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Original Paper

10 Years' Neuroblastoma Screening in Europe: Preliminary Results of a Clinical and Biological Review from the Study Group for Evaluation of Neuroblastoma Screening in Europe (SENSE)

R. Erttmann,[1] T. Tafese,[1] F. Berthold,[2] R. Kerbl,[3] J. Mann,[4] L. Parker,[5] F. Schilling,[6] P. Ambros,[7] H. Christiansen,[8] M. Favrot,[9] H. Kabisch,[1] B. Hero[2] and T. Philip[9] on behalf of the SENSE group*

[1]Department of Pediatric Hematology, Universitätskinderklinik, Martinstrasse 52, 20246 Hamburg; [2]Universitätskinderklinik, Köln, Germany; [3]Universitätskinderklinik, Graz, Austria; [4]The Children's Hospital, Birmingham; [5]University Department of Child Health, Newcastle-upon-Tyne, U.K.; [6]Olgahospital, Stuttgart, Germany; [7]St. Anna Kinderspital, Wien, Austria; [8]Universitätskinderklinik, Giessen, Germany; and [9]Centre Regional Leon Berard, Lyon, France

Between January 1986 and May 1996, 870 313 children were tested in European neuroblastoma (NB) screening programmes. Among these children, 82 cases of NB (age range 4–24 months, median 11 months) were detected by screening. 83% of the patients had localised NB and 17% were diagnosed with generalised NB (stage 4, 10%; stage 4s, 7%). Unfavourable biological markers (*MYCN* amplification, loss of heterozygosity (LOH) 1p36, DNA di/tetraploidy) were observed in 14% of 76 biologically examined cases. The median follow-up time of all the patients was 21.5 months (range 1–101 months). To date, 69 patients are in complete remission (CR) and 2 patients have died due to therapy (stage 4, 1 patient; stage 3, 1 patient with unfavourable markers). Apart from screened patients, 16 other patients with NB were found who had previously had a normal screening test, i.e. 'false negative' patients (age range 10–41 months, median 31.5 months). The median interval between screening and diagnosis was 24.5 months (range 6–35 months). 11 of the 'false negative' patients suffered from generalised NB (stage 4) and 5 had localised NB at diagnosis. Unfavourable biological markers were observed in 7/12 patients. 5 patients have died, 2 achieved partial remission and 9 CR. 9 of the 11 patients with unfavourable biological markers diagnosed due to NB screening are currently in CR. It is very likely that, among the patients without unfavourable biological markers, we detected tumours which may have regressed spontaneously. These children may have undergone 'unnecessary', but unavoidable, diagnostic procedures and therapy. To reduce the number of 'false negative' patients, a later screening could be helpful and should be evaluated. © **1998 Elsevier Science Ltd. All rights reserved.**

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*The members of the study group are Professor I. Mutz, Dr P. Ambros, Dr R. Kerbl, Professor C. Urban (Austria), Professor T. Philip, Dr V. Combaret, Dr J. Estéve, Professor M. Favrot, Dr D. Frappaz, Dr J. Greffe, Dr C. Lasset, Dr P. Mathieu (France), Professor F. Berthold, Professor J. Michaelis, Professor J. Sander, Professor R. Erttmann, Dr F. Schilling, Dr T. Tafese (Germany), Dr C. Dominici, Dr A. Jenkner (Italy), Professor A. Craft, Professor J. Mann, Dr I. Parker, Dr J. Powell, Mr C. Stiller, Dr D. Worthington (U.K.).
Correspondence to R. Erttmann.
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INTRODUCTION

SINCE THE early 1980s, programmes for biochemical screening for neuroblastoma have been carried out worldwide. In Japan, screening started with testing the urine of children for neuroblastoma at the age of 6 months [1]. Recently, several districts in Japan introduced additional screening at 18 months of age [2]. In 1994, the North-American neuroblastoma screening project ended after examining children's urine at 3 weeks and at 6 months of age [3]. Screening for neuroblastoma in Europe was performed by seven different study groups, in children between the ages of 4 and 18 months. In Austria, neuroblastoma screening is offered from 7 months onwards [4]. In France, it was performed at 4 months [5]. In Germany, the test was suggested between 6 and 18 months and is now carried out at 12 months [6]. In the U.K., screening was advised at 4–6 months [7]. The members of the above-mentioned European groups form the SENSE (Study for the Evaluation of Neuroblastoma Screening in Europe) group. The aims of this article were to collate neuroblastoma cases from neuroblastoma screening projects in Europe and to analyse the clinical and biological characters of the tumours. These findings were then correlated with the prognosis of patients with unfavourable tumour markers detected early by screening. Other aims were to clarify what, if any, is the best time for screening [8] and to compare tumours found by screening with tumours of 'false negative' screened patients, to learn about the natural history of the disease. This article is a report of work carried out within the SENSE group.

