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Neuroblastoma Screening: More Questions than Answers?

A FURTHER contribution to the growing controversy surrounding the efficacy of screening infants for the early detection of neuroblastoma has recently been presented by Kaneko and his colleagues in Japan [1]. They describe the biology of cases of neuroblastoma detected both clinically and by screening and conclude that screening at the age of 6 months, as is currently the case in Japan, may not be optimal.

For almost 2 decades the Japanese have been developing techniques for the screening of infants for the early detection of neuroblastoma—that cancer of childhood, the disseminated form of which has remained unyieldingly aggressive in the face of modern chemotherapy.

The method of screening which has been developed and refined in Japan is based on the assay of catecholamine metabolites in urine samples obtained from nappies (diapers). Clearly such a straightforward and non-invasive screening test should have enormous appeal.

In 1984 Sawada *et al.*, who had been screening children with neuroblastoma since 1973, published a report describing the effect of neuroblastoma screening on survival from this disease in children in Kyoto City [2]. The incautiously optimistic analysis estimated an improvement in 5-year survival from 17% to 73% as a direct consequence of screening at 6 months of age, an improvment of a magnitude hitherto unprecedented in any adult cancer screening programme. The results of these studies undoubtedly played a crucial role in the decision to introduce national screening in Japan the following year. In 1987 Takeda and his colleagues published a paper showing a similarly striking improvement in survival from 21.3% to 87.5% following the introduction of screening in Sapporo City in 1981 [3].

Careful study of the reports presented by Sawada and Takeda, however, has revealed flaws in the chosen methods of presentation of the data which lead to an overestimation of the benefits of screening. Some problems were caused by the nature of neuroblastoma itself. It has long been recognised from *post mortem* studies that *in situ* neuroblastoma may exist [4] and when it became apparent that neuroblastoma screening was increasing the incidence of neuroblastoma (T. Sawada, Kyoto University) it was surmised that some of the cases detected must, therefore, have been in the process of regressing spontaneously. When detected by screening, these "silent" cases were indistinguishable from true neuroblastoma. The inclusion of these silent cases, which would otherwise have 100% survival and which appear to occur at a similar frequency to neuroblastoma itself, clearly influences the overall survival in the group of children with neuroblastoma detected by screening. In addition to this problem of silent neuroblastoma, there are problems inherent in the interpretation of survival data from any screening programme, i.e. lead time and length time bias [5].

There have been continuing reports from Japan of improved survival and, more recently, decreased mortality from neuroblastoma which, it is suggested, could be a consequence of the screening programme [6]. However, a significant component in changes in both survival and mortality in Japan must be the improvement in treatment which has occurred over the past few years [7].

Recent advances in our understanding of the biology of neuroblastoma have lead to speculation as to whether it is in fact one disease or several. Investigations of the biology of the disease have highlighted several markers which appear to be characteristic of an individual tumour and which are strongly correlated with prognosis. Amplification of the n-*myc* oncogene, DNA diploidy, chromosome 1p abnormalities, high serum levels of ferritin and neuron specific enolase are all associated with poor prognosis [8, 9].

There is scant evidence that disease of good prognostic indicators progresses into disease of poor prognosis; indeed, the evidence suggests that the characteristics of a particular tumour are constant. For example serial measurements of n-*myc* amplification have shown that this characteristic is constant over time as well as at multiple sites of the same tumour and in both the primary tumour and its metastases [10].

The recent paper by Kaneko and his colleagues [1] has reported the biological characteristics of 79 patients with neuroblastoma, 39 of whom were diagnosed as a result of the Japanese screening programme and the remainder when they presented clinically. Some of these had been previously negative on the screening test, i.e. they were false negatives. None of the 34 children detected by screening in whom n-*myc* amplification was measured were found to have amplification, though this was found in 2 of the 6 false negative cases examined. Diploid tumours were found in 16% (6/37) of cases detected by screening and 1p abnormalities in 13% (4/30). At the time of writing all the children whose disease was detected by screening were alive. This contrasts with those children whose disease was detected clinically; 38% (9/24) had n-*myc* amplification, 35% (11/31) had diploid tumours and 48% (13/27) had 1p abnormalities. The reduced survival of the group detected clinically reflected the presence of the poor prognostic indicators.

It would appear, therefore, that screening infants at the age of 6 months detects mainly those children with an inherently good prognosis as demonstrated by the favourable biological characteristics of the tumours, especially the absence of n-*myc* amplification. The detection of largely good prognosis cases would certainly contribute to the observed survival rate of over 97% in the 328 children detected by screening so far in Japan, following the introduction of national screening [11].

Kaneko and his colleagues conclude that screening should be repeated at the age of 12 months in order to attempt to detect children who have more aggressive disease. Clearly, this suggestion raises serious economic, ethical and methodological issues. Firstly, if screening at 6 months detects only children with good prognosis disease, is there any justification for doing it at all this time? There is great concern about the detection and treatment of silent cases of neuroblastoma (i.e. cases which would otherwise

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regress spontaneously), by screening at 6 months. Waiting until 12 months may well reduce the number of children falling into this category. The option should therefore be whether to screen at the age of 6 *or* 12 months of age. However, taking into account the normal age distribution of neuroblastoma at presentation, screening at 6 months can only realistically affect the outcome of approximately 55% of cases and this is reduced to 45% if screening at 12 months is considered.

Secondly, the major objective in screening children at the age of 12 months would be to increase the proportion of children with aggressive disease characterised by n-*myc* amplification etc. and by so doing improve the prognosis in this group of children who currently have a relatively poor outcome in spite of very intensive and expensive therapy. There is evidence that early detection of the aggresive, rapidly proliferative form of neuroblastoma is possible since 6 children with n-*myc* amplification have been detected in Japan by screening at 6 months of age, but whether many more would be picked up at 12 months is unknown. That early detection will result of itself in substantial improvements in outcome for children with aggressive disease, however, remains to be established. Finally, there is an economic dimension to be considered. Screening twice would almost double the overall costs and therefore increase the cost per life saved by at least this proportion. This should be a serious consideration when recommending screening twice for such a rare disease.

To determine whether screening at 12 months can detect children with aggressive disease and if such early detection will have a substantial impact on the disease process, a specific epidemiological investigation needs to be established with this as its prime objective. The premature decision to implement national screening in Japan in 1985 removed forever the opportunity to conduct an adequate evaluation of screening in Japan.

The pioneering work of the Japanese has shown that screening for neuroblastoma is possible, but is it worthwhile? Their work has raised many questions to which we must now attempt to find answers.

Woods and his colleagues have established a controlled study of neuroblastoma screening in infants aged 3 weeks and 6 months in Quebec, Canada, in 1989 [13]. They may be able to evaluate the effectiveness of screening at 6 months of age before the turn of the century, but the value of screening infants of 6 months for neuroblastoma has already been questioned. There are serious doubts about the interpretation of the epidemiological data published from the Japanese studies and the latest report from Kaneko and his colleagues confirms what many have been suspecting for some time, i.e. that screening at 6 months is too early. The efficacy of screening at 12 months needs to be explored in a separate study and clearly there is urgent need that this be done.

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