ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Evaluation of Clinical Characteristics of Vitamin D Dependent Rickets Type 1 (VDDR-1) Patients and Importance of Early Diagnosis

D Vitamini Bağımlı Raşitizm Tip 1 (VDDR-1) Hastalarının Klinik Özelliklerinin Değerlendirilmesi ve Erken Tanının Önemi

Ruken Yıldırım* (0000-0002-9558-3856), Edip Ünal** (0000-0002-9809-0977), Aysel Tekmenüray*** (0000-0001-8730-3968)

*Diyarbakır Children's Hospital, Clinic of Child Endocrinology, Diyarbakır, Turkey

**Dicle University Faculty of Medicine, Department of Child Endocrinology, Diyarbakır, Turkey

***University of Health Sciences Turkey, Gazi Yaşargil Research and Training Hospital, Clinic of Genetic, Diyarbakır, Turkey

Abstract

Introduction: Vitamin D-dependent rickets type 1 (VDDR-1) is an autosomal recessive disorder caused by 1-α-hydroxylase enzyme deficiency. This rare disease occurs due to biallelic pathogenic variants in the CYP27B1 gene. We evaluated VDDR-1 patients retrospectively in terms of clinical and biochemical characteristics, treatment response, and genetic results.

Materials and Methods: VDDR-1 cases with biallelic variants in CYP27B1 from 12 families were included. Demographic and clinical data were extracted from records. Following DNA isolation and standardized PCR, we performed next-generation sequencing with Miseq device. Data analysis was performed using IGV 2.3 software.

Results: The cohort included 22 patients, 11 (50%) female and 11 male. Median age at diagnosis was 12 (7.75-18) months. Mean calcium, phosphorus, alkaline phosphatase (ALP) and vitamin D concentration was 7.6±0.98 mg/dL, 2.9±0.77 mg/dL, 1149±692 IU/L, 391±181 pg/mL, and 55±38 ng/mL, respectively at diagnosis The most common reasons for presentation were growth retardation, short stature, convulsions, and extremity deformity. The most common variant was the previously identified c.195 + 2T>G substitution, which was detected in 5 families. The second most common variant was another previously reported c.574A>G (p.Lys192Glu) variant, which was detected in 3 families. c.171delC (p.Leu.58Cfs*20), c.240delT (p.Phe80Leufs*79), and c.1166G>A(p.Arg389His) homozygous variants and c.1215_1215+2delinsCGA/c.1474C>T (p.Arg492Trp) compound heterozygous variant were detected in one family each.

Conclusion: VDDR-1 should be considered in rickets patients not recovering with high-dose vitamin D therapy. Delayed diagnosis of VDDR-1 may lead to unnecessary orthopedic surgery in some cases. We are of the opinion that providing early diagnosis, treatment and genetic counseling will give reliable and important information to families.

Öz

Giriş: Vitamin D'ye bağımlı raşitizm tip 1 (VDDR-1), 1-α-hidroksilaz enzim eksikliğinin neden olduğu otozomal resesif geçişli bir hastalıktır. Bu nadir hastalık, CYP27B1 genindeki bialelik patojenik varyantlar nedeniyle oluşur. VDDR-1 hastalarını klinik ve biyokimyasal özellikler, tedavi yanıtı ve genetik sonuçlar açısından retrospektif olarak değerlendirdik.

Keywords
CYP27B1, vitamin D-dependent rickets type 1A, hypocalcemia, hypophosphatemia

Anahtar kelimeler
CYP27B1, D vitaminine bağlı raşitizm tip 1A, hipokalsemi, hipofosfatemi

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Address for Correspondence/Yazışma Adresi: Ruken Yıldırım MD, Diyarbakır Children's Hospital, Clinic of Child Endocrinology, Diyarbakır, Turkey
Phone: +90 507 242 92 62
E-mail: rukmay21@hotmail.com

