Neuroblastoma Screening in Japan: Population-based Cohort Study and Future Aspects of Screening

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Abstract

Introduction: It is unknown whether screening for neuroblastoma has the benefit of reducing the incidence of advanced disease or mortality due to neuroblastoma. Japanese nationwide mass-screening for 6 month old infants was launched in 1985 and was performed using quantitative high-performance liquid chromatography (HPLC) between years 1990 to 2003. Materials and Methods: We compared the incidence rates (IR) and the mortality rates (MR) per 100,000 births of neuroblastomas diagnosed before 6 years of age between 2 cohorts: children born during the years 1980 to1984 (Pre-screen cohort, n = 7,620,203) and 1990 to1998 (Screen cohort, n = 10,878,918). We then proposed the optimal timing and procedures for future screening. Results: Cumulative IR in the Screen cohort was significantly higher than the Pre-screen cohort (29.80 vs. 11.96, *P* <0.0001). On the other hand, IR of neuroblastoma diagnosed after 24 months old in the Screen cohort was significantly lower than in the Pre-screen cohort (*P* <0.0001). The cumulative MR of the Pre-screen cohort was 5.35, whereas that of the Screen cohort was 2.82 (*P* <0.0001). Conclusions: HPLC mass-screening for neuroblastoma at 6 months of age found a marked increase in incidence in younger children (less than 12 month old) and a significant decrease in mortality rates overall. To reduce overdiagnosis of regressing cases and to identify preclinical stages of unfavourable cases, we propose using HPLC-screening at 18 months of age.

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Introduction

Neuroblastoma, one of the most malignant childhood solid tumours, accounted for about 15% of cancer mortality in children.[1,2] Since neuroblastoma usually produces catecholamine, urinary levels of their metabolites vanillylmandelic acid (VMA) and homovanillic acid (HVA) are useful markers for diagnosis. To improve outcomes in neuroblastoma by the early detection of preclinical tumours in infancy,[3,4] nationwide mass-screening test for neuroblastoma at 6 months of age was launched in Japan between 1984 and1985.[5] Initially, this test used a qualitative spot test for VMA and was replaced by the quantitative HPLC test in 1990. In 2003, acknowledging that there was overdiagnosis of occult tumours that would have spontaneously regressed or matured, the Japanese government decided to halt neuroblastoma screening. In response to this, a research group had been established to clarify the effects of screening at 6 months of age for neuroblastoma and recently reported the effectiveness of this, using a retrospective population-based cohort study.[6]

In this study, we reconsidered the effectiveness of nationwide Japanese neuroblastoma mass screening, especially quantitative HPLC screening, and proposed an adequate screening system for 18 month old children.

Materials and Methods

Study Design

Quantitative HPLC analysis of urinary VMA and HVA levels for screening was introduced around 1990 in most areas of Japan.[6] Using HPLC, the positive criterion was that the value of VMA or HVA was higher than the mean + 3 SD μg/mg creatinine. We compared the incidence (IR) and mortality rates (MR) in the patients diagnosed until 72 month of age in the cohort born between 1980 and 84 (Pre-screen) and that born between 1990 and1998 (Screen). Data on patients with neuroblastoma were obtained via the

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cancer registry of 2 major Japanese societies caring for neuroblastoma patients (Japanese Society of Paediatric Surgeons and Japanese Society of Paediatric Oncology). Both registries had data of all screening cases registered and follow-ups for at least 5 years. These databases were approved for use by our consortium by the ethics committee of each of these societies, as well as that of Hiroshima University. Patients were staged according to the INSS or Evans staging system.[7,8] Patients of any age with stage 1 or 2 disease, and those less than 12 months with stage 3 or 4S disease treated with either surgery or surgery plus chemotherapy, and patients aged 12 months or older with stage 3, and those with stage 4 disease were typically treated according to the protocol by the Japanese Neuroblastoma Study Group.[9]

Matching the death cases in our database to the cases in the death certificate files from the Ministry of Health, Labor and Welfare in Japan revealed that our database included 62.5% of all neuroblastoma cases diagnosed in Japan.[6]

Statistical Analysis

IR and MR per 100,000 births of neuroblastoma diagnosed at less than 72 months of age were estimated using the registry data. Multiple comparison for proportions were performed after applying variance stabilisation using arcsin transformation to evaluate the significance level for a large number of comparisons.

