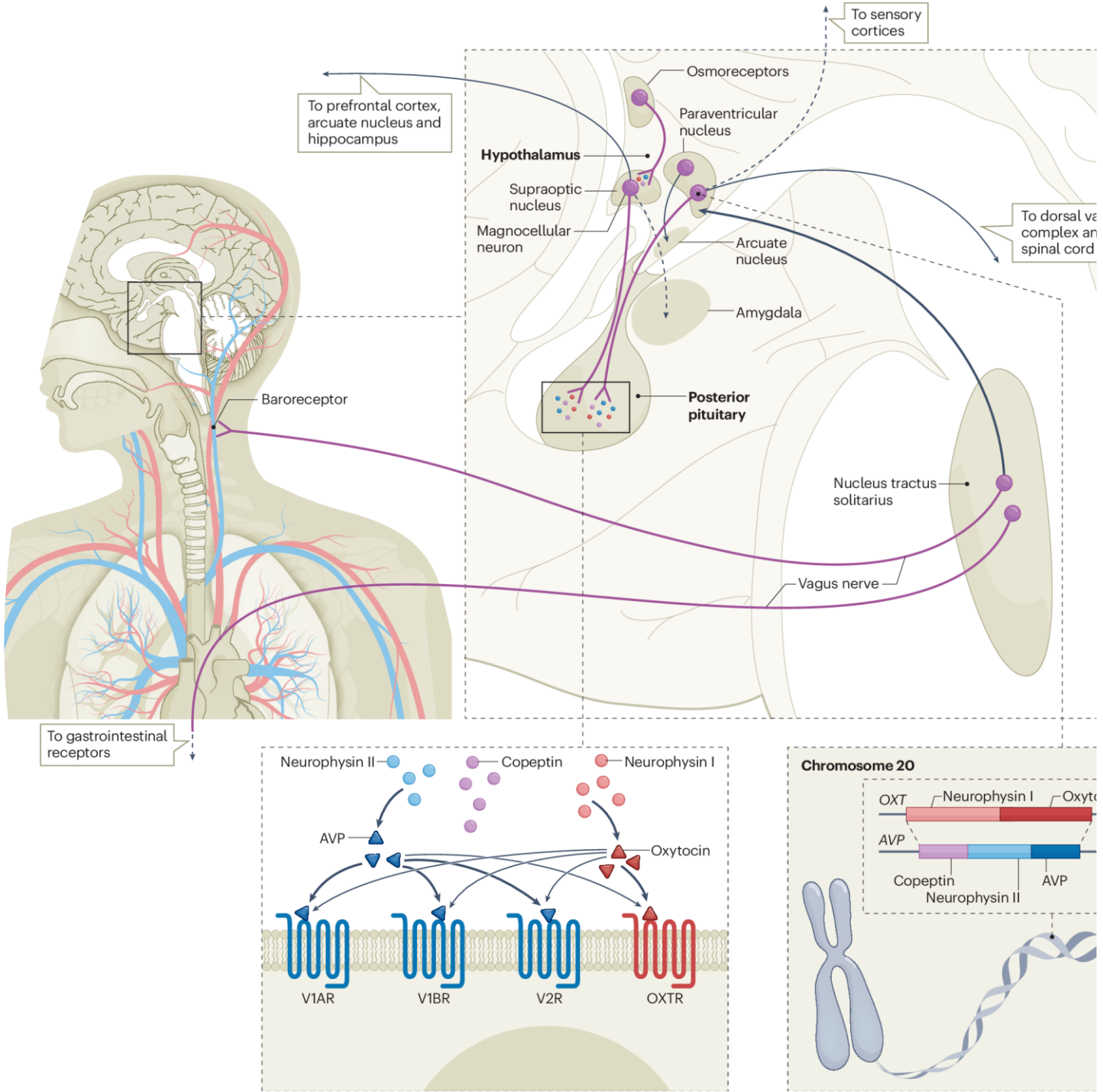
- בירור חוזר אחרי לילה עם הגבלת שתיה (לא הצליח, שתה 2 כוסות)
- אוסמולריות דם 305 ואוסמולריות שתן 113
- נתרן 151
- לציין כי אחרי "צום" של לילה רמת קריאטינין 0.89 ואוראה 45
- חצי שנה קודם לכן קריאטינין 0.59



Etiology of polyuria-polydipsia syndromes

Basic defect	Acquired causes	Hereditary causes
Arginine vasopressin deficiency		
Deficiency in AVP synthesis or secretion	▪ Trauma (surgery and deceleration injury) ▪ Neoplasia (craniopharyngioma, meningioma, germinoma and metastases) ▪ Vascular (cerebral or hypothalamic hemorrhage and infarction or ligation of anterior communicating artery aneurysm) ▪ Granulomatous (histiocytosis and sarcoidosis) ▪ Infectious (meningitis, encephalitis and tuberculosis) ▪ Inflammatory or autoimmune (lymphocytic infundibuloneurohypophysitis and IgG4 neurohypophysitis) ▪ Drug or toxin exposure ▪ Osmoreceptor dysfunction (adipsic AVP deficiency) ▪ Others (hydrocephalus, ventricular or suprasellar cyst, and degenerative diseases) ▪ Idiopathic	▪ Autosomal dominant: *AVP* mutations ▪ Autosomal recessive: *AVP* mutations ▪ Autosomal recessive: *WFS1* mutations ▪ Autosomal recessive: *PCSK1* mutations ▪ X-linked recessive: gene unknown

Nature Reviews Endocrinology volume 20, pages487–500 (2024) Atila et al.



