A RARE CAUSE OF FANCONI SYNDROME- DENT'S DISEASE

DR.G.KALAIVANI
Dept. of Pediatric Nephrology
Mehta Children's Hospital

History

- 2 years 10 months male child born to consanguineous parents (9.06.2012)
- Birth Wt: 2.8kg
- Presented elsewhere at 15 months of age with delayed milestones, generalized bony deformities and found to have glycosuria

Contd…

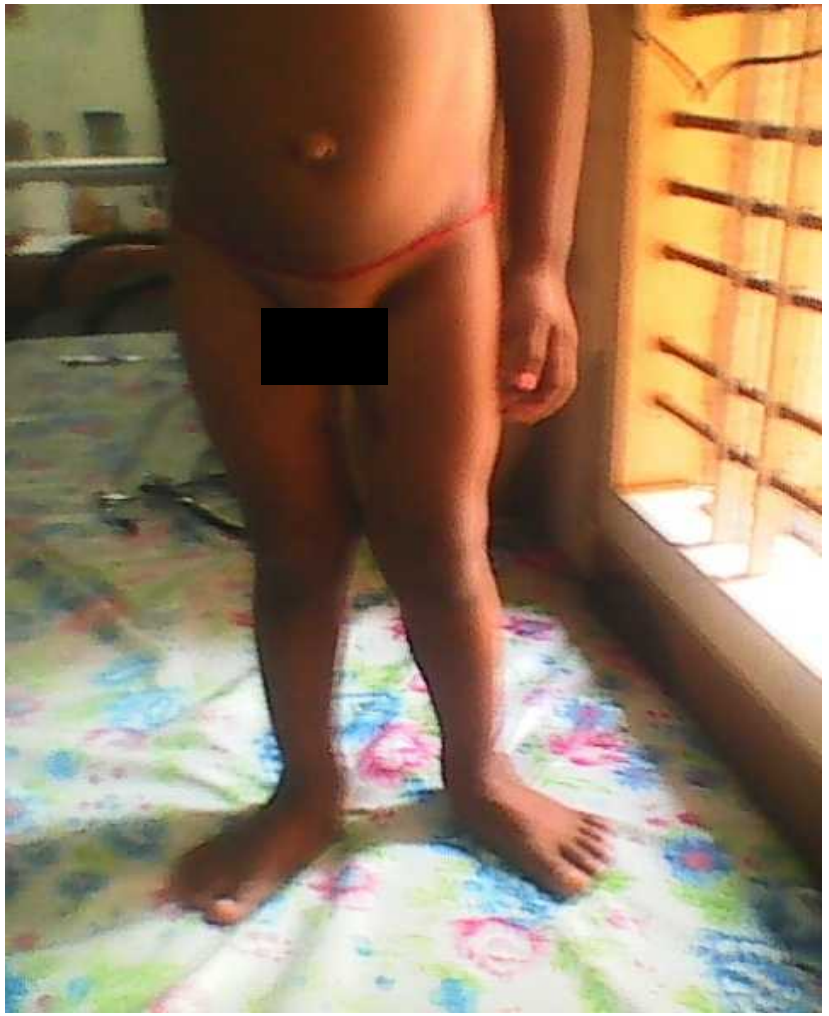
- Diagnosed as Vitamin D deficiency rickets
- Treated outside with Vit.D and Ca supplements for 6 months
- In view of persistent bony deformities child was referred here.

