An overview of CYP27B1 enzyme mutation and management: A case report and review of the literature

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Abstract

Vitamin D-dependent rickets type 1 (VDDRIA) is an autosomal recessive disease caused by mutations in the Cytochrome P450 Family 27 Subfamily B Member 1 (CYP27B1) gene encoding the enzyme 1 alpha-hydroxylase. We report a known VDDRIA case presenting with hypotonia, growth and developmental disorders.

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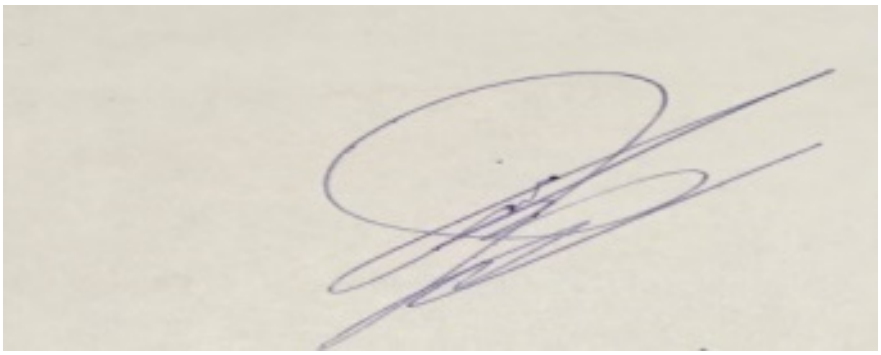

Abstract

Vitamin D-dependent rickets type 1 (VDDRIA) is an autosomal recessive disease caused by mutations in the Cytochrome P450 Family 27 Subfamily B Member 1 (CYP27B1) gene encoding the enzyme 1 alpha-hydroxylase. We report a known VDDRIA case presenting with hypotonia, growth and developmental disorders.

Keywords

CYP27B1 gene, 1, 25-dihydroxyvitamin D, VDDR1A, Rickets, autosomal recessive mutation

Introduction

Vitamin D is a hormone commonly produced by UV exposure in the skin and is hydroxylated twice in the liver and renal tubules to produce the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25 $(OH)_2$ D). Vitamin D plays an important role in nutrient absorption, and vitamin D deficiency reduces calcium and phosphorus absorption by 10-15% and 60%, respectively. Vitamin D plays an immunomodulatory role against infections and cancer, and its levels are controlled by phosphorus, parathyroid hormone (PTH) and calcium. Impaired production of the active form of vitamin D is an inherited disorder that is the most common autosomal recessive form of rickets. Mutations in the CYP27B1 gene caused a form of rickets called VDDRIA by interfering with the active form of vitamin D (located on chromosome 12q13)(1). Symptoms usually appear in the first year of life and caused decreased serum calcitriol levels by inactivating synthesis of the enzyme 1 alpha-hydroxylase (2-4).

In contrast to the nutritional type of rickets, the vitamin D-dependent form is characterized by low serum calcitriol but not low levels of 25-hydroxyvitamin. The clinical laboratory profiles of these patients included high levels of PTH and alkaline phosphatase (ALP), but low serum calcium and phosphate level (2, 3). Typical signs in rickets patients who present with these symptoms, despite vitamin D supplementation, are increased fractures, rachitic rosary, growth failure, genu valgum, and hypotonia (2).

As a result, these patients respond well to products (calcitriol), substrates (1a-hydroxyvitamin D), vitamin D, and calcium supplementation and high cholecalciferol level is not helpful in these patients. Despite the efficacy of calcitriol in these patients, it is also associated with complications such as nephrocalcinosis, hypercalcemia, and hypercalciuria (5). We will introduce a 7-year-old girl, diagnosed as a case of VDDRIA and discuss her clinical and paraclinical findings.

Case presentation

A 4-year-7month-old girl (currently 18-month-old girl) presented with hypotonia, weakness, impaired mobility, and poor growth. The patient had laboratory findings supporting hypocalcemia. Her hospitalization history was associated with severe shortness of breath noted by the impression of pneumonia. The patient was the second child in a family with a positive family history of metabolic disorders. She had never had a seizure before. The patient was delivered by cesarean section, weighed 3.3 kg at birth. There were no reports

of miscarriage in the family history. The first child died of hypophosphatemic rickets. Perhaps her illness was misdiagnosed, resulting in a case of VDDR. Her parents were consanguineous and asymptomatic. The patient was normal regarding nutrition and perinatal care. The patient had no complaints of constipation and lost her appetite recently. Her weight and height were 8.800g and 73.5cm, respectively, both of which were below the 3rd percentile.

