

NEUROBLASTOMA SCREENING AT ONE YEAR OF AGE

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ABSTRACT

Background Neuroblastoma is the second most common type of childhood tumor. It is not known whether screening for neuroblastoma at one year of age reduces the incidence of metastatic disease or mortality due to neuroblastoma.

Methods We offered urine screening for neuroblastoma at approximately one year of age to 2,581,188 children in 6 of 16 German states from 1995 to 2000. A total of 2,117,600 eligible children in the remaining states served as controls. We compared the two groups in terms of the incidence of disseminated disease and mortality from neuroblastoma.

Results A total of 1,475,773 children (61.2 percent of those who were born between July 1, 1994, and October 31, 1999) underwent screening. In this group, neuroblastoma was detected by screening in 149 children, of whom 3 have died. Fifty-five children who had negative screening tests were subsequently given a diagnosis of neuroblastoma; 14 of these children have died. The screened group and children in the control area had a similar incidence of stage 4 neuroblastoma (3.7 cases per 100,000 screened children [95 percent confidence interval, 2.7 to 4.7] and 3.8 per 100,000 controls [95 percent confidence interval, 2.9 to 4.6]) and a similar rate of death among children with neuroblastoma (1.3 deaths per 100,000 screened children [95 percent confidence interval, 0.7 to 1.8] and 1.2 per 100,000 controls [95 percent confidence interval, 0.7 to 1.7]). Comparison of the screened group and the children in the control area revealed substantial overdiagnosis in the former group (an estimated rate of 7 cases per 100,000 children [95 percent confidence interval, 4.6 to 9.2]); the overdiagnosis rate represents children who had neuroblastoma that was diagnosed by screening but who would not benefit from earlier diagnosis and treatment.

Conclusions The present findings do not support the usefulness of general screening for neuroblastoma at one year of age. (N Engl J Med 2002;346:1047-53.)
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NEUROBLASTOMA is the second most common tumor of childhood. Between 1987 and 1991, the incidence of neuroblastoma in Germany was 1.1 per 100,000 children under the age of 15.¹ The prognosis of patients with neuroblastoma depends on their age² and the stage of disease³ at the time of diagnosis; infants have the best prognosis. In unscreened populations, fewer than 50 percent of all neuroblastomas are lo-

calized at the time of diagnosis.¹ In Europe, the overall survival of children with this disease has improved only slightly over the past two decades⁴; there has been particularly little improvement among older patients with advanced disease.⁵ Early detection has thus been considered a promising approach to improving the outcome in patients with neuroblastoma.⁶ Most neuroblastomas produce catecholamines, and the catecholamine metabolites vanillylmandelic acid and homovanillic acid can easily be measured quantitatively in the urine as a screen for the disease.^{7,8} However, it is known that neuroblastomas may undergo spontaneous regression, and therefore some cases diagnosed by screening might never have become clinically apparent. This possibility must be considered when screening is evaluated.

In Japan, programs of screening for neuroblastoma at six months of age have been in place since the early 1970s.⁹ A North American study of neuroblastoma screening^{10,11} in which screening was performed at three weeks and six months of age in Quebec, Canada, found a substantial increase in the number of cases of neuroblastoma that were identified in children under one year of age but no reduction in the number of cases diagnosed at older ages and no decrease in the incidence of advanced-stage neuroblastoma. Since the mid-1980s, European studies have made an important contribution to the understanding of the background behind the benefits and risks of screening for neuroblastoma.¹² We initiated the German Neuroblastoma Screening Project in 1995 to assess whether screening for neuroblastoma at one year of age would lead to decreased mortality from the disease.

METHODS**Study Design**

Screening for neuroblastoma was implemented in 6 of the 16 German states, which were selected on the basis of the feasibility of implementing the screening program.¹³ The remaining 10 states

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served as contemporaneous controls. The study design was similar to that of a cluster randomized trial.¹⁴ The study was approved by the state ethics committee of the German Medical Association in the state of Baden-Württemberg. Parents and their infants participated on a completely voluntary basis. The ethics committee agreed that the parents implicitly gave informed consent by providing a urine sample for testing.