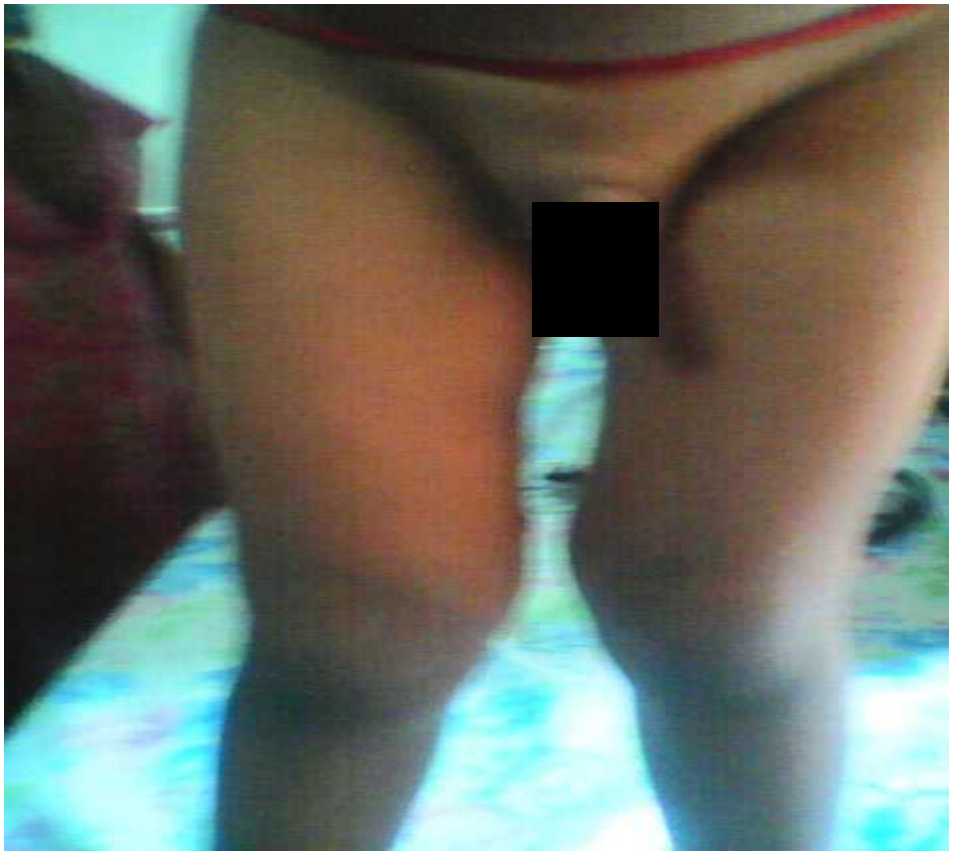
ANTHROPOMETRY

- Height – 76 cm (<10th percentile)
- Weight – 9.5 kg (<10th percentile)
- Head circumference – 46 cm (<50th)

Examination

- Alert
- No edema
- Normotensive
- Genuvalgum
- Widening of wrist
- Dentition normal
- Eyes normal
- Systems normal





Investigations

Date	S.Cr	Na	K	HCO3	Cl	Alb	Ca	P	SAP	Vit.D
3.9.13							8.6	2.9	1372	5.9
16.5.14	0.3	139	3.4	17	108		9.0	2.7	921	

