Clinical Characteristics, Genetic Profile And Outcomes Of Children With Non-azotemic Refractory Rickets: A Cohort Study

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Introduction

- Refractory rickets is a group of rare diseases that do not respond to vitamin D therapy.
- There is paucity of data on the etiology and clinical profile of refractory rickets [1] with only few published studies from India [2–4]

Materials and Methods

- Retrospective cohort study
- 72 children (< 18 years) with non-azotemic refractory rickets who presented to the pediatric nephrology clinic from 2005-2024 were recruited.
- Children with renal dysfunction (CKD-MBD) due to CAKUT, cystic kidney diseases, nephronophthisis, etc) were excluded.
- Data on etiology, clinical features and complications was collected
- Next generation sequencing performed- funded by ICMR
- Outcomes at last follow-up noted
- Genotype-phenotype correlation

Acknowledgements

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References

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Results

Single centre in south India

72 patients from 65 families

Age at presentation : 2 [1, 4] years

Failure to thrive: 68.1%

Polyuria: 51.4 %

Nephrocalcinosis: 45.8%

Table 1: Etiology and clinical presentations of refractory rickets

Etiology /Clinical features	Distal RTA n=34; 47.2%	Fanconi syndrome n=19; 26%	HHR n=11; 15.3%	VDDR n=4; 5.5%	Bartter syndrome n=2; 2.8%	FHHNC n=2; 2.8%
Age at onset of symptoms (years)	3 (1, 4)	2 (0.75, 4)	1 (1, 4.75)	2 (1, 7)	1.5	6
Failure to thrive	22 (64.7)	18 (94.7)	4 (36.4)	2 (50)	2 (100)	1 (50)
Polyuria	21 (61.8)	12 (63.2)	-	-	2 (100)	2 (100)
Nephrocalcinosis	24 (70.6)	6 (31.6)	-	-	1 (50)	2 (100)
Pathological fractures	3 (8.8)	2 (10.5)	1 (9.1)	2 (50)	2 (100)	-
Hypokalemic paralysis	3 (8.8)	1 (5.3)	-	-	-	-
Hypokalemic myopathy	3 (8.8)	-	-	-	-	-
Hyperpigmented teeth	5 (14.7)	-	-	-	-	-
Hearing loss	2 (5.9)	-	-	-	-	-
Ovalocytosis	14 (41.2)	-	-	-	-	-
Consanguinity	19 (55.9)	8 (42.2)	3 (27.3)	2 (50)	2 (100)	1 (50)
Secondary NDI	1 (2.9)	1 (5.3)	-	-	1 (50)	-
Intellectual disability	-	3 (15.8)	-	-	-	-
Cataract	-	3 (15.8)	-	-	-	-
Hepatomegaly	-	2 (10.5)	-	-	-	-
Hypoglycemic seizures	-	2 (10.5)	-	-	-	-
Hepatosplenomegaly		1 (5.3)	-	-	-	-
Jaundice	-	1 (5.3)	-	-	-	-
Disproportionate lower limb involvement	-	-	10 (90.9)	-	-	-
Delayed dentition	-	-	-	4 (100)	-	-
Alopecia	-	-	-	3 (75)	-	-
Carpopedal spasm	-	-	-	2 (50)	-	-
Hypocalcemic seizures	-	-	-	1 (25)	-	-

Fig 2: Genetic spectrum of Refractory rickets

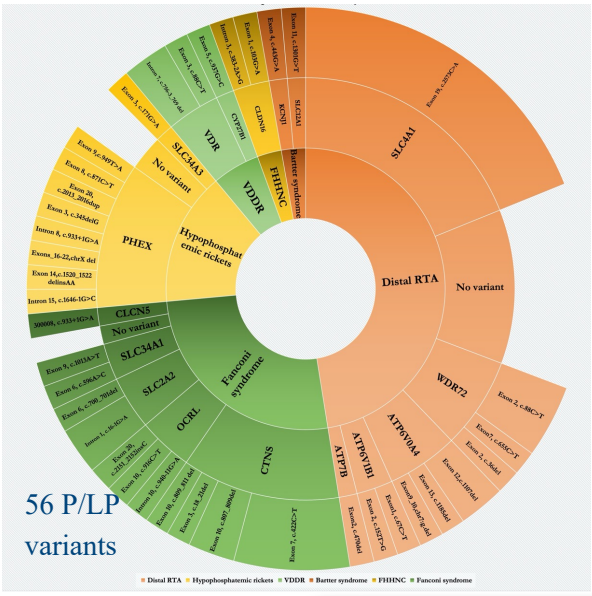
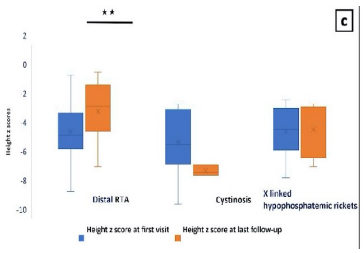


Fig 3: Height z scores at last follow-up



Progression to CKD stage 2 or greater on follow-up:

- Cystinosis- 5 cases
- *SLC4A1*-dRTA- 2 cases
- *WDR72*-dRTA- 2 cases
- Bartter syndrome- 2 cases
- Total- 11 patients

Conclusions

- Distal RTA, X-linked hypophosphatemic rickets and cystinosis were the commonest cause of refractory rickets.
- The c.2573C>A in exon 19 was the most frequent mutation of *SLC4A1*-dRTA