Primary Hyperoxaluria

Prof: Naziha Rhuma
Tripoli Children Hospital
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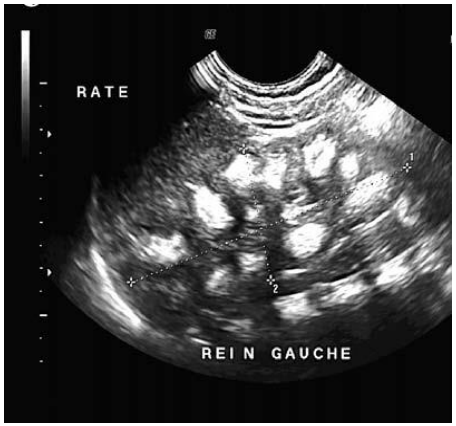
Content:

- Introduction
- Oxalate metabolism
- Types of PH
- Epidemiology
- Diagnosis
- Management
- Pattern of Primary Hyperoxaluria Type I in Libyan Children at TCH (1998-2018)

Introduction:



- **Primary Hyperoxaluria (PH) are a group of autosomal recessive disorders involving the over production of oxalate.**
- **PH is divided into three types, (PH1), (PH2), and (PH3). Primary hyperoxaluria type 1 (PH 1) is the most common and severe form especially when it occurs in infancy.**
- **PH 1 is due to deficiency of alanine glyoxylate aminotransferase (AGT) which is a hepatic peroxisomal enzyme, leading to excessive oxalate production.**

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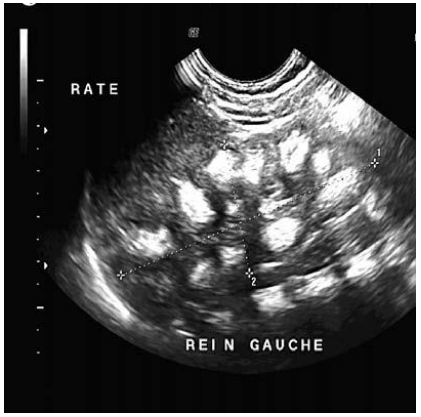

- The high amounts of oxalates exceed the renal filtration threshold, rendering high amounts in the body, which form calcium oxalates, resulting in crystalluria, nephrocalcinosis, and renal stone formation and significant morbidity and mortality.

- Family screening is important to identify cases who may possible benefit from early initiation of treatment.

- The incidence and severity of PH1 vary in different geographic regions and are much more prevalent in Mediterranean country.

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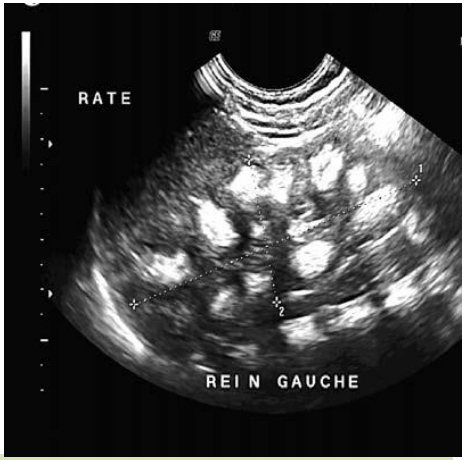


- 20- 50% of patients have advanced Chronic Kidney disease (CKD) or even End Stage Renal Disease (ESRD) at the time of diagnosis.
- Mutations in the alanine glyoxylate aminotransferase (AGXT) are the only gene known to encode in PH1.
- The c.731T> C (p.lle 244 thr) mutation is especially common in North Africa and Spain.