Examination of linear growth revealed a slow progression in height growth trend and inappropriate weight gain. Her developmental assessment noted that the patient was beginning to walk with assistance. Vision, cognition, perception, motor skills and expressive language comprehension were normal. At initial assessment; the patient was able to crawl and stand, and no pathological signs such as abnormal head circumference or impaired tooth development were observed. Her skull examination was normal. No evidence of alopecia was observed and hair distribution was normal. On her musculoskeletal assessment; her wrists were wide and her left ankle was slightly deviated. The patient was able to lift limbs in supine and upright positions. Pretreatment radiographs of her wrists and ankles were consistent with rickets. Muscle assessment; muscle weakness, reduced subcutaneous fat, and global hypotonia have been observed. Pathologic findings after patient exposure; small chest wall with normal expansion. Rachitic rosary was observed on her skin examination. Her chest inspection showed no harrison's sulcus.

Laboratory profile at baseline; hemoglobin : 11.2 mg/dl, mean corpuscular volume : 75.7 fL, calcium : 8.9 mg/dl and Phosphorus: 3.4 mg/dl. Based on her symptoms, a treatment regimen was initiated according to her medical history and her first clinical evaluation; Rocaltrol capsule 0.25 microgram every 12 hours, Calmerz syrup 5 cc every 4 hours, PHOSPHATE SANDOZ tablet 500 mg every 6 hours, ferrous sulfate tablet 50 mg and folic acid 1 mg. After two months, she was referred to our center and treated with a diagnosis of hypophosphatemic rickets. On her next visit; she was mobile and had no problems for walking or running. The patient had a normal appetite and no history of constipation. The patient's mental status was normal, and examination of the lower extremities showed no evidence of Coxa vara and Coxa valga. Her weight and height were and , respectively, both of which were below the 3rd percentile. Lab tests included PTH: 95.4 pg/ml, ferritin: 64 micg/L, ALP: 780 U/L, Hb: 11.7 mg/dl, MCV: 77.1 fL, thyroid stimulating hormone : IU/L, Free T4 m IU/L: 1.20, Ca: 10.2 mg/dl, phosphorus: 4.3 mg/dl and vitamin D: 25.7 ng/ml. Only Calmerz syrup was changed to 5 cc every 6 hours compared to her previous regimen.

At the next visit in 2 months; she had no trouble walking. She has no signs of a rachitic rosary. The patient has a normal appetite and does not complain of constipation. Also, she had flat feet and suffered from orthopnea. The patient's weight and height were 9 kg and 77.5 cm, respectively, both of which were below the 3rd percentile. In her lab tests; PTH: 7.66 pg/ml, creatinine (Cr): 0.4 mg/dl, ALP: 343 U/L, Ca: 11.1 mg/dl, phosphorus: 5 mg/dl and vitamin D: 20.6 ng/ml. The patient's diet was thus changed compared to the previous treatment regimen; PHOSPHATE SANDOZ 500 mg tablets every 6 hours, Calmerz syrup 5 cc every 8 hours and Rocaltrol capsule(5 capsules) every 12 hours. The patient complained of anorexia and polydipsia and was referred to our hospital one month later. Her mobility was acceptable and she had no problems with her gait. Evaluation of her renal and urinary tract ultrasound; Grade 3 hydronephrosis has been reported in her left kidney. Lab tests included; PTH: 22.1 pg/ml, ferritin: 79.6 micg/L, fasting blood sugar (FBS): 88 mg/dl, 2-hpp glucose: 106 mg/dl, Bun: 44 mg/dl, Cr: 0.6 mg/dl, ALP: 337 U/L, Hb: 10.5 mg/dl, MCV: 71.5 fL, Ca: 10.3 mg/dl, phosphorus: 4 mg/dl, vitamin D: 36.1 ng/ml , growth hormone (GH): 4.3 IU/L and insulin-like growth factor 1 (IGF-1): 51 IU/L. The possibility of renal tubular acidosis (RTA) was ruled out based on no history of polyuria and normal blood potential of hydrogen (pH).

