Neonatal neuroblastoma

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Abstract

Over nine years, 33 children with neonatal neuroblastoma were registered with the UKCCSG (United Kingdom Children's Cancer Study Group). Tumours of all stages were found, but stage 4S disease predominated. Five tumours were detected prenatally by ultrasonography. Treatment varied according to tumour stage. The overall survival of the group was 91%. Ten children have had long term complications as a result of their disease, usually as a result of spinal tumour involvement. The good overall prognosis in this age group is encouraging, but the poor neurological outcome of patients with intraspinal extension is of concern.

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Neonatal tumours—those occurring in the first 28 days of life—are rare. They comprise 2% of all paediatric malignancies, with an incidence of 1.58 to 3.65 per 100 000 live births.¹⁻³ A neonatal unit with 3000 deliveries a year might expect to see a case once every 10 to 20 years. The most common neonatal tumour is neuroblastoma, accounting for 28–39% of tumours in this period, with an estimated incidence of 0.61 per 100 000 live births.²⁻⁵

The prognosis of neuroblastoma is influenced by many factors, the most important of which are age and degree of tumour spread. Overall survival for infants under 12 months of age is 81%, while for children over 12 months it is only 31%.⁶⁻⁷ Similarly, survival for stage 1 and 2 disease, irrespective of age, is greater than 85%, while stage 4 neuroblastoma has a survival of around 50% in the first year of life and less than 20% in those aged over 1 year.⁶⁻¹⁰ Biological factors, especially amplification of N-myc (an oncogene located on chromosome 2) and loss of parts of chromosome 1 (1p36-), adversely affect prognosis.¹¹

With the increasing use of prenatal ultrasonography to detect fetal anomalies, the possibility of early detection of children with neuroblastoma is also increasing, with potential implications for the management of these children.

Our study aimed to review the clinical features and outcome of neonatal neuroblastoma in Great Britain, as recorded by the UKCCSG (United Kingdom Children's Cancer Study Group).

Methods

All newly diagnosed children with malignant disease who present to the 22 centres of the

UKCCSG are registered centrally. Analysis of this register revealed 33 cases of neuroblastoma diagnosed in the neonatal period over the 9 years between 1 January 1986 and 31 December 1994, an incidence of 0.52 per 100 000 live births. During this time, a comparison of UKCCSG data with those of the National Registry of Childhood Tumours, showed that 94–97% of neuroblastoma cases were registered with the UKCCSG.

We reviewed the records of these 33 patients and noted information regarding tumour location and stage, histology, clinical presentation, urinary catecholamines, serum and biological markers of disease, treatments received, outcome and complications. Additional questionnaires were sent to the treating physician. Obstetric data were sought wherever possible. Tumours were staged according to the Evans system before 1992, and by the INSS (International Neuroblastoma Staging System) from 1992 onwards.

Kaplan–Meier analysis was used to produce survival curves.

Results

These 33 patients represented 4% of all 860 children with neuroblastoma registered with the UKCCSG during the same period, and 15% of infants under 1 year of age. The mean age at diagnosis was 13.4 days (fig 1).

Prenatal maternal ultrasound scans were documented for 12 of these 33 children. Five scans suggested a possible diagnosis of neuroblastoma prenatally. There were two further abnormal prenatal scans; one was reported to show a cyst on the right kidney, the other reduced fetal movements. Retrospectively, these abnormalities can be attributed to neuroblastoma but were not regarded as suspicious at the time. The remaining five scans (from 17 weeks of gestation to term) were normal (table 1).

Table 1 shows details of the tumours. Histological confirmation of the diagnosis (either primary tumour biopsy or compatible tumour cells in the bone marrow, together with raised

Figure 1 Numbers of children registered with the UKCCSG over study period.