Gereç ve Yöntem: On iki aileden CYP27B1'de bialelik varyantları olan VDDR-1 vakaları dahil edildi. Demografik ve klinik veriler kayıtlardan çıkarıldı. DNA izolasyonu ve standart PCR sonrası Miseq cihazı ile yeni nesil dizileme gerçekleştirdik. Veri analizi IGV 2.3 yazılımı kullanılarak yapıldı.
Bulgular: Kohort, 11'i (%50) kadın ve 11'i erkek olmak üzere 22 hastayı içeriyordu. Ortanca tanı yaşı 12 (7,75-18) aydı. Ortalama kalsiyum, fosfor, alkalin fosfataz (ALP) ve D vitamini konsantrasyonu 7,6±0,98 mg/dL, 2,9±0,77 mg/dL, 1149±692 IU/L, 391±181 pg/mL ve 55±38 ng/mL idi., sırasıyla tanıda En sık başvuru nedenleri büyüme geriliği, boy kısalığı, konvülsiyonlar ve ekstremite deformitesi idi. En yaygın varyant, 5 ailede tespit edilen daha önce tanımlanmış c.195 + 2T>G ikamesiydi. İkinci en yaygın varyant, 3 ailede tespit edilen, daha önce bildirilen bir başka c.574A>G (p.Lys192Glu) varyantıydı. c.171delC (p.Leu.58Cfs*20), c.240delT (p.Phe80Leufs*79) ve c.1166G>A(p.Arg389His) homozigot varyantları ve c.1215_1215+2delinsCGA/c.1474C>T (p.Arg492Trp) bileşik heterozigot varyantı her bir ailede tespit edildi.
Sonuç: Yüksek doz D vitamini tedavisi ile iyileşmeyen raşitizm hastalarında VDDR-1 düşünülmelidir. VDDR-1'in gecikmiş teşhisi bazı durumlarda gereksiz ortopedik cerrahiye yol açabilir. Erken tanı, tedavi ve genetik danışmanlık verilmesinin ailelere güvenilir ve önemli bilgiler vereceği kanaatindeyiz.

Introduction

The term vitamin D is used for both vitamin D3 (cholecalciferol), which is synthesized in the skin by ultraviolet rays, and vitamin D2 (ergocalciferol) of vegetable origin (1-3). All forms of vitamin D are usually transported in serum by binding to vitamin D binding proteins, while 1-3% of the available vitamin D is in free form. For vitamin D to be effective on the receptors in the target tissue, it must first be converted to 25-hydroxy (OH) vitamin D3 in the liver by 25-hydroxylase and then to 1-25 (OH) 2 vitamin D3 by 1 alpha-hydroxylase in the kidneys (4-6).

Of the hereditary diseases of vitamin D metabolism, vitamin D-dependent Rickets type 1 (VDDR1) is divided into two subgroups. In type 1A (OMIM, #264700), the conversion of 25 (OH) D to 1.25 (OH) 2 D cannot occur due to the lack of 1-α-hydroxylase. In Type 1B (OMIM, #600081), however, the conversion of vitamin D to 25 OH Vitamin D3 cannot occur due to 25-α-hydroxylase deficiency. In VDDR type 2, another hereditary disease, vitamin D receptors (VDR) cannot provide a normal physiological response to 1.25 (OH) 2 D (7). Both conditions are inherited in an autosomal recessive manner. The gene encoding 1-α-hydroxylase, which is responsible for VDDR1, is *CYP27B1*, is located on chromosome 12q14 and consists of 9 exons (8). Patients with 1-α-hydroxylase deficiency may suffer from joint pain and deformity, hypotonia, muscle weakness, growth retardation and, sometimes, hypocalcemic seizures (9-12). Laboratory tests may show hypocalcemia, hypophosphatemia, elevated alkaline phosphatase (ALP), and secondary hyperparathyroidism. Serum 1.25 (OH) 2D levels are low in VDDR1 and high in type 2, which is the differential finding for diagnosis.

Today, more than 70 mutations in the *CYP27B1* gene have been identified (13). In this study, we sequenced the *CYP27B1* gene in 22 VDDR1A patients from 12 different families and detected eight mutations. In this article, we describe the genetic, clinical and biochemical characteristics and treatment of VDDR1A patients.

Materials and Methods

In this study, patients who were diagnosed with VDDR1A were retrospectively analyzed. Age, sex, biochemical parameters, clinical follow-ups, and treatment doses were recorded. Clinical findings of rickets, namely genu varum or genu valgus deformity, greenstick fracture, rachitic rosary, frontal bossing, caput quadratum, Harrison's groove, wrist enlargement, hypotonia, hypocalcemic convulsion, and short stature and physical examination findings were analyzed from patient files. In addition, calcium, phosphorus, ALP, parathyroid hormone (PTH), and 25 (OH) D levels in serum were recorded. 1.25 (OH) 2D levels could not be checked because of the unavailability in our laboratories. Decreases in bone density, enlargement in the growth plate area, irregularity at the metaphyseal margin, brushing, cupping, and bending of the bones were radiologically recorded. Nutritional rickets due to malnutrition, secondary rickets due to chronic diseases, and long-term drug use were excluded. Only patients with pathogenic variants in the *CYP27B1* gene were included.

Verbal and written consent for genetic testing was obtained from patients' families.