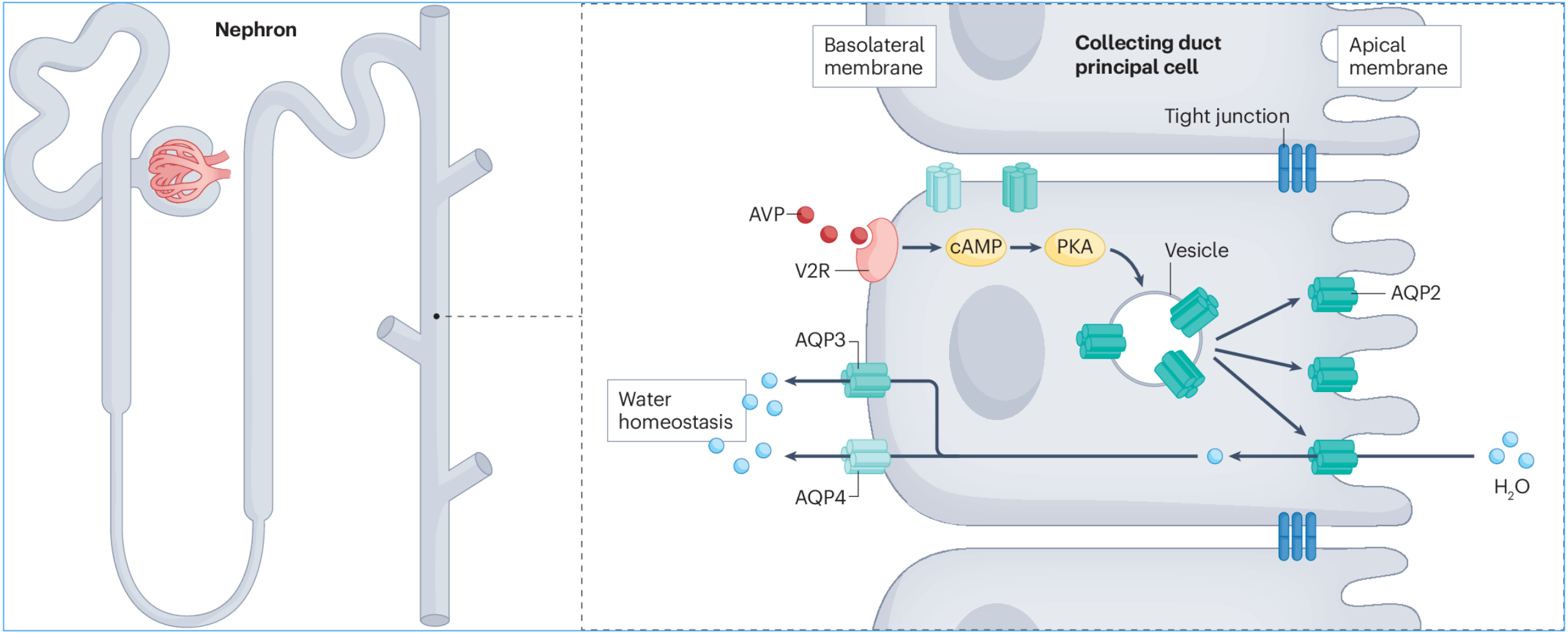
Arginine vasopressin resistance		
Reduced kidney sensitivity to antidiuretic effect of physiological AVP levels	▪ Drug exposure (lithium, demeclocycline, cisplatin, etc) ▪ Hypercalcemia or hypokalemia ▪ Infiltrating lesions (sarcoidosis, amyloidosis, multiple myeloma, etc) ▪ Vascular disorders (sickle cell anemia) ▪ Mechanical (polycystic kidney disease and urethral obstruction)	▪ X-linked: *AVPR2* mutations ▪ Autosomal recessive or dominant: *AQP2* mutations
Primary polydipsia		
Excessive fluid intake at a diminished set point	▪ Psychosis intermittent hyponatremia-polydipsia (PIP) syndrome ▪ Compulsive water drinking ▪ Drugs (eg, synthetic cathinones, methamphetamine and 3,4-methylenedioxymethamphetamine [ecstasy]) ▪ Health enthusiasts ▪ Dipsogenic* (idiopathic or similar lesions as with arginine vasopressin deficiency)	None identified

Causes of acquired forms of NDI and secondary NDI.

Drugs	Antibiotic/antifungal/antiviral therapy	Antineoplastic agents	Metabolic imbalances	Inherited disease/autoimmune disease
Lithium	Demeclocycline	Ifosfamide	Hypokalemia	Acute/chronic renal failure
Orlistat	Ofloxacin	Cisplatin	Hypercalcemia	Urinary tract obstruction
Methoxyflurane	Didanosine	Vinblastine		Sickle cell disease
Colchicine	Cidofovir	Cyclophosphamide		Renal amyloidosis
Sulfonylureas	Foscarnet			Sjögren's syndrome
	Amphotericin B			Cystinosis Bartter syndrome (type 1 and type 2)
				Familial hypomagnesemia with hypercalciuria
				Nephrocalcinosis/cystic kidney disorders:
				Autosomal dominant polycystic kidney disease/medullary cystic kidney disease
				Bardet-Biedl syndrome, nephronophthisis

NDI, nephrogenic diabetes insipidus.

Duicu et al Exp Ther Med. 2021 May 11;22(1):746. doi: 10.3892/etm.2021.10178l.



Nature Reviews Nephrology volume 21, pages83–96 (2025) Levtchenko et al consensus statement

מבחן צמא

- בדיקות בתחילת המבחן (לא בצום):
  - אוסמולריות דם 292
  - אוסמולריות שתן 107
  - UA 6 נתרן 140 אוראה 59 קריאטינין 0.99
- שעתיים אחרי מתן מינרין:
  - נפח השתן 620 מ"ל שתן בשעתיים (ללא שינוי)
  - אוסמולריות שתן 121
  - אוסמולריות בדם 300 מילי אוסמ/קג

- מה האבחנה?
- DI נפרוגני

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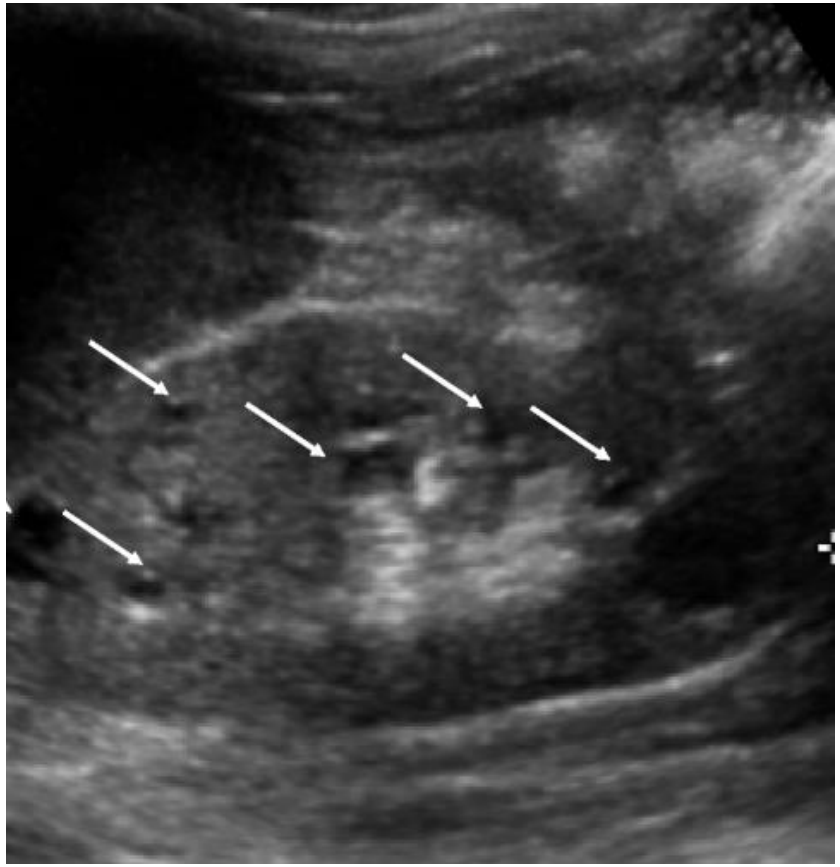
המשך הבירור