Results

Compliance rates for screening between 1990 and1998 was 85.9%. In the Pre-screen and Screen cohorts, 570 and 2025 cases were diagnosed respectively. The Screen cohort included 1537 cases detected by screening.

The IR in the Screen cohort was significantly higher than in the Pre-screen cohort. (29.80 vs. 11.56, P <0.0001, Table 1). In cases diagnosed before 5 months of age, IR in both cohorts remained within similar ranges. The IR of neuroblastomas diagnosed between 6 and 72 months of age was 10.27 in the Pre-screen cohort and 27.80 in the Screen cohort (P <0.0001). IR of clinically diagnosed neuroblastomas between 6 and 72 months in the unscreened group of the Screen cohort (11.35) was similar to that of the Pre-screen cohort (10.27). In the Screen cohort, IR of both localised and stage 4S neuroblastomas were markedly elevated, while IR of disseminated stage 4 was not. The IR of neuroblastomas diagnosed between 24 and 72 months of age significantly declined in the Screen cohort (3.24 *vs.* 1.87, P <0.0001). In all neuroblastomas diagnosed before 72 months of age, stage 4 disease was also significantly lower in the screened subgroup of the Screen cohort (P <0.05).

Out of the 570 and 2025 cases in the Prescreen and Screen cohorts, 255 and 192 patients died respectively; cumulative MR were 5.35 and 2.82 respectively. (P <0.0001). In comparison with the MR of cases diagnosed between 6 and 72 months of age in the Pre-screen cohort, that of the Screen cohort were significantly lower (P < 0.0001). MR in patients with neuroblastomas diagnosed between 6 and 72 months of age in the Pre-screen cohort was similar to that in unscreened subgroup in the Screen cohort (4.89 vs. 4.79).

Discussion

In 2 well-known prospective studies of neuroblastoma screening,[10,11] screening did not seem to reduce mortality, although a high incidence of early-stage disease was noted in these studies. Previous reports from Japan have commonly noted an increased incidence in these infants, but some of them had also observed a reduction in mortality rates.[12,13] Our recent population-based study, using a nationwide Japanese cohort, revealed a significant reduction in mortality by screening.[6] The controversy surrounding this issue may be derived from several factors, including age at screening, screening methodology, compliance rates, study design, diagnostic activity/ability, and socio-economic factors. The most critical problems for this controversy were the low mortality rates for neuroblastoma and the difference in incidence. In a previous effort initiated in Quebec using a cohort consisting of about 500,000 children, the number of observed neuroblastoma death cases was only 22, which may be too small to adequately evaluate for a reduction in mortality rate. In a Germany study which was larger than the Quebec programme, IR of neuroblastoma in the control cohort was 7.3, which was clearly low compared to the incidence typically reported.[1,2] In the present study, IR in the control cohort was 11.96 and more than 100 deaths occurred in each cohort, allowing us to detect significant differences in MR. Only then can the effectiveness of screening for neuroblastoma become apparent for HPLC-screening. In fact, the IR of advanced (INSS 4) neuroblastoma detected more than 2 years of age was significantly decreased. The difference in cumulative MR due to neuroblastoma diagnosed before age 72 months between screened and unscreened groups in the Screen cohort was 22.3 per million.

The MR of the unscreened subgroup in older patients did not show any decrease during these 2 decades. These data indicate that no major advances have been made in neuroblastoma treatment in cases of disseminated disease in older patients. The recent advent of intensive myeloablative therapy with stem cell transplantation may significantly improve survival in advanced disease but would not increase the total number of cases cured. Thus

Table 1. Numbers of Patients, IRs, and MRs of Neuroblastoma Diagnosed Younger than 72 Months of Age

	Pre-screen	**Quant-screen**
Year of birth	**(1980-1984)**	**(1990-1998)**
No. of birth	**7,620,203**	**10,878,918**
No. of screened children (%)	**–**	**9,342,132 (85.9%)**
Total cases of neuroblastoma	570	2026**
Total IR	11.96	29.80
RR (95% CI)	–	2.49 (2.27-2.73)
Cases diagnosed at 1-5 months (IR)	81 (1.70)	135 (1.99)
Cases diagnosed at 6-72 months(IR)	489 (10.27)	1891(27.81)**
Cases in screened children (IR)		1781(30.52) [1536(26.31)]
Cases in unscreened children(IR)		109(11.35)
Localized stage (1-3) (IR)	199 (4.18)	1478(21.74) [1434(24.56)]
Disseminated stage 4 (IR)	251 (5.27)	291(4.28) [231(3.96)]
Stage 4S (IR)	10 (0.21)	101(1.49) [97(1.66)]
Total deceased cases among children with	255	192**
neuroblastoma diagnosed at 0-72 months		
Total MR	5.354	2.824
RR (95% CI)		0.53 (0.44-0.64)
Deceased cases diagnosed at 0-5 months (MR)	22(0.462)	18(0.264)*
Deceased cases diagnosed at 6-72 months (MR)	233(4.892)	174(2.558)**
Screened children (MR)		128(2.091) [20(0.343)]
Unscreened children (MR)		46(4.789)