PTH :71.6 (16.5.14)
RBS : 85

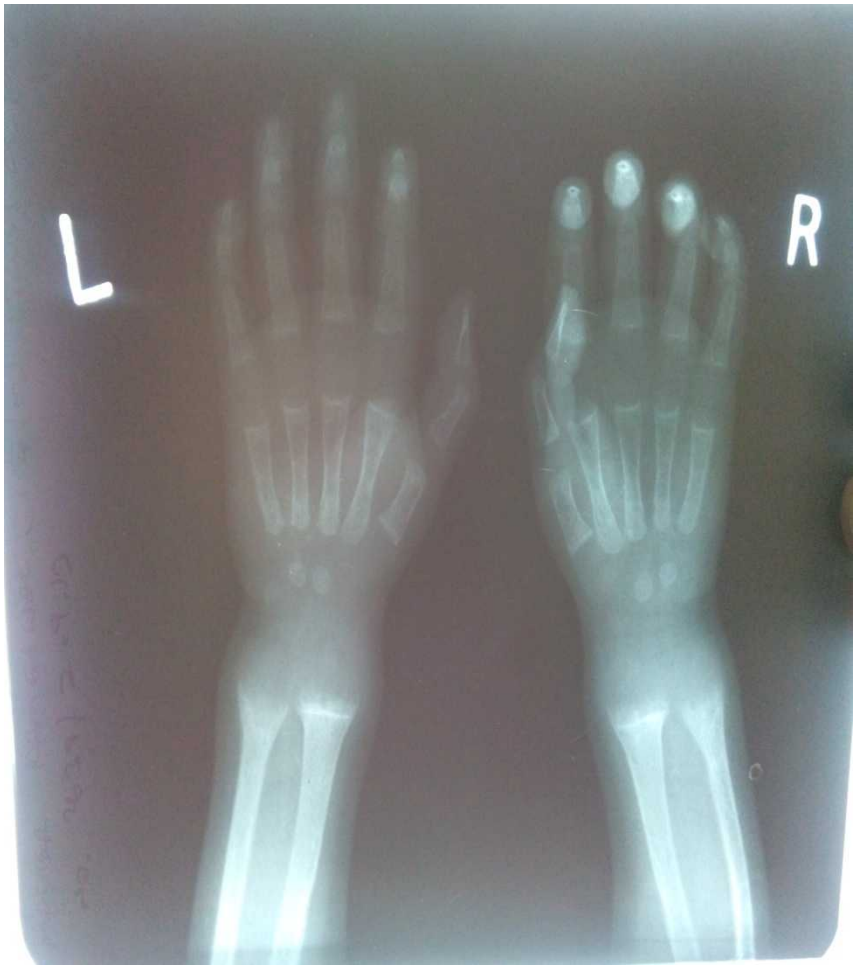
Urine analysis

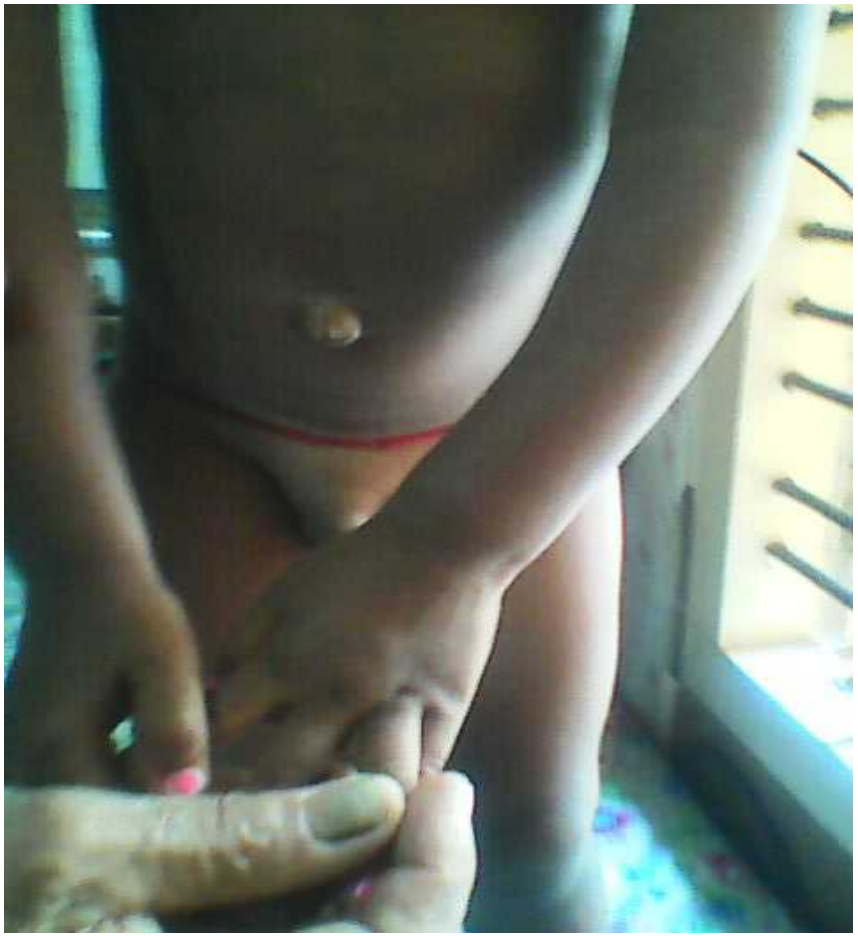
DATES	2.7.13	17.5.14	4.9.14	8.3.15
SP GR	1.010	-	-	-
PH	7.0	7.2	7.0	7.0
Proteins	++	+++	++	++
Sugar	+++	++	++	++++
PC	10	OCC	3	OCC
RBC	2	6-8	4	Nil
Ca/Cr	1.2	1.50		0.36