- קריאטינין בדם 0.78 עם eGFR מחושב של 60
- אנמיה נורמוציטית קלה
- 80 PTH
- קריאטינין אחרי הלידה היה תקין
- סונר כליות ודרכי שתן: כליה ימין 7.8 ס"מ כליה שמאל 7.6 ס"מ. בפרנכימה של שתי הכליות הודגמו ציסטות, הגדולה בכליה ימנית בקוטר עד כ-1.8 ס"מ ומוקדים זעירים אקוגניים – חשודים כהסתיידויות. ללא הפרדה ברורה בין קורטקס ומדולה דו"צ
- מה האבחנה?

Nephronophthisis

- Nephronophthisis (NPHP) is a monogenic autosomal recessive tubulointerstitial nephropathy / cystic kidney disease
- One of the most frequent genetic disorders causing end-stage renal disease (ESRD) in children and adolescents
- Nephronophthisis is caused by mutations in eleven different genes called nephrocystins (NPHP1-11, NPHP1L)
- The term “nephronophthisis” derives from the Greek and means “disintegration of nephrons”, which is one aspect of the histopathology.

Nephronophthisis

- The most frequent form of NPHP, called NPHP type 1, is characterizied by ESRD at a mean age of 13 years
- Symptoms are very subtle and may start as early as 6 years of age.
- They consist of polyuria, polydipsia, secondary enuresis, growth retardation and anemia.
- NPHP has a rare infantile form with age of onset of ESRD prior 4 years of age and an adolescent form with a median age of onset of ESRD of 19 years

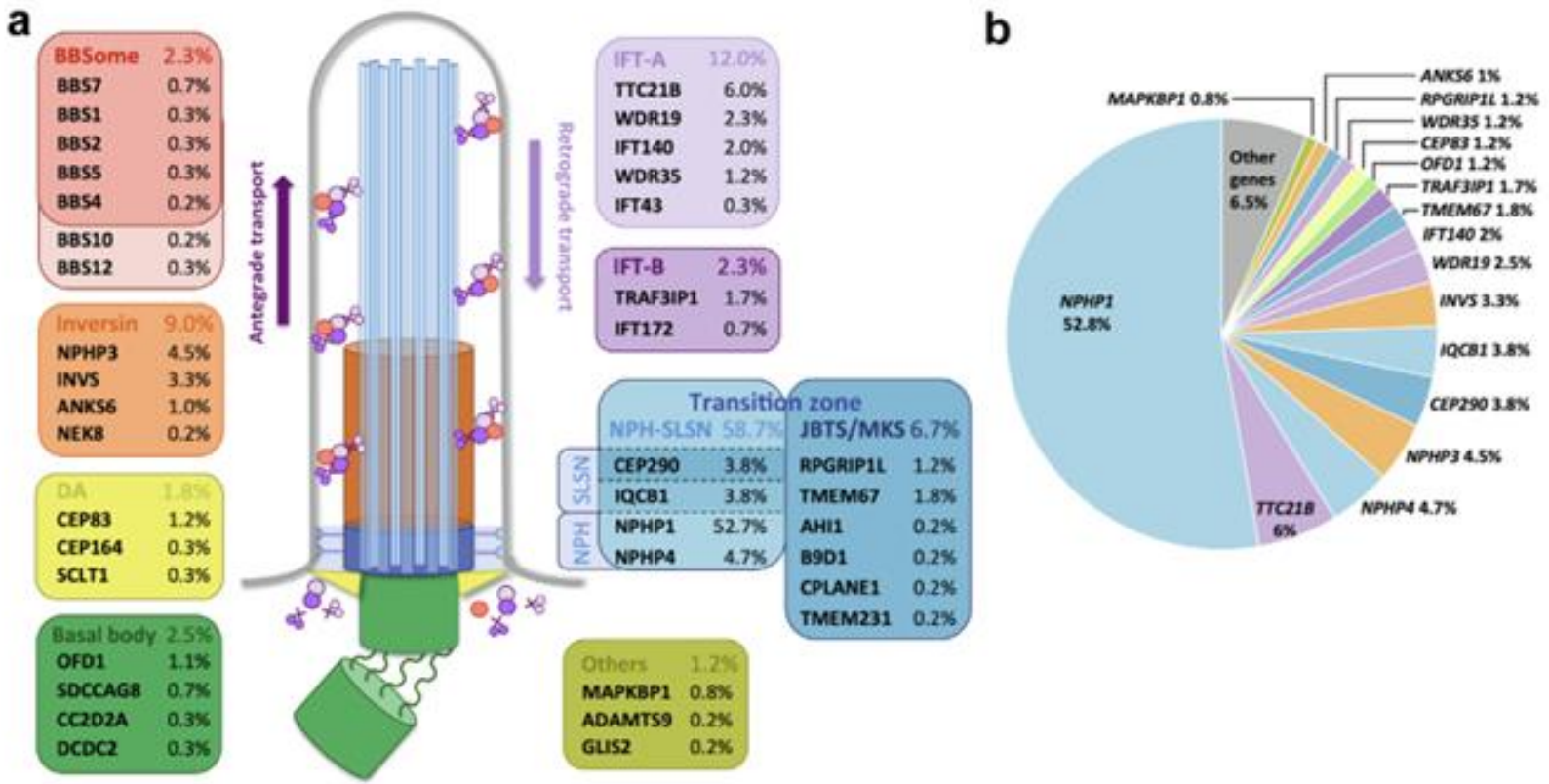


Figure 1 | (a) Composition of the primary cilium. The mother centriole with the distal appendages (DAs) connects to the cellular membrane and forms the basal body, which produces the microtubule-based ciliary axoneme. Distal, the transition zone including 2 distinct protein complexes, the nephronophthisis (NPH) and Joubert syndrome/Meckel syndrome subdomain, controls protein entry and exit and joins to the Inversin compartment. The intraflagellar transport (IFT) system carries cargo along the microtubules and interacts with the cargo adapter BBSome to mediate export of ciliary proteins. NPH genes/proteins localize to the functional and phenotypically based ciliary compartments (except MAPKBP1, ADAMTS9, and GLIS2 without ciliary localization). The portion refers to the frequencies of the causative genes/compartments analyzed in the cohort. (**b**) Relative frequencies of disease-causing genes in the cohort of 600 patients with NPH. BBS, Bardet-Biedl syndrome; SLSN, Senior-Løken syndrome.

