Risk Factors for Leukemia Occurrence among Growth Hormone Users

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A matched case-control study on leukemia occurrence among growth hormone (GH) users was performed to elucidate any risk factor for leukemia. The total doses of GH and administration of other hormones, such as thyroxine, gonadotropin, gonadal hormones, glucocorticoid and anabolic steroid, did not lead to any apparent difference between cases studied and controls. Neither doses of diagnostic X-rays nor therapeutic cranial irradiation was related to leukemia risk. Scintigraphy for thyroid function using radioactive iodide was the only significant risk factor ($P=0.03$). Hematological changes and liver function before and one month after GH administration were compared and the cases studied showed more proliferative reaction of white blood cells with rapid increase of neutrophils, but lymphocyte response was variable. Lactic acid dehydrogenase, alkaline phosphatase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase tended to decrease after GH treatment when the patients had shown abnormally increased levels. Other environmental and familial factors did not show any abnormal clusters.

Key words: Leukemia — Growth hormone — Case-control study — Risk factors

Leukemia occurrence among patients treated with growth hormone (GH) was estimated to be 1 per 6,000 receiving such treatment in Japan and the rates in other countries surveyed range between 1 per 12,000 and 1 per 35,000 patient years.^{1,2} In Japan, the observed/expected ratio of leukemia occurrence was 9.4, but after a review of cases at the international workshop in Bethesda in May 1988, the current estimate of individual risk, assuming a 10-year GH treatment course, would be one chance in 2400. The lowest estimate, however, showed significant excess of leukemia, so that the clarification of leukemia risk is urgently required to provide a basis for efforts to prevent leukemia occurrence in particular individuals. This paper describes the results of a 1:2 matched case-control study to elucidate risk factors for leukemogenesis.

PATIENTS AND METHODS

The patients consisted of five acute leukemia cases occurring in Japan between 1985 and the end of 1987. A brief list of the patients was reported in a letter to The Lancet¹ and individual case reports were published elsewhere.³⁻⁶ Initially five controls were selected for each case from the computerized data base of all Japanese GH users (7,000 patients) by sex, age (± 2 years), time of initial treatment (± 1 year), duration after GH treatment (always longer than the corresponding case), with

as much similarity in residential area and hospitals as possible. A questionnaire was sent to the doctors and each doctor filled in the questionnaire from the clinical chart, with reference to the parents if necessary. The items on the questionnaire included birth date, basic diseases, height and body weight before and after GH treatment, gains in these parameters, time and dose of GH treatment, usage of other hormones and drugs, presence of any anomaly, mental and physical disturbance, history of pregnancy, maternal drug usage, hormonal status at diagnosis of GH deficiency, radiation dose for diagnosis, therapeutic history before GH treatment, white blood cells (WBC), red blood cells (RBC), platelets and other hematologic changes before and after GH administration, liver function, history of life habits, such as diet, health condition, familial smoking habit, occupation of parents, and others.

We had responses for 18 controls from doctors (72%), but 6 of them were not eligible due to insufficient clinical and laboratory data. Finally two controls, for which full data were available, were selected for each case, and a 1:2 matched case-control analysis was performed according to the method of Breslow and Day.⁷

RESULTS

Major factors distinguishing cases and controls are listed in Table I. The type of leukemia is common acute lymphoblastic leukemia (ALL) in 3, stem cell ALL in 1 and acute myeloblastic leukemia (AML) in 1. The basic

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Table I. Risk Factors in Cases and Controls

	Cases	Controls
Birth year		
1961-63	1	2
1968-70	2	4
1971-73	1	2
1978-79	1	2
Basic diseases		
Breech delivery	3	7
Neoplasms	1	3
Genetic anomaly	1	0
Anomaly: Present	3	0
Absent	2	10
Premature baby: Yes	1	2
No	4	8
Newborn jaundice: Present	2	6
Absent	3	4
Abnormal EEG: Present	1	4
Absent	4	6
Diagnostic X-ray for hands:		
less than 5 times	3	2
more than 5	2	8
Therapeutic cranial radiation: Present	1	2
Absent	4	8
Thyroid RI scintigram: Present	5	2
Absent	0	8
Dose of GH:		
less than 1,500 IU	4	1
over 1,500 IU	1	9
Usage of thyroid hormone:		
Yes	3	7
No	2	3
HCG: Yes	0	2
No	5	8
Anabolic steroid: Yes	0	2
No	5	8
Glucocorticoid: Yes	0	1
No	5	9

Table II. Laboratory Data Concerning Cases and Controls

	Cases	Control
Pretreatment WBC:		
less than 4,000	1	0
4,000-5,999	3	4
more than 6,000	0	4
Posttreatment WBC:		
less than 4,000	0	2
4,000-5,999	1	4
more than 6,000	3	4
WBC change more than 20%:		
Increase	4	1
Decrease	0	1
Unchanged	0	8
Neutrophil change more than 5%:		
Increase	2	2
Decrease	1	5
Eosinophil change more than 3%:		
Increase	0	6
Decrease	1	1
Unchanged	2	3
Lymphocyte change more than 5%:		
Increase	1	3
Decrease	2	1
Unchanged	0	3
Alkaline phosphatase change more than 20%:		
Increase	0	2
Decrease	0	4
Unchanged	1	2
GOT and/or GPT change:		
Decrease to normal range	0	5
Unchanged	1	3

Laboratory data were obtained about one month before and after GH treatment.

