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Alkaline Phosphatase and Insuline-Like Growth Factor-1 Levels in Tayanç-Prasad Syndrome: A Case Report

Tayanç-Prasad Sendromu Olgusunda Alkalen Fosfataz ve İnsülin Benzeri Büyüme Faktörü-1 Düzeyi: Bir Olgu Sunumu

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ABSTRACT

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Tayanç-Prasad Syndrome is characterized by geophagia, iron deficiency anemia, hepatosplenomegaly, skin changes, hypogonadism, and retardation of growth and development. A 13.5 year-old female patient who had geophagia for approximately 5–6 years, presented with an ongoing diarrhea 3–4 days a week for the last 4–5 years, headache, loss of appetite, palpitations, and pallor for one year. The patient had an iron deficiency anemia, and low levels of ALP (alkaline phosphatase) and IGF-1 (insulin-like growth factor-1). The patient was treated with ferroglycine sulfate and zinc sulfate. After the 6 month follow-up, there were an increase in height of approximately 2 cm, a weight gain of 6.7 kg, a chest girth increment of 5.5 cm, and an increment of the upper mid-arm circumference of 4 cm. The hepatosplenomegaly disappeared. Anemia and ALP level improved significantly. As a result, zinc deficiency should be suspected in a patient with iron deficiency anemia, low ALP levels, as well as geophagia. Although decreased levels of zinc, ALP and IGF-1 were detected in this particular case, more research is required in a larger number of patients.

Key words: *alkaline phosphatase; anemia; insulin-like growth factor 1; iron deficiency; pica*

ÖZET

Tayanç-Prasad sendrom'u geofaji, demir eksikliği anemisi, hepatosplenomegali, deri değişiklikleri, hipogonadizm, büyüme ve gelişme geriliği ile karakterizedir. Yaklaşık 5–6 yıldan beri geofajisi olan 13,5 yaşındaki kız hastanın 4–5 yıldan beri haftada 3–4 gün devam eden ishali, bir yıldan beri baş ağrısı, iştahsızlığı, çarpıntısı ve solukluğu vardı. Demir eksikliği anemisi tespit edilen hastanın, ALP (alkalen fosfataz)'ı ve IGF-1 (insulin-like growth factor-1)'i düzeyleri düşüktü. Hastaya ferroglycine sülfat ve çinko sülfat başlandı. Yaklaşık 6 aylık takibinde 2 cm boy uzaması, 6,7 kg kilo alımı, göğüs çevresi artımı 5,5 cm, üst/orta kol çevresi artımı 4 cm oldu. Karaciğer ve dalak büyüklüğü kayboldu. Hastanın anemisi ve ALP belirgin bir şekilde düzeldi. Sonuç olarak; demir eksikliği anemisi olan ve ALP'ı düşük bulunan bir hastada geofaji de varsa çinko eksikliğinden şüphelenilmelidir. Bir olgu nedeniyle çinko, ALP ve IGF-1 düzeyinde azalma saptanmış olmakla birlikte daha fazla hasta grubunda araştırma yapılmalıdır.

Anahtar kelimeler: *alkalen fosfataz; anemi; insülin benzeri büyüme faktörü 1; demir eksikliği; pika*

Introduction

Tayanç-Prasad Syndrome is characterized by iron deficiency anemia, hepatosplenomegaly, skin changes, hypogonadism, retardation of growth and development and geophagia (eating soil, clay, etc.). Anemia, growth retardation and hepatosplenomegaly in soil-eating children was first reported by Dr. M. Memduh Tayanç in 1942 and the disease was named as Tayanç syndrome. Syndrome was described by Prasad in Iranian patients in 1960 as well. In his studies in Egypt in 1963, Prasad demonstrated the presence of zinc deficiency in patients with Prasad Syndrome. He reported that the zinc deficiency is usually accompanied by iron deficiency anemia in developing countries[1].

In patients with geophagia chronic zinc deficiency was responsible for changes of the small intestines. Chronic zinc deficiency causes malabsorption of zinc and iron as well[2] and both elements are necessary for normal growth and development.

Growth factor (GF) is one of the most important factors needed for growth and development, and

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it is the main regulator of the IGF-1 (insulin-like growth factor-1) in a human being with an optimum nutritional supply. It provides the growth through its actions on IGF-1 and by stimulation of its main binder, IGFBP-3 (insulin-like growth factor binding protein-3)[3]. In a study conducted on children with zinc deficiency and growth retardation, but no systemic disease, serum IGF-1 and IGFBP-3 levels were decreased and serum levels of IGF-1 and IGFBP-3 were elevated after the zinc treatment[4].