Vitamin D 1-alpha hydroxylase deficiency was suspected on the basis of clinical and laboratory findings, and balance according to therapy, and a complete exome sequencing (WES) plan was considered. The results was the known c.195 + 2T> G homozygous mutation in the CYP27B1 gene, which has an autosomal recessive inheritance. This mutation is located in exon 1 of chromosome 12q13 and is a Splice Site Pathogenic variant. Based on her clear diagnosis of VDDRIA and the patient's symptoms, Rocaltrol capsules were administrated once in the morning and twice in the evening. PHOSPHATE SANDOZ 500 mg tablets were administered once every 8 hours, and vitamin D drops prescribed 2 drops daily. Calmerz syrup was also discontinued. The

patient was followed up regularly and her symptoms improved. A follow-up radiograph showed her findings to be resolve. Due to persistent hydronephrosis during follow-up, periodic nephrology visits were considered. Her final weight and height were 10.8 kg and 89 cm, respectively, both of which were in the 3th percentile. She also had normal serum levels of vitamin D, calcium, phosphorus, and ALP. Her appetite was normal. She did not experience walking problem anymore.

Discussion

Vitamin D has two main forms, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). The source of ergocalciferol is food such as liver oil, milk, fish and eggs, while the source of cholecalciferol is the skin under the influence of ultraviolet B. The next step is for the synthesized vitamin D to be transported to the liver via its carrier protein. Then it is modified by 25-hydroxylase, where hydroxylation first occurs. Synthesized calcidiol or calcifediol is absorbed by proximal convoluted tubule (PCT) receptors such as megalin and cubilin by endocytosis(6). Calcitriol or 1,25-dihydroxy vitamin D (the active form of vitamin D) is synthesized by 1 alpha-hydroxylase in the kidney, where the secondary hydroxylation takes place(7). CYP2R1 and CYP27B1 encode hydroxylating enzymes of primary (calcidiol) and secondary product (calcitriol), respectively(6, 7).

Calcitriol binds to its receptor on the surface of enterocytes and subsequently increases expression of the Transient Receptor Potential Cation Channel Subfamily V Member 6 (TRPV6) calcium channels, resulting in increased calcium absorption. Balance of bone metabolism is maintained by intericate interaction between PTH, fibroblast growth factor-23 (FGF-23), and 1,25 dihydroxy vitamin D hormones. This interaction helps us to understand the correlation between these and the mechanisms of skeletal demineralization in rickets patients. Calcitriol synthesis in the kidney is increased by factors such as PTH, hypocalcemia, and hypophosphatemia. These two hormones (PTH and calcitriol) increase FGF-23 level. FGF-23 is a hormone produced by osteocytes and is regulated by two major bone proteins, including Phosphate Regulating Endopeptidase Homolog X-Linked(PHEX) and Dentin matrix protein 1(DMP1). Decreased expression of these two proteins promotes osteomalacia. This hormone lowers the calcitriol and PTH levels. FGF-23 plays a role in renal excretion of phosphate by acting on its (FGF) receptor in the kidney. This hormone acts through a tubular membrane protein called klotho downregulating the major sodium / phosphate co-transporters in the proximal tubules, including NaPi-2a and NaPi-2c, resulting in increased phosphaturia(8, 9).

The finding of bone deformities due to disruption of bone mineralization in the area of the growth plate is a hallmark of rickets, the most common form of which is nutritional related(10). In general, impaired vitamin D metabolism is associated with four types of rickets, including VDDR1A, VDDR1B, VDDR2A or VDDR and VDDR2B, and is characterized by defects in proper expression of CYP27B1, CYP2R1, vitamin D receptors, and protein related to vitamin D receptor function, respectively(1, 11). Pseudo-VDDR (PDDR) or VDDR1 presented with hypotonia, hypoplasia of dental enamel, growth retardation, weakness, and developmental delay at the age of 6-24 months. It can also manifest as a seizure in the first year of life (12). Alterations in the VDDRIA gene can be compound heterozygous or homozygous, both of which are inherited in an autosomal recessive manner(13). Referring to the Human Gene Mutation Database (HGMD), as of January 2020, 81 different CYP27B1 gene mutations associated with VDDR-IA disease have been reported (14). Mutations in this gene are more commonly associated with missense and nonsense forms, although deletions, splice site alterations, duplications, and insertions have also been reported(15).The location of CYP27B1 gene is on the long arm of chromosome 12. The locus from 12q13.1 - q13.3 is 5Kb in size and contains 9 exons(16) and 8 introns translated into 508 amino acids (17).

