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Review

Screening for Neuroblastoma: 20 Years and Still No Answer

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IF PREVENTION is not possible, then early diagnosis must be the goal in any form of cancer. There is now ample evidence that screening for some adult cancers is worthwhile, cost-effective and saves lives [1, 2], but, to date, the same is not true for children. The lives of many children with cancer are saved, but at the cost of expensive multimodality therapy and with the 'late effects' of the treatment, including an increased risk of second malignancy [3]. The opportunities for screening for childhood cancer in the population are limited, for a variety of reasons. Firstly, the relative rarity of cancer in the young (only one child in 1800 develops leukaemia, the most common cancer of childhood before the age of 15 years) makes screening appear expensive per case detected, although this cost might be counterbalanced by the large number of potential life years saved by an effective programme. Secondly, the relative effectiveness of current therapy, with an overall survival rate in excess of 65–70%, argues against screening for most childhood cancers. For example, screening might be possible for Wilms' tumour using serial abdominal ultrasound examinations, but the high 'cure' rate (80–85%) with current treatment would suggest that even this would not be worthwhile.

Neuroblastoma is the one childhood cancer for which screening might be beneficial. The prognosis for disseminated (stage 4) neuroblastoma diagnosed in clinical practice has only improved slightly over the last 20 years, and where progress has been made, it has included the use of very intensive chemotherapy, often with autologous or allogeneic bone marrow rescue [4]. The outlook for children diagnosed with localised disease or those diagnosed at a young age, particularly those under the age of 1 year, is very much better than for older children or those with stage 4 disease [5]. In addition, at least 85% of children diagnosed as having neuroblastoma have raised urine levels of catecholamine metabolites, detectable by simple biochemical tests on spot urine samples, and which could be undertaken on whole populations of babies at an early age [6, 7]. The ease of the collection of urine from filter papers placed on wet nappies seems to complete the 'setting of the scene' for an ideal screening programme, as the major prerequisites of a potentially successful screening programme are all apparently present: a serious disease, a simple test, a disease with an asymptomatic preclinical phase and a better prognosis for diagnoses made at earlier stages.

Sawada, working in Kyoto, Japan, pioneered the idea, in the early 1970s, of setting up a screening programme for neuroblastoma in that city. His initial results were encouraging, indicating that neuroblastoma could be detected by screening infants at the age of 6 months [8]. The system was improved when he switched from using a qualitative thin layer chromatography (TLC) technique, that could only detect urinary vanillyl mandelic acid (VMA) in 65% of cases to the quantitative technique of high performance liquid chromatography [9]. The results were apparently encouraging, with screen-detected cases having excellent survival. In Japan, others began to follow the example of Sawada, and the work of Takeda in Sapporo has led to a greater understanding of the problems that are faced when trying to evaluate the effectiveness of whole population screening for neuroblastoma. Sapporo is on the island of Hokkaido to the north of the main island of Honshu and is an ideal place in which to carry out epidemiological studies. Firstly, the population is relatively isolated from the rest of Japan and the vast majority of babies born there remain for the whole of their childhood and, secondly, a good public health system with comprehensive cancer registration makes it possible to look at the incidence of and survival from neuroblastoma, both before and after screening. The screening programme was implemented in Sapporo in 1980 and in the rest of Hokkaido in 1985, along with the remainder of Japan, which had by then been persuaded of the efficacy of screening by Sawada's pioneering work. A seminal paper from Takeda's group, published in 1987, was the first to really excite the rest of the world about the benefits that might be achieved by screening programmes [10]. Pilot programmes were established in the U.K. [11], Germany [12, 13], France [14], Austria [15], North America [16] and Autralia [17].