Although the Tayanç-Prasad Syndrome, which is thought to result from geophagia in the pediatric age group is well known among the physicians in Turkey, publications dealing with the details of the syndrome is lacking. Therefore, we aimed to present a case of a Tayanç-Prasad Syndrome, with its pathological anthropometric measurements, accompanied by iron deficiency anemia, and decreased serum levels of zinc, IGF-1 and ALP to take attention on the presentation of the syndrome.

Case report

A 13.5 year–old girl who ate soil, lime, ash or specify what else she ate, approximately for 5–6 years was admitted to our clinic. Approximately for 4–5 years, she had complaints of bloodless diarrhea of watery consistency, without mucus, 3–4 times a day, continuing 3–4 days a week. She also had a foul-smelling defecation and vomiting right after eating. In addition, she complained of headache, dizziness, tinnitus, sweating, fever, loss of appetite, fatigue, palpitations and had pallor for the last one year.

From her medical and social background we learned that the patient had been breast-fed for four years and began to talk at 4 years of age. Having poor socioeconomic conditions, she had a diet poor in animal protein and rich in grains. There was no consanguinity between parents, and she had a 21 year-old brother and an 8 year-old sister, who were both healthy.

Initial physical examination findings were as follows: body temperature: 37º C, heart rate: 96/min, blood pressure 100/60 mmHg, height: 131 cm (SDS: -4.2), body weight: 24kg (SDS: -3.9), chest circumference: 61 cm, upper/mid-arm circumference: 16 cm, body mass index: 14 kg/m^2 (3%), bone age: 8 years of age.

The conjunctiva and the face were pale; there was sparse hair, no axillary or pubic hair growth, no breast development (Tanner 1). The liver was palpable 5 cm under the costal arch, and the spleen was 3 cm palpable (Figure 1). Vitamin B_{12} and folic acid levels were within normal ranges, and the serum antibodies to gliadin and endomysium were negative. There was no parasites and blood in stool.

The laboratory findings at the time of initial admission and duing the follow up visits were summarized in Table 1. In addition to the findings summarized in Table 1, at the time of initial admission the serum iron binding capacity, luteinizing hormone, follicle stimulating hormone, thyroid stimulating hormone, triiodothyronine, zinc and insulin-like growth factor 1 levels were 348 μg/dL, <0.10 (0.20 to 5 mIU/mL), 0.30 (1 to 10.8 mIU/mL), 1.45 (0.25–5μIU/mL), 3.59 (4 –8.3 pmol/L), 60 (64–118 μg/dl) and 80 (220–616 ng/mL), respectively.

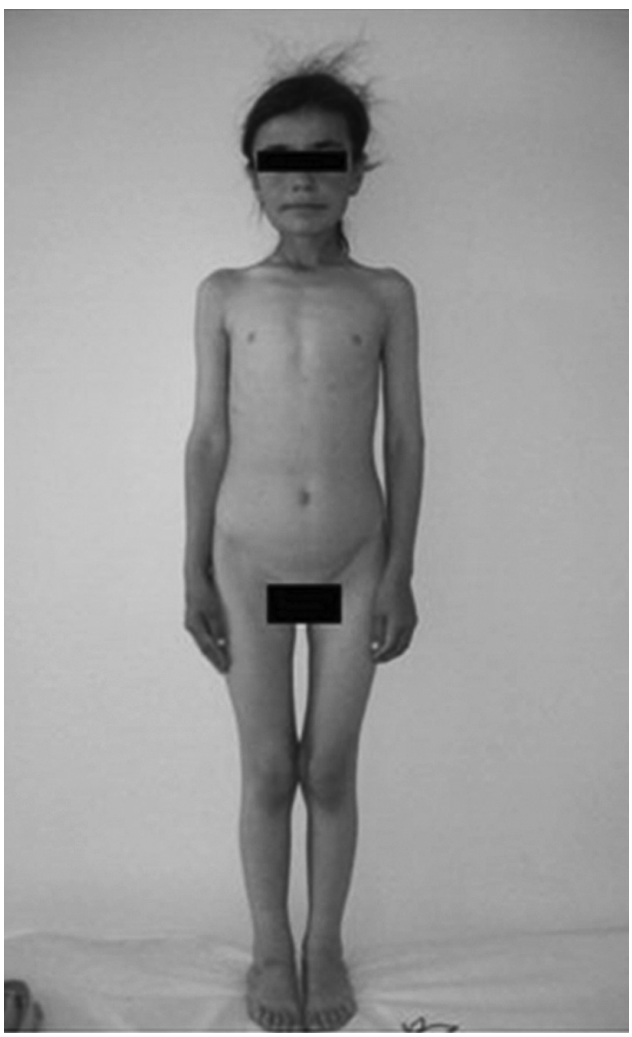

Figure 1. *Although the calendar age was 13.5 years (bone age 8 years), the patient with Tayanç-Prasad Syndrome had no signs of puberty.*