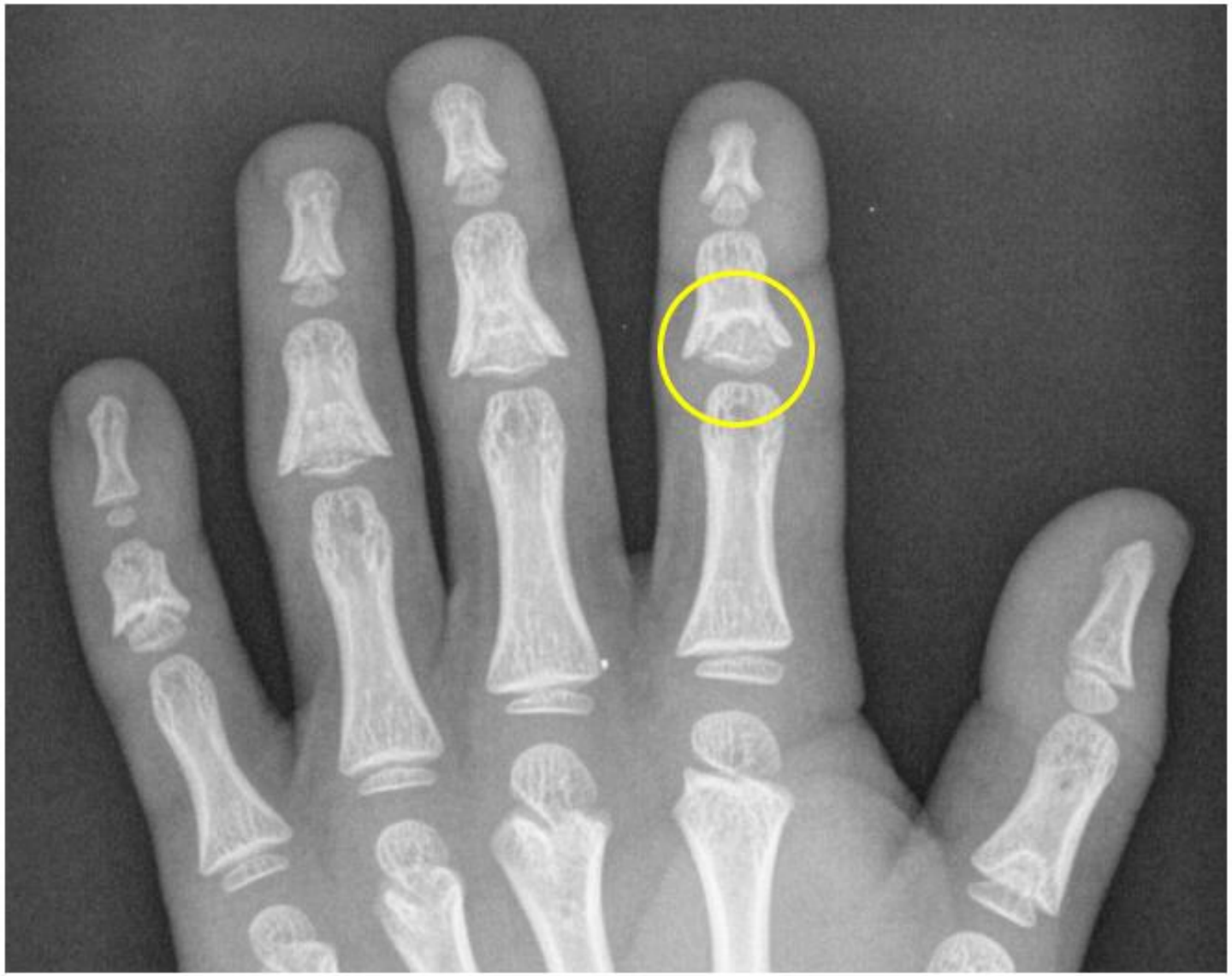
Epidemiology

- The incidence in Canada 1:50,000
- The incidence in Finland 1:61800

Extrarenal manifestations

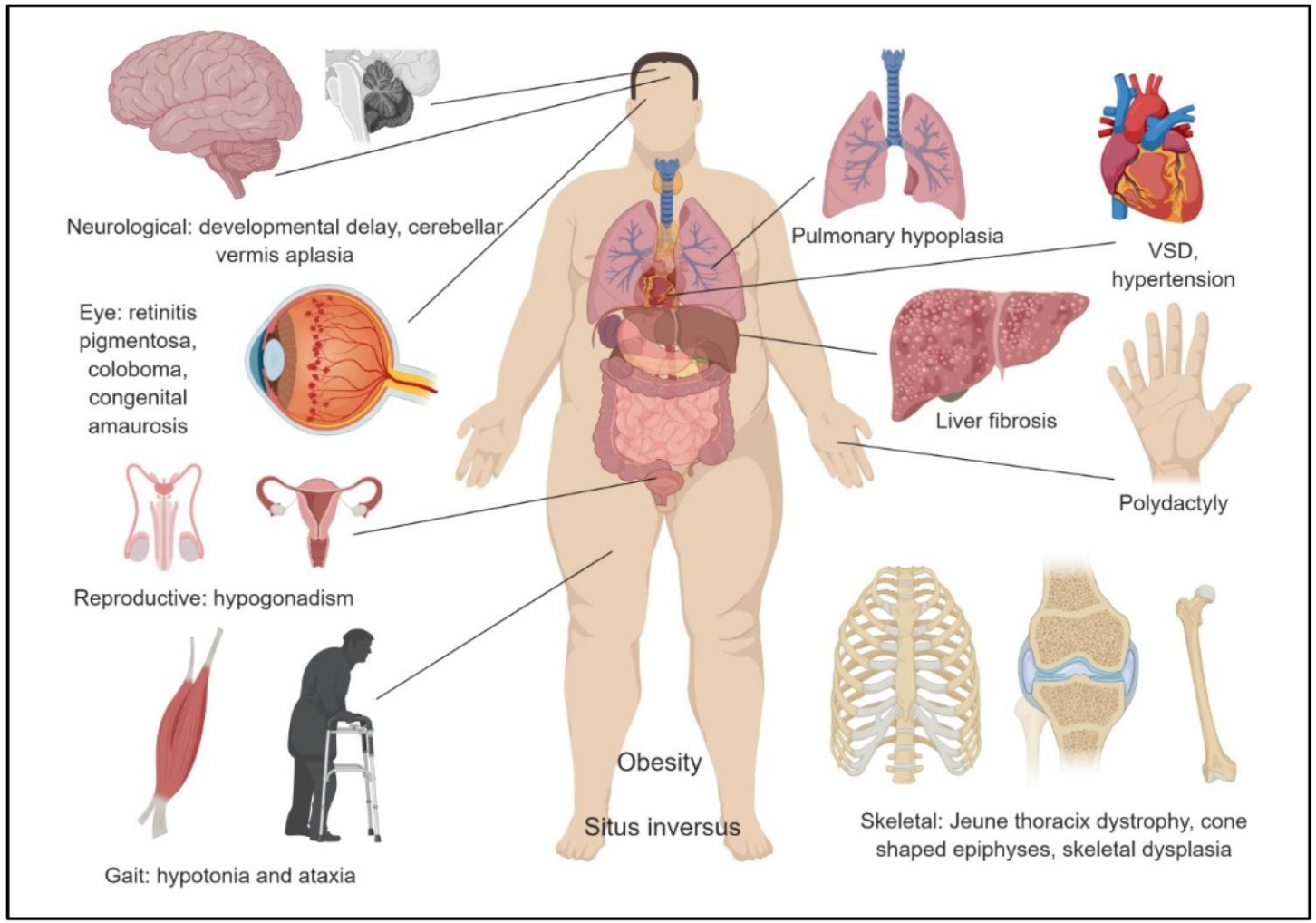
- Found in 10–15% of NPHP patients
- Retinal degeneration (Senior-Loken syndrome)
- Cerebellar vermis aplasia (Joubert syndrome)
- Liver fibrosis
- Oculomotor apraxia (Cogan syndrome)
