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Editorial

Screening for neuroblastoma in children

Neuroblastoma is the third most common tumour among children after leukaemia and brain tumours,[1] with five deaths per million children under 15 years of age in Great Britain from 1986 to 1990.[2] It is a malignant tumour of embryonal cells in the neural crest and may arise in the medulla of the suprarenal gland, or anywhere along the sympathetic nervous chain from the neck to the pelvis. It is a tempting candidate for screening. Children with advanced disease at diagnosis have a much poorer prognosis than children with less advanced disease.[3] It should be feasible to detect them before clinical presentation since at the time of diagnosis more than 90% of patients excrete homovanillic acid (HVA) and vanillylmandelic acid (VMA) in higher than normal amounts.[4] These can be easily assayed in random urine samples obtained by blotting wet nappies with filter paper and sending the filter paper to a laboratory for analysis.

A national screening programme for neuroblastoma has operated since 1985 in Japan, confirming that mass screening is technically feasible.[5] There is no evidence, however, that the screening programme has reduced the mortality from neuroblastoma.[6] Chamberlain, in a paper in the *Journal of Medical Screening* published in 1994,[7] concluded that there was insufficient evidence to recommend screening for neuroblastoma but that future results from a large North American study might be informative. Preliminary results from this and other studies have now been published and so it is timely to review the current evidence on screening for neuroblastoma.

The North American study was the first controlled study of screening for neuroblastoma, though not a randomised trial.[8] All 476 603 children born in the Canadian province of Quebec between May 1989 and April 1994 were offered screening at 3 weeks and 6 months of age. There were two control populations, the American state of Minnesota and the Canadian province of Ontario. The average follow up was three and a half years. Incidence increased in Quebec as expected, because screening resulted in more cases being diagnosed, but the size of the increase was unexpected—the incidence more than doubled (SIR = 2.17; 95% confidence interval 1.79 to 2.57). From the age-specific incidence rates, screening appears to detect cases that would never have presented clinically. This is serious when one considers that the children are given chemotherapy. These results on incidence are in agreement with other studies. It is too early for the mortality from neuroblastoma to be compared in the Quebec study, but other studies have shown no reduction in the incidence of unfavourable advanced stage disease in older children.[9 10]

The original screening programmes were all aimed at screening children under 1 year of age. Children who present clinically with neuroblastoma before the age of 1 year have a much better prognosis than those presenting at a later age because there are two types of neuroblastoma—one with a good prognosis generally being presented before the age of 1; and one with a bad prognosis generally being presented after the age of 1.[11–15] Therefore most tumours detected at screening have been found to be those destined to have a favourable outcome, perhaps even spontaneously regressing as has been reported in a few cases,[16] regardless of early or late detection. Those with a bad prognosis are too small to be detected at 6 months, but may be detected at 12 to 18 months.

Screening children later, at 12 and 18 months, may avoid the problem of detecting spontaneously regressing tumours and increase the detection of those tumours with worse prognosis. Many centres in Japan have now introduced a second screen at 12–18 months,[17] but without abandoning the early screen that led to overdiagnosis. The SENSE Group (Study for the Evaluation of Neuroblastoma Screening in Europe) in cooperation with the International Agency for Research on Cancer plans a trial involving 1.5 million children screened twice at 12 and 18 months, with 1.5 million unscreened controls.[18] Recruitment has just started in Germany; the results are not expected until 2004.

The evidence to date indicates that, although screening for neuroblastoma is technically possible, it is not recommended for children under 1 year of age; it is unlikely to improve the mortality rates; and it seems to detect some spontaneously regressing tumours. The benefits of screening children aged 12–18 months must be

proved before any further screening programmes are implemented.

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