

Neuroblastoma and Leukemia after Induction of Maternal Ovulation

Motoi Nishi, Masako Tanimura

Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, 1757 Tobetsu, Hokkaido 061-0293 Japan

Masako Tanimura, Department of Pediatrics, School of Medicine, Kyorin University, Japan

Correspondence to: Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, 1757 Tobetsu, Hokkaido 061-0293, Japan. motoi@hoku-iryu-u.ac.jp

Tel: +81-133-23-1211

Fax: +81-133-23-1669

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ABSTRACT

AIM: To estimate the contribution of ovulatory agents to the occurrence of neuroblastoma and leukemia in children.

MATERIALS AND METHODS: We studied cases registered in the Japan Children's Cancer Registry from 1985 to 2004. Among them, the mothers of 15155 pediatric patients received no medications before pregnancy (group without medications) and those of 95 patients were given ovulatory medications (ovulatory group). The frequency of each disease (%) in the groups was calculated. If medications before pregnancy make no contribution to the occurrence of malignant neoplasms of children, the frequency of each disease in the ovulatory group should be the same as that in the group without medications. Based on this assumption, an expected value was calculated for each disease. P values were calculated through Poisson distribution, employing "expected numbers" and "observed numbers."

RESULTS: In the ovulatory group, there were significantly more neuroblastoma patients (31 cases) than expected (18.32) ($P=0.001$), and significantly less acute lymphocytic leukemia patients (19) than expected (26.78) ($P=0.037$). There was no significant difference concerning acute non-lymphocytic leukemia patients (5 vs 9.00) ($P=0.074$). In the subgroup whose ages ranged from 1 to 4 years, there were significantly more neuroblastoma patients, too. In the subgroups of both males and females, there were significantly more neuroblastoma patients. In the subgroup of females, the number of cases with acute lymphocytic leukemia was significantly low.

CONCLUSIONS: Ovulatory agents promote the occurrence of neuroblastoma whereas they suppress the occurrence of acute

lymphocytic leukemia.

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Key words: Cancer registry; Children; Leukemia; Neuroblastoma; Ovulatory agents

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INTRODUCTION

The causes of malignancies, including environmental ones, for the most part remain unknown. In Australia, 5 children with neuroectodermal tumors (3 neuroblastomas, 1 medulloblastoma, and 1 PNET) who were born through artificial fertilization were reported, and the necessity of investigating the relation between artificial fertilization and these malignancies was pointed out^[1]. The mothers of these 5 children had taken ovulatory agents. Considering this fact, we examined the intake of ovulatory agents with regard to 6236 cases of malignancies that were registered in the Japan Children's Cancer Registry from 1985 to 1989. There was a significant correlation between neuroectodermal malignant tumors of children and ovulatory agent intake^[2-3].

In the present study, we report the relationships between intake of ovulatory agents and neuroblastoma and leukemia, employing many more cases from the Japan Children's Cancer Registry with other analytical methods.

The registration form of the Japan Children's Cancer Registry has a record of medications of mothers before pregnancy. A total of 23011 cases were registered from 1985 to 2004. The present subjects were 17218 whose mothers' histories of medications before pregnancy were recorded. Among them, there were 15155 cases with a record of their mothers having received no medications before pregnancy (group without medications). For 95 cases the mothers had been given ovulatory medications (ovulatory group).

MATERIALS AND METHODS

Analysis as a whole

Malignant neoplasms were classified using the ICD 9. If medications before pregnancy make no contribution to the occurrence of

malignant neoplasms of children, the frequency of each disease in the ovulatory group should be the same as that in the group without medications.

The frequency of each disease (%) in the group without medications was calculated. The frequency (%) multiplied by 95 was regarded as the "expected number" of cases for each disease in the ovulatory group. *P* values were calculated through Poisson distribution, employing "expected numbers" and "observed numbers."