PATIENTS AND METHODS

The aim of early neuroblastoma detection was achieved differently by the participating groups. The details of methods used have been published by each group [4–7]. Briefly, the Austrian project has been running since January 1991. In Austria, parents are offered the test for their children at a general check-up and advised to carry it out from the seventh month onward. Between January 1991 and May 1996 148 381 children were tested in Austria and 17 neuroblastoma cases were detected by screening. In France, screening was performed in the Lyon area, from May 1990 until December 1995 when patients were 4 months of age, and parents were reminded about the test by a letter. In this project, 103 777 children were tested and 12 cases of neuroblastoma were found by screening. In Germany, three different studies were established and finally combined. A pilot study in Hamburg from February 1991 to April 1995 tested children at 6 months of age until May 1994 and then changed to 12 months of age. The Stuttgart pilot study tested children from February 1991 to April 1995 at 6 months of age. In Bremen, Lower Saxony and Northrhine Westphalia, children were tested between April 1992 and April 1995 from 12 to 18 months of age. Since May 1995, the three pilot study groups combined in the ongoing German project, testing children at 12 months of age. The parents were approached by the local paediatrician at routine check-up visits. Until May 1996, 584 490 children had been tested in Germany and 50 neuroblastoma cases were detected by screening. In the U.K., screening was performed in Birmingham from January 1992 to December 1995, in 4- and 13-month-old children and in Newcastle upon Tyne from January 1986 to December 1990 in 6-month-old children. The parents of the children were approached by the public health nurses. In these two projects, 33 665 children were screened and three tumours were detected. Table 1 shows a summary of these data as of 31 May 1996. In all screening projects, children with elevated test results on two occasions were referred to paediatric oncology centres for further investigation, including abdominal ultrascan and thoracic X-ray. The true positive neuroblastoma patients were staged according to INSS [9] and treated according to the national protocols [10–14]. In all patients, tumour surgery was performed at diagnosis or following neoadjuvant chemotherapy. Response evaluation was also according to INSS.

The details of the urine analysis will be described in a separate paper from the SENSE group. In brief, urine was analysed for homovanillic acid (HVA) and vanillylmandelic acid (VMA) by enzyme-linked immunoassay and/or thin-layer chromatography, gas chromatography/mass spectometry and/or high performance liquid chromatography, the last being the most commonly used method.

Tumour samples for histopathological and biological studies were obtained surgically from the primary lesion before any therapy was given. The methods of tumour examination for *MYCN*, loss of heterozygosity (LOH) 1p36 and DNA ploidy have been previously published [15]. The classification of markers as favourable or unfavourable is shown in Tables 2 and 3. Representative sections of the tumours were classified according to Shimada. Serum levels for neuron specific enolase and/or lactate dehydrogenase and/or ferritin were measured before therapy. Clinical data from the individual cases with follow-up information after 1–101 months (median 21.5 months) from diagnosis were collected.

RESULTS

870 313 of approximately 2 158 187 children were tested in European mass screening projects resulting in an overall participation rate of 40.3%. There were remarkable differences in the compliance rates between the local studies, ranging from 30.9% in Austria to 80.5% in France.