Ethical approval was received for this study from the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (decision number: 186, date: 14.12.2018).

CYP27B1 Gene Sequencing

DNA was isolated from peripheral blood sample of patients using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Then, the exons and exon-intron boundaries of the *CYP27B1* gene were amplified for targeted sequencing. Sequencing was carried out using Illumina MiSeq NGS System (Illumina Inc., San Diego, CA, USA). Sequenced data were analyzed with Integrative Genomics Viewer (IGV). The variants were evaluated according to ACMG criteria, DANN, Mutation Taster, SIFT, and Polyphen2. For the splicing defects, we also used Human Splicing Finder program for the prediction. All variations were checked in HGMD-Public version, ClinVar, LOVD, 1000 genome databases, Pubmed and Google search.

Results

The study included 22 patients (11 females, 11 males) diagnosed with VDDR-1A. The median age of the patients at the time of diagnosis was 12 (7.75-18) months. The most common reasons for presentation were slow growth, hypotonia, delay in walking, and convulsions. All patients had elevated PTH and ALP levels. The calcium levels were low in 17 (77.3%) patients, at the lower limit or in the normal range in five (22.7%). Similarly, phosphorus levels were low in 19 (86.4%) and normal in the remainder at diagnosis. Two patients (9.1%) had very high 25OHD levels because they were diagnosed with nutritional rickets and treated with vitamin D. The laboratory and auxological findings of all patients are given in Table 1. Eight of the twelve families had consanguineous marriages.

The *CYP27B1* gene was sequenced in all patients (Table 2). The most common variant was the c.195 + 2T>G splice donor site mutation detected in 12 of 22 (54.5%). This variant was homozygous in 11 patients in the first five families except the 4th patient of the first family who was compound heterozygous with c.1215_1215+2delins CGA variant. Both c.195 + 2T>G and c.1215_1215+2delinsCGA variants were previously identified.

The homozygous c.574A>G (p.Lys192Glu) variant was detected in six patients in the 6th, 7th, and 8th families, the homozygous c.171delG (p.Leu58Cfs*20) variant was detected in the 9th family, the homozygous c.240delT (p.Phe80Leufs*79) variant was detected in the 10th family, and the homozygous c.1166G>A (p.Arg389His) variant was detected in the 11th family. The compound heterozygous c.1215_1215+2delinsCGA/c.1474C>T (p.Arg492Trp) variant was detected in the 12th family. Clinical and laboratory findings were normal in all heterozygous parents. All variants were previously described in the literature (11,12,14,15).

All patients were started on active vitamin D (calcitriol) treatment. The duration of treatment with calcitriol ranged from six months to seventeen years. Biochemical improvement with treatment occurred over 6 to 12 months. The mean calcitriol dose required for clinical, biochemical, and radiological

Table 1. Auxological and biochemical characteristics of VDDR1A patients (n=22)

	Baseline values (n=22)	Last value	Normal
Median age of diagnosis (month)	12 (min-max: 3-180)	-	-
Mean height (SDS)	-1.9 (min-max: -4.03-0.4)	-0.98	-
Mean calcitriol dose (ng/kg/day)	30 (min-max: 14-45)	18	-
Mean follow up (months)	72 (min-max: 24-210)	-	-
Calcium (mg/dL)	7.6±0.98 (min-max: 5.8-9)	9.58±0.5	(8.5-10.5)
Presented with hypocalcemia, n (%)	17 (76.19 %)	-	-
Phosphorus (mg/dL)	2.9±0.77 (min-max: 1.3-4.8)	4.45±0.4	(3.4-6.7)
Presented with hypophosphatemia n (%)	18 (81.8%)	-	-
ALP, (IU/L)	1149±692 (min-max: 349-3054)	291.2±116.3	(30-500)
PTH, (pg/mL)	391±181 (min-max: 129-903)	67.4±49.2	(15-60)
25OHD, (ng/mL)	55±38 (min-max: 23-160)	37.3±10.2	(20-100)

PTH: Parathyroid Hormone, ALP: Alkaline Phosphatase, 25OHD: 25-hydroxy (OH) vitamin D, min: Minimum, max: Maximum

improvement was 30 ng/kg/day. The predicted dose range for calcitriol differed between patients (14-45 ng/kg/day). However, non-adherence to treatment was observed in some patients and such lack of adherence was associated with the differences in dose range. No convulsions observed during the follow-up, significant improvement was observed in leg deformities and height SDS, and none of the patients developed nephrocalcinosis. The clinical and laboratory data of the patients are summarized in Table 2.

