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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

The relationship between idiopathic chest pain, Vitamin D deficiency and insufficiency in school children and adolescents

Okul çocuğu ve ergenlerde nedeni belli olmayan göğüs ağrısının vitamin D eksikliği ve yetersizliği ile olan ilişkisi

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ABSTRACT

Objective: The aim of this study is to determine an association between vitamin D status and idiopathic chest pain in school children and adolescents.

Methods: Included in the study were a control group of 60 healthy children for comparison with 120 school children and adolescents referred to our pediatric cardiology department, after being diagnosed with idiopathic chest pain. A patient's examination included taking a history and doing a physical examination, chest radiograph, electrocardiogram, echocardiogram complete blood count, and 25-hydroxyvitamin D and troponin I levels.

Results: Age, gender distribution, and body mass index were not statistically different between the control and study groups (p=0.7, p=0.2 and p=0.3, respectively). Histories of the patients with idiopathic chest pain revealed 22% with heart disease and 6% with recent death in the family. Chest pain was present for 1 month in 19.2%, and for <1 month in 79.2% of the patients. Location of the patients' chest pain was in the left precordium (64%), right precordium (32%) and midsternal area (18%). Frequency and duration of the pain were variable. Serum vitamin D levels were significantly lower in the study group than in the controls (p<0.0001), but except for alkaline phosphatase, other biochemical parameters did not differ to a statistically significantly degree. The duration of symptoms and episodes increased as vitamin D levels decreased (r= 0.621, p=0.002 and r=0.213, p=0.02, respectively).

Conclusion: In pediatric patients, there is a significant association between vitamin D deficiency/ insufficiency and the duration and frequency of idiopathic chest pain in pediatric patients.

Key words: Idiopathic chest pain, vitamin D deficiency, child

ÖZET

Amaç: Okul çocuğu ve ergenlerde, nedeni bilinmeyen göğüs ağrısı ile vitamin D düzeyinin ilişkisini belirlemek amaçlanmıştır.

Yöntemler: Çalışmamıza, nedeni bilinmeyen göğüs ağrısı şikayeti ile pediatrik kardiyoloji birimimize başvuran 120 okul çocuğu ve ergen ile genel polikliniğimize başvuran 60 sağlıklı kontrol hastası alındı. Öykü alınması ve fizik muayenenin ardından, biyokimyasal testler (tam kan sayımı, kan biyokimyası, troponin I ve vitamin D düzeyi) akciğer grafisi, elektrokardiyogram, ekokardiyogram tüm hastalarda değerlendirildi.

Bulgular: Çalışma grubu ile kontrol grubu arasında yaş, cinsiyet dağılımı ve vücut kitle indeksi açısından anlamlı fark saptanmadı (sırasıyla, p=0,7, 0,2 ve 0,3). Çalışma grubunda %22 hastanın aile öyküsünde kalp hastalığı, %6 'sında ani ölüm olduğu saptandı. Çalışma grubunda, göğüs ağrısının %19,2 hastada 1 aydır, %79,2 hastada 1 aydan uzun sürdüğü; %64'ünde sol prekordiyumda, %32'sinde sağ prekordiyumda, %18'inde midsternal alanda olduğu öğrenildi. Göğüs ağrısı sıklığı ve süresi değişkendi. Serum vitamin D düzeyi çalışma grubunda kontrol hastalarına göre anlamlı derecede düşüktü (p< 0,0001). Alkalen fosfataz dışında biyokimyasal parametrelerde iki grup arasında fark saptanmadı. Göğüs ağrısı süresi ve ağrı sıklığı serum vitamin D düzeyi düşüklüğü ile ilşikili bulundu (r= 0,621, p=0,002 ve r=0,213, p=0,02).

Sonuç: Çocukluk çağında sebebi bilinmeyen göğüs ağrısının süresi ve sıklığı ile serum vitamin D eksiliği ve yetersizliği arasında ilişki saptanmıştır.

Anahtar kelimeler: nedeni belli olmayan göğüs ağrısı, vitamin D eksikliği, çocuk

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INTRODUCTION

Chest pain, a common presenting symptom in general pediatric clinics, causes anxiety in both patients and their families. Pediatricians are also concerned because chest pain may indicate an underlying cardiac disease. An emergent evaluation is required for acute chest pain because of its association with fatal heart diseases; however, serious organic causes are unlikely in children, whether the chest pain is acute or chronic [1-6].

