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Carotene rich diet and hypogonadism
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·*Case Report*·

Association of carotene rich diet with hypogonadism in a male athlete

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Abstract

Aim: To report on a unique case of hypogonadism associated with excessive carotene intake in a young male athlete. **Case report:** A 20-year-old patient presented with a gradual decline in muscular and physical activity, sexual interest and erectile ability associated with a high in carotene and low in animal fat diet of his own design a year prior to the clinical manifestations. Clinically, he presented with very overt signs of carotene excess: his palms and soles were yellow. Moreover, 2 weeks after normalization of his diet, carotene B levels were at the upper end of the normal range. **Methods:** Repeated stimulation tests of hypothalamic, pituitary and testicular function were performed before and at 3, 6 and 12 months after the introduction of a balanced diet. **Results:** Very low basal and stimulated values for gonadotropins and gonadal steroids were found at the initial evaluation with a progressive recovery shown after months of a balanced diet and carotene B restoration. Complete androgen secretion and sexual response recovery were observed only after 9–12 months from diagnosis. **Conclusion:** This is the first report associating excessive carotene intake with a hypothalamic form of hypogonadism in a young man. (*Asian J Androl 2006 Jul; 8: 488–492*)

Keywords: carotinoids; hypogonadism; male

1 Introduction

Carotenoids are a large group of vitamin A-related compounds with pigmenting properties that are present in large quantities in carrots, broccoli, spinach, pumpkins, tomatoes and other vegetables. Diets addressing the needs of young people for body building or for athletic performance improvement are rich in this type of vegetables and natural carotenoids [1, 2].

Average dietary or supplementary intake of carotenoids has been credited with important biological actions on several tissues [3]. However, excessive consumption of these substances has been associated with hepatic, blood and central nervous system disorders [4, 5]. Moreover, high carotenoid intake has been linked to reproductive system problems in female athletes with amenorrhea without weight loss [6–8]. In a study by Kemmann *et al.* [7], normalization of dietary habits resulted in restoration of the menstrual cycle.

Information regarding the potential effects of excessive carotenoid intake on male gonadal function has never been reported. This is probably related to the fact that gonadal failure in men is not as easily manifested as in women and certainly needs more time to become clinically evident.

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The purpose of this report is to describe a case of hypogonadism that developed after a very high dietary carotenoid intake in a young male athlete. Restoration of his eating habits resulted in normalization of gonadal function.

2 Clinical case

2.1 History

A 20-year-old amateur boxer reported to the endocrine clinic with a gradual drop in sexual desire, progressive erectile dysfunction (ED) and an inability to ejaculate during the last 3–4 months. The patient had an unremarkable medical history and led a healthy life (no smoking or alcohol) with a 3-h daily-training schedule for the last 4 years. He denied the use of any prohibited substances such as anabolic steroids, cannabis and androgens.

2.2 Diet

His daily diet included fish, milk and eggs and liberal quantities of bread and fruit. Moreover, his routine included daily consumption of 500 g of carrots, 500 g of broccoli and large portions of lettuce, tomatoes, cabbage and garlic. These are all vegetables rich in carotenoids. A notable feature of his diet was a total restriction on animal meat and fat. This type of diet was introduced more than a year before the problem became evident and the diet was of his own design.

2.3 Physical examination

The patient had a normal body habitus (height: 178 cm, weight 73.6 kg) with well-developed sexual characteristics. On palpation testicular volume was approximately 10 mL in each side and a left varicocele was present (grade II). A diffuse enlargement of his thyroid gland (~30–35 g) was evident on palpation. A striking feature of his appearance was the yellow color of his palms and soles. Moreover, from his very entrance to the examination room, an intense fishy-like odor from his body was evident.

3 Investigations

Investigations included a general health examination and evaluation of the hypothalamic-pituitary-gonadal axis. Most of the latter tests were performed on several occasions during his care whereas carotene B measurements were made twice.

3.1 Initial laboratory evaluations

Basal values for testosterone (T: 55 μg/mL, normal range: 270–1 100 μg/mL), estradiol (E_2: 10 pg/mL, normal range: 10–40 pg/mL), sex hormone binding globulin (23 nmol/L, normal range: 10–55 nmol/L), follicle stimulating hormone (FSH: 0.3 IU/L, normal range: 1.0–8.0 IU/L), luteini-zing hormone (LH: 0.5 IU/L, normal range: 1.4–11.0 IU/L) and inhibin-B (74 μg/mL, normal range: 140–260 μg/mL) were well below the normal range. Following initial evaluation, dynamic assessments were performed per level of the endocrine axis:

a. A battery of hematological and biochemical tests was within the normal range with the exception of marginal increases for serum glutamic-oxaloacetic transaminase (SGOT) (49.0 IU/mL, normal range: 10–43 IU/mL), folic acid (21.3 ng/mL, normal range: 3.0–16.0 ng/mL), total bilirubin (1.4 mg/dL, normal range: 0.1–1.2 mg/dL), and direct bilirubin levels (1.2 mg/dL, normal range: 0.1–0.3 mg/dL). Serum cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides were all at the lowest end of the normal range. Measurements of vitamin A (470 ng/mL, normal range: 200–850 ng/mL) and vitamin $1.25(OH)_2D_3$ (39 pg/mL, normal range: 10–74 pg/mL) were satisfactory, whereas carotene B levels were at the upper end of the range (73 μg/mL, normal range: 10–80 μg/mL). Sampling for this substance was made 2 weeks after normalization of the patient's diet.