Study Population and Screening Procedure

Children who were born between November 1, 1993, and June 30, 2000 (who were between 9 and 18 months old between May 1995 and April 2001), and who lived in one of the six German states where screening was performed were eligible to participate in the study. The birth cohorts in the screening and control areas were of similar size (2,581,188 and 2,117,600 live births, respectively). The age range was chosen in part on the basis of recommendations of the investigators in the Study for the Evaluation of Neuroblastoma Screening in Europe against screening at younger ages¹⁵ and in part on the basis of the results from a German pilot study on the feasibility of screening for neuroblastoma in 12-month-old children.¹⁶

The parents of each child in the screening area were offered screening once at the time of a general checkup when the child was about one year of age. Details of the procedure have been described elsewhere.¹⁷ Children in both the screening area and the control area who were given a diagnosis of neuroblastoma were treated according to the same national treatment protocols.⁵

A positive urine test for catecholamine metabolites was followed by another test on a second urine sample. If the second test was also positive, the parents were contacted and asked to bring the child for a clinical examination. Considerable efforts were made to increase the rate of participation, including repeated mailings to physicians and parents, press releases, and appeals on radio and television. Testing kits were distributed through December 2000, and the last samples were accepted by April 30, 2001 (confirmatory tests were concluded on June 30, 2001).

Epidemiologic Monitoring

Cases of neuroblastoma were identified by the German Childhood Cancer Registry, which receives information on all cases of childhood cancer in Germany, including all neuroblastomas.¹⁸ Follow-up of all cases was conducted in cooperation with the neuroblastoma treatment trial of the German Society of Pediatric Hematology and Oncology.⁵ Ascertainment of deaths is almost complete. Of the children given a diagnosis of neuroblastoma between 1991 and 1995, two were lost to follow-up before five years. The median duration of follow-up among the survivors in this group is currently six years eight months.

Encrypted personal-identification data and the screening result (positive, negative, or not analyzable) for each participating child were sent from the laboratories to the registry, where they were regularly linked to the registry data by stochastic record linkage¹⁹ and compared with the data from the treatment trial. Positive matches were confirmed by means of decryption in the study centers. The ascertainment of cases that were not detected by urine screening is considered to be virtually complete.

Evaluation of Effect

The primary analysis of the effectiveness of screening was based on the intention-to-screen approach, whereby the outcomes in the screening area were compared with those in the control area.²⁰ This approach was also the basis for the power calculations. In secondary analyses, we compared the outcomes among the children who participated in screening with those in the control area.²¹ The main end point of the study, which is ongoing, is mortality due to neuroblastoma.^{13,22,23} Final results are expected in approximately 2008.

We report here interim results for that end point, as well as for the secondary end point of incidence of stage 4 disease. A decrease in this secondary end point is assumed to be a necessary prerequisite for a decrease in mortality. Statistical tests were based on the assumption of a Poisson distribution at a two-sided significance level of 0.05.

Estimation of Overdiagnosis and Lead-Time Distribution

The lead time is defined as the interval between the time of diagnosis with screening and the time the case would have been diagnosed without screening. Overdiagnosis refers to the diagnosis of cases by screening that would not have become clinically apparent and that therefore represent patients who would not benefit from earlier diagnosis and treatment. This group presumably consists mostly of children with tumors that would have spontaneously regressed.²⁴⁻²⁶

To estimate how much of the increase in the incidence of neuroblastoma with screening can be attributed to overdiagnosis, we compared the group that participated in screening with the children in the control area in terms of the distribution of ages at the time of diagnosis. We divided the cases diagnosed in the screened group at the screening age into three categories: cases that would have been diagnosed at that age regardless of screening, the number of which we estimated on the basis of the incidence of neuroblastoma in the control area; cases that were detected early due to screening, the number of which we estimated as the difference between the incidence of neuroblastoma after the screening age in the control area and the incidence after the screening age in the screened area; and cases that represented overdiagnosis by screening and would not have become clinically apparent — the remainder of the cases diagnosed.

Statistical Analysis

To calculate sample sizes, we used the formula proposed by Casagrande et al.²⁷ as modified by Fleiss et al.²⁸ for groups of unequal size, with a one-sided α of 0.05. On the basis of the size of the population, it was estimated that the study would have 70 percent power to detect a 50 percent reduction in mortality in the screened group, assuming that there was no change in mortality in the control group.

RESULTS

Participants and Test Results

Before the study began, children in the screening area and the control area had similar treatment regimens for neuroblastoma, levels of completeness of registration of cases, stage distribution at the time of diagnosis, and mortality from neuroblastoma (Table 1). Of the 2,581,188 children who were eligible for screening through April 30, 2001, 1,475,773 children participated (61.2 percent of those who were born between July 1, 1994, and October 31, 1999). Of 1841 children who had a second positive urine test, 1759 underwent clinical examination. One child died from sudden infant death syndrome after two positive screening tests but before clinical examination; no autopsy was performed, and the child is therefore classified here as having had a false positive test. A total of 149 cases of neuroblastoma were detected by screening. The current status of all children with neuroblastoma is known. The results of urine screening for neuroblastoma are presented in Table 2.