Table 1. *Summary of patients in European neuroblastoma screening projects (as of* 31 *May* 1996*)*

Country	Screening age	No. of children tested	No. of neuroblastoma detected	False negative cases	Detection rate
Austria	at 8 months	148 381	17	1	1:8 728
France	at 4 months	103 777	12	5	1:8 648
Germany	at 6 months 12 months and 18 months	584 490	50	7	1:11 690
U.K.	at 4–6 months and 13 months	33 665	3	3	1:11 222
All		870 313	82	16	1:10 614

Table 2. 65 screened patients with favourable biological markers

Screening centre	Patient	Age (months)	Ferritin	Ploidy	LOH 1p36	*MYCN*	Stage	Histology*	Status
NC.UK	01	9	nd	nt	nd	neg	2a	Unknown	CR
NC.UK	02	6	n	nt	nd	neg	4s	Unknown	CR
B.UK	03	10	n	nt	neg	neg	1	Favourable	CR
G.A.	04	9	n	nt	neg	neg	1	Favourable	CR
G.A.	05	10	n	nt	neg	neg	3	Favourable	CR
G.A.	06	11	n	nd	neg	nd	3	Unknown	VGPR
G.A.	07	9	n	nt	neg	neg	2b	Favourable	CR
G.A.	08	8	n	nt	neg	neg	3	Unknown	CR
G.A.	09	9	n	nt	neg	neg	2b	Favourable	CR
G.A.	10	10	n	nt	neg	neg	1	Favourable	CR
G.A.	11	10	n	nt	neg	neg	2b	Favourable	VGPR
G.A.	12	9	n	nt	neg	neg	2b	Favourable	CR
G.A.	13	11	n	nt	neg	neg	1	Favourable	CR
G.A.	14	9	n	nt	neg	neg	3	Unknown	PR, relapse
G.A.	15	8	n	nt	neg	neg	3	Unknown	CR
G.A.	16	16	n	nd	neg	neg	4	Unknown	PR
S.G.	17	11	n	nt	neg	neg	1	Favourable	CR
S.G.	18	8	n	nt	neg	neg	1	Favourable	CR
S.G.	19	10	n	nt	neg	neg	3	Favourable	CR
S.G.	20	8	e	nt	neg	neg	4s	Unknown	CR
S.G.	21	14	n	nt	neg	neg	2a	Unknown	CR
S.G.	22	10	n	nd	neg	neg	4	Unknown	Dead
S.G.	23	11	n	nt	neg	neg	2a	Favourable	CR
S.G.	24	10	n	nd	neg	neg	4	Unknown	CR
S.G.	25	11	n	nt	neg	neg	1	Favourable	CR
S.G.	26	12	n	nt	neg	neg	2a	Favourable	CR
S.G.	27	10	n	nt	neg	neg	1	Favourable	CR
S.G.	28	9	n	nd	neg	neg	4	Favourable	PR
S.G.	29	11	n	nt	neg	neg	1	Unfavourable	CR
S.G.	30	11	n	nt	neg	neg	2b	Favourable	CR
S.G.	31	13	n	nt	neg	neg	3	Unknown	CR
S.G.	32	13	n	nt	neg	neg	1	Favourable	CR
S.G.	33	14	n	nd	neg	neg	3	Unknown	CR
S.G.	34	19	n	nd	neg	neg	2b	Favourable	CR
S.G.	35	13	n	nd	neg	neg	2a	Unknown	CR
L.F.	36	4	n	nd	neg	neg	4s	Favourable	CR
L.F.	37	6	e	nt	neg	neg	4s	Favourable	CR
L.F.	38	7	n	nt	neg	neg	1	Favourable	CR
L.F.	39	6	n	nt	neg	neg	2b	Favourable	CR
L.F.	40	8	n	nd	neg	neg	2a	Favourable	CR
L.F.	41	5	n	nt	neg	neg	2a	Favourable	CR
L.F.	42	8	n	nt	neg	neg	2a	Favourable	CR
L.F.	43	6	n	nt	neg	neg	1	Unfavourable	CR
L.F.	44	6	n	nt	neg	neg	2a	Unknown	CR
L.F.	45	6	n	nd	neg	neg	3	Unknown	CR
HH.G.	46	9	n	nt	neg	neg	1	Favourable	CR
HH.G.	47	8	n	nt	neg	neg	1	Unknown	CR
HH.G.	48	13	n	nd	neg	neg	1	Favourable	CR
HH.G.	49	15	n	nt	neg	neg	1	Favourable	CR
HH.G.	50	14	n	nd	neg	neg	1	Favourable	CR
CO.G.	51	19	nd	nd	nd	neg	3	Unknown	CR
CO.G.	52	13	nd	nt	neg	neg	2b	Unknown	CR
CO.G.	53	15	nd	nd	nd	neg	1	Favourable	CR
CO.G.	54	11	n	nt	neg	neg	4	Unknown	CR
CO.G.	55	13	n	nd	nd	neg	1	Unknown	CR
CO.G.	56	14	nd	nd	nd	neg	1	Favourable	CR
CO.G.	57	13	n	nd	nd	neg	2b	Unknown	CR
CO.G.	58	13	n	nd	nd	neg	1	Favourable	CR
CO.G.	59	12	e	nd	neg	neg	1	Unknown	CR
CO.G.	60	15	n	nd	nd	neg	1	Favourable	CR
CO.G.	61	24	n	nd	nd	neg	2a	Unfavourable	CR
CO.G.	62	17	n	p	neg	neg	1	Unknown	CR
CO.G.	63	15	nd	nd	nd	neg	2b	Favourable	CR
CO.G.	64	16	n	nd	nd	neg	2b	Favourable	CR
CO.G.	65	14	n	nd	nd	neg	1	Favourable	CR