USG abdomen (3.9.13): RK- 6.1cms, LK-6.0cms

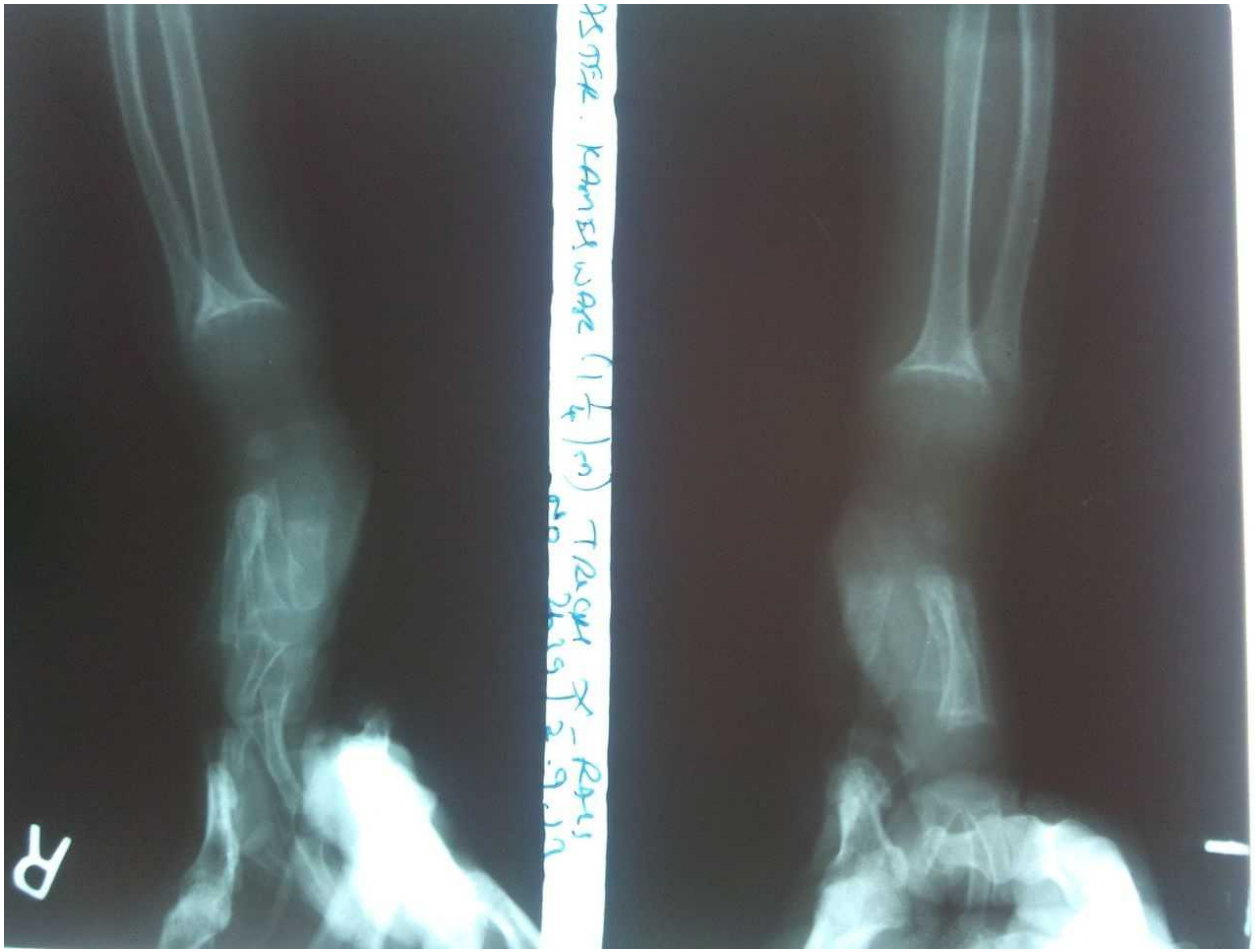
Increased cortical echoes

X-ray wrist (2.9.13)– features of rickets





X- Ray Ankles

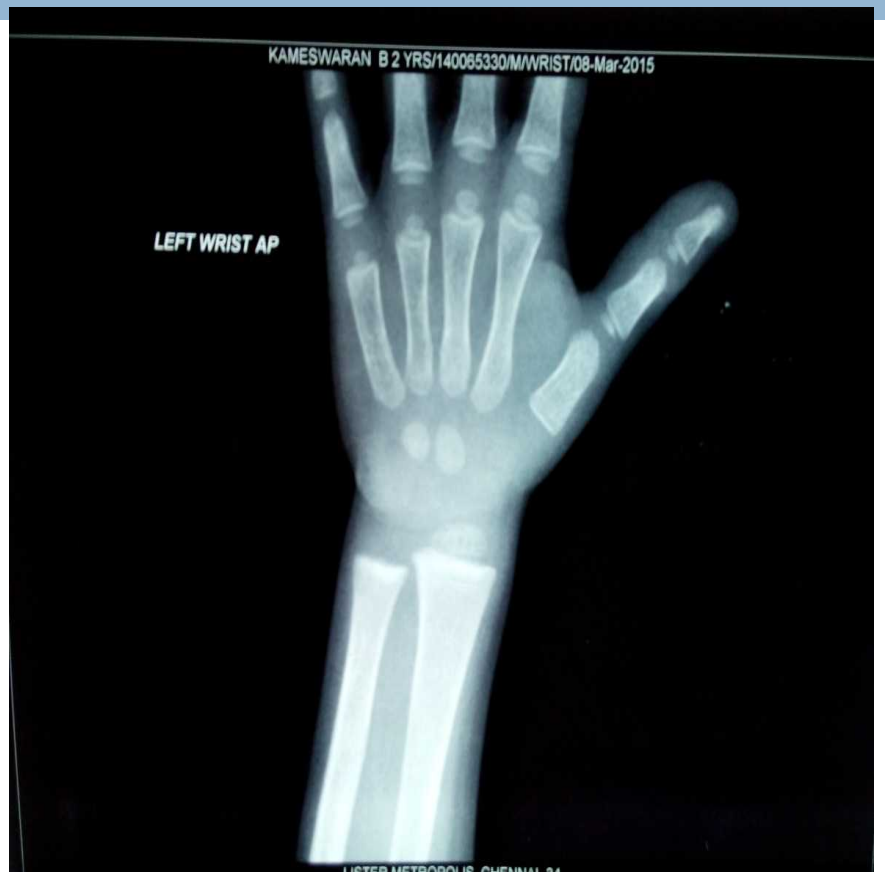


SUMMARY OF FINDINGS

- Hypocalcemia
- Hypophosphatemia
- Increased alkaline phosphatase
- Metabolic acidosis
- Vitamin D deficiency
- Hypercalciuria
- Glycosuria
- Proteinuria
- Increased PTH
- X-ray features of Rickets
- Increased cortical echoes by USG

Treatment

- Vit D supplementation
- Alkali therapy
- Phosphorus



After Treatment

Date	S.Cr	Na	K	HCO3	Cl	Alb	Ca	P	SAP	Vit.D
3.9.13	0.8						8.6	2.9	1372	5.9
16.5.14	0.3	139	3.4	17	108		9.0	2.7	921	
4.9.14		138	4.1	22				3.2	618	17.7
27.9.14		139	4.1	20	102	3.8	8.6	3.8	560	
8.3.15	0.4	137	4.3	21	108	4.0	9.7	4.7	584	29.40

After Treatment

Date	S.Cr	Na	K	HCO3	Cl	Alb	Ca	P	SAP	Vit.D
3.9.13	0.8						8.6	2.9	1372	5.9
16.5.14	0.3	139	3.4	17	108		9.0	2.7	921	
4.9.14		138	4.1	22				3.2	618	17.7
27.9.14		139	4.1	20	102	3.8	8.6	3.8	560	
8.3.15	0.4	137	4.3	21	108	4.0	9.7	4.7	584	29.40

Beta-2-microglobulin >20,000 (670-2143ng/ml)

Discussion

Introduction

- X-linked recessive renal fanconi syndrome
- Synonyms:
  - Dent disease I
  - X-LR hypercalciuric hypophosphataemic rickets
  - LMWP with hypercalciuria and nephrocalcinosis
  - Dent disease II
- Caused by mutation in CLCN5 gene which encodes the electrogenic chloride / proton exchanger located in chromosome Xp11-22