OXALATE

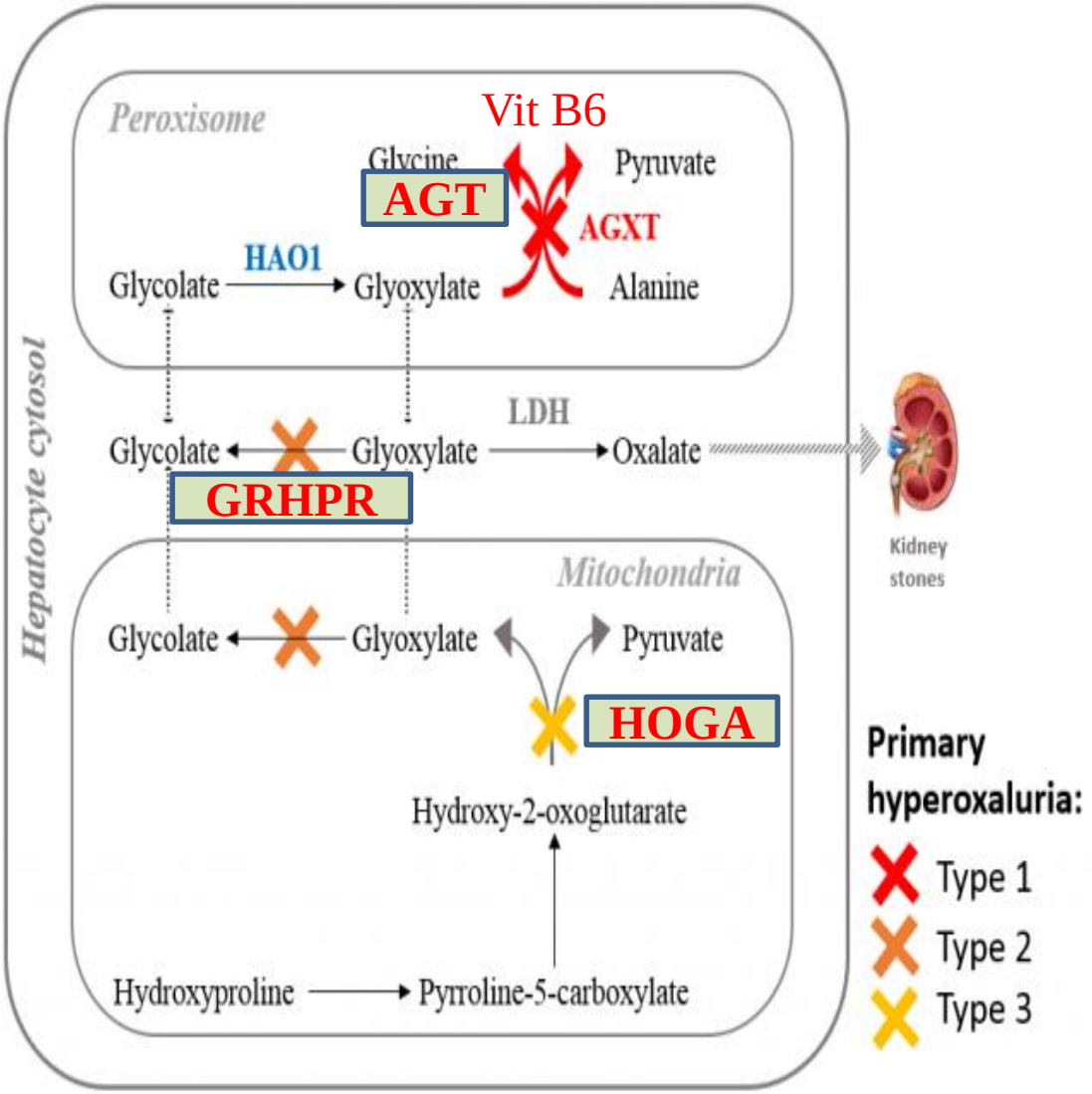
Dicarboxylic acid highly insoluble end product of metabolism in human

- **It excreted in kidney in form of Ca OX.**
- **Had tendency of crystallization in renal tubule.**
- **Leading to CKD and ESRD (obstruction, toxicity and infection).**
- **When GFR 30-45ml/min/1.73m2 kidneys is unable to excrete OX.**
- **At this point serum OX is increased.**
- **Leading to Oxalosis (skeleton).**

Glyoxylate metabolism in Normal hepatocyte

Enzyme deficiency in primary hyperoxaluria:

- Type 1 – Alanine:glycine aminotransferase (AGXT)
- Type 2 – Glyoxylate reductase/ hydroxypyruvate reductase (GR)
- Type 3 – Hydroxy-2-oxoglutarate aldolase (HOGA)



- HAO1 – hydroxyacid oxidase 1
- LDH – lactate dehydrogenase
- Passive transport

Primary hyperoxaluria:

- Type 1
- Type 2
- Type 3

Types

Primary hyperoxaluria

PH1

AGXT
Genetic mutation

AGXT
Enzyme deficiency

PH2

GRHPR
Genetic mutation

GR/HPR
Enzyme deficiency

PH3

HOGA1
Genetic mutation

HOGA1
Enzyme deficiency

Secondary hyperoxaluria

Due to excessive dietary intake of oxalate, oxalate poisoning, bowel obstruction and Ca sequestration in the gut.