Analysis of subgroups

The age distribution of occurrence is different among diseases. For example, most cases of neuroblastoma, are found at under 5 years. Moreover, in the period of the present study, many cases found by mass screening for neuroblastoma and consequently diagnosed at 0 years of age were included. The accuracy of mothers' recall of things before or during pregnancy is different among those whose children's ages at diagnosis are, e.g., 1 year and 10 years. Therefore, we performed analysis for subgroups whose ages at diagnosis were 0 years, 1-4 years and 5-14 years of age, in addition to the subgroups of males and of females.

RESULTS

Table 1 shows the percentages of each of the diseases in the group without medications.

Table 2 shows the number of each of the diseases, the expected

Table 1 Frequency of diseases in the group without medications.

Subgroup		ALL	ANLL	NB
Whole group (<i>n</i> =15155)	No. of cases	4058	1364	2776
	%	26.78	9.00	18.32
0 years (<i>n</i> =3262)	No. of cases	157	159	1724
	%	4.81	4.87	52.85
1-4 years (<i>n</i> =5125)	No. of cases	1746	405	785
	%	34.07	7.90	15.32
5-15 years (<i>n</i> =6768)	No. of cases	2155	800	267
	%	31.84	11.82	3.95
Male (<i>n</i> =8183)	No. of cases	2335	750	1525
	%	28.53	9.17	18.64
Female (<i>n</i> =6972)	No. of cases	1723	614	1251
	%	24.71	8.81	17.94

ALL: acute lymphocytic leukemia; ANLL: acute non-lymphocytic leukemia; NB: neuroblastoma.

numbers, and *P* values in the ovulatory group. In the ovulatory group, there were significantly more neuroblastoma patients (31 cases) than expected (18.32) (*P*=0.001), and significantly less acute lymphocytic leukemia patients (19) than expected (26.78) (*P*=0.037). There was no significant difference concerning acute non-lymphocytic leukemia patients (5 vs 9.00) (*P*=0.074).

In the subgroup whose ages ranged from 1 to 4 years, there were significantly more neuroblastoma patients as well. In both the male and female subgroups there were significantly more neuroblastoma patients. In the female subgroup, the number of cases with acute lymphocytic leukemia was significantly low.

DISCUSSION

Yanaihara *et al.*^[4] estimated that the number of women who were taking ovulatory agents in February 1999 in Japan was 165500. According to the national census in 2000, the number of married women aged from 20 to 49 years was 15687392. The percentage of those who take ovulatory agents in Japan is, therefore, about 1%.

The risk of developing neuroblastoma was significantly high in the ovulatory group. Since the present study employed many more cases

Table 2 Results in the ovulatory group.

subgroup		ALL	ANLL	NB
Whole group (<i>n</i> =95)	No. of cases observed	19	5	31
	% expected	26.78	9.00	18.32
	No. expected	25.44	8.55	17.40
	<i>P</i>	0.037 ¹	0.074	0.001 ²
0 years (<i>n</i> =29)	No. of cases observed	0	1	21
	% expected	4.81	4.87	52.85
	No. expected	1.40	1.41	15.33
	<i>P</i>	0.248	0.344	0.034
1-4 years (<i>n</i> =33)	No. of cases observed	8	3	10
	% expected	34.07	7.90	15.32
	No. expected	11.24	2.61	5.05
	<i>P</i>	0.083	0.218	0.019 ²
5-15 years (<i>n</i> =33)	No. of cases observed	11	1	0
	% expected	31.84	11.82	3.95
	No. expected	10.51	3.90	1.30
	<i>P</i>	0.118	0.079	0.272
Male (<i>n</i> =54)	No. of cases observed	14	2	18
	% expected	28.53	9.17	18.64
	No. expected	15.41	4.95	10.06
	<i>P</i>	0.099	0.087	0.007 ²
Female (<i>n</i> =41)	No. of cases observed	5	3	13
	% expected	24.71	8.81	17.94
	No. expected	10.13	3.61	7.36
	<i>P</i>	0.035 ¹	0.212	0.019 ²

¹ *P*<0.05, Expected>Observed; ² *P*<0.05, Expected<Observed; ALL: acute lymphocytic leukemia; ANLL: acute non-lymphocytic leukemia; NB: neuroblastoma.

than previous studies, its reliability does not seem to be inferior to them. Therefore, ovulatory agents are probably one of the risk factors for the development of neuroblastoma.