b. Hypothalamic-pituitary-gonadal tests (Figure 1):

i. Tamoxifen citrate (TMX) administration (20 mg/day) with FSH, LH and T estimations before and after 10 days [9]. Basal and stimulated gonadotropins were low before and after TMX (FSH: 0.4 IU/mL, LH: 0.2 IU/mL).

ii. Gonadotropin Releasing Hormone (GnRH) challenge (bolus 100 μg i.v.) failed to increase the low basal gonadotropin secretion.

iii. Human chorionic gonadotropin (hCG) stimulation (bolus 1 500 IU, i.m. × 3 days) showed very low basal secretion and a relatively small rise for T, but a decline for E_2.

c. Basal concentrations of deydroepiandrosterone sulphate, prolactin, TSH, ACTH, GH, insulin-like growth factor-I, cortisol, free-triiodothyronine and free thyroxine, were all within the normal range.

d. Gas chromatography-mass spectrometry at the Athens Olympics Control Laboratory failed to identify any anabolics, androgens, *etc*. in a supervised collection

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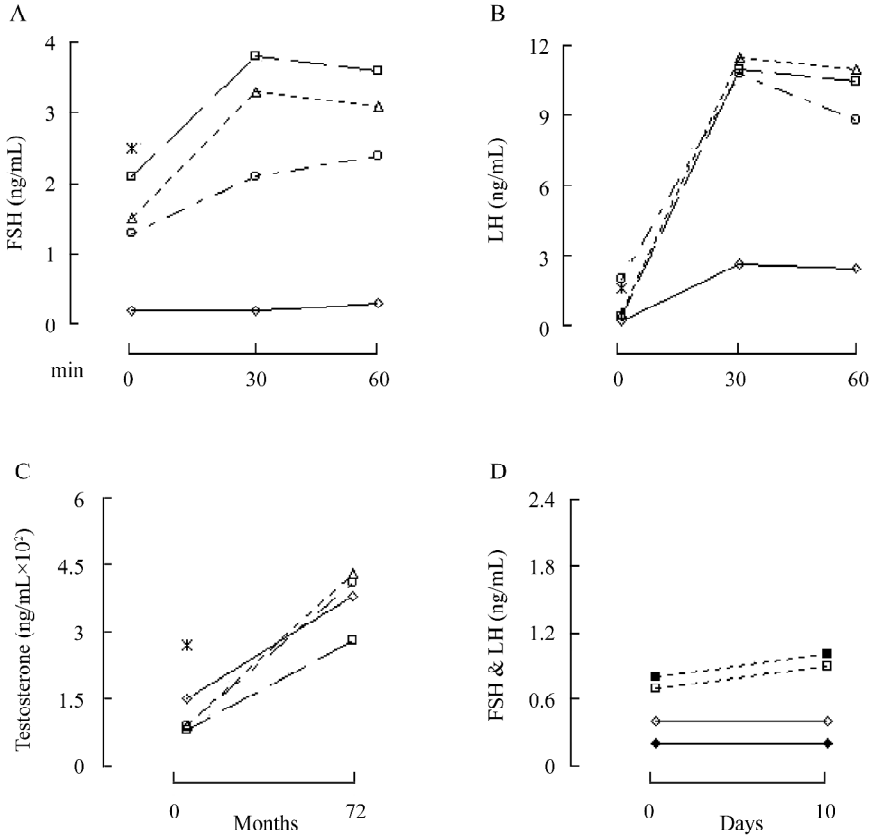

Figure 1. (A): Follicle stimulating hormone (FSH) and (B): Luteinizing hormone (LH) response to GnRH challenge. (C): Testosterone response to hCG. (D): FSH and LH response to tamoxifen citrate. (A)-(C): ◇, initial; □, 3 months; △, 6 months; ○, 12 months; ∗, basal at 18 months; (D): ◇, FSH initial; ◆, LH initial; □, FSH 3 months; ■, LH 3 months.

of a 24 h urine sample.

e. Magnetic Resonance Imaging (MRI) of the hypothalamic-pituitary region revealed no lesions except for a 2.0 mm formation towards the posterior part of the fossa described as of no consequence. On ultrasound, the testes were homogeneous (left 9.0 mL, right 10.2 mL), and a left varicocele was present (II to III grade, World Health Organization criteria).

f. Semen analysis was requested but could not be performed because of the patient's inability to achieve erection and ejaculation.

3.2 Physical and gonadal activity

Physical and gonadal activities were properly evaluated. The patient experienced a significant decline of his muscular power, was unable to train and had to withdraw his participation from an amateur boxers' tournament.

He also reported a total lack of sexual drive, with lack of morning erections, failure to masturbate and inability to ejaculate. Prior to the problem, this young man was very keen in pursuing female companionship.