The most common causes of chest pain among children are musculoskeletal conditions (e.g., costochondritis, slipping rib syndrome, or precordial catch), gastrointestinal disorders, pulmonary diseases, and psychogenic causes. Cardiac etiology is reported in 0-15% of patients [7-11]. Chest pain may have a psychogenic etiology in as many as 30% of cases [5,6,9] and may also be accompanied by other recurrent somatic complaints [12,13]. After thorough evaluation, a substantial proportion of cases of chest pain are found to have no obvious cause and are therefore classified as idiopathic [6,7].

Vitamin D deficiency is often an underestimated issue in children with idiopathic chest pain. Vitamin D is essential for mineralization of bone, calcium, phosphorus homeostasis, and neuromuscular conduction [14]. Low vitamin D levels can lead to rickets in children and osteomalacia and muscle weakness in adolescents and adults [15,16]. Moderate osteopenia that leads to musculoskeletal pain might be the underlying condition in idiopathic chest pain in children. The aim of this study is to determine if idiopathic chest pain in school children and adolescents correlates with low vitamin D status.

METHODS

Patients

This prospective study involved 120 school children and adolescents referred to our pediatric cardiology department with the primary complaint of chest pain. A control group of 60 healthy volunteers living in the same city were evaluated during the same period. Excluded from the study were cigarette smokers and drug users and children whose chest pain was the result of a cardiac problem (e.g., myocarditis, acute rheumatic fever, pericarditis, or mitral valve prolapse), pulmonary problems (severe asthma, pneumonia, pleural effusion, etc.), gastrointestinal problems (such as esophagitis, gastritis, and motility disorders), or other chronic diseases. Also excluded were overweight and obese patients those whose body mass index was >95.

All the patients were examined by both a pediatrician and a pediatric cardiologist and were evaluated according to a protocol which included taking a history and doing a physical examination, chest radiograph, electrocardiogram, and echocardiogram. Serum biochemical markers included calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), a complete blood count, and 25OHD and troponin I levels. We evaluated the chest radiograph, echocardiogram, and electrocardiogram of each patient for an indication of chest pain and any patient with an abnormal electrocardiogram or echocardiogram were excluded from the study.

The study was conducted between September 2011 and April 2012 in our clinic. We obtained written informed consent from parents and approval from our university's ethical committee.

Metabolic analysis and cardiac imaging

Vitamin D levels were analyzed by the electrochemiluminescense enzyme immunoassay method (ECLIA) (ADVIA Centaur, USADPC Co., USA). Levels between 10 and 20 ng/ml were considered insufficient and < 10 ng/ml were considered deficient [17]. Troponin I levels were analyzed by ELİZA (Siemens Centaur, USA) and complete blood counts were analyzed by the impedance technique (Rosch, Sysme XP1800i). We measured serum Ca, P, and ALP levels with the calorimetric method and determined serum PTH by electrochemiluminescense enzyme immunoassay method using the PTH kit (ADVIA Centaur, USADPC Co., USA).

Transthoracic echocardiography was performed using the Royal Philips Electronics of the Netherlands Philips HG-11 System with a 3.5 or 5 MHz transducer. Electrocardiograms were evaluated by the pediatric cardiologist using the Mortara Instruments electrocardiography system.

Statistical Analysis

The SPSS statistical program for Windows version 19 (SPSS Inc., Chicago, Illinois, USA), was used to perform data analysis. The Shapiro-Wilk test was

used for the analysis of compliance with normal distribution. Normally distributed continuous data is presented as a mean ± standard deviation (SD) and normal variables are presented as counts and/or percentages. Non-normally distributed continuous data is presented as a mean ± SD with the median parameters in brackets. For statistical comparison of group data, Student's t test was used for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables. Spearman correlation analysis was used for multiple comparisons. Incidences in groups were tested for significance using the Chi-square test. All statistical tests were two-sided. A p value of < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

The study group consisted of 120 children (57 boys, 63 girls) aged 9-17 (mean 11.66 ±2.17 years) and a control group of 60 healthy children (28 boys and 32 girls) aged 9-17 (11.73 ±2.04 years). Age, gender distribution, and BMI were not statistically different between the control and study groups (p=0.7, p=0.2, and p=0.3, respectively).