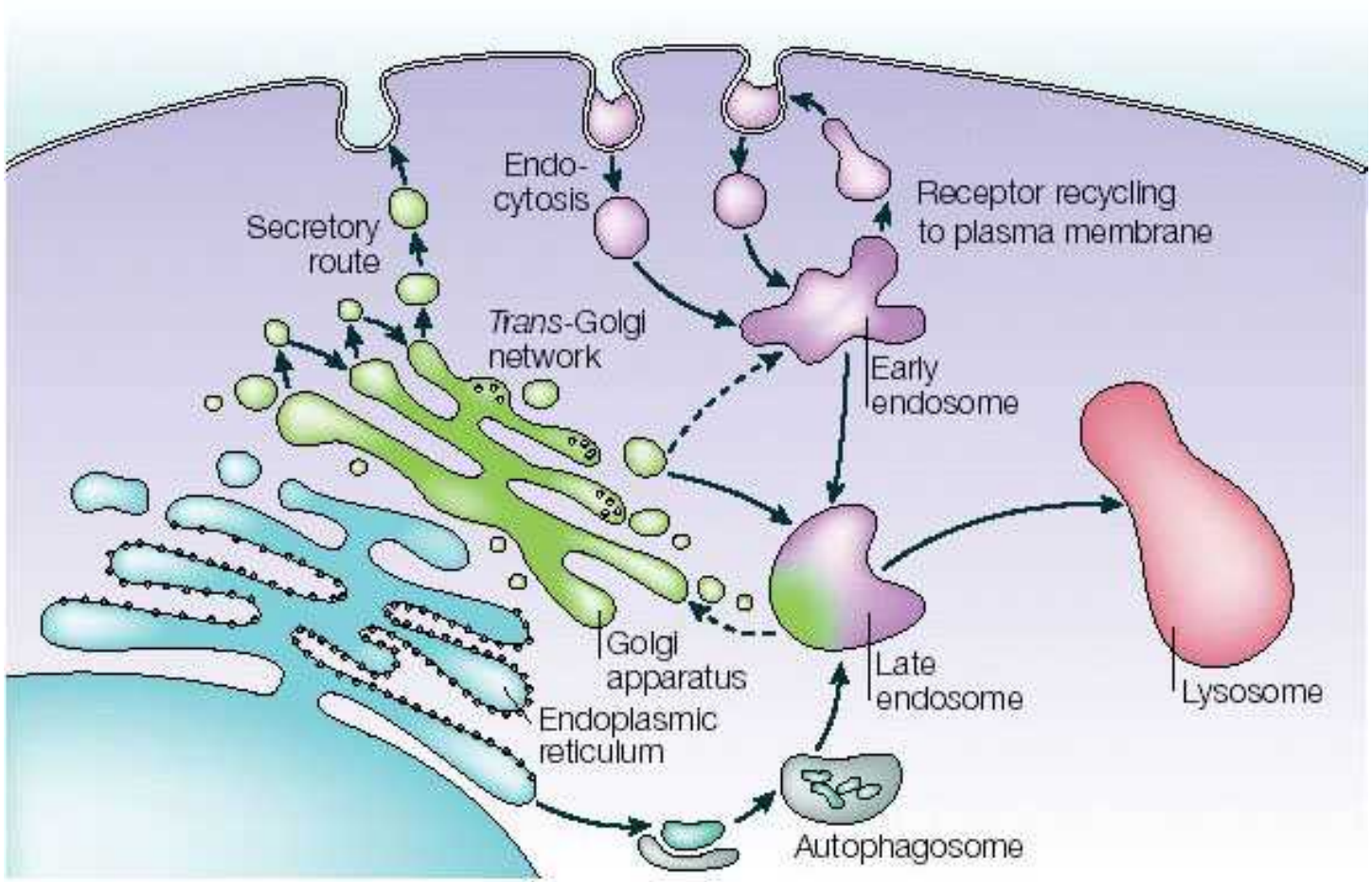
Contd…

- Disruption or mutations in CIC-5 impairs or alters membrane trafficking via receptor mediated endocytic pathway that involves megalin and cubulin and significantly reduce or eliminate the chloride transport.