Table 2. Laboratory, clinical and genetic characteristics of the patients at diagnosis

		Age of diagnosis/ sex (months)	Clinical findings	Ca (mg/dL)	P (mg/dL)	ALP (IU/L)	PTH (pg/mL)	25(OH) D (ng/mL)	Genetic
1	a (sibling)	8 female	Genu varum	8.7	2.5	1677	903	62	c.195 + 2T> G (homozygous)
	b (sibling)	6 male	Convulsion	6.6	4.8	349	129	45	c.195 + 2T> G (homozygous)
	c cousin	8 female	Hypotonia	8.6	2.3	549	421	56	c.195 + 2T> G (homozygous)
	d cousin	8 female	Fracture	9.2	2.6	564	306	53	c.195 + 2T> G/ c.1215_1215+2delinsCGA (p.T460Efs*69) (compound heterozygous)
2	a (sibling)	12 female	Hypotonia + delay in walking	7	2.5	1388	456	31	c.195 + 2T> G (homozygous)
	b (sibling)	12 female	Hypotonia + delay in walking	7.6	2.5	1194	590	34	c.195 + 2T> G (homozygous)
	c cousin	10 male	Delay in walking	5.8	3.3	644	622	71	c.195 + 2T> G (homozygous)
3	a (sibling)	6 male	Hypotonia + delay in walking	7.8	2.5	3054	390	31	c.195 + 2T> G (homozygous)
	b (sibling)	8 male	Hypotonia + delay in walking	7.2	3.3	461	336	45	c.195 + 2T> G (homozygous)
	c (sibling)	6 male	Convulsion	7	2.5	714	329	70	c.195 + 2T> G (homozygous)
4	-	18 male	Delay in walking	8.1	2.4	2092	427	81	c.195 + 2T> G (homozygous)
5	-	12 female	Delay in walking	7.2	3.7	1042	361	27	c.19S+2T>G (homozygous)
6	a (sibling)	12 female	Hypotonia+ growth retardation	9.3	2.9	1425	370	35	c.574A>G (p.Lys192Glu) homozygous
	b (sibling)	18 male	Short stature	9	2	1281	160	27	c.574A>G (p.Lys192Glu) (homozygous)
	c cousin	36 male	Short stature	7.1	3	547	216	42	c.574A>G (p.Lys192Glu) (homozygous)
7	a (sibling)	54 female	Short stature + genu varum	8.3	4	1230	401	160	c.574A>G (p.Lys192Glu) (homozygous)
	b (sibling)	180 female	bone deformity+ inability to walk	7.9	1.3	2114	304	23	c.574A>G (p.Lys192Glu) (homozygous)
8	-	30 female	Short stature+ genu valgus	6.4	3.3	1847	672	23	c.574A>G (p.Lys192Glu) (homozygous)
9	-	3 male	Convulsion	6.9	4.1	466	189	53	p.L58Cfs* (c.171_171delC) (homozygous)
10	-	7 female	Convulsion	6.3	3.5	382	224	68	c.240_240 delT (p.Phe80Leufs*79) (homozygous)
11	-	13 male	Hypotonia + delay in walking	7.6	2.7	1140	449	160	c.1166G>A (p.Arg389His) (homozygous)
12	-	16 male	Hypotonia + delay in walking	7.4	3	1119	365	23	c.1215_1215+2delTGTinsCGA/ c.1474C>T (p.Arg492Trp) (compound heterozygous)

Discussion

The clinical, biochemical, and genetic characteristics of 22 patients with VDDR-1A were examined. We detected eight previously reported pathogenic variants in the *CYP27B1* gene in 22 patients. The most frequently detected genetic variantion was the c.195 + 2T> G, which affected more than half of the patients. This splice region variant was first described in 2 cases by Durmaz et al. (14) and then in 10 cases by Tahir et al. (15). Clinically, delay in walking, hypotonia, genu varum deformity, and hypocalcemic convulsions were the main findings of our patients. The patients with the same variant were similar to those in previous studies, both in terms of age at presentation and clinical characteristics (14,15). Patients with this variant had a relatively mild clinical phenotype. Hypocalcemic seizures were seen in one case in the report of Tahir et al. (15) and in two cases in our study. The c.1215_1215+2delinsCGA variant detected in patient 1d was earlier described by Demir et al. (16). In patient 1d, unlike other patients, a greenstick fracture was observed. The case reported by Demir et al. (16) presented with delay in walking and growth retardation. There was no consanguinity in non of the first five families with c.195 + 2T> G variant. In these five families, the parents were asymptomatic and were heterozygous carriers for the variant.