TABLE 1. CUMULATIVE INCIDENCE ACCORDING TO STAGE OF NEUROBLASTOMA AND RELATED MORTALITY IN THE SCREENING AND CONTROL AREAS FOR THE PRESTUDY BIRTH COHORT (1990–1993) AND IN THE CONTROL AREA FOR THE BIRTH COHORT INCLUDED IN THE STUDY (1994–1999).*

| VARIABLE | PRESTUDY BIRTH COHORT (1990–1993) | | STUDY BIRTH COHORT IN CONTROL AREA (1994–1999) |
|--|--------------------------------------|---------------|---|
| | SCREENING AREA | CONTROL AREA | |
| | no. per 100,000 births (95% CI) | | |
| Cases of neuroblastoma | | | |
| Cumulative | 7.0 (5.8–8.3) | 6.5 (5.2–7.8) | 7.3 (6.1–8.5) |
| Localized disease (stage 1, 2, or 3) | 2.8 (2.1–3.6) | 2.6 (1.8–3.4) | 3.5 (2.6–4.3) |
| Disseminated disease (stage 4) | 4.1 (3.2–5.0) | 3.8 (2.8–4.8) | 3.8 (2.9–4.6) |
| Deaths among children with neuroblastoma | 2.9 (2.1–3.7) | 2.9 (2.1–3.7) | —† |

*Data include cases diagnosed at 12 to 60 months of age. CI denotes confidence interval.

†Mortality in the control area during the study period cannot yet be compared with mortality in the earlier birth cohort, because of shorter follow-up time.

Staging of Neuroblastomas

The distribution of the cases detected by screening is summarized according to the International Neuroblastoma Staging System²⁹ in Table 3. In 87 percent of the cases detected by screening, the neuroblastoma was localized (stage 1, 2, or 3), and in the other 13 percent, there was asymptomatic disseminated disease. All but three children with neuroblastoma that was diagnosed by screening are alive. Two children died from complications of surgery (one with stage 2B disease and the other with stage 3 disease), and one died from complications of chemotherapy (for stage 2B disease).

As of June 30, 2001, 55 children who had had negative screening tests presented with neuroblastoma (median age at diagnosis, 36 months; range, 13 to 64 months). Of these children, 48 had elevated levels of catecholamine metabolites in the urine at the time of diagnosis (87 percent); 31 presented with disseminated stage 4 disease (56 percent); and 14 have died (25 percent).

Incidence of Neuroblastoma and Related Mortality

The cumulative incidence of neuroblastoma was 14.2 cases per 100,000 screened children and 7.3 cases per 100,000 controls (Table 3). A greater proportion of cases were diagnosed at stages 1 and 2 in the screened group than in the control area.

As of June 30, 2001, there was no decrease in the incidence of stage 4 disease or in mortality in the screened group or in the screening area (Table 4). There was a higher incidence of stage 4 disease and a higher mortality rate among children who were eligible for screening but did not participate in the

TABLE 2. RESULTS OF URINE SCREENING TESTS FOR NEUROBLASTOMA AMONG CHILDREN SCREENED BETWEEN 9 AND 18 MONTHS OF AGE.*

| VARIABLE | SCREENED GROUP |
|--------------------------------------|----------------|
| Neuroblastomas detected by screening | |
| No. | 149 |
| Rate per 100,000 | 10.1 |
| False positive results† | |
| No. | 1605 |
| Rate per 100,000 | 108.8 |
| False negative results‡ | |
| No. | 55 |
| Rate per 100,000 | 3.7 |
| Neuroblastomas diagnosed | |
| No. | 204 |
| Raw incidence per 100,000 | 13.8 |
| Test characteristics | |
| Sensitivity (%) | 73.0 |
| Specificity (%) | 99.8 |
| Positive predictive value (%) | 8.5 |

*Results are as of June 30, 2001.

†Data are for children with a positive urine screen but a negative clinical evaluation for neuroblastoma.

‡Data are for children with a negative urine screen but a subsequent diagnosis of neuroblastoma.

screening program than among the controls. Follow-up is not yet complete in terms of mortality.