CI: confidence interval; HPLC: high-performance liquid chromatography; HVA: homovanillic acid; IR: cumulative incidence rate until 72 months of age (per 100,000 births); RR: relative risk; VMA: vanillylmandelic acid
[ ]: Number of screening-detected cases, ** $P < 0.01$, * $P < 0.05$.

early diagnosis and prevention of dissemination in unfavourable disease, in particular screening, may be the most effective means of improving outcomes in neuroblastoma. Thus, the most appropriate age for screening to detect unfavourable disease at early stages with minimum detection of favourable tumours should be elucidated. Most neuroblastomas detected through screening at 6 months of age had favourable characteristics[14] and would either spontaneously regress or mature into ganglio-neuromas.[15] In one study it was observed that for restricted local neuroblastomas detected by screening approximately 40% to 60% regressed spontaneously.[16] However, a whole genome expression profiling study of neuroblastomas detected by screening failed to molecularly differentiate tumours at high risk for progression from those in which the natural history was instead likely to be that of spontaneous regression or differentiation.[17] This phenomenon suggested that some favourable infant tumours might turn into unfavourable types and early detection of these unfavourable tumours is most desired (Fig. 1).[18] According to several studies which adopted "wait and see" strategies,[16,19] urinary VMA and HVA levels would have declined to normal ranges by 18 months of age in almost all regressing tumours (Fig. 1). To decrease overdiagnosis without sacrificing efficacy, a pilot programme of neuroblastoma screening for 18-months-old children has been proposed and launched in several prefectural committees. In the recent report evaluating Japanese screening,[6] neuroblastoma cases that were not picked up during screening at 6 months of age (false negatives) were estimated as 15.2% within the whole cohort of neuroblastoma cases diagnosed between 6 and 72 months of age. In this report, sensitivity, specificity and positive predictive values of HPLC screening were calculated as 84.7%, 99.9%, and 21.1% respectively. Neuroblastoma screening for 18 month old children is also expected to reduce false negative cases.

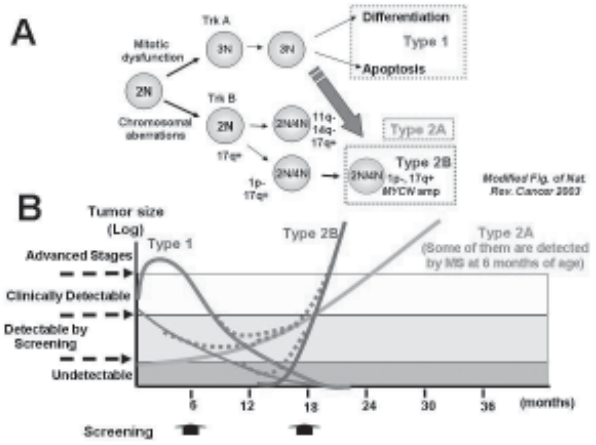

Fig. 1. Neuroblastoma development hypothesis.
A. This was modified figure described previously.[20] Usually, neuroblastoma was divided into 3 types: Types 1 (low risk), 2 (intermediate) and 2B (high risk). Type 1 tumours were infant low risk tumours which show triploid (3N) and regress/mature spontaneously. Type 2 tumours which were diagnosed at older children, have several genetic aberrations and progress into advanced stages. Type 2B tumours are the most aggressive ones with *MYCN* gene amplification. In the present study, early stages of Type 2 tumours are not found out in the tumours detected by screening but Type 2 tumours in elder children significantly decreased, suggesting that some Type 1 tumours might turn to become Type 2 tumours.

B. Time course of each type of tumour in neuroblastoma. According to several studies adopting "wait and see" strategies,[16,19] most regressing or maturing tumours were diminished until 18 months of age and majority of unfavourable type 2A or 2B tumours progress after 18 months of age. Thus, we propose a pilot programme of neuroblastoma screening for 18 months old children.

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