Both the Japanese national programme and the pilot studies elsewhere in the world confirmed Sawada's observation that cases of neuroblastoma could be detected by screening at 6 months of age. However, it soon became apparent that screen-

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ing at this age dramatically increased the incidence of neuroblastoma, apparently by detecting cases which would otherwise have regressed spontaneously and never have become clinical disease. The most convincing evidence for this came from Sapporo, where screening at 6 months of age was shown to double the cumulative incidence of neuroblastoma from 1:8400 to at least 1:3515 by the age of 5 years [18]. It has long been known that cases of neuroblastoma do undergo spontaneous resolution. Stage 4 neuroblastoma is the most dramatic example of this process, but regressed neuroblastoma is occasionally found in the adrenals of elderly people at routine autopsy and neuroblastoma *in situ* has been reported in approximately 1:250 routine autopsies of babies under the age of 3 months [19]. If half of the cases would have enjoyed 100% survival without any intervention whatsoever, it is not altogether surprising that survival figures for neuroblastoma in screened populations have improved. Rather than incidence rates, evaluation of the effectiveness of neuroblastoma screening must therefore rely on examination of mortality rates. In Japan, the whole population has been offered screening since 1985 and here the only possibility is to look for a 'before and after' effect. Clearly any sequential improvements in the therapy for children with neuroblastoma will confound the analysis of data from Japan, as would any changes in case registration and diagnostic accuracy over time. There is, as yet, little convincing evidence of a fall in mortality rates from neuroblastoma in Japan that is attributable to screening [20–22].

The first controlled epidemiological study of neuroblastoma screening was set up in North America in 1989 [23, 24]. It had the good fortune to be able to link up with a programme of urine screening for inborn errors of metabolism that was already in existence, established in Quebec by Scriver some 20 years previously. Babies were screened at 3 weeks, this being the time for the established 'metabolic disease' screening, and again at 6 months of age. The whole of the province of Quebec was to be screened, with neighbouring Canadian provinces, the State of Minnesota and the Greater Delaware Valley acting as control, non-screened areas. There were comprehensive case ascertainment procedures in place in all areas and, unlike Japan, an agreed common policy on the treatment of neuroblastoma whether detected clinically or by screening. The ultimate endpoint of the study is, appropriately, to be a comparison of the mortality rate from neuroblastoma between the screened and control areas. The last babies were entered into the screening programme in 1994, and it will be at least 1998 before preliminary data are available on mortality in the study cohorts. However, there are some intermediate endpoints that may give an indication of the likely results of the study. Mortality is clearly related to extent of the disease at presentation, so the stage distribution should be a good early indicator of outcome. A reduction in the absolute incidence rate of cases with stages 3 and 4 in older children within the screened cohort would be a clear indication that screening is effective in detecting cases of neuroblastoma at an earlier stage than would be possible clinically. The early results of the Quebec screening programme were presented at the American Society of Pediatric Hematology/Oncology (ASPHO) meeting in 1994 [25], with an update at the Fourth International Neuroblastoma Screening meeting held in Stuttgart in November 1995 [26]. The number of babies eligible for screening was 470000 and there was 91% and 75% compliance, respectively, with screening at 3 weeks and 6 months of age. In the whole cohort, 113 cases of neuroblastoma have now been diagnosed compared with the expected number of 53, a more than doubling of the rate and, as in the Sapporo study, this increase was seen in infants of less than 1 year in age. However, there has, so far, been no reduction in the incidence of neuroblastoma diagnosed in older children, despite the fact that 75% have been screened twice for neuroblastoma. In the control areas, there has been no change in the incidence of neuroblastoma, and there has also been no change in the incidence of children diagnosed with stages 3 or 4 of the disease. Mortality data in the screened and control cohorts will not be available for at least another 4 years but, based on the preliminary data, it seems unlikely that there will be any reduction in the death rate from neuroblastoma as a consequence of screening for this disease. A very interesting early finding of the Quebec study has been the 'halo effect'. The increased publicity surrounding the screening programme has generated an increased awareness of neuroblastoma amongst health care professionals and, even prior to infant screening at 3 weeks of age, an increased number of cases were detected by means of either routine clinical examination, including abdominal palpation, or prenatal ultrasound examination.