Pathophysiology

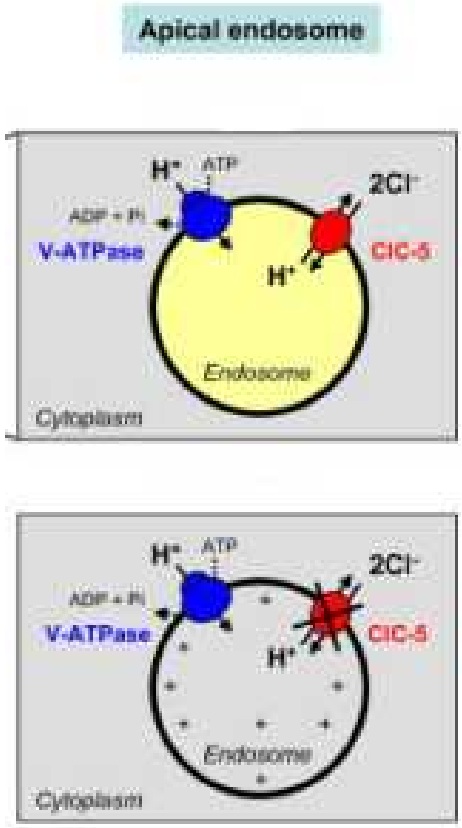
- Selective urinary loss of LMW proteins in Dent's indicates that glomerular filter is undamaged and only problem in proximal tubular endocytosis
- CIC-5 protein seems to be critical for acidification of the endosomes that participate in solute reabsorption and membrane recycling in PTC