Lead Time and Overdiagnosis

Empirically, the maximal lead time appears to be approximately three years (from the 25th month to the 60th month), since the distributions of age at di-

TABLE 3. DISTRIBUTION OF CASES OF NEUROBLASTOMA ACCORDING TO STAGE IN THE SCREENED GROUP AS COMPARED WITH THE CHILDREN IN THE CONTROL AREA.*

| STAGE | SCREENED GROUP | | CONTROL AREA | |
|--------------------------------|-----------------------|--------------------|--------------------|--------------------|
| | DETECTED BY SCREENING | DIAGNOSED 12-60 MO | DIAGNOSED 12-24 MO | DIAGNOSED 12-60 MO |
| Stage 1 | | | | |
| No. | 66 | 75 | 13 | 28 |
| Incidence per 100,000 (95% CI) | 4.5 (3.4-5.5) | 5.1 (3.9-6.2) | 0.6 (0.3-0.9) | 1.5 (0.9-2.0) |
| Stage 2 | | | | |
| No. | 39 | 44 | 9 | 14 |
| Incidence per 100,000 (95% CI) | 2.6 (1.8-3.5) | 3.0 (2.1-3.9) | 0.4 (0.1-0.7) | 0.7 (0.3-1.1) |
| Stage 3 | | | | |
| No. | 25 | 35 | 18 | 27 |
| Incidence per 100,000 (95% CI) | 1.7 (1.0-2.4) | 2.4 (1.6-3.2) | 0.9 (0.5-1.2) | 1.3 (0.8-1.8) |
| Stage 4 | | | | |
| No. | 19 | 50 | 28 | 74 |
| Incidence per 100,000 (95% CI) | 1.3 (0.7-1.9) | 3.7 (2.7-4.7) | 1.3 (0.8-1.8) | 3.8 (2.9-4.6) |
| Any stage | | | | |
| No. | 149 | 204 | 68 | 143 |
| Incidence per 100,000 (95% CI) | 10.1 (8.5-11.7) | 14.2 (12.2-16.1) | 3.2 (2.4-3.9) | 7.3 (6.1-8.5) |

*Data are for the cohorts born between 1994 and 1999 and include cases registered by June 30, 2001. Staging is according to the International Neuroblastoma Staging System. Almost all children with neuroblastoma detected by screening were between 12 and 24 months of age at the time of diagnosis; data on diagnoses in control children of this age range are therefore presented for comparison. CI denotes confidence interval.

TABLE 4. INCIDENCE OF STAGE 4 NEUROBLASTOMA AND MORTALITY AMONG CHILDREN WITH NEUROBLASTOMA DIAGNOSED BETWEEN 12 AND 60 MONTHS OF AGE.*

| END POINT | CONTROL AREA | SCREENING AREA | | |
|---|---------------|----------------|-------------------------------|-----------------|
| | | ALL CHILDREN | PARTICIPANTS (SCREENED GROUP) | NONPARTICIPANTS |
| Stage 4 neuroblastoma | | | | |
| No. | 74 | 105 | 50 | 55 |
| Incidence per 100,000 births (95% CI) | 3.8 (2.9-4.6) | 4.4 (3.6-5.3) | 3.7 (2.7-4.7) | 5.4 (4.0-6.8) |
| Death among children with neuroblastoma | | | | |
| No. | 24 | 33 | 17 | 16 |
| Rate per 100,000 births (95% CI) | 1.2 (0.7-1.7) | 1.4 (0.9-1.9) | 1.3 (0.7-1.8) | 1.5 (0.8-2.3) |

*All children were born between 1994 and 1999, and all cases of neuroblastoma were registered by June 30, 2001. There was no significant difference in the rate of either end point between the entire group offered screening and the control group or between the participants in the screening program and the control group. CI denotes confidence interval.

agnosis become similar in the screened group and the control group around the fifth birthday. There was an excess of 7.8 cases per 100,000 children during the second year of life (Table 5). There were 0.8 fewer cases per 100,000 children 24 to 60 months of age — a finding that is consistent with the early diagnosis of these cases. So there remains an unexplained

excess of 7.0 cases per 100,000 children during the second year of life, which we interpret as overdiagnosis. On the basis of the rates in the control area, we estimate that 39 of the 149 cases diagnosed by screening would have been diagnosed clinically during the second year of life (the screening age), that 11 of the 149 were diagnosed earlier than they would