The histories of the study group patients revealed 22% with heart disease in the family and 6% with recent death in the family. The frequency and duration of the pain were variable (Table 1). Chest pain was found to be present for 1 month in 19.2% and < 1 month in 79.2% of the patients. Chest pain was located in the left precordium (64%), right precordium (32%), and mid-sternal area (18%), but none radiated to an upper extremity or shoulder. Most of the patients described their pain as sudden and sharp (<1 minute), both with exercise and at rest. There was no relationship between chest pain and deep breathing or body position. Associated symptoms (palpitations, dyspnea, dizziness, syncope, vomiting, regurgitation, painful swallowing, or heartburn) were not reported in all children.

Table 1. Pain characteristics of the study group

		n (120)	%
Duration of symptoms	Single episode	12	10
	< 1 week	23	19.2
	1week to 1 month	60	50
	>1 month to 6 months	23	19.2
	>6 months	2	1.6
Frequency of pain	Single episode	10	8.3
	<1 per month	21	17.5
	1 week to <1 per week	19	15.8
	1 week to <1 per day	23	19.2
	Once or more per day	47	39.1
Duration of episodes	<1 minute	59	49.1
	1-15 minutes	57	47.5
	15 minutes-1 hour	4	3.3
	> 1 hour to 1 day	-	0
Quality of pain	Sharp	102	85
	Pressure	12	10
	Tightness	2	1.6
	Squeezing	2	1.6
	Burning	2	1.6
Location of pain	Left	64	53.3
	Right	32	26.6
	Diffuse	6	30
	Mid-sternal	18	15
	Radiation to left upper extremity or shoulder.	-	0

Physical exams detected pectus excavatus in two children although their blood pressure as well as cardiological and respiratory signs were normal.

All the patients had troponin I levels performed at the first assessment; no abnormal results were obtained. Their serum biochemical markers included calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), 25OHD, parathormone (PTH), and a complete blood count were measured. Serum vitamin D levels were significantly lower in the study group than in the controls ($p<0.0001$) (Figure 1), but those patients with vitamin D levels <20 ng/ml showed normal initial biochemical parameters except alkaline phosphatase (Table 2).

Spearman correlation tests showed that the duration of the symptoms and the duration of the episodes increased to a statistically significant degree as serum vitamin D levels decreased significantly ($r= 0.621$, $p=0.002$ and $r=0.213$, $p=0.02$, respectively). Vitamin D levels did not change the frequency, location, and quality of pain statistically (Table 3).

Table 2. Laboratory examinations of the patients with idiopathic chest pain

Variable	Group 1* mean± SD (n=120)	Group2 ** mean± SD (n=60)	p
25(OH)D (ng/ml)	11.5±5.3	23.8±3.3	0.0001
Ca (mg/dl)	9.6±0.4	10.2±0.4	0.547
P (mg/dl)	4.69±0.6	5.2±0.4	0.328
ALP(U/L)	200.3±79.8	152.2±50.2	0.006
PTH(pg/ml)	58.2± 5	56.1±5	0.79
Hb (g/dl)	12.4±1.2	12.6±1.3	0.99
Hct (%)	37.7±3.2	39.4±3.2	0.86
MCV (fl)	82.9±5.5	84.8±5.5	0.85
Troponin I	0.001±0.001	-	-

SD: standard deviation, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase, PTH: parathormone, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume

*Group 1: Children with chest pain**Group 2: Healthy children(control group)

Table 3. The correlation analysis of features of the pain with vitamin D levels

		Duration of symptoms	Frequency of pain	Duration of episodes	Quality of pain	Location of pain
25OHD (ng/ml)	r	0.621[a]	0.212	0.213[b]	-0.403	-0.243

*Spearman correlation test, [a]Correlation is significant at the 0.01 level (2-tailed); [b]Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

The etiology of chest pain depends on whether the symptoms are acute or chronic, but in children rarely is the pain due to cardiac disease. The most common causes of the chest pain in children and adolescents is idiopathic (21-59%), which may, however, be accompained by pulmonary (12-24%), physiologic (17-19%), musculoskeletal (7-16%), or gastrointestinal (5-7%) disorders [18]. These accompanying disorders are what lead doctors to require an extensive diagnostic work-up. In the present study, all the children with chest pain had normal physical findings on their detailed cardiological evaluation (i.e.,chest radiogragh, electrocardiogram, troponin I, and echocardiogram), except two children with pectus excavatus. No pathologies were detected in any chest radiogragh, electrocardiogram, troponin I levels, or echocardiogram.