Table 1. *The change of the hematological findings after the treatment of the 13.5 year old girl diagnosed with Tayanç-Pradas Syndrome*

Date	ALP	Hb	Hct	MCV	MCH	MCHC	RDW	SI	TIBC	Ferritin
Month 0	91	5.9	20.9	56	15.7	28.1	20.01	22	348	1.96
Month 1	59	5.2	18.5	56	15.8	28.1	20.9	49	406	–
Month 2	68	5.7	20.2	57	16.1	28.3	18.7	30	440	–
Month 3	33	6.5	23.4	57	16	27.9	19.9	–	336	–
Month 4	192	9	29.5	57	17.4	30.4	16.9	39	450	<1.5
Month 5	181	9.6	31.3	57	17.6	30.7	17.4	39	439	2.17
Month 6	205	12,6	37,9	67	22,2	33,3	16	40	405	2,6

ALP: Alkaline phosphatase (105–420 U/L), Hb: Hemoglobin (12–16 g/dl), Hct: Hematocrit (%37–47), MCV: Mean corpuscular volume (80 fL), MHC: Mean corpuscular hemoglobin (26,5–33,5 pg), MHCH: Mean corpuscular hemoglobin concentration (31,5–35 g/dlL), RDW: Red distribution width (%10–15), SI: Serum iron (22–184 µg/dL), TIBC: Total iron binding capacity (250–400 µg/dL), Ferritin: (7–140 ng/mL)

Since the condition was chronic, we considered that the anemia was compensated. Therefore, we did not give red blood cells, but 6mg/kg ferroglycine sulphate in three doses, and 2mg/kg zinc sulfate in three doses. After the first week of treatment, the appetite improved and the diarrhea disappeared in the second week. All the complaints disappeared six months after the initiation of the treatment. After a 6 month follow-up, her height and weight increased two cm and 6.7 kg, respectively. She also had a chest girth increment of 5.5 cm, and an increment of the upper/mid-arm circumference of 4 cm. The hepatosplenomegaly resolved, and the anemia and ALP levels improved significantly. The patient and her parents gave informed consent for publication.

Discussion

Zinc in human body was first identified by Erasmus Ebender in 1509. The importance of zinc for the growth of Aspergillus niger was first described in 1869. Its deficiency in animals was first demonstrated in mice in 1934.

In 1940, it was found that the enzyme carbonic anhydrase requires zinc for its catalytic activity, which established the biological function of zinc. Anemia, growth retardation and hepatosplenomegaly in soil-eating children was first reported by Dr. M. Memduh Tayanç in 1942. In 1963, the human dietary zinc deficiency was reported by Prasad, for the first time. Prasad was also the first researcher who stated that zinc is essential in humans.

In 1974 the National Academy of Food and Nutrition Council of America considered zinc as an essential element for humans and the statement was supported by the subsequent studies. Phytate is abundantly present in grain and possibly causes zinc deficiency by inhibiting its absorption. In later years, some investigators began to question the zinc deficiency in humans. Thanks to a significant improvement in the early 1970s, the discussion ended. A genetic disorder, acrodermatitis enteropathica, a fatal disease, characterized by a disorder of the absorption of zinc in the diet was reported and the disease was completely cured by zinc[5].

Zinc takes place in the growth and the proliferation of all cells, and in the active structure of the enzymes. It serves as a structural support for intracellular proteins of the molecular interactions. It provides the stability and the integrity of the biological membranes and the ion channels and is involved in receptor function and structure of the steroid hormones. In addition it plays a role in the catalytic regions of the enzymes[6]. Although the first zinc metalloenzyme, carbonic anhydrase, was defined by Keil and Mann in 1940, in the early 1960s, only three of the other zinc metalloenzymes (alcohol dehydrogenase, carboxypeptidase and alkaline phosphatase) were known. Today, the zinc metalloenzymes have been reported in all classes of enzymes. More than 300 catalytically active zinc metalloproteins have been described[1].