NC.UK, Newcastle, U.K.; B.UK, Birmingham, U.K.; G.A., Graz, Austria; S.G., Stuttgart, Germany; L.F., Lyon, France; HH.G., Hamburg, Germany; CO.G., Köln, Germany; n, normal; e, elevated; nt, near triploid; p, polysom; LOH, loss of heterozygosity; neg, negative; CR, complete remission; PR, partial remission; VGPR, very good partial remission; nd, not done. *Shimada classification.

Table 3. 11 *screened patients with unfavourable biological markers*

Screening centre	Patient	Age (months)	Ferritin	Ploidy	LOH 1p36	*MYCN*	Stage	Histology*	Status†
G.A.	66	9	n	nt	neg	5–30	3	Favourable	Dead
G.A.	67	8	n	nt	neg	10–100	1	Unfavourable	CR
G.A.	68	10	n	4	neg	neg	2b	Unfavourable	Relapse
G.A.	69	9	n	nt	neg	3	3	Unknown	CR
S.G.	70	10	n	2	pos	neg	1	Favourable	CR
L.F.	71	6	n	>4	pos	neg	4s	Unfavourable	CR
HH.G.	72	8	n	2	pos	100	4	Favourable	CR
HH.G.	73	15	n	nd	pos	neg	2b	Favourable	CR
HH.G.	74	14	n	4	neg	neg	2a	Favourable	CR
CO.G.	75	15	nd	2	neg	neg	1	Favourable	CR
CO.G.	76	13	nd	2	nd	neg	3	Unknown	CR

Abbreviations as in Table 2. pos, positive. *Shimada classification. †Last follow-up November 1997.

Among 870 313 children tested, 82 neuroblastoma cases (age range 4–24 months, median 11 months) were detected by screening. Eighty-three per cent of the patients had localised neuroblastoma (INSS stage 1, 35%; stage 2, 29%; stage 3, 18%) and 17% were diagnosed with generalised neuroblastoma (stage 4, 10%; stage 4s, 7%). 16 neuroblastoma cases were detected clinically after a normal screening test (false negative cases). 92 of all 98 patients were evaluable. From their clinical and biological data three different groups could be defined.

The largest group consisted of 65 patients, detected by neuroblastoma screening, without biological risk factors (*MYCN* assessed in 64 patients, LOH 1p36 assessed in 52 patients, *MYCN* and LOH 1p36 assessed in 51 patients, DNA ploidy assessed in 40 patients). Table 2 shows a summary of these patients. The age at diagnosis varied from 4 to 24 months (median 11 months). The stage distribution was as follows: stage 1, 25 patients; stage 2a, 10 patients; stage 2b, 11 patients; stage 3, 10 patients; stage 4, 5 patients; stage 4s, 4 patients. 3 patients showed an unfavourable histology according to Shimada (2 stage 1 and 1 stage 2a patients). Serum ferritin was elevated in 2 4s patients. To date 1 (stage 4) of the children (pt 22) in this group has died, due to toxic shock during therapy. 2 children (pts 16, 28) have partial remission of the disease, another has partial remission with relapse (pt 14), 2 children (pts 6, 11) have very good partial remission of the disease and the other 59 patients are in complete remission of the disease. The median follow-up in this group is 27 months (range 6–101 months). The overall survival of this patient group seems to be very good (probability of survival 0.98).

