Pediatric Renal Rickets at a Tertiary Center

We report clinical and etiological profile of 19 children (10 males) with renal rickets managed in the years 2021-2022. Median (IQR) age of presentation was 60 (18-96) months. The commonest cause was renal tubular acidosis (*n*=8). Genetic analysis revealed the diagnosis in 83% subjects (5 out of 6 tested).

Keywords: *Hypophosphatemic rickets, Renal tubular acidosis, Vitamin D*

The reported etiology of renal rickets have been renal tubular acidosis (RTA), chronic kidney disease (CKD), hypophosphatemic rickets, vitamin D dependent rickets (VDDR), chronic liver disease and malabsorption [1,2]. Hypophosphatemic rickets is the commonest form of renal rickets reported in the Western population [3]. A pragmatic and protocol based approach is required to address the diagnosis and therapeutic aspects of this challenging disorder [4]. There is a paucity of recent data from Indian centres on renal rickets. We, therefore, report our observation on cases of renal rickets.

This was a retrospective case record analysis over a period of two years from January, 2021 to December, 2022. Data of all cases of diagnosed renal rickets i.e., RTA (proximal and distal), chronic kidney disease with rickets, hypophosphatemic rickets and VDDR were included in study. The protocol of the study was approved by institutional ethics committee. The clinical features, biochemical investigations, radiological feature and response to therapy were noted. In addition, results of genetic analysis performed in six children was also noted. The diagnosis of RTA, CKD, VDDR and hypophosphatemic ricket was made as per standard [1]. The investigation results noted included complete blood count, kidney function test, liver function test, arterial blood gas, serum calcium, phosphate, alkaline phosphatase, urine microscopy, urine calcium/ creatinine ratio, *X*-ray bilateral wrist, and ultrasonography of kidney, ureter and bladder. Vitamin D levels (25-OH Vitamin D, 1,25 $(OH)_2$ vitamin D3) were performed in VDDR to establish its diagnosis. Ophthalmological and hearing evaluation was performed, as and when indicated.

The present study included 19 patients (10 males); age group being 3 months to 14 years (median 60 months). Four cases (21.1%) presented during infancy, 5 (26.3%) during 1-5 years and the rest 10 (52.6%) belonged to 6-14 years of age (**Web Table I**).

Failure to thrive, polyuria, polydipsia, were consistently present in all RTA patients. Nephrocalcinosis was present in all dRTA patients. Skeletal deformity (genu valgum) was present in four RTA, three hypophosphatemic and 1 CKD patient, and Parental consanguinity was present in one of 19 patients.

Hypokalemia (serum potassium<3.5 meq/L) was present in 6(75%) RTA patients and metabolic acidosis in all RTA patients (*n*=8) and CKD (*n*=7) patients. Two of the dRTA patients had hemolytic anemia, and of these, one had a pathogenic variant in *SLC4A1*. Of the three pRTA patients, one child was diagnosed as nephropathic cystinosis based on the detection of recurrent pathogenic point variation (c.922G>A (p. Gly308Arg) in exon 11 in *CTNS* gene. He also had diabetes insipidus and hypothyroidism. There were three cases of hypophosphatemic rickets. One girl aged 7 years was found to have pathogenic variation in *PHEX* gene (c.1735G>A; p. Gly579Arg). The child was given treatment as phosphate granules, vitamin D, and oral calcium and showed dramatic response to therapy over two years. One boy aged 14 years had pathogenic variation in *CLCN5* gene (c.473G>A p. Gly158Asp), confirming it to be Dent disease. Cystinosis and Dent disease had features of renal Fanconi syndrome.

A rare form of refractory rickets (vitamin D dependent rickets type 2 A) was diagnosed in a 2-year-old boy, who presented to us with alopecia and rickets. Genetic study showed homozygous splice acceptor variant in exon 7 of *VDR* gene, located on chromosome 12. There were two deaths among this group of 19 patients. One child had nephropathic cystinosis and the other had chronic kidney disease.

The present study was a case record analysis of 19 cases of rickets with renal defects. commonest etiologies were RTA and CKD. The median age of presentation was much less in pRTA than dRTA and CKD. Five dRTA patients had metabolic acidosis, hypokalemia, and medullary nephrocalcinosis. *SLC4A1* variation is known to cause hereditary hemolytic anemia in dRTA patient [5]. Bone disease or rickets is relatively uncommon in dRTA patient, but it was present in two of the five patients [6].

Another form of renal rickets, which presents with knee deformity in adolescents, is hypophosphatemic rickets. Three cases had this form of rickets and 2 revealed genetic variations. This variation as p.Gly88Asp has been previously reported in patients affected with Dent disease [7]. This child had additional findings as hypercalciuria and

proteinuria. Molecular confirmation could not be done in third child.

One child had vitamin D dependent rickets type 2A. Alopecia is present in two-third of cases and it is a marker of disease severity [8]. Alopecia differentiates it from VDDR type 1. Gupta, et al.[9] first reported it in two siblings from India [9]. This child is under treatment with high doses of calcitriol and calcium phosphate. The disease is resistant to treatment with very poor response in cases with alopecia.

RTA and CKD have been the common causes of renal rickets as reported in other Indian series also [10, 11]. We had no patient in category of malabsorption and chronic liver disease, which has been previously reported [12].

The limitations of study are being retrospective case records analysis and restricted genetic analysis. Early pointers for non-nutritional forms of rickets are: growth failure, metabolic acidosis and azotemia. Clinicians should be aware of these pointers for timely diagnosis and management of such cases.

Ethics clearance: Ethical approval was obtained from IEC; No.2023/EC/6177.

Contributors: AS and Sucheta collected the data and AS conceptualized the idea and wrote the manuscript. RG, AA, RP helped in case management and literature search. OPM critically analysed the manuscript.

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