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Table 1 Neuroblastoma in the neonatal period; characteristics of 33 tumours 1986–94

Stage	Age at diagnosis (days)	Prenatal ultrasound	Presentation	Primary site	Other sites	Treatment	Outcome	Complications
1	1	Normal	Abdominal mass	Adrenal	Nil	S	Alive	
1	2	? Neuroblastoma	Prenatal ultrasound	Adrenal	Nil	S	Alive	
1	10	Normal	Neck mass	Cervical	Nil	S	Alive	
2	0	Not documented	Tachycardia, sweaty, hypertensive	Abdominal	Nil	S	Alive	Infarcted left kidney post operatively
2	15	Not documented	Stridor	Cervical	Nil	S+C	Alive	
2	16	Not documented	Abdominal mass	Adrenal	LN	S	Alive	
2	16	Not documented	Lower limb neurology, incontinence	Intraspinal L1/L2	Nil	S	Alive	Neuropathic bladder, walking aids
2	18	Not documented	Abdominal mass	Adrenal	Nil	S	Alive	
3	0	Not documented	Birth asphyxia	Thoracic	Paraspinal extension	S	Alive	Abnormal sweating
3	6	Normal	Abdominal mass	Adrenal	LN	S+C	Alive	
3	11	Not documented	Abdominal distension	Thoracic	Intraspinal extension	S+C	Alive	Kyphoscoliosis
3	18	Reduced movement of lower limbs	Lower limb neurology	Adrenal	Intraspinal extension	S+C	Alive	Flaccid paralysis lower limbs
3	22	Not documented	Lower limb neurology	Thoraco-abdominal	LN, paraspinal extension	S+C	Alive	Scoliosis
3	26	Not documented	Respiratory distress	Thoracic	Intraspinal extension	S+C	Alive	Flaccid paralysis lower limbs
3	27	Not documented	Urinary dribbling	Adrenal	Intraspinal extension	S+C	Alive	Incontinent, walking aids
4	0	Normal	Hydrops	Adrenal	Liver, brain, heart, bone, muscle, lungs	Nil	Stillbirth	
4	1	? Neuroblastoma	Abdominal distension, hydrops	Adrenal (bilateral)	Liver	C	Died	
4	1	? Neuroblastoma	Prenatal ultrasound	Adrenal	Liver, BM, pleura	S+C	Alive	
4	27	Normal	Abdominal distension	Adrenal	Liver, BM, LN	S+C+BMT	Alive	High tone deafness
4S	0	? Neuroblastoma	Prenatal ultrasound	Adrenal	Liver	S	Alive	
4S	0	? Neuroblastoma	Prenatal ultrasound	Adrenal	Liver	C	Alive	Learning difficulties
4S	1	Not documented	Skin nodules	Unknown	Skin	Nil	Died	
4S	2	Not documented	Intestinal obstruction	Adrenal	Liver	S	Alive	
4S	2	Not documented	Abdominal mass	Adrenal	Liver, LN	C	Alive	
4S	5	Not documented	Abdominal distension	Adrenal	Liver	S+C+R	Alive	
4S	8	Not documented	Abdominal mass	Adrenal	Liver	Nil	Alive	
4S	9	Not documented	Abdominal mass	Liver	Liver	R	Alive	
4S	13	Not documented	Abdominal mass	Adrenal	Liver, BM	Nil	Alive	
4S	14	Cyst right kidney	Abdominal mass	Adrenal	Liver, BM	C	Alive	
4S	19	Not documented	Skin nodules	Adrenal	Liver, BM, skin	Nil	Alive	
4S	21	Not documented	Skin nodules	Adrenal	Liver, skin	Nil	Alive	
4S	26	Not documented	Abdominal distension	Adrenal	Liver, BM	C	Alive	
4S	26	Not documented	Abdominal mass	Adrenal	Liver	S	Alive	

S = surgery; C = chemotherapy; R = radiotherapy; BMT = bone marrow transplant; LN = lymph nodes; BM = bone marrow.

urinary catecholamines), was obtained in all but one infant (right sided perirenal mass and liver secondaries together with raised urinary catecholamines). Most tumours were adrenal in origin and they were predominantly stage 4S. Many of the children were asymptomatic, including those with masses found on routine examination of the abdomen (n=6), four of the five children identified prenatally by ultrasound scan, and the infant whose prenatal scan showed a cyst on the right kidney (diagnosed when this ultrasound scan was repeated after birth). The others presented with various symptoms related to the site of their tumour. There was one registered stillbirth.

