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Vitamin D status in children with Crimean-Congo hemorrhagic fever

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ABSTRACT

Background & objectives: Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral disease, causing severe viral hemorrhagic fever outbreaks. This study aimed at determining the serum vitamin D levels and investigated the association between Crimean-Congo hemorrhagic fever (CCHF) and serum vitamin D levels in children with CCHF.

Methods: A total of 45 children aged between 5 and 15 yr, *viz.* 15 healthy control (HC) and 30 pediatric patients diagnosed with CCHF with real-time polymerase chain reaction (PCR) (patient group) were selected for the study.

Results: Analysis of the blood serum samples taken from the said individuals revealed that vitamin D, parathyroid hormone and calcium levels of the patients and the control groups were statistically different.

Interpretation & conclusion: It was found that the serum vitamin D levels of the pediatric patients with CCHF were lower when compared to those of the controls, and that a low vitamin D level could negatively affect the reaction of the body to infections in children having CCHF.

Key words Children; Crimean-Congo hemorrhagic fever; immune response; infection; vitamin D

INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF), caused by viruses (Nairovirus) of the Bunyaviridae family, is a viral hemorrhagic disease having a severe course and carrying a high mortality rate (5–30%)[1–2]. CCHF was first reported in the West Crimean region in 1994. Along with Africa, many Asian and Eastern European countries, including Turkey, are among the countries reporting CCHF, which is a zoonotic disease. CCHF is transmitted to humans either by the bites of infected tick or by direct contact with infected animal blood or other body fluids. Similarly, health workers may be infected with the disease by contact with the blood and other body fluids of an infected person. CCHF symptoms include myalgia, hemorrhage (i.e. petechiae, epistaxis, hematuria, *etc.*), nausea and vomiting[1, 3].

Receptors of active vitamin D have been identified in many tissues such as hypophysis, ovaries, skin, stomach, pancreas, thymus, breast, kidney, parathyroid glands and lymphocytes along with the bone tissue[4]. Presence of vitamin D receptors in different tissues indicates that vitamin D does not only have a regulatory affect on the bone and calcium metabolism but also has some additional functions. Vitamin D maintains the maturation, differentiation and migration in dendritic cells, suppresses the activation in T-cells, stimulates the regulator T-cells and activates the cells of the myeloid and erythroid series, which is an indicator that vitamin D is an important modulator, controlling some of the processes during the reaction of the body to infection[5].

Özkan and Döneray[6] reported that low or insufficient vitamin D levels are related with high incidence of infections in children. The same researchers reported that vitamin D deficiency predisposes the infections. They also indicated that the symptoms of infection occur before the symptoms of skeleton system[6].

Antimicrobial activity of vitamin D has been reported in several studies[7–8]. There are many reports stating that vitamin D deficiency increases susceptibility to diseases such as tuberculosis, otitis media, tonsillitis, respiratory syncytial virus (RSV) infections and influenza[9].

There is no study evaluating the relationship of the vitamin D metabolism in children with CCHF, till now. Therefore, the present study was undertaken for evaluation and determination of the serum vitamin D levels; and investigatation of the association between CCHF and serum vitamin D level in children with CCHF.

MATERIAL & METHODS

The study was conducted on blood and serum samples obtained from a total of 45 children aged between 5 and 15 yr old; which included 30 pediatric patients (study group) reported to the pediatric service of Cumhuriyet University in a four month terms between April and July

of 2011–13, diagnosed with CCHF with real-time PCR and 15 healthy controls (HC), all residing in the same region. Exclusion criteria were as follows: presence of rickets, hyperparathyroidism, hypoparathyroidism, systemic diseases including chronic renal failure, diabetes mellitus, ischemic heart disease and malignancy; trauma, heavy exercise, and the use of drugs with potential effects on biochemical parameters. An ethical approval was obtained from the Ethical Committee of the Medical Faculty of Cumhuriyet University (Decision No: 2011-02/03).

Real-time PCR analyses for CCHF diagnosis were carried out at Refik Saydam Hygiene Center, Turkey which is a national reference laboratory. Serum biochemical analyses were conducted by an autoanalyzer (Mindray BS 200; PRC). Serum 25-hydroxy vitamin D [25(OH) vitamin D] and parathyroid hormone (PTH) levels were determined using chemiluminescence (Abott I 2000; USA) method. Levene test was used to evaluate the changes in serum biochemical values and haematological parameters while the homogeneity of the group variances were tested using the Student's *t*-test. Statistical comparisons of the groups were made by SPSS 14.0 package program (SPSS Inc, Chicago, Illinois, USA).

RESULTS

The average vitamin D, PTH, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium (Ca), phosphorus (P), haemoglobin and white blood cell (WBC) values of the children with CCHF and HC of the same age are depicted in Table 1. Moreover, serum vitamin D, PTH, ALT, AST, Ca, *p*-values of the patient and HC are compared in Fig. 1.

When the HC and the patient group were compared in terms of vitamin D, PTH, ALT, AST, Ca, P and WBC values, it was found that serum vitamin D, Ca and P levels were lower and PTH, ALT, AST and WBC values were higher in the patient group. In terms of all the said values, there was a statistically significant difference between the groups.

Table 1. The average serum vitamin D, PTH, ALT, AST, Ca, P, haemoglobin and WBC values of the patient and control groups in children

Measurements	HC		CCHF		*p*-value
	N	Mean±SE	N	Mean±SE	
Vitamin D	15	31.25±1.25	30	16.99±1.54	6.04*
PTH	9	27.24±2.63	26	43.33±5.47	2.93**
ALT	14	17.50±2.77	30	48.67±9.57	3.13**
AST	14	32.07±2.18	30	119.97±20.38	4.29*
Calcium	15	10.18±0.10	30	8.65±0.08	11.63*
Phosphorus	12	5.05±0.09	30	3.66±0.16	7.69*
WBC	13	8.02±0.74	29	2748.97±228	11.98*

HC— Healthy control; N—Number of samples; PTH—Parathyroid hormone; ALT— Alanine aminotransferase; AST—Aspartate aminotransferase; WBC—White blood cell; *p<0.001; **p<0.01.