Why is neuroblastoma screening probably not effective? The answer seems to be that what appeared 20 years ago to be one disease is now at least two, and maybe more, distinct entities [27]. Besides age and stage, these subtypes of neuroblastoma can probably best be defined on molecular and biological grounds, with *NMYC* amplification, ploidy [28] and chromosomal 1p deletions [29] being the major agreed markers, although more are being defined, such as the tyrosine kinase (TRK) group of growth factors [30]. It seems that the biological properties of a tumour are largely inherent and in most cases, there is no progression from 'good' to 'bad' features [31]. In both the Japanese and Quebec studies, the vast majority of screen-detected cases of neuroblastoma were of the favourable biological category. In the Quebec cohort, biological data are available for 117 patients, 44 of whom were detected by screening and the remaining 73 detected clinically. None of the screen cases had amplified *NMYC* (an unfavourable feature), compared with 17% of the cases detected clinically. There were no diploid tumours (also considered unfavourable) in the screened cases compared with 15% in the clinical group [32]. In Japan, 862 cases of neuroblastoma were detected by screening between 1984 and 1992. Of the 315 for whom biological data are available, only 6 had *NMYC* amplification: 5 had four copies and only 1 had more than 100 copies [33]. There is clear evidence from unscreened populations that the prognosis for neuroblastoma is dependent on the biological properties of the tumour [34] and it is, therefore, no surprise that cases detected by screening, the vast majority of which have favourable biological characteristics, should have such an excellent prognosis.

The timing of screening may well be important. Virtually all screening programmes to date have been in infants of approximately 6 months of age or earlier, and, in all cohorts, there is evidence that tumours with poor prognosis have been missed by the screening programme (false-negative cases) with these presenting later, clinically. The observation has been made that not only are there two types of neuroblastoma with good and bad prognosis, but these two groups also have a different, slightly overlapping, age profile. It appears that screening at 6 months of age detects many of the tumours

with good prognosis, some of which would otherwise have regressed spontaneously, but misses many of those with a prognosis, which at 6 months are too small (or not present) to produce a sufficient level of catecholamine metabolites for detection by urine screening. Would screening at a later stage be more effective? Many centres in Japan have now introduced a second screen at 12–18 months and cases have been detected [35]. In Europe, screening programmes in Germany, Austria and France have also now moved to a later stage of screening, but it is clearly too early to determine whether this screening will be more effective.

There has been considerable interest in screening for neuroblastoma in Europe, and, following the Third International Symposium in Minneapolis in 1991, a Study group for the Evaluation of Neuroblastoma Screening in Europe (SENSE) was established, with members from the U.K., Germany, France, Italy, Austria and Norway [36]. The original objectives were to establish a large Inter-European evaluation study of the effectiveness of neuroblastoma screening. However, data from both Japan and Quebec, as well as the European pilot studies, indicate there is a need for more basic information on the biology and epidemiology of neuroblastoma in unscreened populations before a definitive screening study can be evaluated and understoood. One of the most important tasks completed so far has been an evaluation of the statistical aspects of screening for neuroblastoma. It is quite clear that, in any evaluation study the only endpoint must be a reduction in death rate when compared with a well-chosen control group with identical methods of ascertainment, treatment and follow-up. Based on screening twice at 12 and 18 months, it is estimated that the best that could be achieved would be a 25% reduction in mortality and, in order to demonstrate this difference, a study would need to recruit between 2.5 and 3.5 million children, with a similar number in the control group [37]. A large controlled study has just started in Germany which should be able to accrue sufficient numbers of screened children in a reasonable period of time [38]. However, it will be at least 8 years before the preliminary results of their study are available. In the meantime, the advice given by the International Society of Paediatric Oncology (SIOP) in 1990, that widespread screening should not be implemented except in the context of a controlled evaluation study, is still valid [39]. Profession Nick Day [40], writing about screening for breast cancer [40], said "The major problem of breast screening at present is the need for greater understanding of the heterogenous natural history of the disease. The extent to which earlier diagnosis improves prognosis is poorly understood, but crucial to determining the full potential of screening." This statement is even more true of neuroblastoma.

