

Screening for neuroblastoma in children

J K Morris

Screening does not reduce mortality from neuroblastoma

Twenty years after Japan started mass screening for neuroblastoma in children, conclusive evidence has finally emerged that screening for neuroblastoma in children does not reduce mortality from the disease.¹⁻³ Screening appears to detect tumours that would have remitted spontaneously without treatment.⁴

Neuroblastoma in children is a tempting candidate for screening because (i) children who present before the age of 1 year have a better prognosis than those who present later⁵; (ii) children with advanced disease have much worse prognosis than those with early disease⁶; (iii) there is a simple, cheap and acceptable screening test available (the measurement of catecholamine metabolites sampled by blotting wet nappies with filter paper)⁷; and (iv) the test detects 90% of children with neuroblastoma.⁷

Before screening for neuroblastoma is recommended, it must be shown that it reduces the number of deaths from neuroblastoma. This can only be shown by conducting controlled trials that measure mortality. Following the introduction of mass screening in Japan, many feasibility studies were started in the early 1990s in France, Austria, Germany, Italy, Norway, the United States, Canada, and Australia. The only studies measuring mortality were in Germany and Canada. These two studies have now been published.^{2,3}

The first study was carried out in Quebec, Canada where almost half a million children born from May 1989 to April 1994 were screened at three weeks and six months of age.² All children were followed up for a minimum of 6 years: 118 children with neuroblastoma were diagnosed, 43 detected by screening, 20 detected clinically prior to screening at three weeks of age, and 55 detected clinically after three weeks of age having negative screens (n = 52) or never having been screened (n = 3). Twenty two children died (19 screen negatives and 3 children detected clinically prior to

screening at three weeks of age). The standardised mortality ratio for the Quebec cohort compared with the rest of Canada was 1.39 (95% CI:0.85–2.30) and the standardised incidence ratio was 2.17 (95% CI 1.79–2.57). The authors concluded that screening for neuroblastoma in children under age 1 increased the incidence of this disease, but did not appear to reduce the mortality due to this disease. The authors also noted that there was one child in the screened group who was severely disabled from complications from the surgery to remove the neuroblastoma.

The second study was carried out in Germany where over 2.5 million children in 6 of 16 German states from 1995 to 2000 were screened for neuroblastoma at one year of age.³ Just over 2 million children from the remaining states in Germany acted as the controls. All children were followed up for a median duration of six years and eight months. Two hundred and four children with neuroblastoma were diagnosed between the ages of 1 to 5, 149 detected by screening, and 55 detected clinically after having normal screens. Thirty three children died; three children with neuroblastomas detected by screening (two from complications of surgery and one from complications of chemotherapy), 14 screen negatives and 16 never screened. The death rate was 1.4 per 100 000 births compared with the death rate in the control area of 1.2 per 100 000. The incidence rate of neuroblastoma was 14.2 per 100 000 in the screened group compared with 7.3 per 100 000 in the control group. The authors concluded that screening for neuroblastoma in children at 1 year of age might cause some children to undergo unnecessary and potentially harmful treatment of a tumour that would otherwise spontaneously regress.

Screening for neuroblastoma illustrates how easily one can fall into the trap of assuming that because a disease can be detected early, screening must be worthwhile. In general, in cancer screening, randomised controlled trials are

necessary to determine if screening is worthwhile. These two studies were not randomised; nonetheless, bias was unlikely to have occurred. Ascertainment of deaths was extremely high in both study and control populations, reducing the possibility of ascertainment bias arising. The mortality rates from neuroblastoma in the case and control areas prior to the studies commencing were similar, which indicates that selection bias is unlikely to have occurred. These two studies therefore provide enough evidence to conclude that screening does not reduce mortality from neuroblastoma, despite the fact that they were not randomised controlled trials.

The two studies demonstrate how neuroblastoma screening was not only worthless, but led to “over-diagnosis” and must have identified tumours that would have spontaneously regressed. Screening caused significant harm. Both studies mentioned children in the screened group suffering severe complications due to the treatment. It is now time to withdraw such screening in Japan. Taking such action is always difficult, but this should not be a reason for failing to act. Hopefully these lessons will be learned when considering the implementation of other screening programmes—for example, screening for prostate cancer.

J Med Screen 2002;**9**:56

Author's affiliation

J K Morris, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK; j.k.morris@qmul.ac.uk

REFERENCES

- 1 Sawada T, Takeda T. Screening for neuroblastoma in infancy in Japan. In: Brodeur GM, Sawada T, Tsuchida Y, Voute P, eds. *Neuroblastoma*. Amsterdam: Elsevier Science B.V., 2000:245–64.
- 2 Woods WG, Gao R-N, Shuster J, Robison L, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med* 2002;**346**:1041–6.
- 3 Schilling FH, Spix C, Berthold F, et al. Neuroblastoma screening at one year of age. *N Engl J Med* 2002;**346**:1047–53.
- 4 Yoneda A, Que T, Imura K, et al. Observation of untreated patients with neuroblastoma detected by mass screening: a “wait and see” pilot study. *Med & Ped Onc* 2001;**36**:160–2.
- 5 Takeuchi LA, Hachitanda Y, Woods WG, et al. Screening for neuroblastoma in north America. Preliminary results of a pathology review from the Quebec project. *Cancer* 1995;**76**: 2363–71.
- 6 Craft AW, Parker L. Poor prognosis neuroblastoma: is screening the answer? *Br J Cancer* 1992;**66**:S96–101.
- 7 Tuchman M, Ramnaraine MR, Woods WG, et al. Three years of experience with random urinary homovanillic and vanillylmandelic acid levels in the diagnosis of neuroblastoma. *Pediatrics* 1987;**79**:203.