The second group consists of 11 patients detected by screening who had biological risk factors (*MYCN*, LOH 1p36, DNA ploidy). The age at diagnosis varied from 6 to 15 months (median 10 months). The stage and biological marker distribution are shown in Table 3. Four tumours showed di/tetraploidy as a single unfavourable marker. Unfavourable histology according to Shimada was diagnosed in 3 patients (stage 1, stage 2B and stage 4s). None of the patients showed elevated serum ferritin. To date, 1 of the children with neuroblastoma with unfavourable biological markers detected by screening has died (surgical complication, stage 3, *MYCN* amplified), 1 child had a relapse (stage 2B, tetraploid tumour) and the other 10 patients are in complete remission after adequate therapy according to the national protocols. The median follow-up time is 17 months (range 4–46 months). Although the tumours show unfavourable biological factors, the patients of this group still seem to have a very good prognosis (probability of survival 0.91).

Table 4. *'False negative' patients*

Screening centre	Patient	Interval since screening (months)	Age (months)	VMA	HVA	Ferritin	Ploidy	LOH 1p36	*MYCN*	Stage	Histology*	Status
NC.UK	77	21	27	e	e	e	nd	nd	nd	4	Unknown	Dead
NC.UK	78	26	32	e	e	e	ne	nd	nd	4	Unknown	Dead
NC.UK	79	24	30	e	e	nd	nd	nd	nd	4	Unknown	CR
HH.G.	80	35	41	e	e	e	nd	pos	neg	4	Unknown	PR
HH.G.	81	27	33	n	n	n	nd	nd	neg	1	Unknown	CR
L.F.	82	33	38	e	e	e	nd	nd	20	4	Unknown	Dead
L.F.	83	6	10	e	e	e	2+4	nd	e	3	Unknown	Dead
L.F.	84	28	33	n	n	n	nt	neg	neg	3	Favourable	CR
L.F.	85	25	30	e	e	e	nd	neg	nd	4	Unknown	CR
L.F.	86	26	32	e	e	e	nd	nd	nd	4	Unknown	PR
G.A.	87	28	37	e	e	n	2	neg	neg	4	Unfavourable	Dead
CO.G.	88	21	33	e	e	e	2	nd	30	4	Unknown	CR
CO.G.	89	19	31	e	e	e	nd	nd	neg	4	Unknown	CR
CO.G.	90	9	21	e	e	e	2	pos	40	4	Unfavourable	CR
CO.G.	91	13	25	e	e	e	2	neg	neg	2b	Favourable	CR
CO.G.	92	14	24	e	e	n	nd	nd	neg	1	Unknown	CR

Abbreviations as in Table 2. pos, positive; VMA, vanillylmandelic acid; HVA, homovanillic acid. *Shimada classification.

The third group is 16 children with clinically detected neuroblastoma after a normal screening test (false negative cases). Only 12 patients had biological risk factors assessed. These children presented in screening centre-related hospitals and were not systematically sought. The age at diagnosis ranged from 10 to 41 months (median 31.5 months). The interval between screening and diagnosis varied between 6 and 35 months (median 24.5 months). All but 2 children had elevated HVA and VMA at diagnosis. The stage and biological marker distribution is shown in Table 4. Two tumours showed unfavourable histology according to Shimada. Serum ferritin was elevated in 11 patients. To date 5 patients have died of the disease, 2 achieved partial remission and 9 children have complete remission. The median follow-up time is 15 months (range 17–87 months). The prognosis of patients in this group is by far the worst (probability of survival 0.66).

Comparing the overall probability of survival of the three different patient groups, we find the most striking difference between patients with unfavourable biological markers detected by screening (0.98) and clinically presenting 'false negative' patients. Using Fisher's exact test for comparing the survival of the different patient groups, there is a significant difference between the screened patients and the 'false negative' patients ($P = 0.0017$). No significant difference in mortality can be shown between screened patients with favourable and unfavourable biological markers ($P = 0.27$). The numbers of patients are too small to allow comparison of the outcome of patients with unfavourable biological markers with that for 'false negative' patients. We found an even distribution of tumours with unfavourable biological markers (14%) among the children with tumours detected by screening regardless of the age when the screening test was performed (46 infants < 1 year, 7 with biological risk factors; 30 children > 1 year, 4 with biological risk factors). However, among the 'false negative' patients, there was a considerable excess of tumours with unfavourable biological markers (50%) in children over 20 months old.

