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**Case report**

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## Pubertal arrest due to Zn deficiency The effect of zinc supplementation

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### ABSTRACT

The Prasad Syndrome is characterized by iron deficiency anemia, hepatosplenomegaly, skin changes, hypogonadism, dwarfism and geophagia. Hypogonadism is a major manifestation of zinc (Zn) deficiency in both humans and animals. The mechanism of hypogonadism caused by Zn deficiency has not been clarified. We present a 19 year-old boy with short stature, pubertal arrest, iron deficiency anemia and Zn deficiency. Based on the dynamic tests, the hypogonadism seems to be due to hypothalamic dysfunction. The growth retardation was associated with low IGF-I and normal growth hormone (GH) secretion, indicating GH receptor or post receptor defect. Growth acceleration and testicular development was observed after Zn supplementation. Zn deficiency, although very rare, should be considered in patients with poor growth and hypogonadism associated with skin changes and anemia.

**Key words:** Anemia, Gonadal axis, Hypogonadism, Pubertal arrest, Zinc deficiency

### INTRODUCTION

The Prasad Syndrome, first reported by Prasad et al in 1960, is clinically characterized by iron deficiency anemia, hepatosplenomegaly, skin changes, hypogonadism, dwarfism and geophagia. Since these findings could not be solely explained by iron deficiency, the possibility of Zn deficiency was suggested.<sup>1</sup> Zn deficiency was first documented in Egyptian

subjects with growth retardation.<sup>2</sup> Further studies showed that the growth rate was higher in subjects who received supplemental Zn than in those who received iron instead or an adequate animal-protein diet. Gonadal changes were also reversed by Zn supplementation.<sup>3</sup>

It was initially suggested that hypogonadism seen in Zn deficiency was due to decreased pituitary gonadotropin output.<sup>1,4</sup> However, studies later showed that the effect of Zn deficiency was exerted directly on testicular steroidogenesis, whereas gonadotropins were found not to be affected.<sup>4,6</sup> Other studies indicated that Zn deficiency may be associated with increased Follicle stimulating hormone (FSH) and

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normal Luteinizing hormones (LH) levels.<sup>7,8</sup>

In developing countries, zinc deficiency is still present and is usually associated with iron deficiency.<sup>2,9,10</sup> Hypogonadism is a major manifestation of Zn deficiency in both humans and animals. The mechanism of hypogonadism due to Zn deficiency has not been clarified.

Although primary or secondary hypogonadism due to Zn deficiency has been reported, pubertal arrest due to Zn deficiency has not to our knowledge been described. We therefore present a case of Zn deficiency and pubertal arrest, which was reversed by Zn supplementation.

### PATIENT DESCRIPTION

The patient was a 19 year-old male from a rural area of Central Anatolia. He lived with his parents, whose socioeconomical status was low, resulting in his diet generally being poor in animal protein. He was first admitted to the hospital complaining of fatigue and short stature. He had visual problems at school, but an eye examination had not been carried out.

The medical history revealed geophagia and anorexia in his childhood. On physical examination there was scarce scalp hair and no axillary or pubic hair had developed. Hepatosplenomegaly was detected. His height was 141 cm (SDS:-5.2), body weight was 41 kg (SDS:-2.5) and body mass index

was 20.7kg/m<sup>2</sup> (15-50 percentile). The testicular volume was 8 and 10 ml for the left and the right testis, respectively.

The complete blood count was compatible with iron deficiency anemia (Hb 5.3g/dl; MCV 52 fl; peripheral blood smear showed hypochromic-microcytic anemia; serum ferritin 1.3ng/ml (normal range: 22-322ng/ml); serum iron 6µg/dl (normal range: 65-175µg/dl); serum iron binding capacity 444µg/dl (normal range: 70-380µg/dl). Serum concentration of Zn was 0.43µg/ml (normal range: 0.5-1.2µg/ml). Serum biochemistry was normal, except for increased levels of alkaline phosphatase 160U/l (normal range: 38-126U/l). Duodenal biopsy showed normal appearance of the mucosa.

The bone age was 11 years. The thyroid hormone levels and serum prolactin (PRL) levels were within the normal ranges. Gonadotropins, testosterone (T), free testosterone (FT) and insulin like growth factor-1 (IGF-1) levels were low (Table 1). Insulin tolerance test (ITT), Gonadotropin releasing hormone (GnRH) and human chorionic gonadotropin (hCG) stimulation tests were performed and the responses were normal (Tables 2, 3, 4). Pituitary magnetic resonance imaging showed no abnormality.

His eye examination prior to Zn supplementation revealed partial keratopathy and signs of optic atrophy; the optic discs were pale, visual acuity of the patient was decreased and minimal latency was observed in the visual evoked potentials.

