Screening for neuroblastoma

Neuroblastoma is the most common extracranial solid tumour of childhood with an incidence of 6–10 cases per million children (under 15 years) each year.1 The median age at diagnosis is 2 years and few children are diagnosed after 5 years of age. The tumour originates in the adrenal gland in half of the cases and elsewhere in the abdomen in a further 20%. The remaining tumours arise in sympathetic ganglia in the thorax, pelvis, or neck. Children presenting with localised, resectable (stage 1) tumours can be treated by surgical excision with a high expectation of cure (95% five year survival).2 Unfortunately, symptoms from the disease are non-specific (anorexia, malaise, limb pain, etc.) such that over 50% of clinically presenting children will already have advanced metastatic (stage 3 or 4) disease.2 For these children prognosis is very poor (25% five year survival)3 despite such intensive and expensive treatment as delayed primary surgery, chemotherapy, radiotherapy, and high dose chemotherapy with bone marrow rescue. In addition, neuroblastoma has not shown the dramatic improvement in prognosis over the past 10–15 years seen with other childhood malignancies such as acute lymphoblastic leukaemia, Hodgkin’s disease, and Wilms’ tumour.4

The aim of screening is to detect disease preclinically so that children can be treated when younger and with lower stage disease. As children diagnosed under 1 year of age with localised neuroblastoma are known to have a much better prognosis than older cases,5 screening for neuroblastoma is attractive and might be expected to reduce the morbidity and mortality. How, then, can we screen for neuroblastoma?

Children with neuroblastomas have long been known to excrete catecholamine metabolites in their urine.6 When La Brosse presented a simple test for 4-hydroxy-3-methoxy-mandelic acid (VMA) using urine spotted onto filter paper mass screening for neuroblastoma became a possibility.7 Sawada et al were the first to begin mass screening in 1972, testing 42 636 children aged 3 years in Kyoto, Japan, and finding one child with stage 2 disease.8 Mass screening has advanced rapidly in Japan since that time: Nagoya joined the programme in 1977 and Osaka in 1980 and by 1985 a nationwide programme for mass screening was introduced. The age at which children are screened has been reduced to 6 months and the qualitative VMA spot test has been superseded by quantitative measurement of both VMA and homovanillic acid (HVA) by high performance liquid chromatography (HPLC). All 3 month old infants are examined under the Child Health Survey Programme and at this time parents are given a screening kit. When the infant is aged 6 months a urine sample is taken and the filter paper is mailed to the local screening centre. Children with values above mean +2.5 SD for VMA and/or HVA are examined physically, by chest and abdominal radiography, and by abdominal ultrasound scan. By the end of 1988, a total of 4 018 630 children had been screened (78.9% of all infants) and 342 cases of neuroblastoma had been found, an incidence of 1/11 750.

Dr Sawada and his colleagues have presented extensive data regarding the outcome of children detected by the screening programme.4 Seventy eight percent of cases were detected between 7 and 11 months of age and 95.8% of children were asymptomatic. By the end of August 1989, fully 97% of these children were still alive and only three children had died from progressive disease. There has also been a shift away from advanced stage disease at diagnosis.
(55% had stage 4 disease during 1971–6 compared with 8% in 1989) towards children presenting with localised disease (20% stage 1 and 2 1971–6 compared with 65% in 1989). Is there, then, any doubt about the value of screening?

Unfortunately, there have been no population based control trials to study the impact of mass screening for neuroblastoma. Results from any screening programme must take into account lead time bias and length bias. Lead time bias refers to the apparent increase in survival of a case being detected earlier in the course of the disease as a result of screening. Length bias is due to slower growing tumours having a longer preclinical phase of the disease and thus a greater chance of being detected by screening than faster growing, more aggressive tumours. Where screening has been introduced without adequate control studies it is, therefore, possible that improvement in survival may be due in part to the bias of screening. Also there are features of neuroblastoma that makes interpretation of the results from Japan difficult.

Neuroblastoma is known occasionally to regress spontaneously without treatment, and there is evidence that some of the tumours detected by screening might never have come to clinical attention had they not been detected by the urine test. First, the incidence of clinically detected tumours in a screened population ranges from 1/17 000 to 1/10 000.5 When screening by HPLC was introduced in Japan, the incidence was seen to increase to around 1/8000–1/5000 suggesting that some ‘silent’ neuroblastomas were being detected.

Secondly, comparison of prognostic markers between cases detected clinically and by screening suggests that screening picks up tumours with an inherently better prognosis. MYCN amplification, copy number, chromosome lp loss of heterogeneity (1pLOH), and DNA ploidy have been shown to have strong prognostic significance. Cases detected by screening tend to have single copy MYCN, no lp LOH, and aneuploid tumours. On the other hand clinically detected tumours, particularly those negative at an earlier urine test, tend to have tumours with amplified MYCN, lp LOH, and diploidy. As the above markers are consistent throughout the course of the disease, screening as currently undertaken may be failing to detect the very cases being sought, that is, those with a poor prognosis. Therefore, any analysis that suggests the tumours detected by screening have a poorer prognosis must have reached a critical size. Few tumours have been detected under 3 g with the majority weighing between 10 and 50 g at diagnosis. Some tumours may be missed when the child is screened at 6 months of age because the tumour was too small at that time to produce raised concentrations of metabolites.

Finally, epidemiological studies have shown that 18% of cases of neuroblastoma present before the age of 6 months. Indeed, with increasing use of antenatal ultrasound scanning, neuroblastoma can be detected before birth. Screening at 6 months obviously will not affect the clinical outcome of such cases.

In order to assess the value of screening, centres in Quebec and the United States are cooperating in a controlled trial whereby neuroblastoma cases seen in the province of Quebec (where over 90% of 3 week old neonates and over 70% of 6 month old children are being screened) will be compared with cases seen in Quebec before screening, and with cases seen in Ontario, Minnesota, Florida, and the Greater Delaware Valley where there is no screening policy. Craft has also proposed a controlled trial involving six regions in the UK. (AW Craft, personal communication). It is likely to be five to eight years before the results from these trials are available, but it is important that such controlled studies are implemented before widespread arbitrary urine testing renders such research impossible.

If the above studies show that screening for neuroblastoma can reduce the morbidity and mortality from the disease, and cost-benefit analyses are favourable, what methods are available for screening? Urine may be collected from a napkin onto a filter paper, which is then dried and mailed to the screening centre. To increase compliance the help of health visitors may be enlisted, but then the timing of collection should coincide with a routine visit in order to reduce costs. Most screening is now performed at 6 months of age, but this may not be the ideal time and screening later, for example at 18 months, may detect better the more aggressive tumours. Multiple testing may also be desirable.

Once in the laboratory, VMA and HVA may be measured by thin layer chromatography (TLC), HPLC gas chromatography with mass spectrometry (GC/MS), or by enzyme immunoassay. The method chosen should combine low cost with high sensitivity and specificity. Normal values should be determined within each laboratory, cut off concentrations being set to reduce the possibility of false negative results while minimising the parental anxiety of false positive results. The majority of laboratories have a mean ± 2 SD. Once detected, the infant should receive rapid, sympathetic, and up to date diagnostic confirmation and treatment.

Sawada and his colleagues in Japan are to be congratulated on their extensive pioneering work on neuroblastoma screening. Much has been learnt about this enigmatic tumour. Screening is not yet of proved value and the results from Japan and Quebec are eagerly awaited. In the mean time, it is important that every opportunity be taken to study this tumour and anyone involved in establishing a screening programme should at the same time gather as much epidemiological data as clinical and biological details from cases detected both clinically and by screening.

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