patients had calcium levels that are in the lower limit of normal, hypocalcemic convulsion is not frequently encountered.

The clinical presentations of patients with VDDR1A could lead to a misdiagnosis of nutritional rickets or hypophosphatemic rickets. It can be differentiated from hypophosphatemic rickets by a high PTH level and nutritional rickets by a normal 25 OHD level. The hypophosphatemia in VDDR1A is a result of elevated PTH and renal excretion of phosphate. Clinical and laboratory features of VDDR1A are very similar to nutritional rickets; its differential diagnosis can be made by a low or inappropriately normal 1, 25- OH_2D level and unresponsiveness to vitamin D treatment. In our study, 6 patients also had been treated with vitamin D for a long time with the diagnosis of nutritional rickets, and they had extremely high 25-OHD levels. Four patients had normal calcium levels, and one of them had been followed with hypophosphatemic rickets. There were a few patients with normal 1, 25-OH_2D levels diagnosed with VDDR1A in the literature (4, 8). In fact, the expected 1, 25-OH_2D levels in 1α-hydroxylase deficiency are low, inappropriately normal 1, 25- OH_2D levels also indicate that the enzyme activity is insufficient. Recently, Nishikawa N, et al (22) reported that liver mitochondrial CYP27A1 can catalyse 1α-hydroxylation of 25-OHD. A small increase in serum 1, 25- OH_2D level has been observed in CYP27B1 knockout mice after given high dietary vitamin D, suggesting a conversion from 25-OHD to 1, 25- OH_2D by a non-CYP27B1 enzyme. Three of eleven patients of our study had normal 1, 25-OH_2D level. There was a history of high dose vitamin D intake in two of these three patients with normal 1, 25-OH_2D. In these patients, conversion from 25-OHD to 1, 25-OH_2D by a non-CYP27B1 enzyme may contribute to the normal 1, 25-OH_2D.

Maternal 1, 25-OH_2D does not cross the fetoplacental barrier (21, 23). 1, 25-OH_2D is increasing 2-3 fold in the first weeks of pregnancy where as maternal 25-OHD crosses the placental barrier. The rise in circulating 1, 25-OH_2D concentrations in the mother facilitates optimal in utero bone development by attaining a positive calcium balance (24). Edouard T, et al (21) reported that, unlike patients with severe vitamin D deficiency who can present within the first 6 months of age, none of the VDDR1A patients were symptomatic before the age of 6 months. Indeed, the infant who was diagnosed with VDDR1A at the age of 1 month had a low serum level of 1, 25-OH_2D and a positive *CYP27B1* sequencing result but did not have any clinical or radiological signs of rickets (21). This indicates that 1,25-OH_2D is not critical for mineral ion homeostasis and growth plate mineralization in first months of life owing to in utero positive calcium balance in these patients. All patients in this study group were 6-month or older at admission.

Generally, a good response to treatment with alfacalcidol or calcitriol (10- 400 ng/kg/day) is expected in cases with VDDR1A (4, 21). Calcitriol dose was tailored based on biochemical and clinical findings. Edouard T, et al (21) indicated short and long-term outcomes of calcitriol treatment in their patients. They started calcitriol treatment at a dose of 1.0 µg/day, given in two doses of 0.5 µg. Treatment with calcitriol resulted in the normalization of biochemical parameters within 3 months. The aims of the treatment were to achieve normocalcemia, to maintain PTH levels within normal limits, and to avoid hypercalciuria. Our patients did not reach their final height, and their treatment duration ranged between 6 months and 7 years. Improvement of biochemical parameters occurred at a somewhat later period, between 4 months and 12 months.

Study Limitations

The main limitation of our study is the relatively small number of patients.

Conclusion

Although VDDR1A is a rare disease, it is more common in Turkey where autosomal recessive disorders are common. In this study, we evaluated the genetic and clinical features of 11 patients with the diagnosis of VDDR1A. Intron 1 mutation was the most common mutation as in the previous studies, and all patients carrying that mutation were from same city of origin suggesting a "founder" or a "common ancestor" effect. As it may be confused with nutritional rickets and hypophosphatemic rickets, genetic analysis is important for making a correct diagnosis. VDDR1A should be considered when a patient with signs of rickets has a normal 25-OH level or when there is unresponsiveness to vitamin D treatment. We have also emphasized that the concentrations of 1, 25-OH_2D levels could be in normal ranges in patients with VDDR1A and can lead to diagnostic confusion.

Conflict of interest

The author declares that there is no conflict of interest.