Epidemiology of PH1

- A prevalence of PH1 is 1-3 / million population and incidence of 0.12-0.15 per million population. (European surveys)
- It accounted (10%) of ESRD in Kuwait, 13% in Tunisia compared 0.5-2% in Europe, North America and Japan.
- In Libya accounted 10% of cases with ESRD (2022).
- High prevalence is found in Mediterranean consanguineous population.
- Worldwide study found a consanguinity rate was 76% of cases (Libya consanguinity rate is 80%).
- Median age at initial presentation is 4 to 7 years old but ranges from the early neonatal period to the sixth decade of life.

A combination of clinical, radiological, biochemical, histopathological and genetic studies.

Diagnosis of PH

- **U/S (nephrocalcinosis and urolithiasis).**
- **Stone analysis (monohydrate Ca OX (whewellite) a dumbbell shaped form.**
- **24 h urinary oxalate excretion and adjustment to body surface area is recommended.**
- **Urinary oxalate: urinary creatinine ratios can be used but age specific normal values must be known.**
- **GFR declines, need to measure plasma oxalate >80 µmol/ L.**
- **Urinary glycolate and glycerate levels should be measured.**

Definitive diagnosis of PH

- **Noninvasive, is provided by testing of AGXT, GRHPR and HOGA1 genes mutations.**
- **There are 150 known mutations for AGXT, 16 for GRHPR and 15 for HOGA1.**
- **Three most common mutations in AGXT (c.33_34insC, c.508G>A, and c.731T>C).**

Secondary Hyperoxaluria

- **The excretion of urinary oxalate is increased may be > 0.7 mmol/1.73 m^2 per 24 h.**
- **CT may also be helpful in detection of calcium oxalate deposition in various other organ systems like bowel wall, muscle and arteries.**

TREATMENT

Conservative measures

1. High fluid intake 3-4 L/d in infants and children, a gastrostomy tube.

2. Dietary interventions No role in PH.

3. Diet modification is a very important secondary hyperoxaluria.

Role of pyridoxine

1. Pyridoxine functions as a cofactor for the enzyme AGT in PH1.

2. Recommended initial dose of pyridoxine is 5-20 mg/kg.

3. Effective in only 30% of the patients.
4. Certain genotypes (508G>A (Gly170Arg) and 454T>A (Phe153Ile) are known to be more responsive to pyridoxine than others.

5. Early initiation of pyridoxine treatment and compliance help to prevent renal failure in PH1.

Urinary alkalinization

1. To prevent stone formation .
2. Potassium citrate can be used at a dose of 0.10-0.15 g/kg .
3. Urinary pH must be maintained between 6.2 - 6.8.
4. In patients with renal failure, potassium salt can be replaced by sodium citrate.

Management of renal stones

1. Endoscopy is currently the procedure of choice as it allows direct visualization of the stones.

2. Extracorporeal shock waves lithotrepsy may be mistakenly used on areas of nephrocalcinosis instead of stones due to lack of direct visual assessment which is achieved with endoscopy.

3. ESWL procedure may form a nidus for calcium oxalate deposition and recurrent stone formation in patients with hyperoxaluria.

Renal replacement therapy

1. Patients reaching ESRD need RRT to ensure adequate oxalate removal.
2. Hemodialysis (HD) removes oxalate more efficiently than peritoneal dialysis (PD) and should initiated early (GFR 20-30).
3. Dialysis should be done with high flux dialyzers and maximum possible blood flow rate.
4. Oxalate rebound following hemodialysis and levels can reach 80% of the prehemodialysis levels.
5. Additional sessions per week are preferable as compared to more time per session.

Renal replacement therapy

7. Combination of HD and PD may be used to further enhance oxalate elimination.
8. The timing of HD and PD should be coordinated as PD may be more efficient in removing oxalate in the later phases of the intradialytic period when rebound is much higher than in the earlier intradialytic phase.
9. Efforts should be made to keep the oxalate level below 50 μmol/L.

Transplantation

1. Transplantation when GFR falls between 15-30 mL/min / 1.73 m^2.
2. These patients require preemptive liver, sequential liver kidney, or combined liver kidney transplantation.
3. Preemptive liver transplantation can be considered in patients who have progressive renal disease and approach a GFR of 50 mL/min / 1.73 m^2.
4. Sequential liver kidney transplantation can be performed in children who are small for a combined liver kidney transplant.
5. Combined liver kidney transplant is best suited for patients who are on chronic renal replacement therapy and not responsive to pyridoxine.

