CASE REPORT

Secondary Adrenal Insufficiency due to Intra-articular Glucocorticoid Injections

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Background: The most common cause of hypothalamic-pituitary-adrenal axis suppression is systemic glucocorticoids administration. **Case characteristics**: A 14-year-old boy with juvenile idiopathic arthritis receiving repeated intra-articular steroids for last 3 years developed fever, fatigue, nausea and abdominal pain. Stimulation with low-dose Synathen revealed low adrenal reserve, suggesting secondary adrenal insufficiency. **Outcome**: Temporary hydrocortisone substitution therapy improved condition. **Message**: Intra-articular steroids may cause potentially life-threatening suppression of the hypothalamic-pituitary-adrenal axis.

Keywords: *Adrenal insufficiency, Corticosteroids, Fever, Juvenile idiopathic arthritis*.

Secondary adrenal insufficiency is caused by impaired hypothalamic secretion of corticotropin-releasing hormone (CRH) and/or pituitary secretion of adrenocorticotropin hormone (ACTH). Its prevalence is estimated at 150-280 per million [1]. The most common cause is suppression of the hypothalamic-pituitary-adrenal (HPA) axis because of long-term administration of exogenous corticosteroids. The clinical manifestations include non-specific weakness, fatigue, anorexia, fever, and abdominal and musculoskeletal pain. As the symptoms are not characteristic, the diagnosis is difficult and the treatment is often delayed. Topical therapy (*e.g.,* intra-articular, inhaled, skin ointment) is usually considered to have less systemic effects [2-6] .

CASE REPORT

A boy aged 14 years and 11 months diagnosed as juvenile idiopathic arthritis (JIA) at the age of 3 years (oligoarticular JIA, knees and ankles joints involved) was hospitalized in our department because of recurrent, transient (lasting 1-2 weeks) episodes of severe fatigue with fever up to 39 °C along with nausea and abdominal pain. He did not report any other complaints, and his somatic growth was normal (height-for-age at 97th percentile, BMI 19 kg/m^2, puberty completed). He had no Cushingoid features. He was on treatment with methotrexate, sulfasalazine and adalimumab. For last 3 years, every 2-3 months at the time of exacerbation of arthritis, he was also receiving injections of methylprednisolone acetate (MPA) (usually 80 mg) into the left or right knee (depending on the local condition) at another hospital. There were no symptoms suggesting any infection, and acute phase reactants (sedimentation rate, C reactive protein) were in normal range. The most frequent causes of recurrent fever like infections Cytomegalovirus, HIV, Ebstein-Barr virus, *Borrelia burgdorferi*, tuberculosis), other autoimmune diseases, and immunodeficiency (cellular, humoral and complement deficiency) were excluded. The detailed history suggested relationship between steroid administration and these episodes, which occurred after 4-5 weeks of MPA administration. Basal, morning ACTH and cortisol levels were normal (45.8 pg/mL and 285.8 nmol/L, respectively). To evaluate the ability of the adrenal cortex to produce cortisol after stimulation, the low dose Synacthen test (1 µg of Tetracosactid, Sigma-tau, Germany) was performed 8 weeks after last injection. The test revealed significant decrease in the adrenal reserve (cortisol 20 min: 318.6 nmol/L, 30 min: 264.6 nmol/L, 60 min: 350 nmol/L; normal response is a peak cortisol level of ≥430 nmol/L). Mineralcorticoid deficiency was excluded (aldosterone 79.5 pg/mL N: 35-310, plasma rennin activity 1.02 ng/mL/h N: 1.5-5.7). Blood levels of other pituitary hormones *viz.* thyroid stimulating hormone, leuteinizing hormone, Follicle stimulating hormone, prolactin) as well as magnetic resonance imaging scan of the pituitary gland were normal. Based on these results, secondary adrenal insufficiency due to long-term administration of exogenous glucocorticoids was diagnosed. Hydrocortisone substitution therapy (10 mg daily in 3 divided doses) was

prescribed at the each first day of fever and weakness periods, which resulted in reduced intensity and shortened periods of fever and weakness. Intra-articular MPA injections were stopped, and a repeat stimulation test with 1 µg of exogenous ACTH-Synacthen was within normal range.

DISCUSSION

Secondary adrenal insufficiency is the most common form of adrenal insufficiency; however, the diagnosis is difficult. It is caused by the suppression of the HPA axis due to exogenous steroids administration and their subsequent withdrawal. During the time of recovery of the normal axis function, the patient is vulnerable to overt, life-threatening adrenal insufficiency during time of stress such as illness [2-6]. Although the usual HPA suppression lasts for approximately two weeks, duration and strength of suppressive effect on HPA axis seem to depend on the type of preparation and dose of steroids [7,8]. In secondary adrenal insufficiency, basal levels of cortisol and ACTH can stay within the normal range. Low-dose (1 µg) ACTH test diagnoses it with higher sensitivity and specificity than the standard dose test [9].

Intra-articular steroid administration leading to suppression of HPA axis has been earlier described in a randomized controlled study [10]. Habib, *et al*. [10] documented transient secondary adrenal insufficiency in 25% of the asymptomatic patients after single intra-articular injection of MPA; the effect was observed between week-2 and week-4 following the injection. We suggest that children receiving intra-articular steroids should be screened for secondary adrenal insufficiency, especially when they present with symptoms such as recurrent fevers and lethargy.

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