

## Mass Screening for Neuroblastoma Necessity for Rediscussion

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### ABSTRACT

In this article, the history of mass screening for neuroblastoma (NBMS) targeting 6-month-old infants is briefly described, and the change in the mortality after stopping NBMS is reported. Several cohort studies performed to evaluate NBMS are summarized, as well. NBMS was previously performed on a nationwide scale in Japan targeting 6-month-old infants, and after 1992 all the specimens were measured by high performance liquid chromatography (HPLC). But NBMS stopped in most communities by the spring 2004. For the purpose of estimating the influence of stopping NBMS, we investigated the mortality rates of the children who died of neoplasms of the adrenal glands at the ages of 1 to 4 years by birth cohorts from the introduction of HPLC to the period after stopping NBMS. The mortality rate in the birth cohort from 1992 to 2003, most of whose members participated in NBMS with HPLC, was significantly lower than the mortality rate in the cohort from 1989 to 1991 ( $P < 0.01$ ). The mortality rate in the cohort from 2004 to 2006, most of whose members were not screened, was the highest among the cohorts after 1992, and the significant difference from the mortality rate in the cohort from 1989 to 1991 disappeared. Considering the increasing mortality of the neoplasms of the adrenal glands in Japan and the recent results of the cohort studies revealing the effectiveness of NBMS, it is necessary to discuss its restart on a nationwide scale.

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**Key words:** Child; Epidemiology; Mass Screening; Mortality; Neuroblastoma

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### INTRODUCTION

Neuroblastoma (NB) is a frequent solid tumor during childhood. In Japan, before the start of mass screening for neuroblastoma (NBMS), NB was the third most frequent malignancy in children 0-14 years of age, after leukemia and brain tumors<sup>[1]</sup>. In many cases of NB, the original site is the adrenal glands. Though therapeutic methods have become better, even now its prognosis has not improved much. The 5-year survival rate of cases in stage IV is about 30-40%<sup>[2]</sup>.

One feature of NB is the excretion of large amounts of vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine. Taking advantage of this feature, NBMS was previously performed on a nationwide scale in Japan, but this is no longer done except in a few areas. In this article, the history of NBMS in Japan is briefly described and the change in the mortality rate after stopping NBMS is reported, employing the data of vital statistics.

### HISTORY OF MASS SCREENING FOR NEUROBLASTOMA

NBMS was started in Kyoto Prefecture, Japan, by Dr. Tadashi Sawada in 1973<sup>[3,4]</sup>. After 1985, NBMS gradually spread to other areas of Japan. Its subjects were 6-month-old infants. Urine from babies was sampled on filter paper and levels of urinary VMA and HVA were measured using high performance liquid chromatography (HPLC)<sup>[5,6]</sup>. HPLC is a quantitative method. At first, these levels were estimated by qualitative methods, e.g., the spot test, dip test, and thin layer chromatography (TLC). However, after it became known that the efficacy of HPLC was far better than those of qualitative methods, it was gradually introduced and all the specimens were measured by HPLC after 1992 throughout Japan. In fact, there are large differences between the results for NBMS obtained using HPLC and those from non-HPLC methods<sup>[7,8]</sup>.

After several years, however, it turned out that the incidence of true positives in NBMS with HPLC was higher (1 case per 5,000 screened) than the natural incidence previously reported (1 case in 10,000 live births), and more than a few false negatives (patients

who appear to have clinical symptoms after having negative results in MS) were detected (1 in 20,000 screened). The sensitivity was, therefore, about 80%<sup>[7]</sup>.

Therefore, some researchers began to suggest that NBMS found only those whose tumors regressed spontaneously (spontaneous regression cases) without finding those whose symptoms appeared at older ages (proper cases)<sup>[9]</sup>. In fact, several true positives detected by NBMS were followed without any treatment and, in some cases, tumor markers such as VMA or HVA, became normal<sup>[10]</sup>.

In 2000 the study group of Hisashige *et al*<sup>[11]</sup>, which conducted a large-scale retrospective cohort study, concluded that NBMS with HPLC was effective in reducing mortality. Their subjects were 6-month-old infants from the introduction of HPLC to 1997 (children screened, 19,520,000 person-years; children not screened, 3,340,000 person-years). The relative risk of mortality was 0.547 (95% CI; 0.306-0.976). From 2003 to 2004, Hayashi *et al*<sup>[12,13]</sup> reported the results of their large-scale retrospective cohort study in which screened and unscreened children born from 1995 to 1999 were compared. The relative risk of mortality was 0.269 (95% CI; 0.170-0.428).

