Devastating Effect of Uncontrolled Corticosteroid Usage: Severe Growth Retardation in Juvenile Rheumatoid Arthritis

Kontrolsüz Kortikosteroid Kullanımının Yıkıcı Etkisi: Juvenil Romatoid Artritli Bir Hastada Gelişme Geriliği Olgusu

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Abstract
A 22-year-old male patient was admitted to the hospital with complaints of retardation in physical and sexual development. He had been diagnosed with juvenile rheumatoid arthritis 15 years previously and treated with salicylazosulfapyridine 2x2 g and 30 mg prednisolone daily since diagnosis. His height was 109 cm (less than 3rd percentile), and his weight was 24 kg (less than 3rd percentile). He had no beard, mustache, axillary, or pubic hair, and had a cushingoid appearance. He had neither erection nor ejaculation. Growth retardation has been shown in patients with juvenile rheumatoid arthritis. This undesired effect may be due to both severe chronic inflammation and to long-term usage of corticosteroids. Corticosteroids can cause inhibition of pubertal and sexual development by affecting directly or indirectly all components of brain-pituitary-gonad axis. We report this patient to emphasize that although corticosteroids are effective in the treatment of juvenile rheumatoid arthritis, they may have devastating effects on the physical, sexual, and psychological development when used in high doses. Turk Jem 2008; 12: 57-9

Key words: Growth retardation, high dose steroid, juvenile rheumatoid arthritis

Özet

Anahtar kelimeler: Büyüme geriliği, yüksek doz steroid, juvenil romatoid artrit

Introduction
Most known side effects of corticosteroid (CS) treatment are osteoporosis, glucose intolerance, and secondary infections due to immune suppression. Corticosteroids can also inhibit the hypothalamo-hypophysio-adrenal system, resulting in irreversible sexual and physical development delay or retardation (1-3). We here report the effects of inappropriate CS treatment on physical, sexual, and psychological development of a young male patient.

Case Report
A 22-year-old male was seen in our department for evaluation of physical and sexual retardation. On physical examination, his height was 109 cm (less than 3rd percentile), weight 24 kg (less than 3rd percentile), and he had a cushingoid appearance (Figure 1). He had buffalo hump, moon face, and purple striae of the extremities. His knee and hip movements were restricted and painful. Cardiovascular, pulmonary, and abdominal examination were normal. His sexual development was Tanner stage 1. He had no history of erection or ejaculation. When he was 8 years old, he was diagnosed with juvenile rheumatoid arthritis (JRA), after a history of recurrent fever, arthralgia, and swelling of joints, particularly the knee joints. He treated with salicylazosulfapyridine 2x2 g and 30 mg prednisolone daily for 14 years. During follow-up, when corticosteroid therapy was tapered or stopped, symptoms recurred, and CS therapy had to be continued.
restarted. Methotrexate (MTX) 5 mg/week was added to his medications during his tenth year of therapy. Despite this treatment, he had recurrent symptoms of fever, arthralgia, and swelling of joints. He has had two operations for cataract and glaucoma.

On laboratory analysis, biochemical parameters were normal, but hemoglobin level was 10.1 g/dL, leukocyte count was 12,400/mm$^3$, platelet count was 263,000/mm$^3$, and erythrocyte sedimentation rate was 35 mm/hour. He was on folate replacement therapy because of his long-term methotrexate usage. Hormone levels are shown in Table 1.

After initial evaluation and detection of low IGF-1 level, a stimulation test for growth hormone was performed. Growth hormone levels after stimulation by insulin hypoglycemia and L-dopa tests were 57 ng/mL and 10.40 ng/mL, respectively. These results indicated no growth hormone deficiency. Plain radiographs revealed deformations and clear evidence of osteoporosis at vertebrae, pelvis, and hips, as well as aseptic necrotic appearance of both femur heads. All epiphyses were closed, and bone age was consistent with an age of 16 years. Bone mineral densitometry measured the lowest vertebral T score as -5.77 (Z score -5.32), lowest femur neck T score as -5.54 (Z score -5.21).