He reported occasional hot flashes and a marked reduction in his facial hair's growth rate, limiting his shaving requirements from 3–4 times to once per week.

3.2 Follow-up investigations and treatment

a. Routine hematology, biochemistry and hormonal assessments were normal at all evaluation time-points. At 6 months, serum vitamin A (347 ng/mL) and carotene-B (51 μg/mL) were substantially lower than those in the initial evaluation.

b. Endocrine evaluations (Figure 1):

i. TMX test at 3 months showed basal and response values slightly higher than those in the initial test (basal: FSH-0.7 ng/mL, LH-0.8 ng/mL; stimulated:

FSH-0.9 ng/mL, LH-1.0 ng/mL).

ii. GnRH test at 3, 6, 12 months and basal gonadotropin values at 18 months showed a gradual improvement as compared to the initial evaluation.

iii. hCG test at 3, 6 and 12 months showed a normal response at 6 and 12 months, whereas at 18 and 24 months basal T was 263 and 360 ng/mL, respectively.

c. Sperm evaluation became possible at 8 months, with seminal volume 1.8 mL, spermatozoa concentration 26.0×10^6/mL, good motility 34% and normal morphology 39% [10].

d. Physical, gonadal and sexual activity: After the initial work-up and as a result of his poor psychological condition, the patient requested androgen substitution for a short period. For this reason, testosterone undecanoate was prescribed (40 mg × 3/day, for 6 weeks). This androgen at the dose given exerts very little, if any, suppressive action at hypothalamic-pituitary-testicular level. As a result of this treatment, basal T climbed up to 217 ng/mL and a partial muscular and physical fitness recovery was reported, but with poor sexual drive and erectile power. The yellow color of his skin and the fishy-like smell of his body disappeared about 9–10 weeks following normalization of his diet. Testicular size has gradually increased to a volume of approximately 15.0 mL on each side at 12 months. At 18 and 24 months, T (263–360 ng/mL), FSH (2.2–3.2 ng/mL) and LH (2.1–1.4 ng/mL) were normal. At that time, the patient felt strong enough to resume full training in preparation for a tournament and he had morning erections and occasional sexual activity. His body weight climbed gradually from 73.6 to 81.0 kg after 12 months, and following a restrictive diet in preparation for a contest, it was stabilized at 76.0–78.0 kg. It is important to note that his appetite, initially reduced, became satisfactory soon after changing his diet.

4 Discussion

This is the first presentation of a case with secondary hypogonadism associated with excessive carotene intake in a young man. The patient had most of the characteristics of hypothalamic hypogonadism but also evidence of primary testicular failure. Successive challenging tests demonstrated low functional reserves of gonadotropins and T when compared to eugonadal men [9]. Because there was no evidence of other endocrinopathy or carotene raising systemic condition in the patient and his body weight remained relatively constant, his condition was assumed to be related to his dietary habits. Furthermore, drastic changes in his diet led to a drop in carotene B level, gradual reduction of his skin discoloration, disappearance of his body odor, progressive restoration of his muscular power, ability to train and psychological well-being.

Repeated endocrine evaluations during diet normalization showed a slow recovery of gonadotropins and T secretion. Sexual drive, erectile ability and performance were also rather late to return as was testicular volume increase. However, when a moderate increase of gonadotropins and T concentration occurred the young man recovered his erectile ability and produced a reasonable sperm sample. Of interest was the dissociation between the stimulation tests performed at 3-month follow-up when the pituitary response to GnRH was relatively satisfactory whereas the hypothalamic centers were resistant to TMX stimulation. This observation was indicative of a sustained hypothalamic involvement and lends strong support to the central suppressive effect of carotene excess in this case.

Although a large but unspecified number of young men and athletes have been following similar empirical diets for several decades, information regarding hypogonadism developing in men after prolonged, carotene-rich diets has not been presented up to now. The impact of similar diets on the menstrual cycle has been well documented for some time [6–8]. Apparently, the prompt demonstration of reproductive dysfunction in women is more easily recognized as amenorrhea than hypogonadism in men.

A contributing factor might have been the negligible amount of red meat and fat in his diet. In this context, the very lean constitution of his body might have played a role through the leptin-reproductive axis [10, 11]. Unfortunately, leptin concentrations were not determined.

A finding of uncertain origin was the fish-like smell of the patient. One might hypothesize that the abundance of fish and vitamins A and D in his diet had some bearing on it.

Finally, of interest was the low Leydig cell reserve initially observed as compared to an approximate 50% and 100% increase expected for T and E_2, respectively, in eugonadal men [9]. This inadequacy might have been a result of the prolonged LH hyposecretion but also because of a primary testicular involvement. This failure was temporary because a gradual return towards normality was noted at the final stages of recovery. It is of

interest that gonadal involvement has been demonstrated in hyper-carotenemic women with secondary amenorrhea and so described "golden" ovaries [12].

In conclusion, this was a case of a young man with temporary hypogonadism related to a high carotene diet. From the evidence presented it appears that the low central and peripheral activity was brought about by a diet high in carotenes. Introduction of a balanced diet reversed the endocrine failure and restored the gonadal activity.

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