In 2003, however, groups in Canada<sup>[14]</sup> and Germany<sup>[15]</sup> published their findings that NBMS was not effective. That year the Japanese Government decided to stop the nationwide NBMS. By the spring 2004, NBMS stopped in most communities in Japan.

As stated above, there is an opinion that NBMS identifies only "spontaneous regression cases", and misses "proper cases", and that it is therefore ineffective in reducing mortality. If this opinion is correct, after NBMS starts, the mortality rate must increase, because some of those who are true positives detected by NBMS will die of the side effects of chemotherapy or of sequelae of operations, and their mortality rate will be added to that of "proper cases". If this opinion is correct, after NBMS is stopped the mortality rate should decrease because there would be no more deaths of those with "spontaneous regression". The reality is, however, quite the opposite.

## CHANGE IN MORTALITY RATE OF NEOPLASMS OF THE ADRENAL GLANDS

### Mortality rates at 1-4 years of age

For the purpose of estimating the influence of stopping NBMS, we investigated the mortality rates of the children who died of neoplasms of the adrenal glands at the ages of 1 to 4 years by birth cohorts from 1989 to 2006, i.e., from the introduction of HPLC to the period after stopping NBMS<sup>[16]</sup>.

In the vital statistics there are no codes that stand for NB. The codes 194.0 (ICD 9) and C74 (ICD 10) stand for neoplasms of the adrenal glands. Every year the Japanese Government publishes the numbers of deaths at the ages of 0, 1, 2, 3, 4, 5-9, 10-14, etc., up to 95-99, and 100 years of age or older<sup>[17]</sup>. Using these data, birth cohorts can be made. For example, those who died at 0 years of age in 2000, at 1 year of age in 2001, at 2 years of age in 2002, at 3 years of age in 2003, and at 4 years of age in 2004 belonged to a birth cohort whose birth year was 1999 or 2000 (1999-00 cohort). The number of live births of this cohort was estimated to be "the number of live births in 1999×0.5 + that in 2000×0.5". Using the numbers of deaths and live births, the mortality rate (per 100,000 live births) was calculated. Multiplying the mortality rate of the "1989-91 cohort" (the birth cohort before all the babies were screened by HPLC) to the number of live births of each cohort, the expected number of deaths was calculated. Employing the number of deaths and the expected number, chi-square test was performed (Table 1).

**Table 1** Live births, deaths at 1-4 years of age, mortality rates (per 100,000 live births), expected number of deaths (multiplying the mortality rate of the "1989-91 cohort" compared to the number of live births of each cohort), and  $\chi^2$  values.

Birth cohort	Number of live births	Number of deaths	Mortality rate	Expected number of deaths	$\chi^2$ value
1989-91	3,737,012.5	75	2.01	75.00	0
1992-94	3,628,057.5	55	1.52	72.81	4.36 <sup>1</sup>
1995-97	3,608,615.5	58	1.61	72.42	2.87 <sup>2</sup>
1998-00	3,571,922.0	58	1.62	71.69	2.61
2001-03	3,481,595.5	52	1.49	69.87	4.57 <sup>1</sup>
2004-06	3,281,393.0	62	1.89	65.86	0.23
1992-03 total	14,290,190.5	223	1.56	286.8	14.19 <sup>3</sup>

<sup>3</sup>  $P < 0.01$ ; <sup>1</sup>  $P < 0.05$ ; <sup>2</sup>  $0.05 < P < 0.10$ .