- **Skeletal defects** – including shortening of the limbs and ribs, scoliosis, polydactyly, brachydactyly, craniosynostosis, and cone-shaped epiphyses of the phalanges.

Cone-shaped epiphyses in Mainzer-Saldino syndrome



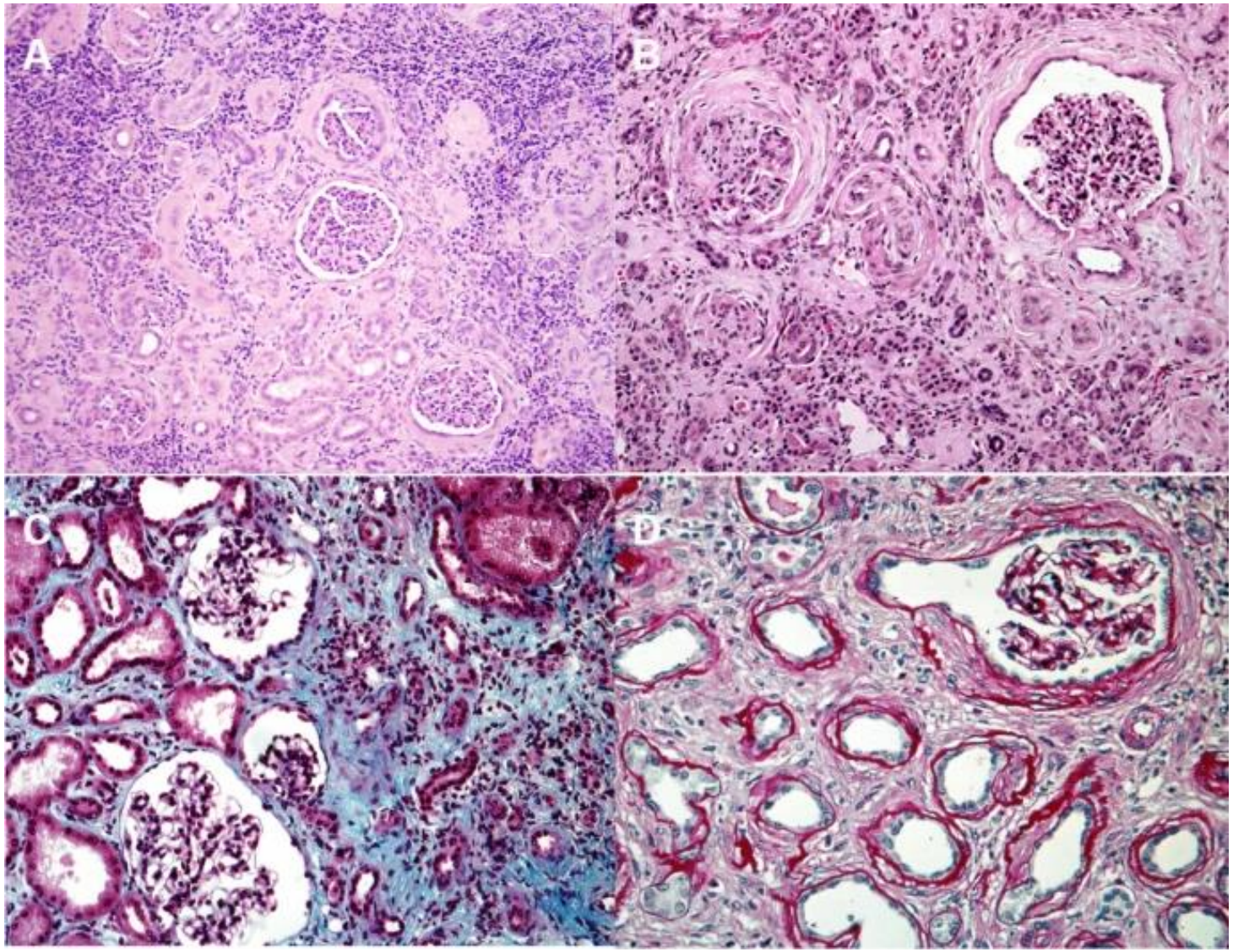
Extrarenal manifestations associated with NPHP and resulting syndromes associated with *NPHP* mutations.

