

Treatment Complications in Children Diagnosed With Neuroblastoma During a Screening Program

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A B S T R A C T

Purpose

The Québec Neuroblastoma Screening Program was put in place to investigate the possibility of decreasing mortality from high-risk neuroblastoma through early screening. We assess treatment complications in the patients diagnosed during this screening program.

Patients and Methods

A total of 476,603 patients born during the screening period were eligible. Parents of 425,838 children (89%) agreed to participate in the 3-week screening, and 73% agreed to participate in the 6-month screening. Forty-five patients had neuroblastoma. We reviewed the medical and research charts for all patients diagnosed by screening. Follow-up was available from 8 to 13 years after screening.

Results

Forty-five patients were diagnosed by screening. All patients were treated according to the Pediatric Oncology Group recommendations of the time. All patients had surgery, and 29 patients received chemotherapy. No patient died from neuroblastoma. Eleven patients suffered complications from treatment. Two patients had life-threatening complications.

Conclusion

In view of the lack of impact of screening programs on neuroblastoma mortality, evidence that many of the tumors detected through screening can be observed without treatment and the serious complications that may arise from therapy, we do not support neuroblastoma screening programs for children.

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INTRODUCTION

Neuroblastoma is the most common solid tumor in young children, affecting one in 7,000 children younger than 5 years of age.¹ Prognosis is strongly correlated with the stage of the tumor, age at diagnosis, and biologic markers in the tumor tissue itself. Approximately 90% of neuroblastomas secrete catecholamines, which are readily detectable in the urines of affected children. On the basis of these facts, a number of screening programs were established with the purpose of detecting neuroblastoma at a preclinical stage of the disease.

The Québec Neuroblastoma Screening Program was designed to study screening for neuroblastoma first by highly sensitive, semi-quantitative, thin-layer chromatography (TLC) on urine samples. Samples with increased homovanillic acid (HVA) or vanillylmandelic acid (VMA) normalized to creatinine were then tested by highly specific quantitative gas chromatography/mass spectros-

copy (GCMS) for confirmation.^{2,3} The first screen was done at 3 weeks of age and the second screen at 6 months. The screening period was from May 1989 until April 1994. Incidence and mortality from neuroblastoma were compared with that of two comparable cohorts in North America and also with historical controls from the Canadian province of Québec. We showed that the incidence of neuroblastoma during the screening period was doubled,⁴ while mortality from neuroblastoma was not reduced.⁵ We now report the complications of therapy in children diagnosed by screening.

PATIENTS AND METHODS

A total of 476,603 infants born in the Province of Québec during the screening period were eligible. Information regarding the study was distributed to the parents at the time of a child's birth. Parents were asked to send urine-saturated, air-dried filter papers to the screening center at both study time points (ie, 3 weeks and 6 months) for TLC for detection of increased HVA or VMA. Posting of the

filter papers was considered to indicate passive consent to participate. Parents of children with positive results on both TLC and GCMS were asked for a second sample for confirmation by GCMS assay. Written informed consent was obtained for assessment of possible neuroblastoma in all patients with confirmed elevation of urinary HVA-VMA.

Parents of 425,838 children (89%) voluntarily agreed to participate in the 3-week screening, and 73% complied with participation in the 6-month screening. Of the 1,175 positive GCMS screening samples, 84 were positive on the confirmation test. All patients with possible neuroblastoma were referred to one of the four pediatric teaching hospitals in the Province of Québec for uniform assessment, staging, treatment, and follow-up. Patients with negative assessment, including history, physical examination, chest x-ray, abdominal ultrasound or abdominal computed tomography scan, if older than 6 months, and repeat negative urine samples for 6 months were contacted every 3 months until 5 years of age and considered false-positive if neuroblastoma did not develop over the period of observation. Of the 84 patients, 39 were false-positive and 45 had neuroblastoma. We reviewed the medical and research charts for all patients screened. Follow-up was available from 8 to 13 years after screening.

RESULTS

Forty-five patients were diagnosed by screening: 18 patients at 3 weeks of age and 27 patients at 6 months of age. Among the patients detected at 3 weeks, six patients were International Neuroblastoma Staging System stage 1, three were stage 2, three were stage 3, two were stage 4, and four were stage 4S. Among the patients detected at 6 months, six patients were stage 1, eight were stage 2, three were stage 3, six were stage 4, and four were stage 4S (Table 1). Biologic aspects of the neuroblastomas are published elsewhere.⁶ All patients were treated according to the Pediatric Oncology Group recommendations of the time.⁷ All patients had surgery on the primary tumor. Eight patients detected at 3 weeks and 21 patients detected at 6 months also received chemotherapy. Chemotherapy agents included anthracyclines, alkylating agents, cisplatin, and epipodophyllotoxins. No patient died from neuroblastoma. One patient, detected at 3 weeks, and 10 patients, detected at 6 months, developed complications of treatment (Table 2).

Chemotherapy induced complications in three patients. One of them was major, T-cell acute lymphoblastic leukemia with an 11q23 rearrangement occurring 5 years after initial diagnosis. This patient is alive in remission of his neuroblastoma and his leukemia with severe bronchiolitis obliterans 8 years after an HLA-matched sibling bone marrow transplantation. The other complications are related to either the tumor or the surgical removal of the tumor. One patient developed a volvulus because of a postoperative adhesion that progressed to hypovolemic shock. This patient suffered severe anoxic encephalopathy and is in a persistent vegetative state. None of the children with a false-positive screen subsequently developed neuroblastoma.