Clinical findings of rickets (vitamin D deficiency form) can be divided into two categories: skeletal and extra skeletal; of the skeletal manifestations, bone changes are a typical feature of the disease and vary according to the site of stress. The areas of greatest bone involvement are usually areas of high growth, such as the epiphyses of long bones and costochondral junctions(18). In toddlers and crawling infants, bone involvement in the form of genu varum or genu valgum and forearm deformities are more predominant(19). Ambiguous presentations in adolescence, such as headaches and lower extremity pain are called florid signs, which are uncommon. Craniotabes, widened fontanelles, bone mass in the frontal region (frontal bossing), delayed growth of teeth, rachitic rosary (which reflects the severe form of rickets caused by enlargement of the

costochondral region) (20), looser's zone, and pathologic fracture(21) have been observed in these patients(19, 22). For extra skeletal findings; irritability, proximal limb weakness, hypotonia(23), laryngospasm, tetany, seizure and cardiomyopathy (uncommon) have been reported(3, 24).

On radiological examination of these patients; the epiphyseal center may be delayed or in ill-defined, small and osteopenic forms. The metaphyseal findings in these patients are regarding its expansion. During the early and advanced stages, changes such as the absence of crisp line and concave or frayed form, respectively occurred (25). All epiphyses in rickets are affected. In particular, the growth plates in area with faster growth, so radiological findings are more pronounced(18). The Rickets Severity Score (RSS) can be used to assess the transformation of metaphysis and growth plates more accurately. RSS is also a useful measure for assessing patient response to treatment and disease severity (26). X-rays are routinely used in the diagnose of rickets, and the role of magnetic resonance imaging (MRI) in showing cartilage changes in rickets was recently reported(27).

As the clinical diagnosis of rickets becomes available to patients, laboratory tests is help to achieve a rapid diagnosis. In addition to diagnosis, these assessments serve to reflect the type and stage of rickets. In patients with bone deformation and epiphysis expansion, measurement of ALP levels may be an salient finding in confirming rickets. Monitoring ALP level may be a useful tool for assessing disease progression and treatment response(18). Recently, Mukai, M. et al., represented that ALP level had bidirectional relationship with the degree of genu varum during a study of pediatric rickets due to vitamin D deficiency with genu varum (28). A common feature of all types of rickets is low serum phosphate levels (29). Indeed, hypophosphatemia in patients with vitamin D-dependent rickets can be managed by adjusting calcium to mean normal serum levels and normalizing PTH levels. Radiographic examination, plasma and urine biochemical concentration, and kidney ultrasound should be checked regularly.

There is evidence that calcitriol or alfacalcidol can be used for high levels of ALP and PTH and low serum calcium and phosphorus levels in patients with VDDR1a (30). There is evidence that calcitriol or alfacalcidol can be used for high levels of ALP and PTH and low serum calcium and phosphorus levels in patients with VDDR1a which clinical and paraclinical findings of patients improved by a physiological dose of 1,25(OH)2D(31-33). The recommended dose for an adequate response in these patients is 1–2 μg/day of calcitriol, and the tolerable calcium intake for these patients is 30–75 mg/kg/day (5). In addition to initiating treatment for patients, it is necessary to re-evaluate calcium and phosphorus (serum-urinary level), ALP, calcidiol, because knowing the values of these findings are a good guide to adjust the patient's treatment. The first expected change after starting treatment is an increase in phosphate, followed by and increase in serum calcium. Six months after starting treatment, the patient's clinical symptoms may have resolved. Although, the first radiologic changes can be seen from the first week(34), its improvement occurs 6-8 weeks after the starting treatment(5). Complications from initiation of treatment with calcitriol include elevated serum, urinary, and tissue calcium levels, and regular evaluation for nephrocalcinosis, hypercalcemia, and hypercalciuria is recommended (5). Urinary calcium/ creatinine ratio can be used to reflect the degree of hypercalciuria in these patients (34).