Ophthalmologic disorder	Syndrome
Retinitis pigmentosa	Senior-Loken syndrome (SLSN)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Alstrom (RP, obesity, DM type 2, hearing impairment)
	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome/Joubert syndrome related disorders
Coloboma	Joubert syndrome/Joubert syndrome related disorders
Skeletal disorder	
Short ribs	Jeune syndrome/asphyxiating thoracic dystrophy
Cone-shaped epiphysis	Mainzer-Saldino syndrome
Postaxial polydactyly	Joubert syndrome/Joubert syndrome related disorders
	Bardet-Biedl syndrome(NPH P, RP, obesity, deafness)
	Ellis van Creveld
Skeletal dysplasia	Sensenbrenner syndrome / cranioectodermal dysplasia
	Ellis van Creveld
Neurological disorder	
Encephalocele	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
Vermis aplasia	Joubert syndrome/Joubert syndrome related disorders
Hypopituitarism	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Hepatic disorder	
Liver fibrosis	Boichis syndrome
	Meckel-Gruber syndrome (occipital encephaolocele, NPHP)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Joubert syndrome/Joubert syndrome related disorders
Others	



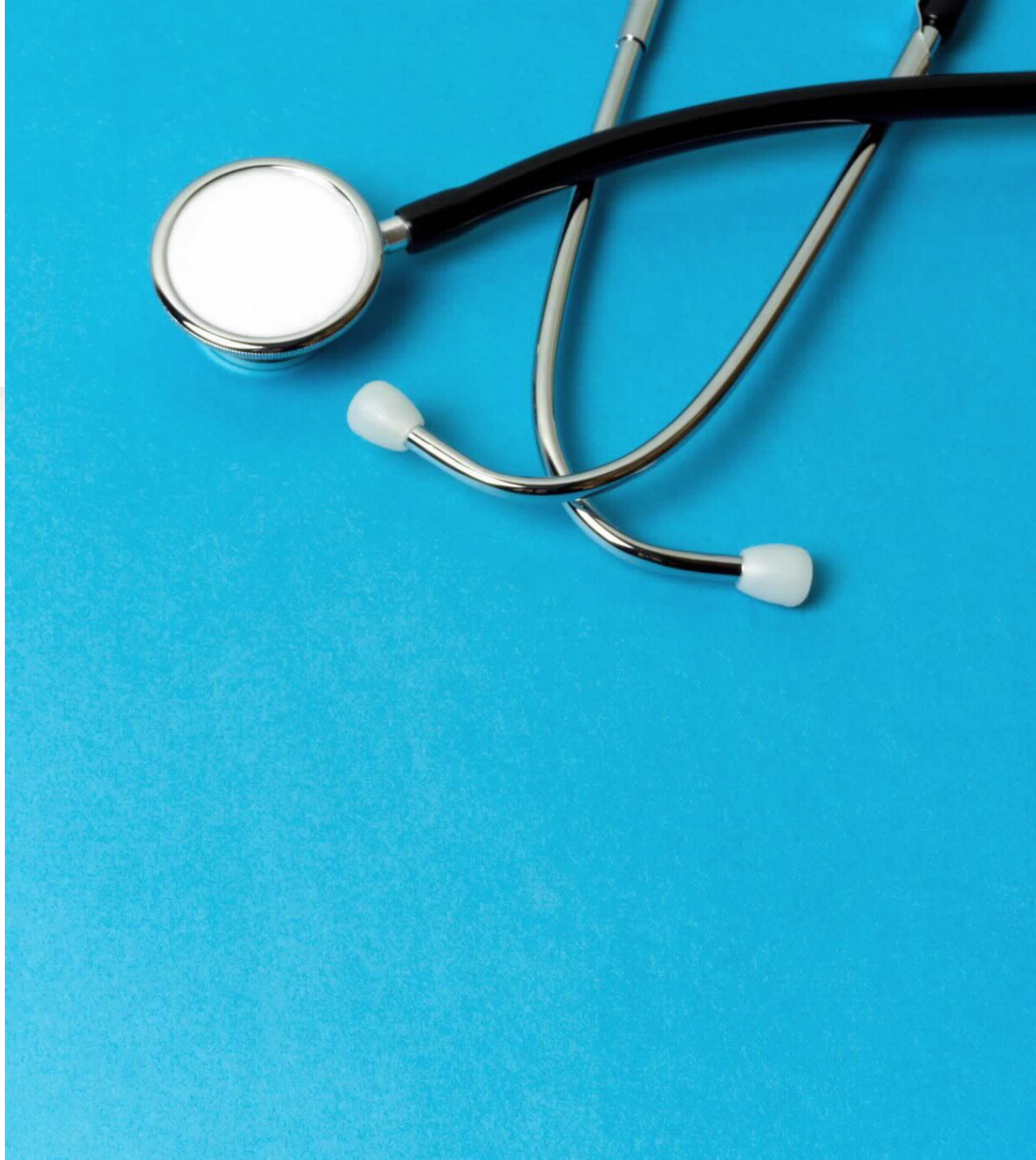
Histology

Tubular atrophy with thickened or thinned tubular basement membrane, cysts at the corticomedullary border and diffuse interstitial fibrosis