1. Miller AB. An epidemiological perspective on cancer screening. *Clin Biochem* 1995, **28**, 41–48.
2. Wald NJ, Chamberlain J, Hackshaw A. European Society of Mastology, Consensus Conference on Breast Cancer Screening, Paris, 4–5 February 1993. Report on the Evaluation Committee. *Bull Cancer* 1994, **81**, 825–834.
3. Ochs J, Mulhern R. Long term sequelae of therapy for childhood acute lymphoblastic leukaemia. *Baillieres Clin Haematol* 1994, **7**, 365–376.
4. Evans AE, August CS, Kamani N, *et al.* Bone marrow transplantation for high risk neuroblastoma at the Children's Hospital in Philadelphia. An update. *Med Pediatr Oncol* 1994, **23**, 323–327.
5. Evans AE, D'Angio GJ, Propert K, Anderson J, Hann HW. Prognostic factors in neuroblastoma. *Cancer* 1987, **59**, 1853–1859.
6. Pritchard J, Barnes J, Germond S, *et al.* Stage and urinary catecholamine metabolite excretion in neuroblastoma. *Lancet* 1989, **2**(8661), 514–515.
7. Tuchman M, Ramnaraine MLR, Woods WG, Krivit W. Three years of experience with random urinary homovanillic and vanillylmandelic acid levels in the diagnosis of neuroblastoma. *Pediatrics* 1987, **79**, 203–205.
8. Sawada T, Todo S, Fujita K, Lino S, Imashuka S, Kusunoki T. Mass screening of neuroblastoma in infancy. *Am J Dis Child* 1982, **136**, 710–712.
9. Sawada T. Laboratory techniques and neuroblastoma screening. *Lancet* 1988, **2**(8620), 1134–1135.
10. Nishi M, Miyake H, Takeda T, Schimada M. Effects of the mass screening of neuroblastoma in Sapporo City. *Cancer* 1987, **60**, 433–436.
11. Parker L, Craft AW, Dale G, *et al.* Screening for neuroblastoma in the North of England. *Br Med J* 1992, **305**, 1260–1263.
12. Erttman R, Schilling FH, Dohrmann S, *et al.* Two years experience of the German pilot study for the early detection of neuroblastoma. 3rd International Symposium on Neuroblastoma Screening. Kyoto, Japan, 1993.
13. Berthold F, Sander J, Baillot A, Hunneman DH, Michaelis J. Neuroblastomscreening-Projekt Niedersachsen/Nordrhein-Westfalen: Zur Notwendigkeit des Epidemiologischen Verleichs. *Klin Padiatr* 1992, **204**, 288–292.
14. Philip TO, Mathieu P, Chauvin F, *et al.* A 5 year study (1990–1994) on screening babies for neuroblastoma in France. Methodological aspects and preliminary observations. 3rd International Symposium on Neuroblastoma Screening. Kyoto, Japan, 1993.
15. Kerbl R, Urban C, Starz I, *et al.* Neuroblastoma with N-myc amplification detected by urine: mass screening in infants after the sixth month of life. *Med Pediatr Oncol* 1993, **21**, 625–626.
16. Woods WG, Tuchman M, Bernstein ML, *et al.* Screening for neuroblastoma in North America. *Am J Pediatr Hematol/Oncol* 1992, **14**, 312–319.
17. Bayliss U, Wiley VC, Wilcken B. Neuroblastoma screening in New South Wales. 3rd International Symposium on Neuroblastoma Screening. Kyoto, Japan, 1993.
18. Craft AW, Parker L. Poor prognosis neuroblastoma: is screening the answer? *Br J Cancer* 1992, **65** (Suppl), 96–101.
19. Beckwith JB, Perrin EV. *In situ* neuroblastomas: a contribution to the natural history of neural crest tumours. *Am J Pathol* 1963, **17**, 1089–1104.
20. Hanawa Y, Sawada T, Tsunoda A. Decrease in childhood neuroblasoma death in Japan. *Med Pediatr Oncol* 1990, **18**, 472–475.
21. Cole M, Parker L, Craft AW. Decrease in childhood neuroblastoma death in Japan. *Med Pediatr Oncol.* 1992, **20**, 84–85.
22. Nishi M, Miyake H, Takeda T, *et al.* Mass screening for neuroblastoma and mortality in birth cohorts. 4th International Symposium on Neuroblastoma Screening. Stuttgart, Germany, 1995.
23. Tuchman M, Woods WG. Introduction: neuroblastoma screening. Laboratory, clinical, and epidemiological aspects. *Am J Pediatr Hematol/Oncol* 1992, **14**, 95–96.
24. Woods WG, Lemieux B, Leclerc JM, *et al.* Screening for neuroblastoma (NB) in North America: the Quebec Project. *Prog Clin Biol Res* 1994, **385**, 377–382.
25. Woods WG, Robison LL, Tuchman M, *et al.* Screening for neuroblastoma (NB) increases the overall incidence of the disease without decreasing the incidence in children over 1 year of age. Presented at American Society of Pediatric Hematology/Oncology (ASPHO), Chicago, October 1994.
26. Tuchman M, Lemieux B, Robison LL, *et al.* Screening for neuroblastoma (NB) increases with overall incidence of the disease without reducing the incidence of advanced stage NB. 4th International Symposium on Neuroblastoma Screening. Stuttgart, Germany, 1995.
27. Brodeur GM, Nakagawara A. Molecular basis of heterogeneity of human neuroblastoma. *Eur J Cancer* 1995, **31A**, 505–510.
28. Look AT, Hayes A, Shuster JJ, *et al.* Clinical relevance of tumor cell ploidy and N-myc gene amplification in childhood neuroblastoma: a pediatric oncology group study. *J Clin Oncol* 1991, **9**, 581–591.
29. Maris JM, White PS, Beltinger CP, *et al.* Significance of chromosome 1p loss of heterozygosity in neuroblastoma. *Cancer Res* 1995, **55**, 4664–4669.
30. Nakagawara A, Arima-Nakagawara M, Scavarda NJ, Azar CG, Cantor AB, Brodeur AM. Association between high levels of