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Authorship Contributions

Concept: FD, BH, Design: FD, HK, EK, Data collection or processing: FD, EK, GÖ, BH, Analysis or interpretation: FD, BH, HK, EK, GÖ, Literature Search: FD, BH, HK, EK, GÖ, Writing: FD, HK, EK, BH, GÖ

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Figure 1: *X-rays of this patient before (A) and at the 6th month of calcitriol treatment (B). A: abnormal cupping, widening and fraying of the metaphyses consistent with rickets. B: recovery of cupping and fraying, and a provisional calcification zone suggesting healing rickets.*
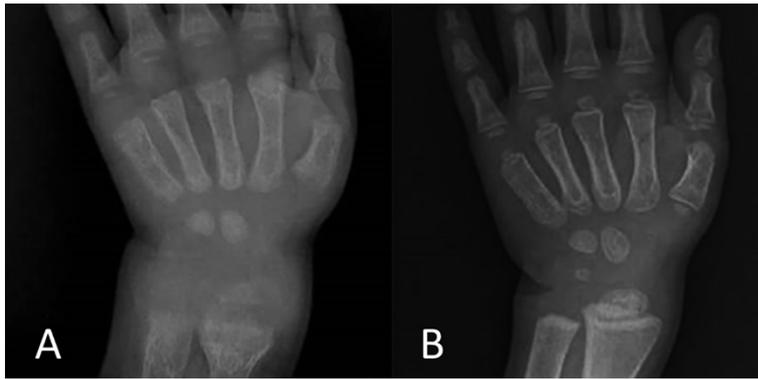
Figure 2: A. *Wild type sequence of exon 8 in CYP27B1 gene.* **B.** *Sequencing analysis of the CYP27B1 gene exon 8 showing the homozygous mutation (1319_1325dupCCCACCC, Phe443Profs*24).*
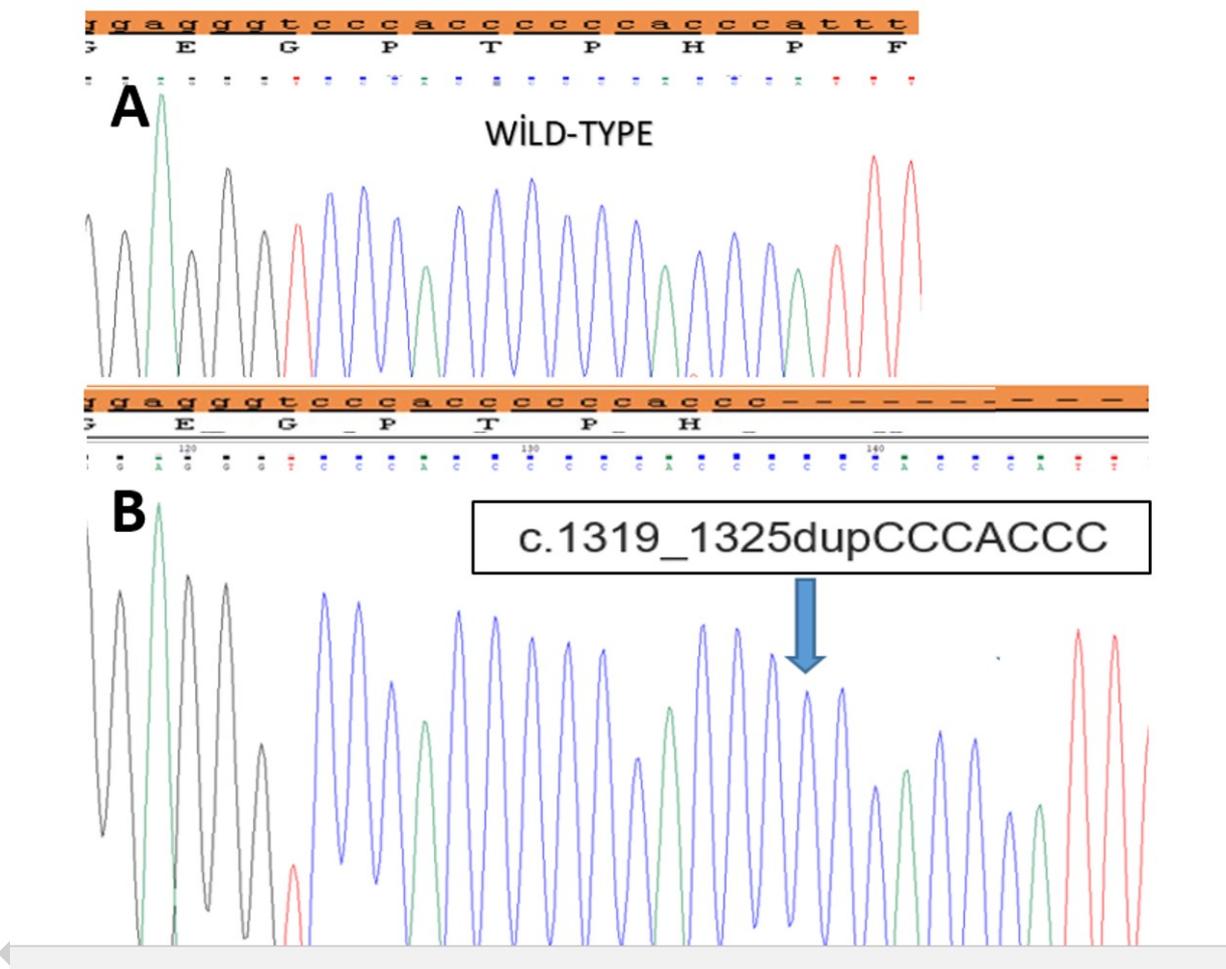

Table 1: List of primers used for polymerase chain reaction amplification of the nine coding exons of CYP27B1 gene.