**Table 1.** Basal values of Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Testosterone (T), Free testosterone (FT), and Insulin growth factor-I (IGF-I) before and after Zn supplementation.

|                | FSH IU/L<br>(1.4-18.1) | LH IU/L<br>(1.5-9.3) | T nmol/L<br>(9.86-21.6) | FT nmol/L<br>(0.04-0.08) | IGF-I µg/L<br>(197-476) |
|----------------|------------------------|----------------------|-------------------------|--------------------------|-------------------------|
| Pre-treatment  | 0.48                   | 1.1                  | 5.63                    | 0.005                    | 119                     |
| Post-treatment | 1.5                    | 3.68                 | 31.6                    | 0.024                    | 480                     |

\*normal values in parenthesis

**Table 2.** Response of cortisol and growth hormone to insulin induced hypoglycemia prior to Zn administration.

|                       | Basal level | Peak response* |
|-----------------------|-------------|----------------|
| Cortisol (nmol/L)     | 370.5       | 735.5          |
| Growth hormone (µg/L) | 0.91        | 11.5           |

\*Simultaneous blood glucose: 0.66 mmol/L

**Table 3.** Response of LH and FSH to gonadotropin releasing hormones (GnRH) stimulation prior to Zn administration.

|            | Basal level | Peak response |
|------------|-------------|---------------|
| FSH (IU/L) | 1.15        | 2.31          |
| LH (IU/L)  | 2.58        | 20.46         |

**Table 4.** Response of serum testosterone (T) and free testosterone (FT) to human chorionic gonadotropin (hCG) stimulation prior to Zn administration

|            | Basal | After 48 hours | After 72 hours |
|------------|-------|----------------|----------------|
| T (nmol/L) | 5.63  | 33.37          | 22.2           |
| FT(nmol/L) | 0.005 | 0.101          | 0.071          |

Based on the physical examination and the laboratory results, the patient's condition was diagnosed as pubertal arrest due to Zn deficiency. Following intravenous replacement of 300mg/day ferric hydroxyl sucrose for 5 days, the patient received 160mg/day ferrous sulphate and 50mg/day Zn for 6 months.

After 6 months, his complaints were resolved. He had a weight gain of 5.5kg and his height increased by 7cm. Testicular volume increased up to 15 and 18 ml for the left and the right testis, respectively. Axillary and pubic hair appeared and there was also increase in scalp hair. His anemia improved markedly (Hb 15.5gr/dl) and basal serum levels of gonadotropins, T, FT and IGF-1, increased to normal range (Table 1). The patient reported that his vision was better after Zn supplementation, but eye examination was not carried out.

## DISCUSSION

The importance of zinc (Zn) for the growth of *Aspergillus niger* was recognized for the first time in 1869. Several decades later, it was reported that Zn should be present in sufficient amounts for the growth of the plant and the rat.<sup>11</sup> Essentiality of Zn in man was first described by Prasad<sup>1</sup> and later studies supported this.<sup>2,3</sup> The presumptive cause of Zn deficiency was phytate, present in cereal grains, which impairs the absorption of Zn.<sup>2,3</sup> During the following decade some investigators questioned the existence of Zn deficiency in humans.<sup>11</sup> An important development in the early 1970s ended the controversy. A fatal genetic disorder, Acrodermatitis Enteropathica caused by a defect in the absorption of dietary Zn, was reported. The disorder was completely cured by Zn supplementation.<sup>12</sup>

Before the recognition of Zn deficiency, a group of patients with the findings of anemia, hepatosplenomegaly and hypogonadism were treated with

1 g/day ferrous sulfate and animal protein. Anemia and hepatosplenomegaly improved, while pubic hair and size of genitalia increased in these patients. Retrospectively, it was thought that the pharmaceutical preparation of iron also contained Zn as a concomitant and along with a well-balanced diet containing animal protein provided sufficient amounts of Zn, which led to improvement of the hypogonadism.<sup>11</sup>

Animal protein is the most important dietary source of bioavailable iron and Zn. Phytate, which is present in cereal proteins, inhibits the absorption of both iron and Zn.<sup>11</sup> Clinical iron deficiency anemia is one of the features of the Zn deficiency syndrome. Therefore, it was not surprising to detect iron deficiency besides Zn deficiency in our patient. Excepting the experimental studies, Zn deficiency without iron deficiency has not been reported. As far as we know, lack of testicular development due to iron deficiency has not been reported either. Thus, the pubertal arrest seen in our patient cannot be explained by iron deficiency alone.

It was initially suggested that Zn deficiency caused hypogonadotropic hypogonadism.<sup>1,4</sup> However, studies later showed that the effect of Zn deficiency was exerted directly on testicular steroidogenesis and that the gonadotropins were not affected.<sup>4,6</sup>

In our patient, we demonstrated a decrease in both serum gonadotropins as well as T and FT levels. Hence, the patient had hypogonadotropic hypogonadism, and since the testicular volume was greater than 4 ml, we assumed that puberty had started but was arrested due to Zn deficiency.

An experimental study in man demonstrated that Zn deficiency was associated with decreased sperm counts and serum T levels. In that study serum FSH levels were found to be increased and there was no change in the serum LH level. The increase in serum T after GnRH stimulation was lower, but the gonadotropin response was greater after Zn restriction in comparison to the stabilization period.<sup>7</sup>

An animal study has demonstrated that Zn deficiency has no effect on pituitary gonadotropin output and that Zn deficiency most likely affects testicular function, either directly through its effect on testicular steroidogenesis and/or indirectly through its

effect on the pituitary synthesis and/or secretion of prolactin.<sup>4</sup> A correlation between serum T levels and cellular Zn levels has been described in healthy adults.<sup>13</sup>

Despite the studies demonstrating an effect of Zn directly on testicular function,<sup>4,12,13</sup> in our patient the findings are compatible with hypothalamic dysfunction. The gonadotropins were decreased, but rose post GnRH stimulation and gonadal response to hCG was preserved. Since the gonadotropins and T levels returned to normal after Zn supplementation, we can suggest that Zn has a role in the function of the hypothalamic pituitary gonadal axis.

In conclusion, Zn deficiency can lead to pubertal arrest, possibly through its effect on hypothalamic function, which is reversible by Zn supplementation. More studies are needed to understand the effect of Zn on the gonadal axis.

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