X-LINKED AGAMMAGLOBULINEMIA AND ISOLATED GROWTH HORMONE DEFICIENCY*

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X-linked agammaglobulinemia and isolated growth hormone deficiency was first described in 1980 and then classified as a different primary immune deficiency. Delayed puberty in patients with X-linked agammaglobulinemia may result in delayed secretion of growth hormone (GH). To determine true isolated growth hormone deficiency, GH stimulation tests and other hypophyseal hormone evaluations must be performed. In this paper, we report a 15-year-old boy with X-linked agammaglobulinemia and isolated growth hormone deficiency, and review related literature. *Key words: agammaglobulinemia, growth hormone deficiency, delayed puberty.*

The first case of X-linked agammaglobulinemia (XLA) and growth hormone deficiency (GHD) was described in 1980 by Fleischer et al.[1]. Although sharing some clinical and laboratory features with classical XLA, this unusual association is currently classified as an independent primary immunodeficiency[2]. The molecular pathogenesis of XLA/GHD is controversial.

Since growth hormone insufficiency may result from delayed puberty, some prepubertal XLA patients were misdiagnosed as GHD. As a result, several investigators advised administering sex steroids before performing GH evaluation studies[3,4]. In this paper, we report a 15-year-old boy with agammaglobulinemia and isolated GHD without family history.

Case Report

A 15-year-old boy was admitted to hospital with diffuse bilateral bronchiectasis and marked growth retardation. He was the third child of nonconsanguineous parents. Three male siblings and a female sibling were healthy. He had recurrent respiratory tract infections from infancy. His weight was 27 kg (<3rd percentile) and height was 131 cm (<3rd percentile); SDS for height was –4.625. He had

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pectus carinatum deformity and digital clubbing, and pubertal development was consistent with Tanner 1. Laboratory studies revealed hypochromic, microcytic anemia and normal WBC count. Bone age was 11 years, sweat chloride was 8 mmol/L. The levels of serum immunoglobulins were too low, and CD19, which is a marker of B lymphocytes, was below one percent. Immunologic parameters are presented in Table I. Because of growth and pubertal retardation, the patient was evaluated endocrinologically. While serum T3, T4, TSH, basal cortisol and IGF-I levels were within normal ranges for age, basal serum levels of testosterone, FSH and LH were consistent with prepubertal stage. Basal and post-hCG stimulation testosterone levels were 7.74 and 220.06 ng/ml, respectively.

Because gonadotropin levels were consistent with stage 1, a LH-RH test was performed. After LH-RH stimulation, serum FSH and LH levels rose to 2.17 and 4.11 mIU/ml, respectively. Growth hormone stimulation tests with L-dopa and insulin hypoglycemia were performed three days after administration of 100 mg intramuscular testosterone (Sustanon®)[5]. Growth hormone levels were below the value of 7 ng/ml for two tests. Hormone evaluation studies are presented in Table II.

The patient was treated with antibiotic, chest physiotherapy and monthly intravenous immunoglobulin at a dose of 200 mg/kg of body weight. He had gained 6 cm of height during 20 months of follow-up.

Table I: Immunologic Parameters

WBC: 7,400/mm³
Absolute lymphocyte count: 2,812/mm³
Serum immunoglobulins:
IgG : 180 mg/dl (Normal ranges for age: 800-1900)
IgA : 25 mg/dl (Normal ranges for age: 85-220)
IgM : 25 mg/dl (Normal ranges for age: 75-197)
Lymphocyte subsets (flow cytometric)
CD45 : 99.9%
CD3 : 82.4%
CD4 : 25.7%
CD8 : 56.2%
CD16 : 17.8%
CD19 : 0.0%

Table I: Immunologic Parameters

T3: 152.50 (ng/dl)

T4: 11.76 (mg/dl)

TSH: 0.70 (mIU/ml)

Cortisol: 18.28 (mg/dl)

IGF-I: 224.48 ng/ml (Normal ranges for Tanner 1: 215 ± 71 ng/ml)

Testosterone (ng/ml):
Basal: 7.74 After hCG stimulation: 220.06

Gonadotropin-RH Stimulation Test

	Basal	20 min	40 min	60 min	90 min
FSH (mIU/ml)	0.63	0.84	2.17	1.83	1.61
LH (mIU/ml)	0.5	3.04	3.94	0.91	4.11

*Growth Hormone Stimulation Tests**

Time (min)	0	20	40	60	90	120
L-DOPA GH (ng/ml)	1.2			0.89	5.80	
Insulin Hypoglycemia Test						
Blood Glucose (mg/dl)	80	27	44	85	76	78
GH (ng/ml)	0.70	0.34	3.84	6.48	2.14	0.76

* After 100 mg testosterone administration.

Discussion

This boy had proportionate short stature and agammaglobulinemia without circulating B cells and normal cellular immune function. Responses to GH stimulation tests and other endocrinologic evaluation led to the diagnosis of isolated GH deficiency.

Bruton's agammaglobulinemia is characterized by an X-linked recessive mode of inheritance of a defective humoral immune system with intact cell mediated immunity[6]. Controversial results have been reported with regard to the molecular pathogenesis of XLA/GHD. Both linkage analysis and evaluation of X chromosome inactivation suggested a gene other than the classical XLA gene in the first pedigree, but were consistent with a typical XLA mutation in the second and third families[7,8].

Since this patient was a boy and had no family history consistent with XLA, he was suspected to be a sporadic XLA patient.

Some prepubertal children with decreased growth velocity have a temporary partial GH deficiency. Penny and Blizzard[9] observed very low values (<3 ng/ml) of GH after insulin or arginine stimulation tests in three prepubertal

boys with short stature. They had a significantly higher response after entering stage IV of sexual development. The delayed secretion of sexual hormones presumably would play a role in the impaired GH release in these subjects. For the diagnosis of true GH deficiency in delayed growth and puberty it seems worthwhile to repeat GH stimulation tests after a brief administration of sexual hormones[5].

This patient's basal serum testosterones, FSH and LH levels were consistent with the prepubertal stage. Follicle-stimulating hormone and LH levels were increased sufficiently after LH-RH stimulation[10]. In fact, interpretation of the LH-RH test may be difficult in GH deficient patients until the bone age has reached 12.5-13 years in males and 10.5-11 years in females[11]. Serum testosterone levels increased to 220.06 ng/dl after hCG stimulation. After priming with testosterone, GH levels, after stimulations with L-dopa and insulin hypoglycemia, were below the value of 7 ng/ml. This picture was consistent with isolated growth hormone deficiency.

As a result, we would like to suggest that in the case of hypogammaglobulinemia and short stature, GH deficiency should be kept in mind.

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