In a case-control study of 504 neuroblastoma cases conducted in the USA and Canada, the odds ratio was 1.4, though it was not significant^[5]. The odds ratio of the group aged 1-2 years was higher than that of the group aged 0 years. Their results are not contradictory to ours.

In Denmark, 51 malignancies occurred in 30364 children born from 1960 to 1990 whose mothers took ovulatory agents. In that study the incidences of sympathetic nervous tumors including neuroblastoma was high (observed, 7 cases; expected, 3.3; relative risk, 2.14), though it was not significant (95% CI, 0.9-4.4)^[6]. Since the number of observed cases was only 7, and the lower limit of the 95% CI was 0.9 which is very near to 1.0, their findings do not completely deny the effects of ovulatory agents to promote the occurrence of neuroblastoma.

There are several factors associated with an increased risk of neuroblastoma in offspring, such as two or more prior induced abortions^[7], a shorter gestational duration and low birth weight^[8]. Bluhm *et al.*^[9] reported that maternal recreational drug use and marijuana use during pregnancy increased the risk of neuroblastoma. (In Japan, however, marijuana use is strictly prohibited, and there are very few pregnant women who use it). Since the present study is not a case-control one, we could not take account of confounding factors. In this sense, the present conclusion is not necessarily decisive.

For the purpose of the present study, the most precise method was to longitudinally follow those who were given medications before/during pregnancy and those who were not given any medications, and to observe the occurrence of malignant diseases in their children. This method was, however, not practical, since it required a long period, and since the incidence of malignant diseases during childhood is low. In the present analysis, therefore, we regarded the frequency

of each malignant disease in the group without medications as the "natural frequency", and we compared the natural frequency and the frequency in the group with medications.

Generally, 30-40% of the malignant neoplasms occurring in the children younger than 15 years of age are leukemia, and about 10%, neuroblastoma. However, the distribution of malignancies in the group without medications was different from this general one. Since the present study period included the years when a nationwide program of mass screening for neuroblastoma was performed, the percentage of neuroblastoma in the group without medications was relatively high. These conditions, however, had no influence on the present calculations. In the group aged 1-4 years, where the risk was significantly high, there were smaller numbers of neuroblastoma patients found through mass screening for neuroblastoma than in group aged 0 years. Thus the influence of the mass screening on the group aged 1-4 years was not large.

The reason why a single agent has a protective effect on one cancer type and a promoting effect on another type cannot be clarified in the present study. But growth factors, such as the vascular endothelial growth factor, induced by clomiphene especially in ovarian hyperstimulation syndrome, might have something to do with the promotion of neuroblastoma which is a solid tumor. Bruinsma *et al*^[10] reported that children conceived using in-vitro fertilization and related procedures did not have a significantly increased incidence of cancer. 24.3% (1060 cases) of their subjects were given clomiphene, and 3 male cases with leukemia, but no female cases with it were found. This is not contradictory to the present results that the number of female cases with acute lymphocytic leukemia was significantly low.

Using the same analytical methods as in the present study, one of us^[11] reported that children with Down syndrome did not develop neuroblastoma, whereas they developed significantly more leukemia. The present study showed that ovulatory medications promoted the occurrence of neuroblastoma, whereas they suppressed the occurrence of acute lymphocytic leukemia. Thus, the contribution of ovulatory agents is nearly inverse to that of Down syndrome.

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Peer reviewers: Thomas Roujeau, Head of the Pediatric Neurosurgical Unit, Department of Neurosurgery, Hôpital Gui de Chauliac, 80 av Augustin Fliche, 34 295 Montpellier cedex 5, France; Daniel Satgé, MD, PhD, ONCODEFI Project, Epidemiology and Biostatistics Department (EA 2415), University Institute for Clinical Research, Montpellier University, 34093 Montpellier, France.