Biological data were incomplete: urinary catecholamines were documented in 29 of the 33 children, and were raised in all but two. Ferritin concentrations were not recorded in 18 patients, but were raised in all stage 4 and 4S patients for whom results were available, and normal in all others, with the exception of one child with a stage 3 tumour. Lactate dehydrogenase activity was raised in all eight patients in whom it was measured. N-myc amplification was examined in six tumours (one stage 2, five stage 4S) and all had normal copy number.

Treatment depended on the tumour stage (table 1). Chemotherapeutic regimens over the span of the review included vincristine and cyclophosphamide, sometimes with the addition of etoposide and cisplatin (OPEC) or carboplatin (OJEC). The eight infants with stage 1 and 2 disease underwent primary surgical

resection of their tumour. One patient with stage 2 disease had a local recurrence treated successfully with chemotherapy. The seven stage 3 patients were treated with surgery and chemotherapy (6 patients) or surgery alone (1 patient). One of the stage 4 patients was stillborn. The remaining three patients received chemotherapy, and one patient autologous bone marrow transplantation. One patient with stage 4 disease died of toxicity during initial chemotherapy. Five children with stage 4S disease required no treatment for their disease. Four stage 4S patients had total resection of their primary site; this was the only treatment for three. Six children with stage 4S disease received chemotherapy, and two radiotherapy to relieve respiratory compromise.

Overall survival of the cohort was 91% (confidence limits 86.1–95.9%), with a mean follow up of 48 months (SD 32 months, range 0–105 months, median 52.5 months). There were 3 deaths, including the stillbirth; one had stage 4S and two stage 4 disease. When analysed by stage, the survivals in our study were: stages 1–3, 100%; stage 4, 50% and stage 4S, 93%. Fig 2 shows the Kaplan–Meier survival curves.

Long term complications occurred primarily as a result of intraspinal extension of tumour (table 1). Four patients have persisting neurological deficit of varying degrees—either problems with walking or incontinence. Two children also had clinically significant scoliosis. One child has abnormal sweating on one side secondary to laminectomy. The child who

Figure 2 Kaplan-Meier survival curve for 33 cases of neonatal neuroblastoma, divided by stage.

underwent bone marrow transplantation now has high tone deafness affecting acquisition of normal speech, and one child has learning difficulties, having had vincristine and cyclophosphamide alone as treatment for stage 4S disease.

Discussion

Our overall survival for neuroblastoma in the neonatal age group was very good at 91% and better than for any other age group. De Bernardi found an overall survival for infants under 1 year of age of 82%, compared with 31% for children over 1 year of age.⁷ He found that those under 6 months of age did better than those between 6 and 12 months (86% *vs* 78%). Survival of prenatally diagnosed neuroblastoma is around 90%.¹² The survival results for the neonatal age group when analysed by stage are similar to published results for infants with neuroblastoma.^{8 13-15}

Stage 4S disease comprises a primary tumour at stage 1 or 2, with spread limited to the liver, skin, or bone marrow, in a child under 12 months of age. Differentiating stage 4 and 4S disease can be difficult, which the introduction of the INSS has attempted to address. Stage 4S neuroblastoma is an unusual tumour, because in most patients the disease will spontaneously remit without any treatment. In only 1-2% of patients does the disease progress to stage 4. The major risk for infants with stage 4S disease comes from the systemic effects of the disease, chief among which is respiratory compromise caused by an often massively enlarged liver.^{14 15} The risk of respiratory compromise is at its greatest in infants under 6 weeks of age.^{6 15 16} Treatment with radiotherapy or chemotherapy may be urgently required, and frequent review of such infants is necessary. Our study confirms the good prognosis of stage 4S disease (93% overall survival). In our series six patients with stage 4S disease were treated (42%), similar to the numbers in other reported series.¹⁴

Two of the three live born stage 4 patients survived following intensive chemotherapy. The one death resulted from renal failure during induction chemotherapy. Including the stillborn child, survival in half of the stage 4

cases is similar to the prognosis of stage 4 disease throughout infancy.