Transplantation

6. Isolated kidney transplantation may be the procedure of choice for adult patients who are sensitive to pyridoxine.
7. In PH2 Isolated kidney transplantation is the preferred treatment of choice.
8. In PH3, there are no reports of ESRD to date and as a result, no recommendations for renal transplantation have been made in this subset of PH3 patients.

Research on PH1

Original Article Saudi J Kidney Dis Transpl 2018;29(1):30-38

1- Mutational Analysis of AGXT Gene in Libyan Children with Primary Hyperoxaluria Type 1 at Tripoli Children Hospital

Naziha R. Rhuma[1], Omar A. Fituri[1], Laila T. Sabei[2]

Departments of [1]Pediatrics and [2]Community and Family Medicine, Faculty of Medicine, University of Tripoli, Tripoli, Libya

Research Article (Tripolitana Medical journal (***Received 7 May 2019 / Accepted 5th January 2020***

2- The pattern of Primary Hyperoxaluria Type I in Libyan children at Tripoli Children Hospital, (1998-2018)

Naziha Rhuma*@1*, Marya Elazibi[2],Miluda Elhamadi[3] and Marrwa Tilmon[4]

[1]Nephrology Unit at Tripoli Children Hospital, faculty of medicine, University of Tripoli ,[2]Faculty of Medicine, University of Tripoli, Tripoli, Libya,[3]Family and Community Medicine, Faculty of Medicine, University of Tripoli, Tripoli, Libya [4]Nephrology Unit at Tripoli Children Hospital.

Aims of this presentation

1. To define the clinical and epidemiological patterns of PH1 in Libyan children at Tripoli Children Hospital.

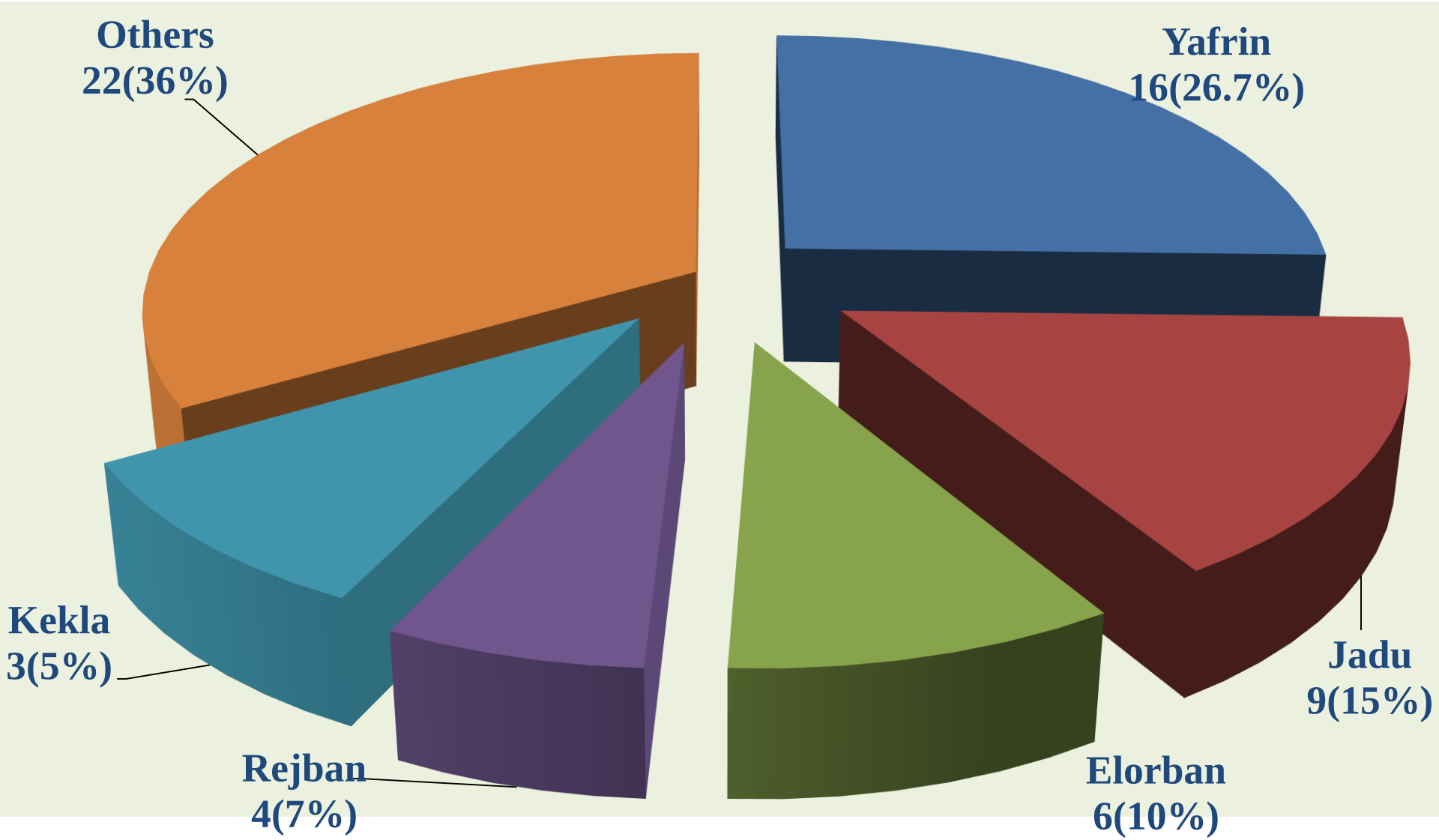
2. To highlight the genes that caused PH1.