Furthermore, we evaluated sex hormone levels because of the patient’s retardation in sexual development. Although FSH and LH levels were normal, testosterone levels were below the normal range (Table 1). Human chorionic gonadotropin (HCG) stimulation (5000 IU) was performed for consecutive four days. Free testosterone levels were 1.14 pg/mL and 1.22 pg/mL on 4th and 5th days, respectively. Total testosterone levels were 0.12 ng/mL and 0.18 ng/mL on 4th and 5th days, respectively. There was no response to HCG test. Orchidometric volume of both testes were 5 mL. After consulting with colleagues in the rheumatology department, we decreased the CS dose to 12 mg/day methylprednisolone and increased the MTX dose to 10 mg/week. During this treatment, he had an attack of arthralgia and fever, thus we were unable to lower the CS dose further.

Discussion

Corticosteroids in supraphysiological doses may result in severe side effects, such as inhibition of the hypothalamo-hypophysio-adrenal system, Cushing syndrome, short stature, osteoporosis, secondary infections, and aseptic necrosis of the femoral head (1). Growth retardation has been shown in patients with JRA, and this undesired effect may be due to both severe chronic inflammation and adverse effect of long term usage of CS (2,3). Insulin-like growth factor (IGF-I) production is also impaired in patients with active JRA as seen in our patient (4,5). In fact, there is no obvious growth hormone deficiency but marked reduction of the serum concentration of its mediator (IGF-1) (5). Our patient had adequate growth hormone levels in response to provocative tests. In JRA patients, linear growth and final height is impaired during childhood because of the duration and doses of CS treatment. If CS is discontinued after remission of the disease, 70% of patients achieve catch-up growth, but 30% of patients show a persistent loss of height because prolonged CS treatment (≥1 year) can lead to irreversible growth impairment (2,6). Final height is strongly correlated with mean height at the end of CS therapy (3,6).

One of the most serious and frequent complication of CS treatment is osteoporosis, which results in increased risk of fractures. Risk is increased even with low doses, used for three months or longer. Corticosteroids mainly cause augmented bone resorption and inhibition of osteoblastic bone formation that results reduction of bone strength by trabecular thinning in bone microstructures (7-10). CS reduces not only bone mineral density (BMD) but also bone quality; therefore, patients with CS induced osteoporosis have a higher risk of fracture than those with postmenopausal osteoporosis with the same level of BMD (11,12). The cut-off value of the BMD for prediction of fracture was approximately 80% of young adult means (T score, -1.5). This value would give a useful diagnostic point for initiating treatment (12). To prevent CS induced osteoporosis and its undesired and irreversible results, treatment must begin earlier than other osteoporotic conditions.

<table>
<thead>
<tr>
<th>Table 1. Patient hormone levels</th>
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<td>Detected value</td>
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<tr>
<td>FSH (mIU/mL)</td>
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<tr>
<td>LH (mIU/mL)</td>
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<tr>
<td>Free testosterone (pg/mL)</td>
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<td>Total testosterone (ng/mL)</td>
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<td>Prolactin (ng/mL)</td>
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<td>Growth hormone (mIU/mL)</td>
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<td>TSH (μIU/mL)</td>
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<td>IGF-1</td>
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<td>ACTH (pg/mL)</td>
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<td>Vitamin D</td>
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<td>PTH (pmol/L)</td>
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Another important problem of our patient was the severe delay in sexual development that is in Tanner level 1. Onset and regulation of puberty is determined by functional development of the brain-pituitary-gonad (BPG) axis. In experimental studies, CSs cause inhibition of pubertal and sexual development by affecting all components of BPG axis, directly or indirectly. CS usage results in retardation of testicular development due to reduced pituitary LH content; stress also interferes with the functions of the BPG axis [13]. Chronic inflammatory disease, such as JRA, is a major stressor. Menarche is later in girls who have JRA than healthy girls; and those who had taken CSs had later menarche and less pubertal growth than those who had not [14]. Gonadal steroidogenesis increases pubertal GH secretion and further pubertal IGF-I increase. There are close positive correlations between IGF-I concentrations and age, height, and weight and between IGF-I and estradiol or testosterone concentration in girls and boys, respectively. Defects in testosterone production also disturb the IGF-I synthesis [15].

In our patient, CS therapy with high doses for a long period (14 years) has affected all aspects of his life: a 22-year-old man with a height of 107 cm, no sexual development, T and Z scores lower than -5.0, vertebral compression fractures, aseptic necrosis of femoral head, and two operations for cataracts and glaucoma. These complications led to both physical and psychological burdens. We report this patient to emphasize that, although corticosteroids are effective in the treatment of juvenile rheumatoid arthritis, they may have devastating effects on the physical, sexual, and psychological development when used in high doses. Patients for whom CS therapy is planned should be followed diligently, with regard to relevant complications.

References