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BRIEF COMMUNICATION

Number and Percentage of NK-Cells Are Decreased in Growth Hormone-Deficient Adults

J. P. T. SPAN, G. F. F. M. PIETERS, A. G. H. SMALS, P. P. KOOPMANS,* AND P. W. C. KLOPPENBORG

*Department of Medicine, Divisions of Endocrinology and *Internal Medicine, University Hospital Nijmegen, 6500 HB Nijmegen, The Netherlands*

Snell–Bagg mice and Ames dwarf mice repeatedly show severe immunodeficiencies, affecting mostly the thymus-dependent lymphocyte system, probably caused by growth hormone deficiency. In growth hormone-deficient children contradictory data on the immune status have been reported. We investigated indices of cellular immunity in 22 adult patients with proven growth hormone deficiency in comparison to those in 100 healthy volunteers. Cellular immunity was assessed using total leukocyte count, percentage lymphocytes, and percentage and absolute numbers of CD3, CD4, CD8, CD19, and CD3⁻CD56⁺ (NK)-cells. Comparison revealed statistically significantly lower percentage and absolute number of NK-cells ($P < 0.001$). Except for a trend toward an increased CD4/CD8 ratio, no statistically significant differences for B- and T-lymphocytes could be observed. No correlation between the percentage and absolute number of NK-cells, on one hand, and the duration of growth hormone deficiency or prolactin level, on the other hand, could be demonstrated. In all these respects men did not differ from women. So, in growth hormone-deficient adults the percentage and absolute number of NK-cells are decreased. © 1996 Academic Press Inc.

INTRODUCTION

Animal studies demonstrated that growth hormone plays a role in the modulation of the immune response in mice. Two animal models of congenital hypopituitarism, the Snell–Bagg mouse and the Ames dwarf mouse, have severe immunodeficiency affecting mostly the thymus-dependent lymphocyte system (1). In a third model (DW/J dwarf mice) a selective defect in the production of growth hormone and prolactin coexisted with a deficiency of $CD4^+CD8^+$ double-positive thymocytes, which could be corrected by treatment with recombinant growth hormone (2). Growth hormone deficiency also affects thymic immunoresponse in rats and dogs (3).

In untreated children with isolated growth hormone deficiency, reduced natural killer (NK)-cell activity (4) and an increase of B-cells associated with an increase in T-suppressor cells have been described (5). Other studies, however, failed to demonstrate similar data (6, 9). In adult patients with growth hormone deficiency, no data are available yet. Therefore, we studied cellular immunity in adult patients with growth hormone deficiency.

PATIENTS AND METHODS

Twenty-two patients (15 female and 7 male; mean age, 42 years; range, 27–59 years) with growth hormone deficiency were included in this study. The diagnosis of growth hormone deficiency was based on an arginine provocation test with a growth hormone peak concentration ≤10 mU/liter and an IGF-I concentration below the normal value corrected for age and sex. Most patients ($n = 17$) had multiple pituitary deficiencies and received adequate, hormonal replacement therapy, except for growth hormone for the last 2 years. The control group consisted of 100 healthy volunteers (48 male and 52 female; mean age, 43 years; range, 18–70 years).

In all patients the following parameters were studied; hemoglobin, white blood count (WBC), red blood count (RBC), thrombocytes, the percentage and absolute number of lymphocytes, $CD3^+$ (total T-lymphocytes), $CD4^+$ (T-helper cells), $CD8^+$ (T-suppressor cells), $CD19^+$ (B-lymphocytes), and $CD14^+$ cells (monocytes) and $CD3^-CD56^+$ cells (NK-cells). Hematologic indices were measured using a Technicon H1 electronic cell counter. The percentages of CD3-, CD4-, CD8-, CD14-, and CD19-positive cells and the NK-cells were measured using flow cytometry and direct immmunofluorescence.

The unpaired Student t test was used to compare data of patients and controls, and the Spearman rank correlation test was used for the within population comparisons.

All patients signed informed consent to the protocol

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which was approved by the University Hospital Ethical Committee.

RESULTS

Growth hormone deficiency was mostly due to hypophysectomy for the treatment of a pituitary adenoma. Other causes included M. Sheehan, trauma, craniopharyngeoma, and hypothalamic insufficiency (see Table 1).

Standard hematological analysis revealed no statistically significant differences when the patients data were compared with the controls.

Comparison of indices of the cellular immunity of growth hormone-deficient patients with those of the control group revealed a statistically significant lower percentage and absolute number of NK-cells ($P < 0.001$) (Table 2). No statistically significant differences for B- and T-lymphocytes could be demonstrated between patients with growth hormone deficiency and the normal population, except for a trend to an increased CD4/CD8 ratio ($P = 0.053$).

No statistical significant correlation between the number or percentage of NK-cells and the estimated duration of growth hormone deficiency or prolactin levers could be demonstrated. In all these respects men did not differ from women.