Prasad have observed that the low ALP levels returned to the normal values after treatment with a well-balanced diet of animal proteins (that contains sufficiently zinc), and iron preparations (that contains a small amount of zinc). He has attributed this result to the diminished activity of ALP, which is a zinc–dependent metalloenzyme, due to the zinc

deficiency[1]. The ALP was significantly low in our patient. However, as a result of a balanced diet with animal proteins and iron replacement therapy for about 3 months, an increase in ALP levels to the normal range was noticed (Table 1). In communities with an insufficient consumption of proteins, a frequent consumption of grains, and a frequent habit of eating soil, zinc deficiency should be suspected in a patient with an iron deficiency anemia and low levels of ALP.

We have learned from the recent publications that the zinc deficiency frequency increased in our country[7–9]. Because of the high cation-binding capacity of the clay and the soil, the phytate found in the grain protein, inhibits the absorption of both the iron and the zinc[1,5]. The chronic zinc deficiency is responsible for the changes in the small intestine mucosa, in geophagia. A shortening, blunting, and flattening of the villi in the small intestine occur, which in turn leads to an iron and zinc malabsorption[2]. Our patient had all the mentioned factors. She was fed with grain-based foods, consumed too little proteins, ate soil, which resulted in chronic diarrhea, and eventually malabsorption of iron and zinc. The patient was advised a protein-rich and grain-free diet, as far as possible. The drawbacks of eating soil were explained. After the etiological factors were eliminated, and the iron replacement therapy was started, her appetite was improved at the end of the first week, and the diarrhea in the second week, then the other physical examination and the laboratory findings improved.

The GH is particularly important for the cell proliferation. It provides the growth, through IGF-1 and by stimulation of its main binder, IGFBP-3. The IGF-1 is secreted by the liver and it is low in patients with malnutrition. Insulin, thyroid hormone, and cortisol also have an impact on IGF-1 levels. The IGF-1 increases with the increase of sex hormones during adolescence[3].

Growth retardation is a major problem in patients with thalassemia major and the hyperzincuria in thalassemia patients may be a cause of developmental delay. In these patients, a decreased IGF-1 activity due to zinc deficiency was found. In patients with thalassemia major, the zinc therapy has been shown to have positive effects on the development. The zinc therapy, given at an early age at the proper dosage has been reported to be useful in the treatment[10]. In a case study with Tayanç-Prasad's syndrome, Karaca et al. have found low levels of IGF-1, and demonstrated that by iron and zinc treatment, not only the normal IGF-1 levels were achieved, but the anemia, the hypogonadism, and the other clinical findings improved, as well[7]. In another case study with Tayanç–Prasad's syndrome, Demirel et al. have shown decreased levels of IGF-1 and IGFBP-3, and by means of a detailed endocrinological evaluation, a partial growth hormone deficiency and hypogonadotropic hypogonadism were determined[8]. They have reported that anemia, hypogonadism, and other clinical symptoms were all treated by GH, iron and zinc therapy. In our patient, all the anthropometric parameters were pathologically low, and she had no pubertal development despite the age of 13.5 years. Although we were unable to study the growth hormone to evaluate the growth retardation, a very low level of IGF-1 (60 ng/mL) was found. The reason for the low IGF-1 level may be due to the decreased IGF-1 activity related with the zinc deficiency, malnutrition, decreased free T3 levels, iron deficiency anemia and insufficient steroids, because she was not in puberty yet.

Normally, between four years of age and 10–12 years of age, when the puberty begins, there is an increase of 5–6 cm in height annually[11]. The patient's determined FSH/LH levels were equal to the prepubescent levels. She had a hypogonadotropic hypogonadism. We were not able to determine whether there was a partial/full growth hormone deficiency, by a detailed endocrinological evaluation. However, after about 6 months of (zinc and iron) treatment, there was a height increase of approximately 2 cm, a weight gain of 6.7 kg, a chest girth increment of 5.5 cm, and an increment of the upper/mid-arm circumference of 4 cm. The hepatosplenomegaly disappeared. The patient's anemia and ALP improved significantly.

Thyroid hormones have impact on the growth both via the direct effect on the growth of the bone (osteogenesis) and by stimulating the growth hormone-IGF-1 axis[3]. Our patient had a TSH value within normal limits and a low T3 value. The decreased T3 levels may be a result of malnutrition.

As a conclusion, iron deficiency and geophagia are a major problem, especially in the children of the rural communities in countries like ours, in which the main food source is grains, with insufficient consumption of proteins[12]. The association of iron deficiency anemia and decreased levels of ALP in a patient with geophagia should raise the suspicion of zinc deficiency.

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