Treatment

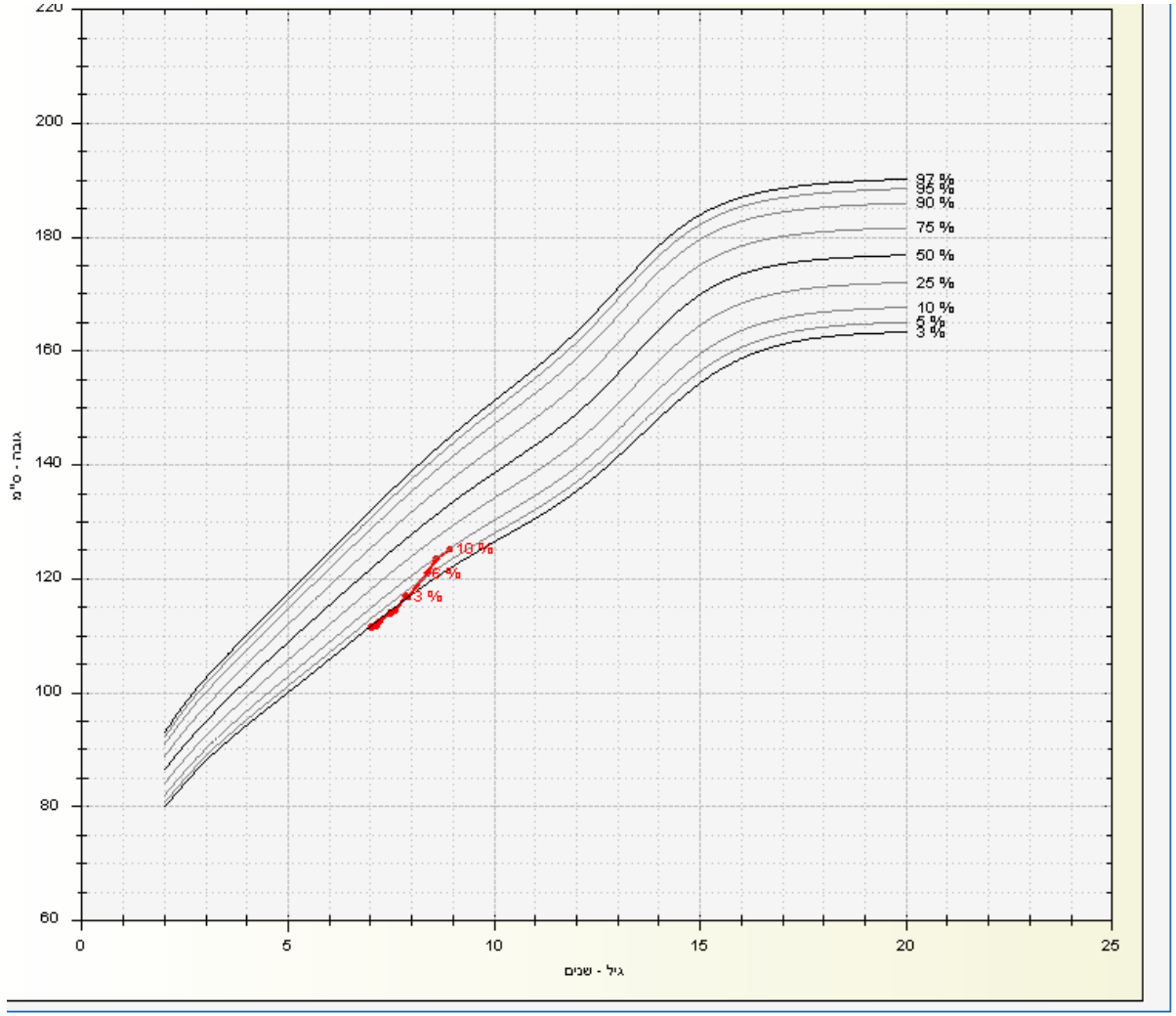
- Mostly supportive with therapy of anemia, secondary hyperparathyroidism, metabolic bone disease, and blood pressure.
- Kidney replacement therapy once fluid overload and uremia become more pronounced.
- Currently, the best therapeutic option for NPHP patients is a kidney transplant as NPHP does not recur in a new organ.



תוצאות בירור גנטי והמשך תיאור המקרה:

- CMA הודגם חסר הומוזיגוטי בגודל של כ-0.5 Mb בכרומוזום 2q13
- **החסר כולל את הגן NPHP1 בשלמותו**
- התוצאות מאשרות אבחנה של נפרונופטיזיס אצל ק.מ

- כיום מ. בן 9 שנים. קריאטינין יציב, eGFR אחרון 96 PTH 60
- מקבל טיפול בהורמון גדילה, ברזל, ויטמין D


220
200
180
160
140
120
100
80
60
0
5
10
15
20
25
גובה - ס"מ
גיל - שנים
97 %
95 %
90 %
75 %
50 %
25 %
10 %
5 %
3 %
10 %
5 %
3 %

NPHP1 gene-associated nephronophthisis is associated with an occult retinopathy.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

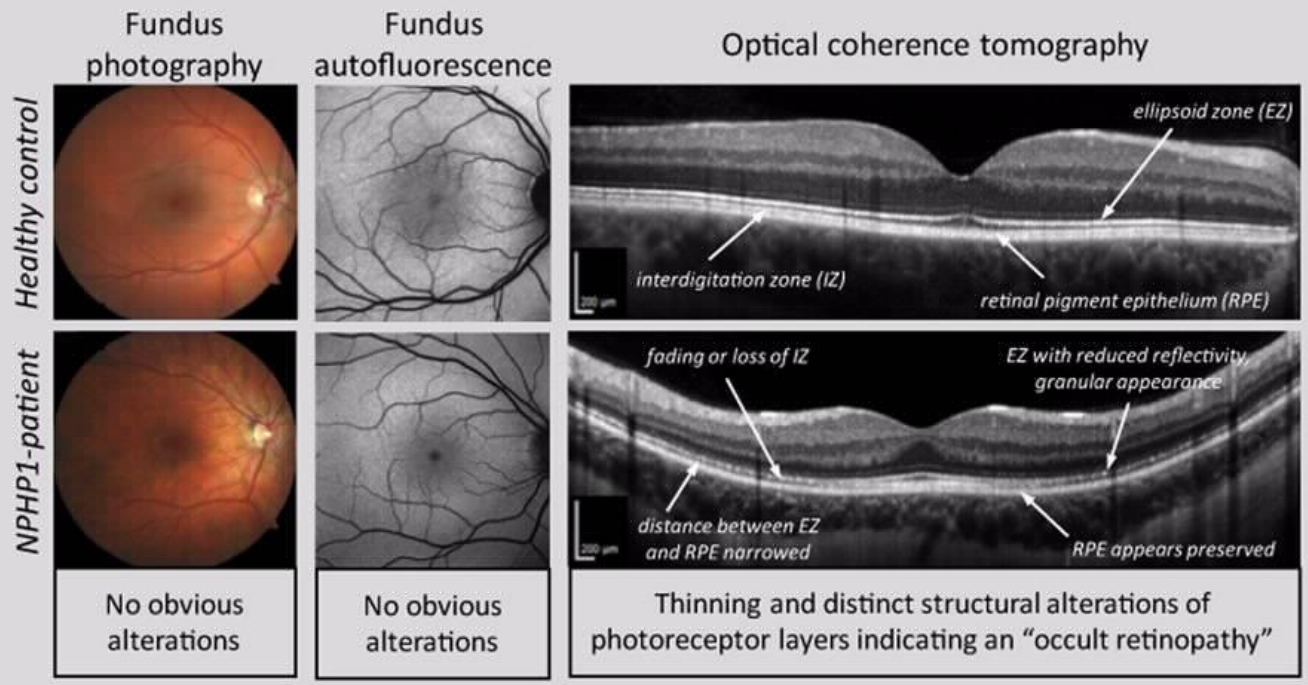
NEOCYST

16 patients with *NPHP1*-associated nephronophthisis

- Diverse age at diagnosis
- Variable renal impairment (normal renal function to ESRD)
- Varying extrarenal disease

Deep phenotyping of ocular disease

- Clinical symptoms
- Visual function
- Retinal imaging
- Genetics



A mild retinal phenotype is seen in patients with *NPHP1*-associated nephronophthisis. Genetic modifiers and ageing might lead to more advanced retinal degeneration.