The c.574A>G (p.Lys192Glu) homozygous variant detected in the 6th, 7th, and 8th families was previously described in six patients by Tahir et al. (15). Their patients presented with hypocalcemic convulsions, greenstick fracture, delay in walking, and bowed legs. Later, Orbak (17) found the same variant in two siblings who presented with short stature and classical findings of rickets. Patient 6a presented with hypotonia and growth retardation, 6b presented with short stature and genu varum deformity, and 6c only had short stature. The first two cases (6a and 6b) were siblings and they were cousins of the third case (6c). Thus, different clinical characteristics can be present in different individuals, even in the same family. Patient 7a with the same variant presented to the orthopedic clinic of another hospital with short stature and genu varum deformity. She was treated with high-dose vitamin D several times and then surgically operated for the genu varum deformity. The patient had recurrent genu varum deformity, despite the operation, and was subsequently referred to our clinic. This patient, who was initiated on calcitriol treatment, achieved both clinical and biochemical improvement. The leg deformity improved and the patient started walking. Family history revealed that she had a wheelchair-dependent fifteen-year-old older sister who could not walk due to bone deformities. The sister (7b), who had a severe clinical course and diagnosed late, initiated on treatment. However, despite the improvement in laboratory parameters, the same extent of improvement could not be achieved in terms of clinical outcome and mobility. Thus, early diagnosis and treatment are of crucial importance in clinical outcome. In the light of this experience, we believe that every patient with short stature and leg deformity should be referred to pediatric endocrinology clinic rather than orthopedics. Thus, unnecessary, repetitive, and ineffective high-dose vitamin D treatment and surgery can be prevented. Patient 8 with the same variant presented with short stature and genu valgus deformity.

The c.171delG(p.Leu58Cfs*) variant detected in the 9th family was first reported by Tahir et al. (15). Severe hypocalcemic convulsions and greenstick fractures were seen in their case. Similarly, our case presented with hypocalcemic convulsions.

The c.240delT(p.Phe80Leufs*79) variant detected in the 10th family was first reported by Kulıkova et al. (18). The case reported by Kulıkova et al. (18) presented at 17 months old when they were diagnosed with significant short stature, genu varum deformity, rachitic rosary, muscle weakness, rachitic findings in the bone, and a history of frequent lung infections. Our case presented to the clinic at 8 months with hypocalcemic convulsion.

The c.1166G>A (p.Arg389His) (Homozygous) variant detected in the 11th family was first reported by Wang et al. (19). Their case was diagnosed at 13 months of age with growth retardation, delay in walking, and poor gross motor development. Our case presented with similar clinical findings, also at 13 months of age. This patient previously received high-dose vitamin D replacement and was subsequently referred to us due to a lack of improvement in their clinical and biochemical parameters.

We detected compound heterozygous c.1215_1215+2delinsCGA/c.1474C>T (p.Arg492Trp) variants in the 12th family. The c.1215 + 2T>A variant was described by Demir et al. (16) in two families. These earlier cases were diagnosed with growth

retardation, inability to walk, blue sclera, and fractures. The c.1474C>T (p.Arg492Trp) variant was previously reported by Dursun et al. (13) in one patient who presented with a delay in walking. Similarly, our case was diagnosed with a delay in walking and hypotonia.

Laboratory findings, non-response to 25 OH Vitamin D treatment, and satisfactory response to calcitriol appear to be supporting findings for the diagnosis of VDDR1. No correlation was found between genotype-phenotype relationship, type of mutation, age of onset, disease severity, or dose requirements for calcitriol treatment. The genetic diagnosis of patients plays a crucial role in the early diagnosis and treatment. Family screening and genetic counseling is very important for the other, seemingly healthy, family members.

Conclusion

We detected eight mutations in the *CYP27B1* gene in 22 patients from 12 different families. We found that a particular variant did not significantly alter the course of the disease and vice versa, clinical severity could be different in patients with the same variant. Short stature, bone deformities (genu varum/genu valgum), and hypocalcemic convulsions in VDDR-1A cases can be prevented with proper treatment. Misdiagnosis or delayed diagnosis may lead to unnecessary high-dose vitamin D treatments and orthopedic surgery. We believe that VDDR-1A should be considered in rickets cases that do not improve with vitamin D therapy, especially in regions where consanguineous marriages are common. This study will make an important contribution to the literature due to the large number of patients and their long term follow-up.

Ethics

Ethics Committee Approval: Ethical approval was received for this study from the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (decision number: 186, date: 14.12.2018).

Conflict of Interest: No conflict of interest was declared by the authors.

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