DISCUSSION

This study revealed no differences in thymic-derived cells between the adults with growth hormone defi-

TABLE 1
Demographic Data

					Isufficiency of other pituitary axes			
Patient	Birth date	Years of somatotropin deficiency	Sex	Cause of somatotropin deficiency	Adrenal	Thyroidal	Gonadal	Posterior lobe
1	10 Sept. 1948	46	Male	Congenital	No	No	No	No
2	21 Oct. 1963	17	Female	Hypophysectomy (chromophobe adenoma)	Yes	Yes	Yes	Yes
3	4 July 1962	32	Female	Congenital	No	Yes	No	No
4	2 March 1968	21	Female	Thalamus tumor (irradiated)	No	No	Yes	No
5	9 July 1943	25	Female	M. Sheehan	Yes	Yes	Yes	No
6	29 Nov. 1952	12	Female	Hypophysectomy (chomophobe adenoma)	Yes	Yes	Yes	No
7	11 Nov. 1945	49	Female	Congenital	No	Yes	No	No
8	15 Feb. 1940	4	Male	Pituitary tumor	Yes	Yes	Yes	No
9	20 May 1956	19	Female	Epipharynx carcinoma (irradiated)	Yes	Yes	Yes	No
10	20 Sept. 1950	12	Female	Hypothalamic insufficiency	No	Yes	No	No
11	23 Feb. 1968	12	Female	Idiopathic	No	Yes	Yes	Yes
12	19 Sept. 1936	10	Female	Hypophysectomy	Yes	Yes	Yes	Yes
13	2 May 1965	18	Female	Craniopharygeoma	Yes	Yes	Yes	Yes
14	16 July 1961	24	Male	Craniopharygeoma	Yes	Yes	Yes	Yes
15	10 Jan. 1956	11	Female	Hypophysectomy (M. Cushing)	Yes	No	No	No
16	30 June 1941	7	Male	Hypophysectomy (pituitary tumor)	Yes	Yes	Yes	Yes
17	27 Aug. 1940	16	Male	Hypophysectomy (chromophobe adenoma)	Yes	Yes	Yes	No
18	9 March 1964	11	Male	Trauma	Yes	Yes	Yes	No
19	2 Feb. 1967	17	Female	Irradiation (cerebral tumor)	No	Yes	Yes	Yes
20	17 June 1954	24	Female	Hypophysectomy (pituitary tumor)	Yes	Yes	Yes	No
21	6 March 1961	20	Female	Trauma	Yes	Yes	Yes	No
22	27 Jan. 1941	3	Male	Hypophysectomy (M. Cushing)	Yes	Yes	Yes	No

TABLE 2
Cell Counts and Percentage of White Blood Cells

		Lymphocytes, ×10⁹/liter	CD-3 positive cells		CD4-positive cells		CD8-positive cells		CD4/CD8 ratio
			×10⁹/liter	%	×10⁹/liter	%	×10⁹/liter	%	
GHD	Mean	2.4	1.75	73.8	1.14	47.5	0.66	28.5	1.99
	25–75%	1.7–3.1	1.14–2.39	71–79	0.74–1.55	43–51	0.43–0.86	22–33	1.34–2.58
Normal	Mean	2.1	1.4	72	0.8	42	0.7	35	1.2
	25–75%	1.6–2.4	1.1–1.7	67–76	0.7–1.1	38–46	0.5–0.9	31–40	1.0–1.5

		CD19-positive cells		CD14-positive cells		$CD3^-CD56^+$ cells	
		×10⁹/liter	%	×10⁹/liter	%	×10⁹/liter	%
GHD	Mean	0.3	14.6	0.43	5.9	0.14**	6.2**
	25–75%	0.2–0.4	8–20	0.28–0.56	4.3–6.8	0.09–0.18	4.0–9.0
Normal	Mean	0.3	13	0.5	8.5	0.3**	14**
	25–75%	0.2–0.4	(11–16)	0.18–0.92	4.0–13.0	0.2–0.4	10–19

* Statistically significant difference, $P < 0.001$ (Student t test).
** Statistically significant difference, $P < 0.001$ growth hormone deficient patients vs controls (Student t test).

ciency and the normal population. The number and percentage of B-cells are also comparable with the values found in the normal population. Remarkably the number and percentage of NK-cells were significantly lower in the patient group than in the normal population.

Hyperprolactinemia has been shown to inhibit immune function (3); moreover, in hyperprolactinemic men, a reduced NK-cell activity was demonstrated compared to hyperprolactinemic patients treated with bromocriptine (7), but these findings could not be reproduced (8). In our study we could not demonstrate a correlation between the absolute number of NK-cells and the prolactin concentration. Therefore, we consider growth hormone deficiency as a possible cause for the decrease found in number and percentage NK-cells.

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