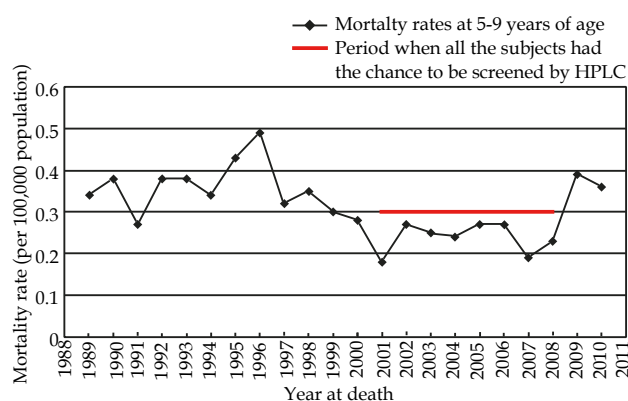
The mean participation rate for NBMS in the 1990s was 86%, according to the report of Hiayama *et al*<sup>[18]</sup>. That of the babies born from 1995 to 2000 reported by Hayashi *et al*<sup>[13]</sup> was 87.4%. Therefore, about 90% of the "2001-03 cohort" participated in NBMS. There were no large differences in the mortality rates among the "1992-94", "1995-97", "1998-00" and "2001-03" cohorts. The total number of deaths in these cohorts from 1992 to 2003 was 223. Since the expected number of deaths was 286.8, the number of deaths was significantly small ( $P < 0.01$ ). The mortality rate of the "2004-06 cohort", most of whose members were not screened, was the highest among the cohorts after 1992-94, and the significant difference from the mortality rate of the "1989-91 cohort" disappeared.

### Mortality rates at 5-9 years of age

As stated above, for the number of deaths at the ages of 5 years or older, only the data by 5-year age-groups (5-9 years, 10-14 years, etc.) are available. Therefore, it is impossible to make birth cohorts. Figure 1 shows the changes in the mortality rates (per 100,000) of children whose age at death was 5-9 years. In the group aged 5-9 years before 1996, there were few children who underwent NBMS with HPLC, since it was first in 1992 that all 6-month-old babies had the chance to be screened by HPLC. The mortality rate had no tendency to decrease. In 1997, however, when the number of children who were screened by HPLC began to increase, the mortality rate started to decrease. The mortality rates from 2001 to 2008, when all the children of this age group had the chance of being screened by HPLC, were the lowest. However, in 2009, when the number of children who were not screened began to increase within this age group, the mortality rate started to increase.

### Effects of mass screening in reducing the mortality of neuroblastoma

As reported before<sup>[19]</sup>, Hanawa *et al*<sup>[20]</sup> published several reports,



**Figure 1** Mortality rates at 5-9 years of age.

using all cases with NB. According to their data, there were 842 deaths at 0-4 years of age from 1979 to 1992. On the other hand, according to the vital statistics during the same period, there were 771 children (91.6% of the cases reported by Hanawa *et al*) who died of neoplasms of the adrenal glands. It is possible that among the 771 cases there were several cases with adrenal carcinoma or pheochromocytoma, but these are very rare during childhood. It is not unreasonable, therefore, to conclude that NBMS with HPLC reduced the mortality rate of children with NB whose original site was the adrenal glands. In 2008 Hiyama *et al*<sup>[18]</sup> published a report of a large-scale retrospective cohort study. They compared the screened cohort and the one not screened. Their conclusion was that the relative risk of mortality for the children screened by HPLC was about 0.53 (0.42-0.63). The present data compare the group whose members all had the chance to be screened by HPLC and the one whose members did not. Though the subjects in the study of Hiyama *et al*<sup>[18]</sup> and the present one are different in character, the conclusions of the two studies are similar.

As pointed out previously<sup>[21]</sup>, the study in Canada<sup>[14]</sup> employed TLC, the efficacy of which is far worse than that of HPLC. The German study<sup>[15]</sup> combined false negatives with true positives to calculate the incidence of the "screened group", but since many cases with spontaneous regression were included as true positives, this method inflated the incidence of the "screened group" and led to underestimation of the effectiveness of NBMS, indicating that it could not reduce the incidence of NB. Furthermore, they employed subjects in a "control area" as controls, not "non-participants" for whom biases would be fewer because of being in the same area as the participants. The incidence of NB among the subjects in the "control area" was about 25% smaller than that of "non-participants". This also led to underestimation of the effectiveness of NBMS.

### Influence of prolongation of survival period

The mortality rate of the "2004-06 cohort" was a little lower than that of the "1989-91 cohort" (Table 1). This might partially have been due to complete cure and/or prolongation of life in some cases as a result of the progress of therapeutic methods. In France, where virtually no NBMS has been performed, there was a slight decrease in the mortality rate of the cases with neoplasms of the adrenal glands at 1-4 years of age from the 1980s to 1990s (Table 2)<sup>[22]</sup>. However, the mortality rate at 5-9 years of age increased, and there was no significant change in the total mortality rate for 1-9 years of age, suggesting that prolongation of the survival period due to the progress of therapy brought about this change.