Birtel et al, 2021

CONCLUSION: Diagnostic awareness about this distinct retinal phenotype may have implications for differential diagnosis of nephronophthisis and for individual prognosis of visual function.

Nephrogenic DI with growth failure? At age 6?

- אני כאנדוקרינולוגית הייתי מאוד מופתעת שילד עם כאבי ראש, הפרעה בגדילה, DI בגיל 6 שנים הוא לא DI מרכזי על רקע בעיה היפופיזרית!
- הרי ברור שהכל הורמונים!

Long-term growth of children with nephrogenic DI

Table 1 Basic anthropometric information of the sample

Family	Case	Age at diagnosis years	Length of follow-up years	Initial weight SD	Final weight SD	Height at diagnosis SD	Final height SD	BMI at diagnosis SD	Final BMI, SD
A	1	1.72	8.56	−3.27	−2.24	−2.0	−2.18	−2.58	−0.94
B	2	0.45	11.33	−3.27	−1.44	−2.8	−1.20	−2.30	−0.50
C	3	1.98	16.20	−3.92	−1.24	−3.42	−1.0	−2.57	−0.60
D	4	5.45	14.32	−2.40	−0.93	−2.70	−1.70	−0.93	0.22
E	5	1.02	14.83	−3.56	0.56	−2.60	−1.23	−2.10	2.70
E	6	0.16	14.16	−0.38	−1.24	−0.65	−1.50	−0.40	−0.10
F	7	0.69	11.63	−3.25	−1.65	−3.40	−0.90	−2.30	−1.10
F	8	0.34	13.83	−1.99	−0.13	−0.42	0.50	−2.78	−0.14
G	9	0.77	10.81	−4.11	−2.97	−2.85	−3.69	−2.79	−0.75
H	10	6.0	14.03	−1.90	1.69	–	0.10	–	2.20
I	11	3.33	6.27	−2.58	−0.62	−3.31	−1.25	−0.37	0.67
I	12	6.29	5.32	−0.16	1.03	−1.03	−0.35	1.34	2.92
J	13	1.57	9.79	−4.21	−3.03	−3.71	−2.47	−2.20	−1.50
K	14	1.64	3.39	−2.73	−1.48	−1.78	−1.39	−1.61	−0.30

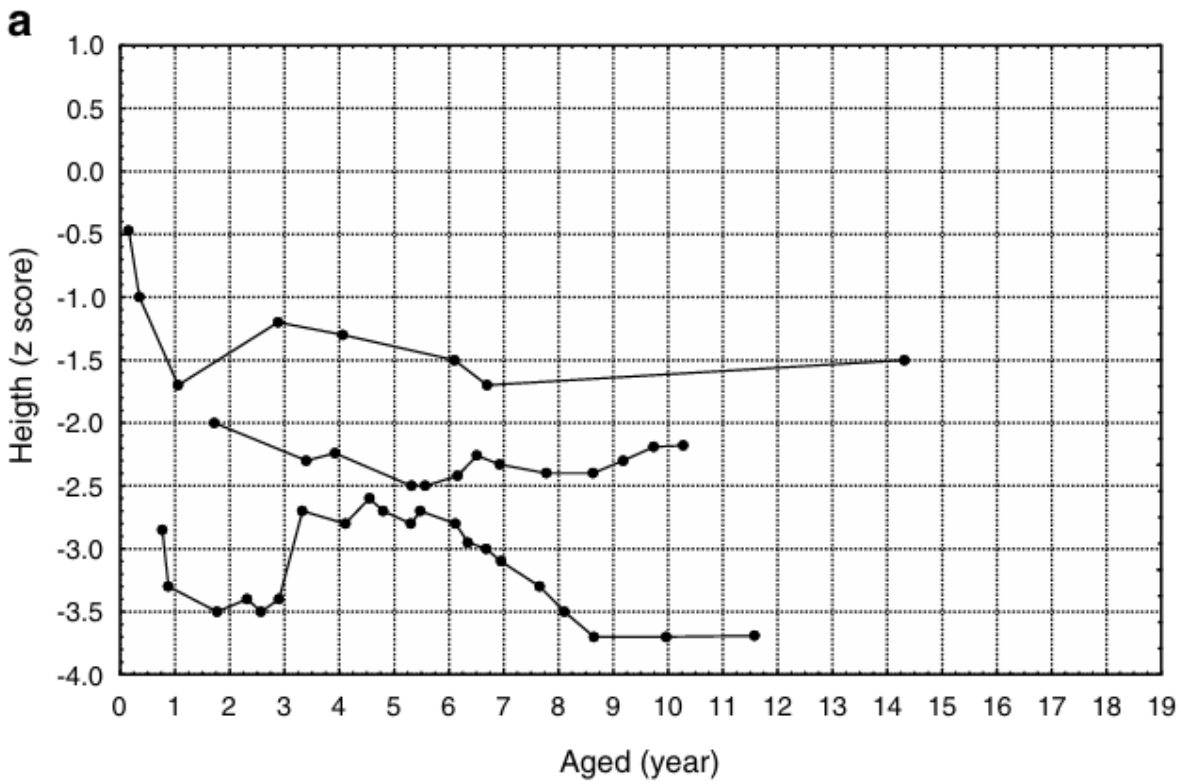
SD standard deviation, *BMI* body mass index
*Letters in the first column represent the family of each patient

Lejarraga et al. *Pediatr Nephrol . 2008 Nov;23(11):2007-12. doi: 10.1007/s00467-008-0844-8. Epub 2008 Jun 27.*

Long-term growth of children with nephrogenic DI

Lejarraga et al. *Pediatr Nephrol . 2008 Nov;23(11):2007-12. doi: 10.1007/s00467-008-0844-8. Epub 2008 Jun 27.*

Fig. 2 **a** Height of three children with no adherence to treatment. **b** Growth of nine children with adherence to treatment



Take home message

- Polydipsia and polyuria, **associated with growth deceleration and headache** does not always indicate central disease!
- Secondary nephrogenic DI can present during childhood, **symptoms can be identical to central disease**
- **Juvenile Nephronophthisis** – may present in mid-childhood with nephrogenic DI, anemia, growth deceleration and headaches