Our patient's mutation was homozygous c.195 + 2T> G in exon 1 (splice site pathogenic form), and its early symptoms were hypotonia, movement disorders and growth retardation. According to our patient's mutation, Fatma Dursun et al. evaluated the genomic DNA of 11 VDDR1A patients. They found that the c.195 + 2T> G splice donor site was the most common mutation reported in 7 patients out of 11 participants, 2 of whom were compound heterozygous, 5 were homozygous(11). For the first time, the mutation c.195 + 2T> G (homozygous) was reported in two Turkish cases from the same family(35). Fatma Dursun et al. reported movement disorders and bowed legs in all patients with intron-1 mutations. They noted that the height percentage of 4 patients with intron-1 mutations was less than 2 standard deviations. In addition, an 11-month-old patient had an episode of hypocalcemic convulsion(11). Tahir et al. assessed the genotype and phenotype of 22 VDDR1 cases, in which they discussed 10 patients with c.195 + 2T> G mutations (splice donor site). They showed that individuals with intron-1 mutations exhibited milder symptoms, with the exception of one patient who presented with hyocalcemic convulsion. No good correlation has been

reported between genotype and phenotype of VDDR1 patients(36). Durmaz et al. evaluated the genotypic and phenotypic findings of 15 cases of VDDR1 from 4 families. They observed 4 cases with the c.195 + 2T> G mutation (homozygous), 2 of whom had severe hypocalcemic convulsion at 4 months of age and the others showed delayed movement along with mild hypocalcaemia at the age of 18-19 months. They reported that there was a good relationship between genotype and phenotype in VDDR1 patients (35).

Demir et al. analyzed CYP27B1 gene mutations of eight patients and their seven families. They found that 3 patients had c.195 + 2T> G mutations (homozygous), 2 patients had movement and growth disorders, and 1 of them had growth disorder and fractures. They reported that half of the patients presented with hypocalcemic convulsion. They stated that intron-1 mutations were associated with the most severe symptoms among the mutations, thus they did not report a pertinent relationship between genotype and phenotype in VDDR1 patients(37). Kaygusuz et al evaluated the correlation between genotype and clinical presentation in 13 patients with VDDR-IA. They argued that the c.195 + 2T> G mutation is one of the most common mutations. Of the 13 patients, 4 patients had movement disorders and only 1 patient had a hypocalcemic seizure. They reported that there was a clear association between genotype and clinical manifestations in VDDR-IA patients, and that patients with intron-1 c.195 + 2T> G mutations had more severe symptoms owing to abnormal height standard deviation score (SDS), so they need higher doses of calcitriol(14). To analyze the genotype and clinical manifestations of VDDR-IA patients, Dodamani et al. designed a retrospective study of 7 VDDR-IA patients and a systematic review of 165. A systematic evaluation of 165 patients showed that c.195 + 2T> G mutation was one of the most common mutations and that mutation was region specific (West Asia, Turkey). All seven patients had abnormal height SDS, deformity, high PTH and ALP, low calcium level, and low 1,25 $(OH)_2D$ at baseline. Of the 7 patients, 4 had episodes of hypocalcemic seizure. In 165 patients, seizures and motor-deformity were more common during infancy(11 of 31 infants) and post-infancy, respectively(38).

The therapeutic dose of calcitriol range in VDDR1 patients is 0.008 - 0.40 µg / kg / day or 0.5 - 2 µg / day(33). Yunfei Li et al. introduced two cases of VDDR1 and discussed that both responded to high doses of calcitriol (case 1: 0.75 µg / day or 0.079 µg / kg / day and case 2: 2 µg / day or 0.18 µg / kg / day)(39). In a study conducted by Durmaz et al., doses of 0.01–0.1 µg / kg / day normalized serum levels of phosphate and calcium and improved growth status in VDDR1 patients (35).

Ningyi Cui et al. examined the CYP27B1 gene in 8 Chinese patients with PDDR and obtained therapeutic response with doses of 0.5–1.0 µg / day of calcitriol (40). Valentina Donghi et al. regarded proper calcium diet with regimen of 25-30 ng / kg / day Calcitriol, which gradually raised up to 50 ng / kg / day for VDDR1 cases. Optimal improvement of clinical and paraclinical findings of VDDR1 patients was achieved after 12 weeks of treatment (41). T. Edouard et al. evaluated clinical findings in PDDR patients during calcitriol treatment. They initially took 0.5 µg of calcitriol twice daily, but after 3 months of acceptable feedback, they reduced the therapeutic dose to 0.50 µg / d. The calcitriol dose was then changed to 0.25 µg / d (0.1-1.0 µg) and 0.25 µg / d (0.1-0.5 µg) after 1 year and 2 years, respectively(42). Kaygusuz et al. noted in their study that the intended dose of calcitriol was 41.01 ± 7.59 ng / kg / day depending on the severity of symptoms and hypocalcemia. Clinical and paraclinical improvements with calcitriol regimen were observed in all patients (calcium level improved after 1-3 months, PTH and ALP levels improved after 3-12 months)(14). Dodamani et al. received optimal therapeutic feedback with a diet of calcium (30–75 mg / kg / day) and calcitriol (10–20 ng / kg / day). At the onset of radiographic changes, the calcitriol dose modified to 0.25-0.5 µg / day. They concluded that physiological doses of calcitriol (0.25-0.75 µg / day) could improve the clinical and laboratory profile of patients (38). Dhull et al. considered doses of 30 ng/kg/day and 2 mmols/kg/day for calcitriol and phosphate, respectively, for both patients. Then, after positive feedback, the calcitriol dosage was modified; it was set to 20 ng/kg/day in the first case and reduced to 10 ng/kg/ day in the second case. Also, over the course of treatment, phosphate supplementation was reduced and then discontinued(43).