3. To define the effect of consanguinity on the prevalence of the disease, the most common presentation in our region, and where the cases are especially clustered.

Table 1: Socio-demographic characteristics of Libyan PH1 patients

Character	No.	%
Sex: Male	34	56.7
Female	26	43.3
Age (year):		
≤1	18	30
2-4	22	36.7
5-7	12	20
8-10	8	13.3
Ethnicity: Arab	30	50
Amazigh	30	50
Residence:		
Western mountain	45	75
Others	15	25
Family history: Yes	55	91.7
No	5	8.3
Consanguinity: Yes	48	80
No	12	20

Distribution of children according to place of residence



AGXT gene mutation

The most common gene mutation was **c.731T>C (plle.244thr)** (84.4%), which mainly diagnosed among Amaziegh children lived in mountain area.

There was a significant statistical difference between gene mutation type and area of residence (p=0.001), but no significant statistical difference between Arab and Amaziegh patients (p=0.1).

As seen in next tables.

AGXT gene mutation among Libyan PH1 patients according to residence area

AGXT	Mountain area No. (%)	Other area No. (%)	Total
c.731T>C(plle.244thr)	33(91.7%)	5(55.6%)	38
c.466G>A(p.GLY156Arg)	0 (0%)	2(22.2%)	2
c.33dupC(p.Lys12GInfsX156)	1(2.8%)	0(0%)	1
c.2_3delinsAT,c.907C>T)	2(5.5%)	0(0%)	2
c.1078C>Tp.(Arg360Trp)	0(0%)	2(22.2%)	2
Total	36 (100%)	9 (100%)	45

Mutations in the AGXT gene according to ethnicity

AGXT	Amaziegh No. (%)	Arab No. (%)	Total
c.731T>C(plle.244thr)	22 (91.7%)	16(76.2%)	38
c.466G>A(p.GLY156Arg)	0 (0%)	2(9.5%)	2
c.33dupC(p.Lys12GInfsX156)	0 (0%)	1(4.8%)	1
c.2_3delinsAT,c.907C>T)	2(8.3%)	0 (0%)	2
c.1078C>Tp.(Arg360Trp)	0 (0%)	2(9.5%)	2
Total	24 (100%)	21 (100%)	45

Limitations of study

- **lack of investigations for PH1 in Libya (24hr urinary oxalate collection and AGXT gene mutation analysis).**

- **The feasibility and financial burden hindered a larger sample size, which in turn may have an impact on the reliability of our data in future analysis.**

Recommendations

- **Increase awareness and knowledge of the families regarding the role of consanguineous marriage and genetic testing.**
- **Family counseling and premarital screening program especially in places where PH1 is prevalent.**
- **Since for the time being the only accessible drug for the treatment of PH1 is Pyridoxine, further study regarding efficacy of pyridoxine on PH1 expressed particularly by the genes is recommended.**

Conclusions

- **PH1 cases in Libya are especially clustered in the West Mountain area.**
- **The most common gene mutation identified was c.731T>C (p.lle244thr), this might be helpful in future screening, counseling, and management of PH1 in Libya.**
- **Around two-thirds of the cases presented in the first four years of life with nephrocalcinosis .**
- **Renal stones were the commonest presentation exhibited in one-third of the cases.**

To take home massage…

Hope

1. **RNAi therapy (Nedosiran) for PH1,PH2, PH3**
   It inhibit lactate dehydrogenase enzyme at liver.
   (Dicerna)

2. **Oxlumo (lumasiran) indicated for PH1 to lower urinary oxalate in kidney (as monthly S/C injection).**
   (alnylam).

Thank you