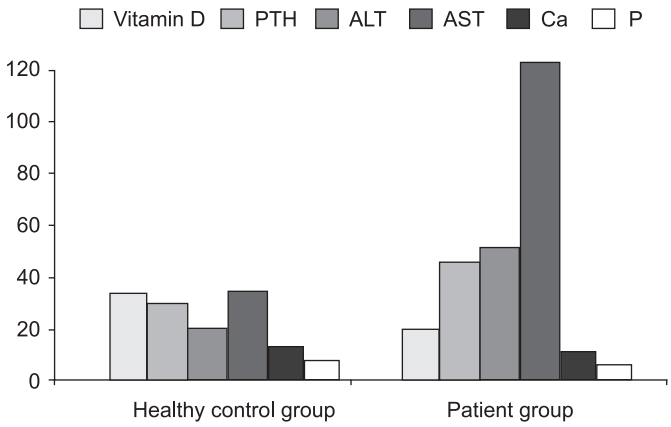

Fig. 1: Comparison of serum vitamin D, alanine amino transferase (ALT), aspartate amino transferase (AST), calcium (Ca), and phosphorus (P) values in children of patient and healthy control groups.

DISCUSSION

CCHF involves the multiorgan systems in which severe cases of CCHF are characterized by hemorrhagic manifestations, disseminated intravascular coagulation, vascular dysfunction, and shock[1–2]. The specific mechanisms underlying the pathogenesis of the CCHF infection have not been clearly explained yet. The most important targets are mononuclear phagocytes, hepatocytes, and endothelial cells for the CCHF virus[10–11]. Active 25(OH)D vitamin receptors are defined in all immune system cells especially T and B lymphocytes, macrophages and dendritic cells[12–13]. All active 25(OH)D vitamin increases the phagocytosis of macrophages and natural killer cells and alteration in its level affects the immune system[14]. Similar study has shown that the secretion of pro-inflammatory cytokines (IFN-γ, IL-2, TNF-α) increases due to potent Th1 response after 25(OH)D vitamin deficiency[15]. These studies demonstrated that the immune response is deteriorated through affected leucocyte chemotaxis, and so disposition to infections becomes more probable. Previous studies have reported that vitamin D deficiency increases susceptibility to infectious diseases (i.e. tuberculosis, otitis media, tonsillitis, upper respiratory infections, RSV infections and influenza)[9]. It has been reported by the researchers that the level of 25 (OH)D, which is an active form of circulating vitamin D

having a half-life 2 to 3 wk, should be assessed in order to decide whether vitamin D level is normal, low or high in patients. It has been proved that a 25(OH)D level should be regarded as insufficient if it is lower than 20 ng/ml, deficient if it is between 21 and 29 ng/ml and normal if it is between 30 and 150 ng/ml[16]. In the present study, conducted on children diagnosed with CCHF with real-time PCR, the serum levels of vitamin D were calculated as 4–19 ng/ml in 20 patients and 23–30 ng/ml in 10 patients, while the average value of vitamin D was 16.99±1.54 ng/ml. The said value can be interpreted as insufficient vitamin D in a great majority of children diagnosed with CCHF. The rate of increase in vitamin D deficiency in children with CCHF is thought to be originated from the winter hold over in Sivas, Turkey and damage caused by CCHF in organs such as liver and kidney which play important roles in vitamin D metabolism.

Shin *et al*[17] reported that 1, 25 (OH)2 D3 produced the expression of CD14 acting as a co-receptor of toll-like receptors (TLRs) playing an important role in the antimicrobial activity against intracellular pathogens. Engin *et al*[18] studied that TLR8 Met1Val, TLR8-129C/G and TLR9-1486T/C polymorphisms are important in clinical course of CCHF disease. Supporting these previous studies, finding out a statistically significant difference between the serum 25(OH)D levels of the patient group and the controls, points out that serum 25(OH)D level should be sufficient in children with CCHF to increase the activation of the body's defence.

It was inferred in the current study that 25(OH)D levels were statistically significantly lower in children with CCHF when compared to the HC groups ($p<0.001$). This forms an opinion that lower serum 25(OH)D levels facilitate the onset of infections. This opinion is supported by a study conducted by Karatekin *et al*[19] reporting that serum 25(OH)D levels are lower in baby with acute respiratory infection but no rickets; and by a study of Muhe *et al*[20] reporting that the risk of developing pneumonia is increased in individuals with rickets. Also, calcium and phosphorus levels of the children with CCHF were found to be lower when compared to the controls; however, these were within the levels considered normal for children both in the patient group and the control group.

The study also proves that the patients had significantly higher PTHs when compared to the controls, which is consistent with the literature data indicating that PTH has a role in vitamin D metabolism, PTH-activated 1-α hydroxylase enzyme regulation in kidney, stimulatation of the synthesis of vitamin 1, 25(OH)D; and there is a negative feedback mechanism between vitamin D metabolites and PTH[21].

As a result, it was concluded that children with CCHF had lower serum vitamin D levels when compared to the control group, and low vitamin D levels could negatively affect the response of body to infection. Hence, serum levels of vitamin D should be tracked in patients with CCHF and lack of vitamin D should be taken into consideration while planning of treatment.

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