It is clear from the therapeutic doses in these studies is that some patients respond to high doses of calcitriol and others respond to low doses of calcitriol, but the dose chosen should be based on the individual patient.

Please note that the decision should be made on a case-by-case basis. However, complications such as hypercalciuria and nephrocalcinosis should be considered.

A typical finding in patients with VDDR1 is decrease serum 1,25-OH_2D levels, although normal 1,25-OH_2D levels have been reported at disease onset(37, 44). Recently, Nishikawa et al proposed that enzymes other than CYP27B1 are involved in 25-OHD catalysis. They showed that in knockout mice (CYP27B1 enzyme), 1,25-OH_2D is recovered from 25-OHD by the CYP27A1 enzyme(45). In contrast to our patient, who had low 1,25-OH_2D levels, Giannakopoulos et al.(46) and Wang et al.(47) reported 1 and 2 cases, respectively, with normal 1,25-OH_2D levels. In a study by Dursun et al., 8 of the 11 patients had normal or above normal levels of 1,25-OH_2D. Of the 5 patients with relatively high 1, 25-OH2D levels, all five received vitamin D treatment due to misdiagnosis of nutritional rickets. Of the 3 patients with normal 1,25-OH_2D levels, 1 patient was treated with phosphate and calcitriol for misdiagnosis of hypophosphatemic rickets(11). Dhull et al. reported 2 cases with mutations in the CYP27B1 gene and both impaired movement and growth. Their baseline laboratory results demonstrated a normal reading of 1,25 $(OH)_2$D(43).

Conclusion

It is important to consider the diagnosis of VDDRI in order to initiate appropriate treatment with the aim of preventing disease complications, including skeletal and non-skeletal disorders. In our article a girl with a confirmed diagnosis of VDDRIA presented and improved laboratory and clinical findings occurred following timely and appropriate treatment.

Abbreviations

VDDRIA: vitamin D-dependent rickets type 1

CYP27B1: Cytochrome P450 Family 27 Subfamily B Member 1

1,25 $(OH)_2$ D: 1,25-dihydroxyvitamin D

PTH: parathyroid hormone

ALP: alkaline Phosphatase

VDDR: vitamin D-dependent rickets

Hb: hemoglobin

MCV: mean corpuscular volume

Ca: calcium

TSH: thyroid stimulating hormone

Cr: creatinine

FBS: fasting blood sugar

2-hpp: 2 hour Post Prandial

BUN: blood Urea Nitrogen

GH: growth hormone

IGF-1: insulin-like growth factor 1

RTA: renal tubular acidosis

Potential of hydrogen:pH

WES: whole exome sequencing

PCT: proximal convoluted tubule

TRPV6: transient Receptor Potential Cation Channel Subfamily V Member 6

FGF-23: fibroblast growth factor-23

PHEX: phosphate Regulating Endopeptidase Homolog X-Linked

DMP1: dentin matrix protein 1

PDDR: pseudo-VDDR

HGMD: human Gene Mutation Database

RSS: rickets Severity Score

MRI: magnetic resonance imaging

SDS: standard deviation score

Authors Contributions

Conceptualization and design: D.Z. and M.G.; management and follow up of the patient: D.Z.; article writing: D.Z. and M.G.; data interpretation: D.Z. and M.G.; final revision: D.Z. and M.G.

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Conflicts of Interest

None declared

Consent

Written consent to write the article has been obtained from the patient's family

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