DISCUSSION

Neuroblastoma screening programmes based on the detection of catecholamine metabolite excretion in urine have been established in the hope of being able to diagnose this disease at an earlier age and clinical stage and to improve outcome. However, data published from early screening programmes show that screening at the age of 6 months may not meet this objective [3]. In populations which were screened in the first 6 months of life, an increased rate of localised neuroblastoma was observed, but this did not lead to a reduction in high-stage neuroblastoma cases in subsequent years of life [1–3]. Therefore, it may be concluded that neuroblastoma screening in the first months of life increases the apparent number of children with neuroblastoma and, hence, the morbidity rate of the disease. Supporting evidence comes from a significant number of cases identified by biochemical screening which have undergone spontaneous regression during a period of 2–18 months after detection without any therapy [1, 16–18].

It may be assumed that a significant number of tumours without biological risk factors (*MYC*N amplification, LOH 1p36 and DNA ploidy assessed as in Table 2) which are presented in this paper belong to this group of 'benign' neuroblastoma. For these patients, screening may represent a harmful risk to the health of the child and also to the psychological well-being of the family.

Additionally, the group of tumours without unfavourable biological markers includes localised neuroblastoma with a low tendency to invasive growth and metastatic potential. In these cases, earlier diagnosis of the disease may not be reflected in any outcome advantage, but it should be remembered that favourable biological markers are not always correlated with a good prognosis. It has been shown recently that some of these tumours may progress, in spite of their 'favourable' markers [19].

However, a small group of localised tumours could be defined which would have been classified as favourable, using clinical prognostic criteria such as age and site, but, after biological studies showed adverse risk factors (*MYC*N amplification, LOH 1p36, DNA ploidy). Similar observations have been reported by some Japanese screening groups [1, 20, 21]. Tumours like these in general have a bad prognosis. It is possible that without early treatment, these tumours would have shown infiltrative growth and development of metastases. To date this patient group seems to have a remarkably high survival. If the favourable clinical course of these high-risk patients continues and has resulted from early treatment, then it is possible to define a small group of patients who may gain clinical benefit from biochemical screening in the first year of life. This group of patients comprises 14% of all cases detected by screening in our study, with an equal age distribution within the screening period. Based on these findings, it is possible that in populations undergoing biochemical neuroblastoma screening around the age of 6–12 months, a reduction of disseminated clinically observed neuroblastoma by this small number may be expected. It will be hard to substantiate such a small positive effect of biochemical neuroblastoma screening statistically, even in a huge epidemiological study [8].

In summary biochemical neuroblastoma screening during the first year of life detects at least three different groups of children (i) Group 1—Subclinical neuroblastoma with an inherent tendency to spontaneous regression which would never be diagnosed without screening. The total incidence of this type of neuroblastoma in the normal population is not known. In screening populations it has been estimated to be one-third of all detected neuroblastoma cases [22, 23]. (ii) Group 2—Localised 'low-risk' neuroblastoma without unfavourable biological markers which have a good prognosis after surgical therapy. This therapy probably could be performed without inducing a prognostic disadvantage even at the time of clinical diagnosis in most cases, but some cases probably would have progressed in spite of their 'favourable' biological markers. (iii) Group 3—Neuroblastoma with unfavourable biological markers in localised or early disseminated clinical stages. With the assumption that the biological markers have the same significance in children under 1 year of age as in older children, it is possible that this group will gain a survival benefit by early complete resection or by early intensive multimodal therapy. These tumours make up only a small proportion of the entire group of screened neuroblastoma (14%).