The complete blood counts and other biochemical markers (except 25OHD and alkaline phosphatase) were found to be normal in both the study and control groups. Biochemical parameters seen in osteomalacia such as hypocalcaemia, hypophosphatemia, and hyperparathyroidism were not detected in these children, probably because the duration of vitamin D insufficiency and deficiency was not long enough to cause abnormal biochemical findings. The major stimulus for PTH secretion is a low level of serum ionized calcium that can be detected in severe vitamin D deficiency (vitamin D level < 10ng/ml), so children with vitamin D insufficiency (vitamin D levels between 10-20 ng/ml) showed no evidence of hypocalcemia or increased production of PTH in our study. Concentrations of 25(OH)D and intestinal calcium absorption did not appear to decline until 25OHD concentrations fell to 4 ng/ml or less, a level generally considered to be indica-

tive of severe vitamin D deficiency [19]. After a thorough evaluation confirmed no specific, obvious organic cause of the chest pain in the children, such cases were considered idiopathic.

This study examines vitamin D status and its possible association with chest pain. In toddlers, vitamin D deficiency can cause severe skeletal symptoms depending on the time of onset. Osteopenia a condition linked with very low levels of vitamin D, may lead to musculoskeletal pain such as school children and adolescents usually suffer [15], but data are limited as to the etiology of the idiopathic chest pain and its relationship with childhood osteopenia. Heidari et al. from Iran [15] found a positive association between vitamin D deficiency and non-specific skeletal pain-particularly in adolescent girls-which could be explained by conservative clothing which blocks exposure of skin to sunlight. The relationship between bone mineral densities, osteocalsin levels, and musculoskeletal chest pain in healthy children was studied by Sanlı et al. who suggested that musculoskeletal chest pain may be due to reduced bone mineral metabolism [20]. Another study conducted by Roberto et al. revealed that bone mineral density was significantly lower in children with hypermotility and musculoskeletal pain than in the healthy control group [21]. In our study, vitamin D levels in study group were significantly lower than those in the healthy controls confirming the recent studies. Our patients typically had no serious underlying organic medical condition and although the pain usually repeated, symptoms in general resolved over time.

The mean age of the occurrence of the chest pain was found to be 11 years, confirming previous studies that pre-adolescents and adolescents (especially those 12-15 years of age) were at high risk of vitamin D deficiency [22]. Since the bone turnover increases because of growth spurts in this age group, if calcium and vitamin D supplementation and exposure of sunlight is insufficient, then vitamin D deficiency could occur with clinical manifestations such as musculoskeletal pain. Considering when this study was conducted (September 2011 - April 2012), we can conclude that the vitamin D stores formed by summer sun exposure were inadequate to maintain sufficient levels throughout the winter. Vitamin D studies in the literature support the finding of seasonal variation [22].

Studies in adults note diffuse skeletal pain in conjunction with low vitamin D levels [23-26]. For patients with documented vitamin D deficiency and nonspecific, persistent musculoskeletal pain, vitamin D replacement therapy is advised. In a double blind placebo controlled study, adult patients with 25OHD levels of 10-25 ng/ml were randomized to receive either high dose vitamin D supplementation (50,000 IU weekly per 8 weeks) or a placebo. Compared to the placebo group the treated group showed significantly greater improvement in fibromyalgia symptom scores [27]. A similar study conducted by Warner et al., [28] showed contradictory results: the patients with diffuse musculoskeletal pain or osteoarthritis were given vitamin D for 3 months but had no improvement in their pain compared with baseline or placebo-treated patients.

According to the 2008 data from the American Academy of Pediatrics, all infants, children, and adolescents should receive 400 IU/day of vitamin D through diet or supplements [29]. Vitamin D supplementation should be continued throughout childhood and adolescence.

The most important limitation of the present study is its cross-sectional design. The statistical interpretation would be stronger if the study were performed as a case- crossover design in patients receiving vitamin D therapy and if the patients were evaluated after vitamin D supplementation.

In conclusion, a substantial proportion of children who present with chest pain, the etiology of the pain, remains unknown even after detailed evaluation. Our findings indicate a significant association between vitamin D deficiency and idiopathic chest pain in pediatric patients, but it is difficult to determine this result is incidental or if low vitamin D level is a cause of their idiopathic chest pain. The relationship between chest pain and vitamin D deficiency and insufficiency should be verified with other studies. In cases where organic causes are excluded by the primary care physicians, those children would be evaluated for musculoskletal pain and osteopenia before being referred to cardiology. Our study also showed the importance of vitamin D supplementation in order to maintain bone health throughout childhood and adolescence.

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