Immunological Abnormalities in Adults Treated with hGH in Childhood; Responses to One Month Trial of hGH.

Kumiko Araki, Mikiya Fujieda, Taisuke Okada, Hiroshi Wakiguchi, Takanobu Kurashige, Atuko Yoshizawa, Toshiaki Tanaka and Itsuro Hibi

Department of Pediatrics, Kochi Medical School (K.A., M.F., T.O., H.W., T.K.), Kochi Endocrine Research Laboratory, National Children's Medical Research Center (A.Y., T.T) and Division of Endocrinology and Metabolism, National Children's Hospital (I.H.), Tokyo, Japan.

Abstract. Twelve adult patients with growth hormone deficiency (GHD) were studied in regard to serum levels of immunoglobulins, immunoglobulin G (IgG) subclasses, natural killer (NK) activities, interferon (IFN) augmented NK activities and lymphokine activated killer (LAK) activities before and after one month of human growth hormone (hGH) treatment. They were compared with 114 age-matched controls. All the patients were diagnosed as having GHD in childhood and had been treated with hGH for more than 5 years. The present study was performed 1 to 7 years after the cessation of hGH treatment.

Serum immunoglobulin G1 (IgG1) levels and IFN augmented NK activities in the patients were significantly lower than in the controls, although NK and LAK activities of the patients were normal. Therefore it was concluded that NK and LAK activities were maintained at normal levels without hGH in adults who had been treated with hGH, although IFN augmented NK activities were reduced without it. It seems that longer treatment with hGH is needed to produce normal levels of serum IgG1 and IFN augmented NK activities.

Key words: GH deficiency, immunological function, adult patient

Introduction

Although immune function in patients with GHD (1-6) is controversial, we have reported previously that NK and LAK activities are depressed in children with GHD and recover with hGH treatment (7,8). In addition, NK activities remain normal after cessation of hGH treatment, although IFN augmented NK and LAK activities return to low levels (9). Such discrepancies among the responses to hGH treatment of various killer activities suggest that the actions of GH on cellular immunity is stimulatory in some aspects and sustaining in other aspects.

We investigated such killer activities in adult patients who had had treatment with hGH since childhood and who had finished
hGH treatment at least one year before this study. The serum levels of immunoglobulins and IgG subclasses in these patients were also examined.

Patients and Methods

Twelve patients (5 men and 7 women) were studied after giving informed written consent. All were diagnosed as having had GHD in childhood by low responses (peak below 5ng/ml) of serum GH in provocation tests of GH secretion. They had been treated with hGH for 6.0 to 13.3 years and had stopped treatment 1 to 7 years before this study (Table 1). When it was necessary, thyroxine and/or sex hormones replacement treatments had been continued. All patients were given biosynthetic hGH (Somatonorm, Kabi Pharmacia AB) in a dose 0.5IU/kg/week by daily subcutaneous injections for one month. Blood samples were taken before and after the hGH trial.

The control group was composed of 50 men and 64 women aged 20 to 40 years.

Serum IgG, IgA and IgM levels were assessed by nephelometry. IgG subclasses (IgG₁, IgG₂, IgG₃, and IgG₄) were assessed by enzyme-linked immunosorbent assay as previously reported (10).

NK activities, recombinant IFN-α (rIFN-α) augmented NK and LAK activities were assessed by a ⁵¹Cr-release assay as previously reported (7,8).

These tests could not be performed on all subjects due to an insufficient quantity of blood being taken. Statistical analysis was performed by Wilcoxon test and Student’s unpaired t test.

Results

Serum levels of immunoglobulins were assessed in 8 patients before the hGH trial and in 4 patients at the end of the trial. Serum levels of IgG, IgA and IgM of the patients were not significantly different from those of the controls and did not respond to hGH administration (Fig. 1). Serum IgG subclasses were assessed in 11 patients before the hGH trial and in 5 patients at the end of the trial. Serum IgG₁ levels of the patients were signifi-
Immunological Abnormalities in Adult GHD

Fig. 1. Changes in serum immunoglobulin levels before and after GH therapy.

Fig. 2. Changes in serum immunoglobulin G subclasses before and after GH treatment.

Significantly lower than in the controls (p<0.05) but showed no response to hGH administration. There were no differences between patients with low levels of IgG1 (−1SD below normal mean) or with normal levels of IgG1 (>−1SD above normal mean) in the duration or age at which hGH therapy was started on the period after the cessation of the hGH therapy. Serum IgG2, IgG3, and IgG4 levels of the patients were not significantly different from those of the controls and showed no response to hGH administration (Fig. 2). NK activities were assessed in 8 patients before the hGH trial and in 4 patients at the end of the trial. NK activities of the patients were not significantly different from those of the controls and showed no response to hGH administration (Fig. 2). Three patients (Cases 1, 6, 8) who had low NK activities (<−1SD below normal mean) had finished the initial course of hGH therapy longer ago than the other patients. rIFN-α augmented NK activities (500IU/ml, 18 hours) of the patients were significantly lower than those of controls (p<0.01) but showed no response to hGH administration. LAK activities of the patients were lower than those of controls, but not significantly, and become normal with hGH administration (Fig. 3).

Discussion

Although hypopituitary animals show a marked deficiency of cell-mediated immune function (11), the role of GH on the development and function of the immune system in humans is not well understand. In children with GHD, both normal (1-3) and abnormal (4-6) immune functions have been observed. Our previous report showed significantly reduced levels of NK and LAK activities stimulated by recombinant interleukin (rIL)-2 or OK432 in children with GHD, which returned to normal with hGH treatment (9). How-
Fig. 3. Changes of NK cell activity, IFN-α augmented NK cell and LAK activity before and after GH treatment.

However, NK activities remained normal after the cessation of GH treatment, although IFN-augmented NK activities and LAK activities returned to low levels (9). Reduced NK activities and impaired IL-2 production have been reported by other investigators (1,2,3). Kiess et al. reported that this immune abnormality was induced when GHD persisted for a long period (1) and that lymphoproliferation was influenced by the addition of hGH in vitro (12). Therefore, GH appears to play an important role in the development and function of the immune system in childhood (13,14).

The present study showed that NK and LAK activities were maintained as normal without hGH in adult patients who had been previously treated with hGH, although rIFN-α augmented NK activities were reduced without it. Therefore, it is concluded that GH is indispensable for the maturation of NK cells but is not essential to maintain their function. On the other hand, GH is indispensable to maintain normal rIFN-α augmented NK activities even in adult patients with GHD. rIFN-α augmented NK activities were of normal levels and did not change with hGH treatment in children with GHD (9). However, they were reduced after the cessation of hGH treatment and did not return to normal in adults with GHD as shown in the present study. Two reasons have been proposed to explain the discrepancy between the levels of LAK activities and rIFN-α augmented NK activities in our patients. First, the killer cells that matured under the influence of hGH therapy showed more responsiveness to rIL-2 than to rIFN-α. Secondly, rIL-2 had more stimulatory effect on the killer cells than rIFN-α. Therefore, normalization of rIFN-α augmented NK activities might occur with longer hGH treatment than that of the present study.

To best of our knowledge, there are no reports on IgG subclasses in GHD. The serum IgG1 level was reduced in adult patients with GHD but did not recover by short-term treatment with hGH. It may be necessary to give longer GH treatment for the serum IgG1 level to become normal in the same way as for rIFN-α augmented NK activities. Further studies are needed to confirm such speculations.

The present study demonstrated that GH was indispensable for the development of maturation of some immune functions and to maintain other immune functions.

References

Immunological Abnormalities in Adult GHD