Therefore, after the detection of a localised neuroblastoma by biochemical screening the question arises as to which group the patient concerned belongs. This classification of the disease is important because a risk-adapted therapeutic decision is desirable. For group 1 a 'wait and see' policy is

plausible, for group 2 surgical intervention is appropriate and group 3 patients may require multimodal therapy. Unfortunately, until now there are no non-invasive methods to discriminate between the different tumours. Therefore, it is necessary to sample tumour material in order to study biological risk factors in every case. Fine needle biopsy as an adequate method to investigate the biological markers as a basis for a proper therapeutic decision has recently been questioned [19, 24]. Whether in future studies there may be a 'wait and see' policy for patients without unfavourable biological markers depends on the development of new minimally invasive, highly predictive diagnostic methods. Currently, complete or gross resection of screened tumours should be performed in the majority of cases, as was done in most patients presented in our study.

It seems that for the group 3 patients active therapeutic intervention improved the outcome. Unfortunately, in order to achieve this, an unknown but significant number of patients may have undergone unnecessary operations; not to mention the psychological burden on themselves and their families. This diagnostic and therapeutic dilemma is one of the main problems of all neuroblastoma screening programmes during the first year of life as it is for all other localised neuroblastomas detected early in life. Therefore, if screening programmes continue, the invention of a minimally invasive test predicting to which risk group a screened neuroblastoma patient belongs would be highly desirable.

This paper addresses another problem which brings the value of neuroblastoma screening in infancy into question. During careful follow-up of the screened infants, a significant group of patients has been defined who were found to be urine catecholamine metabolite negative as infants, but were diagnosed with secreting neuroblastoma during the third year of life. These 'false negative' patients have a higher mortality. As most of these patients were found to excrete catecholamine metabolites at the time of clinical diagnosis, all attempts should be made to include them in early detection programmes, perhaps by postponing screening or by a second screening. The data presented in this paper provide some information about this crucial question. The average interval between a negative screening test and clinical diagnosis was 24.5 (6–35) months. At this time, 81% (13/16) of the 'false negative' tumours showed locoregional or distant dissemination (2 INNS stage 3; 11 stage 4). On the basis of clinical observations, it has been shown that the time from localised to disseminated neuroblastoma is approximately 13 months [25]. Therefore, a screening test around the 18th month of life might be chosen in order to detect this group of high-risk neuroblastoma by screening. This is in accordance with earlier assumptions based on epidemiological considerations [8]. It may be assumed that this time point meets the sojourn time (the period before clinical diagnosis during which the tumour is detectable by biochemical urine analysis) of this group of tumours.

The lessons we have learned by the combined evaluation of clinical, biological and screening data of the SENSE studies are firstly that screening in the first year of life may offer a prognostic benefit to a small group of patients with early stage tumours bearing biological risk factors. However, the screening process creates an artificial morbidity rate reflected by an overdiagnosis of tumours which would normally regress spontaneously. To escape from this dilemma, a minimally invasive method to predict the biological and clinical behaviour of cases of neuroblastoma needs to be developed and implemented before neuroblastoma screening should be considered as a common routine examination in infants.

Secondly, a significant number of high-risk neuroblastomas cannot be detected by screening performed too early. It is possible that screening at 18 months of age may confer a survival advantage on these patients. However, a second screening would increase costs. Therefore, it would be highly desirable to develop cheaper analytical methods than those which are used today.

There are clearly difficulties in implementing neuroblastoma screening. However, in view of the current poor prognosis of neuroblastoma patients, it is worthwhile persevering with it rather than rejecting the screening idea prematurely.