Primer Name	Primer sequence
CYP27B1_1F:	GTCATCACCTCACCCAAAGG

CYP27B1_1R:	TCTGACGCTGTCAAAACCAG
CYP27B1_2F:	GAAGCTCCCTATTCCCAAGC
CYP27B1_2R:	CATGCCCCCAGATTGATAGT
CYP27B1_3-4 F:	CTCCTTCACTGCAGCCAGTC
CYP27B1_3-4 R:	GTGGGTAGAAGGCACGTGAA
CYP27B1_5 F:	GCATTTGGTAAGGCACAGGT
CYP27B1_5 R:	CATAATGGATCCCCTGCAAC
CYP27B1_6-7 F:	CCATAATCTGCACCCTCTGC
CYP27B1_6-7 R:	GGGCCCAAGATAGTGAGGA
CYP27B1_8 F:	TCTTCATGCCTGCCCTATTC
CYP27B1_8 R:	CAGGGGAAAGAGCTCACAAC
CYP27B1_9 F:	CACCCAATCATTGACCATTC
CYP27B1_9 R:	CATACTTCACACATTGGTCAGG

Table 2: Clinical and laboratory findings of 11 patients with VDDR1 from 8 families

Subjects	Age (Month)	Presenting symptoms	Height SD	Ca mg/dL N:9-11.5	P mg/dL N:4-6.5	PTH pg/mL N:11-67	ALP IU/L N<455	25-OHD ng/mL N>20	1,25-OH$_2$D pg/mL N: 20-153
1.1	18	Bowed legs, growth retardation	-2	8.0	2.3	441	2120	26	15
1.2	36	Bowed legs, growth retardation	-2.5	7.1	3.1	784	3100	64	10
1.3	18	Bowed legs, growth retardation	-2.1	6.2	2.8	980	1940	120	12
2	9	O-bine deformity, failure to thrive	-3.1	7.8	3.0	625	1445	45	6
3	14	Hypotonia	-4.7	8.4	2.2	972	3111	194	38
4.1	6	History of VDDR sibling	0.28	8.0	2.9	546	1325	50	11
4.2	7	Inability to work	-1.06	8.9	2.1	423	1400	132	45
5	14	Growth retardation	-2.2	5.91	3.4	925	2531	41	<1.3
6	11	Hypocalcaemic seizure	-0.55	6.7	3.6	467	651	89	15.4

| 7 | 24 | Inability to walk | -2.1 | 8.7 | 2.3 | 1397 | 4479 | 18.7 | 21.5 |
| 8 | 24 | Elevated ALP, inability to walk | -3.1 | 8.2 | 2 | 571 | 1001 | 135 | 5.5 |

The patients were indicated with respective family number and the number of individual in that family. Patients 1.1, 1.2, 1.3. and 4.1 and 4.2 were siblings. SD: standart deviation, Ca: calcium, P: phosphate, PTH: parathyroid hormone, ALP: alkaline phosphatase, N: normal range

Table 3: Characteristics of the mutations detected in 11 patients with VDDR1 from 8 families

Family number	Exon/Intron	DNA description	Zygosity	CF	MO/PO
1.1	Intron 1	c.195 + 2 T>G	HM	yes	Batman/Batman
1.2	Intron 1	c.195 + 2 T>G	HM	yes	Batman/Batman
1.3	Intron 1	c.195 + 2 T>G	HM	yes	Batman/Batman
2	Intron 1	c.195 + 2 T>G	HM	no	Batman/Batman
3	Intron 1	c.195 + 2 T>G	HM	no	Batman/Batman
4.1	Intron 1	c.195 + 2 T>G / c.1215 +2 T>A	CHT	no	Batman/Bitlis
4.2	Intron 1	c.195 + 2 T>G / c.1215 +2 T>A	CHT	no	Batman/Bitlis
5	Exon 8	p.Phe443Profs*24 (c.1319_1325dupCCCACCC)	HM	yes	Erzurum/Erzurum
6	Intron 7	c.1215+2T> A	HM	yes	Mardin/Mardin
7	Exon 9	c.1474C>T p.R492W	HM	yes	Mersin/Mersin
8	Exon 8	p.Phe443Profs*24 (c.1319_1325dupCCCACCC)	HM	yes	Elazig/Elazig

CF: consanguineous family, HM: homozygyous, CHT: Compound Heterozygosity, MO:maternal origin / PO: paternal origin. Locations of origins: Batman, Bitlis, Mardin: South-eastern Anatolia. Erzurum, Elazig: Eastern Anatolia. Mersin:Mediterranean Region