Interleukin-6 serum concentration in patients with impaired growth hormone secretion

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Abstract
There is a growing number of studies which have revealed that the growth hormone (GH) plays a role in regulation of systemic inflammatory response. Interleukin-6 (IL-6) is a well established pro-inflammatory, proangiogenic and adipocyte expressed cytokine that is also involved in pituitary tumors pathophysiology.

In this study, using commercially available kits, we aimed to determine serum concentrations of IL-6, GH and IGF-1 in the following groups of age and sex matched patients expressing impaired growth hormone secretion: patients with active acromegaly (n=11), patients cured from acromegaly (n=14), patients exhibiting growth hormone deficiency (GHD) induced by pituitary tumors (n=12), patients with GHD unrelated to pituitary tumors (n=10) and control group of healthy volunteers (n=15). Concentrations of IL-6 were significantly higher in both GHD groups with reference to controls. Acromegalic patients revealed comparable to healthy subjects IL-6 concentrations. Using segmental regression applied to the group combined of all patients (n=62), a cut off point for GH=2.27 ng/ml was determined below which a negative correlation with IL-6 was confirmed (r=-0.56, p<0.048). Multiple regression failed to reveal any correlation between IL-6 and IGF-1/BMI in groups of patients irrespective of the GH concentration threshold.

Taken together, we conclude that GHD in adults is accompanied by increased serum concentrations of IL-6. Nevertheless, neither adipocytes nor pituitary adenoma cells are the major source of IL-6 in these patients. Lack of correlation of IL-6 with IGF-1 suggests the direct impact of low GH concentrations in IL-6 induction. Noteworthy, increased IL-6 concentrations can be secondary to the atherosclerotic process augmented by GHD via mechanisms which require further investigations.

Key words: growth hormone, interleukin-6, pituitary adenomas, adipocytes.

Introduction
The growth hormone (GH) plays a well-established and important role in the regulation of a variety of physiological processes, including immunological functions and inflammatory reactions. It has stimulatory effects on the immune system mainly through promoting thymic growth and T cell development. It improves T cell function, and may contribute to increased T cell receptor (TCR) diversity [1]. Nevertheless, the interactions of GH with cytokine network remain unknown.
Interleukin-6 (IL-6) is a pleiotropic cytokine with a variety of biological activities, but mainly possesses pro-inflammatory properties. It is produced not only by immune cells but also by endothelial cells and vascular smooth-muscle cells [2]. A number of studies indicated its proangiogenic activity and its role in neoplasia [3]. Moreover, IL-6 has been recently shown to be an adipocyte expressed cytokine. IL-6 serum concentrations are elevated in obesity and diabetes which indicates its possible role as a mediator of insulin resistance [4]. Nevertheless, it has to be emphasized that IL-6 as a crucial inflammatory factor is implicated in the pathogenesis and clinical course of atherosclerotic vascular disease [2].

On the other hand, IL-6 is a well established modulator of anterior pituitary cells function and it is considered to play a role in pituitary tumors pathophysiology. A number of studies have demonstrated that somatotroph adenoma cultures produce IL-6 which triggers secondary GH secretion even stronger than GHRH. This might contribute via autocrine/paracrine mechanisms to excessive GH production in acromegaly [5].

The aim of this study was to assess the concentrations of IL-6 in patients with pituitary disorders in terms of impaired growth hormone secretion.

Materials and methods

The study was performed on 47 patients hospitalized in the Department of Endocrinology of Medical University of Lodz, designated to 4 following, age and sex matched clinical groups applying standard clinical and biochemical criteria (GH and IGF-1 levels, imaging techniques, provocative tests): 1-patients with active acromegaly (n=11), 2-patients cured from acromegaly (n=14), 3-patients exhibiting growth hormone deficiency (GHD) induced by pituitary tumors, other than somatotroph macroadenoma (n=12), 4-patients with GHD unrelated to pituitary tumors (n=10). The sex and age matched control group consisted of healthy population of volunteers (n=15). Ethical approval for this study was granted by the Ethics Committee of the Medical University of Lodz No RNN/126/2001/KE and written consent was obtained from each subject. The following assessments were performed in specimens of obtained serum using commercially available kits: GH (Immunolite DYSIAG System, USA), IGF-1 (Immunolite DYSIAG System, USA) and IL-6 (R&D Systems, USA). Body mass index (BMI) for each patient was calculated using the following formula: 

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\text{BMI} = \frac{\text{body weight (kg)}}{\text{height}^2 (\text{m}^2)}
\]

ANOVA test with post-hoc Student-Newman-Keuls was employed to determine the statistical significance of differences between the groups. Correlation ratios were calculated using either segmental or multiple regression. \( P<0.05 \) was assumed as significant.

Results

Concentrations of IL-6 were significantly higher in both GHD groups with reference to controls. Using segmental regression applied to the group combined of all patients involved in experiment (n=62), a cut off point for GH=2.27 ng/ml was determined. In patients who exhibited GH concentrations below this value a negative correlation with IL-6 was confirmed (r=-0.56, \( P<0.048 \)). Based on the cut off point for GH, all patients were divided into 2 groups. Multiple regression did not reveal any correlation between IL-6 and IGF-1/BMI in both groups.

Discussion

Acromegalic patients do not show any differences in terms of IL-6 secretion, with reference to controls. The outcomes of this study show that human somatotroph pituitary adenoma cells, despite their ability to produce IL-6 in situ, cannot affect blood concentrations of this cytokine.

Untreated GHD patients revealed higher IL-6 concentrations in comparison to healthy subjects without differences between tumor related and unrelated GH deficiency, excluding \textit{ipso facto} the role of tumor in IL-6 secretion.

The present study failed to confirm a correlation of IL-6 with IGF-1. Therefore these results may suggest the direct impact of low GH concentrations in IL-6 induction.
Other authors showed that GH deficient adults who received routine replacement therapy with pituitary hormones other than GH demonstrated increased cardiovascular morbidity and mortality [6]. On the other hand, there is a growing number of evidence showing that IL-6 is an independent predictor of cardiovascular disease [2]. It raises a question whether moderately increased concentrations of IL-6 in GHD patients are either directly linked to the lack of GH or secondary to exacerbated atherosclerotic process which itself courses with chronic subclinical systemic inflammation. The present study did not reveal any correlation of BMI and IL-6 concentration in GHD patients which provides a supporting evidence that adipocites are not a source of IL-6 in GHD patients although subcutaneous and intra-abdominal fat mass have been found to be abnormally high in these patients [7].

Conclusion

Taken together, we conclude that patients with active acromegaly have Il-6 levels similar to healthy subjects. Presence of pituitary adenoma does not impact blood levels of IL-6. GHD in adults is accompanied by increased serum concentrations of IL-6, nevertheless adipocytes are not the major source of IL-6 in these patients. Increased IL-6 concentrations can be secondary to the atherosclerotic process augmented by GHD via mechanisms which require further investigations. Additional studies are needed to clarify the pathological basis and consequence of these findings.

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References