1. Suita S, Zaizen Y, Sera Y, *et al.* Mass screening for neuroblastoma: Quo vadis? A 9-year experience from the pediatric oncology study group of the Kyushu area in Japan. *J Pediatr Surg* 1996, **31**, 555–558.
2. Hayashi Y, Ohi R, Yaoita S, *et al.* Problems of neuroblastoma screening for 6 month olds and results of second screening for 18 months olds. *J Pediatr Surg* 1995, **30**, 467–470.
3. Woods WG, Tuchman M, Robison L, *et al.* A population-based study of the usefulness of screening for neuroblastoma. *Lancet* 1996, **348**, 1862–1687.
4. Kerbl R, Urban CE, Ladenstein R, *et al.* Neuroblastoma screening in infants postponed after six months of age: a trial to reduce 'overdiagnosis' and to detect cases with 'unfavourable' biological features. *Med Pediatr Oncol* 1997, **29**, 1–10.
5. Chauvin F, Mathieu P, Frappaz D, *et al.* Screening for neuroblastoma in France: methodological aspects and preliminary observations. *Med Pediatr Oncol* 1997, **28**, 81–91.
6. Treuner J, Schilling FH. Neuroblastoma mass screening: the arguments for and against. *Eur J Cancer* 1995, **31A**, 565–568.
7. Craft AW, Dale G, McGill A, Seviour J, Spence EM. Biochemical screening for neuroblastoma in infants: a feasibility study. *Med Pediatr Oncol* 1989, **17**, 373–378.
8. Esteve J, Parker L, Roy P, *et al.* Is neuroblastoma screening evaluation needed and feasible? *Br J Cancer* 1995, **71**, 1125–1131.
9. Brodeur GM, Seeger RC, Barrett A, *et al.* International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. *J Clin Oncol*, 1988, **6**, 1874–1881.
10. Berthold F. Multizentrische Therapiestudie zur Behandlung von Kindern und Jugendlichen mit Neuroblastom (Neuroblastomstudie NB 90), 1990.
11. Berthold F, Hero B. Kooperative multizentrische Therapieoptimierungsstudie für die Behandlung von Säuglingen mit Neuroblastom. Säuglings-Neuroblastom-Pilotprojekt NB 95-S(P), 1995.
12. Ladenstein R, Urban C, Gadner H, *et al.* First experience with prognostic factors in unselected neuroblastoma patients. The Austrian neuroblastoma 87 study. *Eur J Cancer* 1995, **31A**, 637–641.
13. Rubie H, Hartmann O, Michon J, *et al.* N-myc gene amplification is a major prognostic factor in localized neuroblastoma: results of the French NBL 90 study. *J Clin Oncol* 1997, **15**, 1171–1182.
14. Pearson A, Pinkerton C, Lewis I. European neuroblastoma group fifth study (ENSG 5). A randomized study of dose intensity in stage 4 neuroblastoma over the age of one. *Advances in Neuroblastoma Research*, 4th edn. New York, Wiley-Liss, 19XX.
15. Favrot MC, Ambros P, Schilling F, *et al.* on behalf of the SENSE Group. Comparison of the diagnostic and prognostic value of biological markers in neuroblastoma. *Ann Oncol* 1996, **7**, 607–611.
16. Matsumara M, Tsunoda A, Nishi T, *et al.* Spontaneous regression of neuroblastoma detected by mass screening. *Lancet* 1991, **338**, 447–448.
17. Nishihara H, Toyoda Y, Ohnuma K, *et al.* Spontaneous regression of tumors in children with neuroblastoma found by mass screening. *Jpn J Pediatr Oncol* 1996, **33**, 379 (in Japanese).

18. Hanada R, Kikuchi A, Ichikawa M, *et al.* Spontaneous regression of neuroblastoma found by mass screening. *Jpn J Pediatr Oncol* 1996, **33**, 380 (in Japanese).
19. Kerbl R, Urban C, Lackner H, *et al.* Connatal localized neuroblastoma. The case to delay treatment. *Cancer* 1996, **77**, 1395–1401.
20. Hachitanda Y, Ishimoto K, Jun-ichi H, *et al.* One hundred neuroblastomas detected through a mass screening system in Japan. *Cancer* 1994, **74**, 3223–3226.
21. Kusafuka T, Nahgahara H, Takeda T, *et al.* Unfavorable DNA ploidy and Ha-ras p21 findings in neuroblastoma detected through mass screening system. *Cancer* 1995, **76**, 695–699.
22. Nishi M, Miyake H, Takeda T, *et al.* Cases of spontaneous regression and true patients detected in mass screening for neuroblastoma. *Int J Pediatr Hematol* 1995, **1**, 557–563.
23. Nishi M, Miyake H, Takeda T, *et al.* A trial to discriminate spontaneous regression from non-regression cases during mass screening for neuroblastoma. *J Clin Oncol* 1994, **24**, 247–251.
24. Lorenzana AN, Zielenska M, Thorner P, *et al.* Heterogeneity of *MYCN* amplification in a child with stroma-rich neuroblastoma. *Pediatr Pathol Lab Med* 1997, **17**, 875–883.
25. Berthold F, Hero B, Breu H, *et al.* The recurrence patterns of stages I, II and III neuroblastoma: experience, with 77 relapsing patients. *Ann Oncol* 1996, **7**, 183–187.

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