diseases of the cases were idiopathic pituitary deficiency due to breech delivery in 3, post-irradiation to suprasellar germ cell tumor in 1, and probable Fanconi's anemia in 1. Among the controls, idiopathic hypopituitarism due to breech delivery numbered 7, post-irradiation status due to histiocytosis X and craniopharyngioma, one each, and post surgical status of sellar cyst, one. It is noteworthy that 3 of the cases showed some kind of anomaly, i.e. various anomalies associated with Fanconi's anemia, anomaly of the ears, and germ cell tumor (teratoma), while there were none in controls. Neither amounts of diagnostic radiation to the hands, lungs and skull nor

amount of therapeutic irradiation to the skull were related to the occurrence of leukemia. All 5 cases, however, had received scintigraphy of the thyroid using radioactive iodide, while it had been performed in only 2 out of 10 of the controls. Risk of scintigraphy was significantly high ($\chi^2=4.225$, with 1.09 lower limit of the 95% confidence interval).

The duration and total dose of GH did not show a dose-dependent relationship with leukemia occurrence. The administration of other types of hormones, such as thyroxine, HCG, etc., seemed to be negatively related to leukemia occurrence. Gain of height and body weight after GH treatment showed no difference between cases and controls.

Changes of WBC were remarkable (Table II). The WBC of cases was within the normal range or less, but it increased in most cases with increased neutrophils. In controls, an abnormally high WBC count was recognized in 4 pretreatment, remaining unchanged after GH treatment. An increase of eosinophils was present in controls,

Table III. Familial and Environmental Factors of Cases and Controls

		Cases	Controls
Brothers:	Present	3	4
	Absent	2	6
Sisters:	Present	4	1
	Absent	1	9
Malignant tumors in the first generation:	Present	0	2
	Absent	5	8
Smokers within family:	Present	3	8
	Absent	2	2

the highest being 11% (968/mm³). Response of the lymphocyte fraction was variable. About half of both cases and controls showed elevated alkaline phosphatase, LDH, GOT and/or GPT, but these became within normal limits after about one month of GH treatment.

Familial background did not show specific findings, but 80% of cases had a sister, while only 10% of controls did (Table III). Malignant tumor in the first generation was present only in controls (one carcinoma and one sarcoma). There was no difference in socioeconomic status, type of occupation or type of residence, or number of smokers in their homes between cases and controls.

DISCUSSION

Fifteen cases of leukemia in patients treated with GH up to the end of 1987 were carefully reviewed at the international workshop in Bethesda in May, 1988, and the incidence of leukemia detected at that time in GH-treated patients was estimated to be about 1 per 21,000 patient-years of risk. In that meeting, the following possible explanations for the relation of GH treatment to leukemia were considered, (a) an effect of GH itself; (b) an effect of a contaminant in the GH preparations; (c) an interaction between GH deficiency and/or GH therapy and factors such as chromosome fragility or immune system abnormalities in GH-deficiency patients; (d) an interaction between GH and environmental factors such as radiation or viruses; or (e) chance, as in earlier unexplained geographical clusters. Possibility (b) was considered unlikely, because leukemia developed following recombinant GH treatment. Possibility (e) is also unlikely, because GH-related leukemia has appeared throughout the world. The rather low incidence of leukemia among GH users, however, suggests that (a) is not the only cause of leukemia.

In this regard, possibilities (c) and (d) require urgent study. The present case-control study revealed that neither diagnostic nor therapeutic irradiation appeared to be a risk factor of leukemogenesis. However, the relative risk of radioactive scintigraphy for the thyroid was extremely high. The mechanism is not known, but the isotope may have initiated hematopoietic stem cells. No other significant risk factor for leukemia was found. Total amount of GH was not related to leukemia occurrence. Other hormones seemed to be negatively related to leukemia, but this may be the result of the long survival of the controls. Sex hormones are used when the patients reach puberty.

It is noteworthy that some kinds of host factors seemed to be closely related to leukemia occurrence. The presence of anomaly, especially chromosomal breakage syndrome seems to be associated with high risk. The relatively low frequency of sisters in the controls could not be explained, but the sex chromosome may be involved in some way in leukemogenesis. A phase II study of GH application for Turner's syndrome is under way in Japan, and for this, careful follow-up will be required. The response of leukocytes to GH appeared to differ in cases, so regular blood tests might be useful to detect pre-leukemic abnormal response.

Familial aggregation of cancer was not present in cases, so the genetic burden may be scant. However, cases of pituitary deficiency within cancer family syndrome or Li-Fraumeni syndrome, or cases where there is glioma among siblings should perhaps not be treated with GH although the administration should be determined from the balance of risk and advantage in each case.

Leukemia is the most sensitively observable iatrogenic malignancy, partly due to the short latent time and onset at young age. GH is well known to have a close relationship to prolactin secretion, and the latter may have some relation to breast cancer occurrence. A long follow-up study will be necessary to check for long-latency side effects of GH. GH therapy is essential for the growth and development of GH-deficient children, but strict indications for GH treatment should be applied.

Two additional leukemia cases among GH users were reported to us in 1988. One was a 17-year-old girl, who had received GH therapy for one year due to growth retardation after multidisciplinary therapy for malignant teratoma of the ovary in 1982, and developed AML. She had received Ga-scintigraphy and ¹³¹I-uptake test. The other case was a 15-year-old boy, who had been treated by both surgery and cranial irradiation for craniopharyngioma in 1985, and developed Ph¹-positive CML after treatment with GH for one year. He had also received Ga-scintigraphy. These cases will be reported separately.

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