expression of the TRK gene and favourable outcome in human neuroblastoma. *N Engl J Med* 1993, **328**, 847–853.
31. Brodeur GM, Hayes FA, Green AA, *et al.* Consistent N-myc copy number in simultaneous or consecutive neuroblastoma samples from sixty individual patients. *Cancer Res* 1987, **47**, 44248–44253.
32. Woods WG, Tuchman M, Brodeur GM, *et al.* Clinical and biologic parameters from patients (PTS) diagnosed with neuroblastoma as part of the Quebec Screening Project (QNSP): differences between cases detected by screening and those diagnosed clinically. 4th International Symposium on Neuroblastoma Screening. Stuttgart, Germany, 1995.
33. Sawada T, Shikata T, Matsumuna T, Kawakatsu H, Sugimoto T. Analysis of 598 cases of neuroblastoma (NB) detected by screening and changes in the age distribution and incidence of NB patients after mass screening in infant Japan. NB Screening Study Group. *Prog Clin Biol Res* 1994, **385**, 371–375.
34. Brodeur GM, Azar C, Brother M, *et al.* Effect of genetic factors on prognosis and treatment. *Cancer* 1992, **70**, 1685–1694.
35. Hayaslin Y, Ohi R. Yaoita S, *et al.* Problems of neuroblastoma screening for 6 month olds and results of second screening for 18 month olds. *J Pediatr Surg* 1995, **30**, 467–470.
36. Parker L on behalf of the SENSE group. SENSE: Study for the Evaluation of Neuroblastoma Screening in Europe. 4th International Symposium on Neuroblastoma Screening. Stuttgart, Germany, 1995.
37. Esteve J, Parker L, *et al.* Is there a need for the evaluation of neuroblastoma screening: would it be feasible? *Br J Cancer* 1995, **71**, 1125–1131.
38. Schilling FH, Berthold F, Erttmann R, Sander J, Treuner J. An epidemiological study to evaluate neuroblastoma screening at 12 months of age in Germany. 4th International Symposium on Neuroblastoma Screening. Stuttgart, Germany, 1995.
39. Ninane J. Consensus statement of SIOP on neuroblastoma screening. SIOP Newsletter, Spring 1991.
40. Day NE. Screening for breast cancer. *Br Med Bull* 1991, **47**, 400–415.