TABLE 5. ESTIMATED RATES OF CASES DETECTED EARLY AND EXCESS CASES NOT EXPLAINED BY EARLY DETECTION.*

| DIAGNOSES | CONTROL AREA | SCREENED GROUP | DIFFERENCE BETWEEN GROUPS |
|-----------------------------------|---------------------|------------------------|--|
| | | | rate per 100,000 births (95% CI) |
| At screening age (12–24 mo) | 3.2 (2.4 to 3.9) | 10.9 (9.3 to 12.6) | 7.8 (5.9 to 9.6) (excess in the screened group) |
| After screening age (25–60 mo) | 4.1 (3.2 to 5.0) | 3.3 (2.3 to 4.3) | 0.8 (–0.6 to 2.1) (cases detected early by screening) |
| Total (12–60 mo) | 7.3 (6.1 to 8.5) | 14.2 (12.2 to 16.1) | 7.0 (4.6 to 9.2) (overdiagnosis — excess not explained by early detection) |

*All children were born between 1994 and 1999. Apparent discrepancies are due to rounding.

otherwise have been and the patients may therefore benefit, and that the other 99 neuroblastomas (two thirds of all detected cases) would never have become clinically apparent and would presumably have regressed.

DISCUSSION

We found that screening for neuroblastoma at approximately one year of age did not reduce the incidence of disseminated disease, nor did it appear to reduce mortality. This study was ethically acceptable, because when it began, expert opinion about the usefulness of screening was divided.^{6,17,30} At first glance, screening for neuroblastoma may seem to be warranted. Younger children and children with localized disease have a better prognosis, disease is more often localized at a younger age,³ and localized disease is often associated with markers of good prognosis.³¹ However, the population-based Quebec Neuroblastoma Screening Project showed that screening at three weeks and six months of age did not reduce the incidence of advanced disease, although it increased the number of cases detected.¹⁰ The final results of that study, published in this issue of the *Journal*,³² confirm that screening at these ages does not reduce mortality from neuroblastoma. An international consensus conference in 1998 recommended against screening six-month-old infants for neuroblastoma.³³

We assessed neuroblastoma screening at 12 months of age, with reliable ascertainment of all cases and deaths in the screening area and a control area by a source that was independent of the study.¹⁹ We thus avoided the bias that would be inherent in a comparison between a screening area and a historical control area or between a screened group and a group that chose not to participate in screening.²¹ Our results are qualitatively similar to the results of the Quebec study.³²

The fact that there was no evidence of any reduction in the incidence of metastatic disease or in mortality argues against any substantial effect of screening on outcome. We estimated that 7 percent of all cases detected by screening (11 of 149 cases) were detected earlier by screening than they would otherwise have been, and that those patients may therefore have at least a chance to benefit. This figure (0.8 per 100,000 children screened) is similar to the rate of 1.1 per 100,000 that was previously estimated on the basis of theoretical considerations regarding screening at 12 to 18 months of age.³⁴

Given the present results, we would expect to find an insignificant reduction in mortality, at best, after further follow-up. The small potential benefit is outweighed by the high proportion of patients with neuroblastoma diagnosed by screening who would not be expected to die of neuroblastoma and might be harmed by treatment (99 of 149 cases, or 7 per 100,000 children). The potential risks of screening are highlighted by the fact that the three children who died in the group with neuroblastoma detected by screening had localized disease and died from causes related to treatment.

In Japan, screening for neuroblastoma at six months of age was reported to result in high survival rates (in excess of 95 percent) among patients whose disease was detected by screening,^{35,36} as well as in reduced mortality as compared with that in a historical control group.³⁷ However, there is no population-based registry of childhood cancers in Japan,⁹ and lead-time bias may result in overestimation of the benefit of screening.^{22,23,38,39} In addition, the detection of neuroblastomas that would otherwise spontaneously regress contributes to an overestimation of the benefits of screening.⁴⁰ Comparison of mortality rates with those of historical controls may be biased by recent advances in treatment.^{41,42} In the present

study, many children who had negative screening tests were identified later as having neuroblastoma by the linking of records at the registry. Thus, it is likely that the ascertainment of cases in the screened cohorts in Japan was not complete.⁴³

The high rate of overdiagnosis that results from screening between 9 and 18 months of age suggests that spontaneous regression is not limited to neuroblastomas in infants.⁴⁴ The majority of neuroblastomas in the screened group as well as in the screening area were in localized stages. These findings support the hypothesis that there are different types of neuroblastoma — a type with a favorable prognosis that may regress spontaneously and a more clinically aggressive type with an unfavorable prognosis. This hypothesis has been suggested by several groups.^{26,45,46}

Our findings do not support mass screening for neuroblastoma at one year of age. On the contrary, our results suggest that many of the children with neuroblastoma that is diagnosed by mass screening may undergo unnecessary treatment of a tumor that would otherwise spontaneously regress.

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