**Table 2** Mortality rates (per 100,000 population) for neoplasms of the adrenal glands in France.

Year of death	1-4 (%)	5-9 (%)	1-9 (%)
1980-83	0.733 (100)	0.247 (100)	0.452 (100)
1984-87	0.655 (89.4)	0.341 (137.7)	0.482 (106.7)
1988-91	0.779 (106.3)	0.317 (128.0)	0.519 (115.0)
1992-95	0.394 (53.8)	0.281 (113.6)	0.331 (73.2)
1996-99	0.535 (73.0)	0.403 (163.0)	0.460 (101.8)

Since the time interval of the present study was about 20 years, the contribution of progress in therapeutic methods cannot be ignored. In Japan, too, many children who would have died at 1-4 years of age died at 5-9 years of age due to prolongation of the survival period. It is probable that this made the mortality rate at 1-4 years of age in the "2004-06 cohort" lower (Table 1). The mortality rate at 5-9 years of age had a tendency to increase by 1996 (Figure 1). This suggests that there were already cases whose survival period was prolonged.

### Influence of NBMS targeting 18-month-old children in several areas

There are several areas that continue NBMS, including the City of Sapporo<sup>[23]</sup>, Niigata Prefecture, Kyoto Prefecture<sup>[24]</sup>, and Osaka Prefecture<sup>[25]</sup>. Now, NBMS in all of these areas targets 18-month-old children, not 6-month-old babies. One of the aims of this change in the age targeted is to reduce the detection of cases of "spontaneous regression"<sup>[26]</sup>.

In Kyoto<sup>[24]</sup> and Osaka<sup>[25]</sup>, the incidence rates of true positives were 1 of 8,060 screened, and 1 of 8,556, respectively, which are lower than that of NBMS targeting 6-month-old infants (about 1 in 5,000), though it was higher in Sapporo (1 of 2,965 screened)<sup>[26]</sup>.

In Sapporo<sup>[26]</sup>, 9 cases were identified from April 2006 to December 2008. In Kyoto<sup>[24]</sup>, 4 cases were identified from 2004 to 2009. In Osaka<sup>[25]</sup>, 8 cases were identified from April 2005 to March 2008. Since most of these cases belonged to the "2004-06 cohort" (Table 1), the mortality rate of this cohort was decreased by saving the lives of these children.

### Biological features of detected cases in NBMS

Biological characterization is one of the important factors which influence the prognosis of NB cases.

In Sapporo City, the NBMS targeting 6-month-old infants were performed from April 1981. On April 1991, the second NBMS was started, targeting 14-month-old children. The 6-month NBMS was stopped on March 2004. On April 2006, the age targeted was changed from 14 months to 18. That is, the 6-month NBMS was performed for 23 years, the 14-month NBMS, for 15 years, and the NBMS targeting 18-month-old children have been performed since April 2006. Hanai *et al*<sup>[23,27]</sup> reported biological aspects of the cases detected in these 3 mass screenings (Table 3). Only 1 case detected in the 6-month MS was in INSS stage 3 (2%). But in the 18-month MS, 4 cases (33%) were in this stage. 50% of the cases detected in the 18-month MS had the unfavorable type of Shimada's classification. Thus, in the 18-month MS, though no cases had amplification of MYCN, so far as Shimada's classification and clinical stages are concerned, more cases with unfavorable prognosis are detected than in the 6- and 14-month MS.

Considering the increasing mortality of the neoplasms of the adrenal glands in Japan and the recent results of the cohort studies revealing the effectiveness of NBMS, it is necessary to discuss its restart on a nationwide scale.

**Table 3** Biological features of the cases detected in the 6-, 14- and 18-month-NBMS (Sapporo City, since 1991).

		6MS	14MS	18MS
MYCN amplification <sup>[23,27]</sup>	+	1	0	0
	-	41	26	12
INSS stage <sup>[23]</sup>	1	30	22	6
	2A	7	2	0
	2B	8	5	2
	3	1	3	4
	4	0	1	0
Shimada's classification <sup>[23]</sup>	4S	1	0	0
	Favorable	36	29	6
	Unfavorable	4	3	6
Histopathology <sup>[23]</sup>	Neuroblastoma	46	28	8
	Ganglioneuroblastoma	1	5	4

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