Contd…

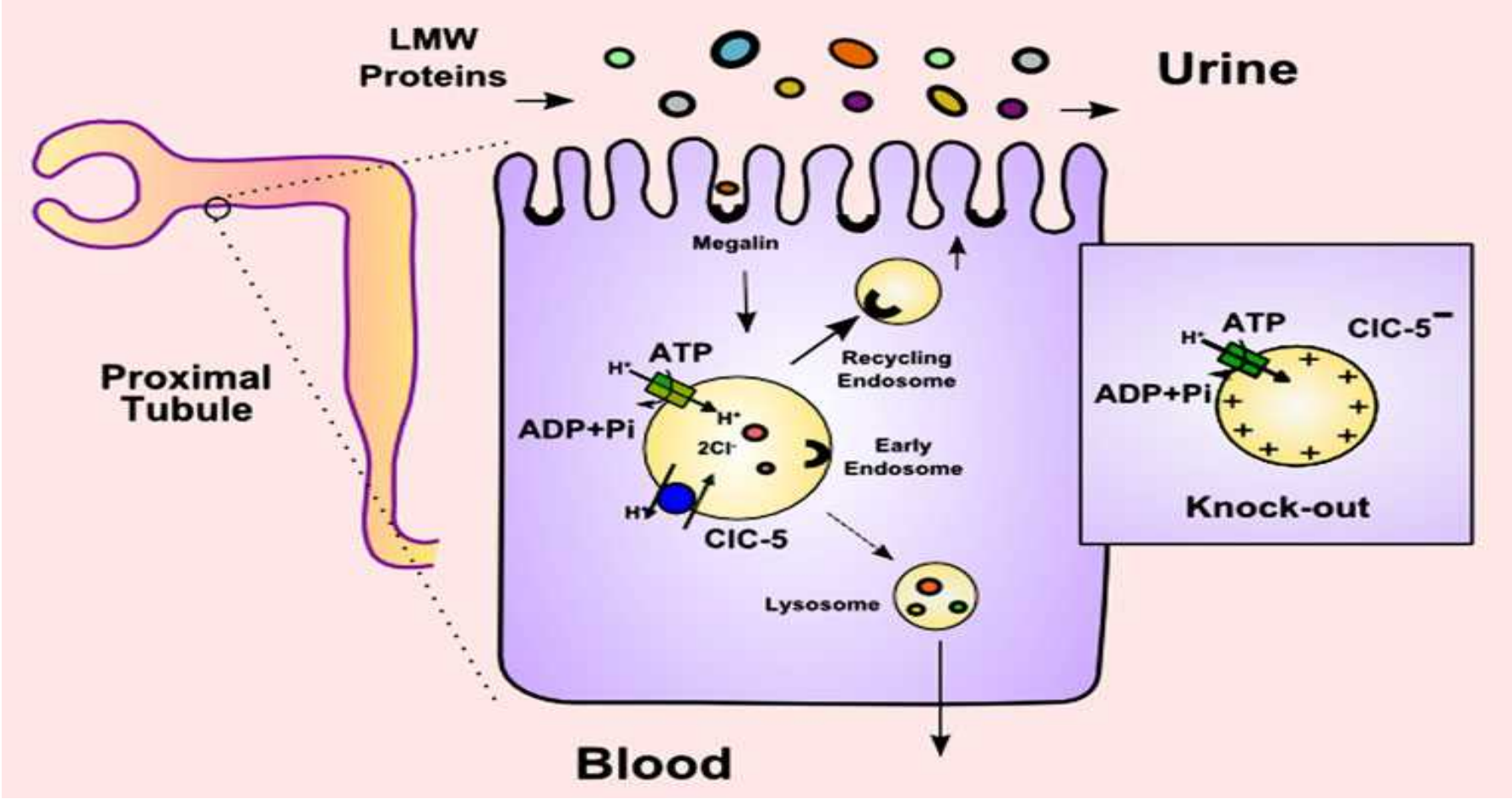


Role of CLC-5

- CLC-5 is a $2Cl^-/H$ exchanger rather than a chloride channel which will facilitate acidification



PATHOPHYSIOLOGY



Contd…

Acidification of the endosomes results

↓

Dissociation of receptor-ligand complexes

↓

Megalin and Cubilin being recycled in apical membrane

↙ ↘

Ligand goes to lysosomes

↓

Degradation

Impaired acidification

↓

Mutation of ClC-5 ability

Cl

Clinical phenotype

- Dent's 1- CLC 5 gene mutation- 60%
- Dent's 2- OCRL1 gene mutation 15%
- Males are affected and females have minor phenotype
- Have variable manifestation of proximal tubule dysfunction (partial Fanconi)
- 10% of patients denova mutation

Clinical and biochemical characteristics of Dent's Disease patients with CLCN5 mutation

Clinical/biochemical characteristics	Consistency of presence in Dent's disease patients with mutations in CLCN5(%)
LMWP	100
Aminoaciduria	44
Glycosuria	19
Hypophosphatemia	32
Hypercalciuria	89
Nephrocalcinosis	76
Nephrolithiasis	41
Renal failure	42
Rickets/osteomalacia	33
Hematuria	94
Concentrating defect	82

PTH

Regulates Na coupled phosphate cotransporter (NaPi-II a)

Uptake of phosphate in PT

PTH not reabsorbed. Accumulates in distal part of PT → Increase PTH in urine

Stimulation of apical PTH receptors in late proximal tubular cells

Internalization &degradation of NaPi-IIa from the membrane

Phosphaturia

PTH is filtered through glomerulus and removed from urine by megalin dependent endocytosis

Contd…

- Urinary loss of vitamin D binding protein leads to bone defects.
- Nephrolithiasis:
  - i) Due to deceased renal function
  - ii) Impaired handling of Ca phosphate and Ca oxalate crystals in CD

Contd….

- Glucosuria and aminoaciduria : failure to recycle their transporters to apical membrane
- ESRD : It has been found potentially bioactive hormones PTH, insulin, IG-F in tubular fluid contributes to hypercalciuria and interstitial fibrosis and progressive renal failure.

Diagnosis

- Dent's Disease is probably under-diagnosed
- Presence of LMWP and atleast one of the variable characteristics or a positive family history
- Clinical diagnosis is supported by history of X-linked inheritance of renal Fanconi syndrome

Diagnostic criteria

- Presence of all three of the following criteria:
  - LMWP –increased ß2 microglobulin (1 gm/day), Clara cell protein, RBP by atleast 5 fold increase
  - Hypercalciuria >4mg/kg or Urine Ca/Cr>0.25mg/mg
  - One of the following:

    Nephrocalcinosis

    Kidney stones

    Hematuria

    Hypophosphatemia

    Renal insufficiency

Treatment

- Supportives – generous fluid intake
- Vit D – indicated only with clinical bone disease
- Phosphate supplements
- Thiazide
- Citrate supplementation
- Genetic counseling

TAKE HOME MESSAGE

- Male Child
- Consanguinity
- Early onset rickets
- Persistent Hypercalciuria
- Early biochemical response
- Parenchymal changes
- 2 microglobulin


THANKS