Table 1. INSS Stage of the Patients Diagnosed by Screening

Age at Screening	Stage 1	Stage 2	Stage 3	Stage 4	Stage 4S
3 weeks	6	3	3	2	4
6 months	6	8	3	6	4

Abbreviation: INSS, International Neuroblastoma Staging System.

DISCUSSION

The Québec Neuroblastoma Screening Program was put in place to investigate the possibility of decreasing mortality from high-risk neuroblastoma through early screening. Unfortunately, the incidence of neuroblastoma was almost doubled and population-based mortality was unchanged.⁵ Most of the neuroblastomas diagnosed by screening were of favorable biology.⁶ These results are consistent with those of other screening programs. A screening program in Japan for children younger than 6 months did not decrease the mortality from neuroblastoma.⁸ Although postponing screening until 7 months to 1 year of age led to an increase in neuroblastomas diagnosed by screening with at least one unfavorable feature in Austria, it did not translate into decreased mortality from neuroblastoma.⁹ Screening at 1 year of age was undertaken in Germany. Their findings, similarly, did not support the usefulness of screening for neuroblastoma at 1 year of age.¹⁰ When surgery is performed following a period of observation, neuroblastomas diagnosed by screening demonstrate maturation.¹¹ Also, a significant proportion of the patients observed without surgery will show a decrease in the size of the neuroblastoma. No patients have shown conversion to unfavorable biology tumors or upgrading of the stage.¹²

Our report is the first describing complications resulting from a neuroblastoma screening program. All patients underwent surgery and two thirds of patients received cytotoxic therapy. One fourth of patients suffered complications. Two were life threatening. Though some of the complications may have resulted from the tumor itself, none were present before treatment. The difference in the complication rate between the group diagnosed at 3 weeks versus the group diagnosed at 6 months is likely multifactorial. Eight of the 18 patients in the first group received chemotherapy, as compared with 18 of 27 patients in the second group, with the chemotherapy delivered mainly through central venous access catheters. More adrenal tumors were found in the 6-month group (19 v five), probably accounting for more kidney injuries in the older patients. The possibility of more extensive surgery having been performed in the older age group is also supported by the larger volume of tissue submitted to pathology, 54 g from the 6-month group as compared with 27 g from the 3-week cohort. Our results are comparable with those reported in the literature. Nishihira et al¹² report a 10% major and minor complication rate from surgery in the MS6M mass screening program, with a 1.1% mortality rate. Schilling et al¹⁰ report a 0.5% mortality from treatment complications in 149 infants diagnosed through screening. Ikeda et al¹³ described surgical complications in 50 infants younger than 1 year of age, half of whom had been diagnosed by screening. Ten infants suffered complications, of which one was lethal. Screening programs can also generate false-positive results, which can be associated with a considerable degree of anxiety and inconvenience on the part of the family.¹⁴ None of the children whose screen was positive but whose assessment for neuroblastoma was negative subsequently developed neuroblastoma. However, we did not study the psychological impact on the families of the false-positive patient cases. In view of the lack of impact of screening programs on neuroblastoma mortality, evidence that many of the tumors detected through screening can be observed without treatment and the serious complications that may arise from therapy,

Table 2. Complications in the Screened Cohort

Patient ID	Screening	INSS Stage	Treatment	Complication
L20	6 months	4	S+C A	Left renal atrophy, secondary to ischemia
L32	6 months	1	S	Intestinal obstruction because of postoperative adhesions; laparotomy; right kidney atrophy
S04	6 months	1	S	Shock, secondary to volvulus because of postoperative adhesions; severe anoxic encephalopathy
M16	3 weeks	3	S+P VP16 C A	Mild hearing loss; hearing aids; speech delay
M26	6 months	4	S+C A	Horner syndrome
M31	6 months	4	S+C A P VP16	Severe hearing loss
M35	6 months	3	S+C A P VP16	Right renal artery thrombosis; right kidney atrophy; hypertension
J51	6 months	2B	S+C A	4 years postchemotherapy: T-ALL with 11q23 rearrangement; BMT; severe cGVHD; bronchiolitis obliterans
J67	6 months	1	S	Intestinal obstruction; intussusception; laparotomy
J69	6 months	2B	S+C A	Left renal artery thrombosis; left kidney atrophy
J100	6 months	3	S+C A P VP16	Right atrial and SVC thrombus on central venous catheter

Abbreviations: INSS, International Neuroblastoma Staging System; S, surgery; C, cyclophosphamide; A, Adriamycin; P, cisplatin; VP16, etoposide; T-ALL, T-cell acute lymphoblastic leukemia; BMT, bone marrow transplantation; cGVHD, chronic graft-versus-host disease; SVC, superior vena cava.

we do not support neuroblastoma screening programs for children. Furthermore, the high rate of surgical complications in infants leads us to support initial observation of localized neuroblastomas incidentally discovered in infants, as suggested by

Fritsch et al.¹⁵ Finally, our results underscore the importance of thoroughly validating any screening program before accepting it as standard of care, since, not only can it be of no benefit, but it could also be detrimental for the patients screened.

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