The increased use of routine prenatal ultrasound over the past few years has resulted in more children with neuroblastoma being diagnosed prenatally.^{12 17 18} The survival of these infants has been very good overall. Acharya *et al* recently reviewed 55 children with prenatally diagnosed neuroblastoma.¹² They found predominantly adrenal tumours with favourable staging and biological features, and an overall survival of 90%. In our series five patients had a prenatal ultrasound scan suggestive of neuroblastoma; two had stage 4S, two stage 4, and only one stage 1 disease. This stage distribution contradicts the findings of other studies where the percentage of stage 1 tumours identified by prenatal ultrasound scan was around 70%.^{12 17} On the basis of their stage distributions, both Ho *et al* and Acharya *et al* recommend a wait and see policy for treatment of prenatally diagnosed patients, but staging investigations are obviously vital before this policy is adopted.^{12 17} The comparable overall survival in our study, despite a lower percentage of stage 1 disease, is probably explained by the large numbers of patients with stage 4S disease who have a similarly good prognosis.

The role of prenatal ultrasonography in the diagnosis of neuroblastoma has many parallels with routine postnatal screening for neuroblastoma, first introduced in Japan over 20 years ago.¹⁹ Screening is performed by measuring urinary catecholamines in all infants. It was hoped that screening would result in earlier diagnosis of neuroblastoma at a less advanced stage, thus leading to improved survival. However, while the prognosis of neuroblastoma diagnosed on screening is very good, an increased incidence of neuroblastoma has been noted in the screened populations, but with no reduction in overall mortality.¹⁹⁻²¹ Screening may therefore be identifying tumours that would previously have resolved without treatment. It is not possible to determine from our study whether prenatal ultrasonography is detecting a similar group of tumours, because the numbers involved are small.

The mode of presentation and diagnosis in children with neuroblastoma is very diverse, and this was seen in our study group. The primary site distribution within the neonatal period is similar to that of other ages, with a large proportion arising from the adrenal gland. Six cases (18%) presented asymptotically, with an abdominal mass noted on routine examination, reinforcing the value of routine neonatal abdominal examination. A palpable abdominal mass in a neonate is most likely to be of renal origin, but the possibility of neuroblastoma cannot be discounted. Three patients (9%) presented with skin nodules associated with stage 4S neuroblastoma. Eleven (33%) presented with diverse symptoms referable to the abdominal and respiratory systems, the true diagnosis coming to light during investigation.

We found six infants (18%) with intraspinal tumour involvement. Although they survived, they have all had long term complications, with

varying degrees of flaccid paralysis of the legs, urinary incontinence, or scoliosis. One child had a laminectomy and all received chemotherapy. In comparison, the neurological outcome for intraspinal neuroblastoma when all age groups are included is much better. Plantaz *et al* found serious neurological sequelae in only six of 42 children with intraspinal tumours (15%).²² However, four of the six children with ongoing neurological problems in their study had deficits present at birth.²² Munro *et al* found a similarly poor neurological outlook for children with congenital paraplegia secondary to neuroblastoma.²³ One of our patients had reduced fetal movements at 28 weeks of gestation on ultrasound scan, and had probably had had spinal cord compression for three months by the time of delivery. Long standing nerve damage is likely to be present in most patients with congenital neuroblastoma and spinal cord involvement, which may explain the poor neurological outcome. In view of the long term deformities often noted following spinal cord surgery and the very poor neurological recovery, caution should be used in considering surgical intervention. As most children with intraspinal disease in our study had stage 3 disease they received moderate dose chemotherapy. Plantaz *et al* showed that in older children with partial neurological deficits, chemotherapy produced good results.²² The historical nature of our study and the long timespan over which patients have accrued makes it difficult to interpret the limited serum and biological marker results. Certainly urinary catecholamines are raised in most neonatal patients with neuroblastoma, confirming this as a useful investigation. Urinary catecholamines can be accurately measured on a spot urine. The technically difficult 24 hour urine collection is unnecessary. Ferritin, LDH, and N-myc amplification are useful prognostic indicators in neuroblastoma, and may provide additional information in this age group.

We conclude that the outlook for infants diagnosed with neonatal neuroblastoma is better than for any other age group. However, three particular groups are at greater risk from their disease. Stage 4 disease has a similar outcome to that in older infants with only a moderate chance of survival. Stage 4S disease, while having a good long term prognosis, needs careful observation to detect potentially life threatening complications. The functional outcome of those with neurological deficit secondary to their tumour is not good. Some tumours may

be picked up prenatally. The high risk of complications, as well as the good survival rates, should be taken into account when counselling parents.

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