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Malignant tumours in the neonate

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SUMMARY One hundred and two cases of neonatal cancers, representing 2% of all paediatric malignancies, were seen during a 60 year period at The Hospital for Sick Children, Toronto, Canada. The neonatal cancers included neuroblastoma (47%), retinoblastoma (17%), soft tissue sarcoma (12%), central nervous system tumours (9%), leukaemia (8%), and a few cases of Wilms' tumour, liver tumour, and miscellaneous tumours. The overall mortality from disease was 41%. Patients with retinoblastoma, Wilms' tumour, and neuroblastoma had the best prognosis. Forty three patients (42%) survived their neonatal cancers; all were treated with surgery or radiochemotherapy, or both, but none suffered long term major handicaps as a result of treatment. There was one instance of second malignancy of the thyroid gland induced by radiation. We conclude that although neonatal cancers are difficult management problems, many patients can be cured. Physicians should discuss with parents the possible risks associated with treatment before treatment is begun.

Cancer in the neonate is a rare event. Except for isolated case reports, there is little information on the prevalence, sites of origin, or tumour types encountered in this age group. Fraumeni and Miller, in a review of death certificates over a five year period in the United States, found the neonatal death rate from malignancies to be 1 per 6·24 million live births.[1] A study of mortality, however, does not represent the true prevalence as only certain malignancies are fatal. Bader and Miller reported that the prevalence of cancer in the first month of life in the United States was 36·5 per million live births,[2] while Barson estimated the prevalence of congenital neoplasia to be 1/12 500 to 1/17 300 total births.[3] There are scant publications on the diagnosis and treatment of these patients, whose management poses unique problems.

We report the outcome of a group of 102 neonates found to have malignant diseases in a single institution over a 60 year period and their management problems.

Subjects and methods

The Hospital for Sick Children in Toronto, Canada, is the tertiary referral centre for most sick neonates and for paediatric malignancies seen in Ontario. During a 60 year period (1922–82), 5290 cases of paediatric malignancy were seen at the hospital, 102 of whom were neonates under 29 days of age. The tumour registry, the medical records, and the pathology registry were examined to determine the prevalence of paediatric malignancies. The clinical records of the patients were reviewed. Histological sections of biopsy specimens or autopsy material, or both, and bone marrow aspirates were available in all patients, except three cases of neuroblastoma with increased urinary catecholamines and two cases of soft tissue sarcoma, and were reviewed by all the authors except ANC to confirm the diagnosis of the malignancy.

Results

One hundred and two neonates were diagnosed as having malignancy in the first 29 days of life. Forty two patients presented on the first day, 13 during the next six days, and the remaining 30 between days 7 and 29. Sixteen diagnoses of neuroblastoma and one of Wilms' tumour were made incidentally at autopsy in neonates who died of unrelated medical problems. There were 64 boys and 38 girls, giving a sex prevalence of 1·7:1. Table 1 shows the prevalence of different cancers and the mortality from disease. Forty two neonates (41%) died from their malignancy, 43 (42%) survived, and 17 died of unrelated medical problems.

Neuroblastoma was the most common neonatal

Table 1 *Prevalence of different cancers and mortality in neonates presenting with malignant diseases*

Diagnosis	*Total No of cases (Ages 0–18 years)*	*No occurring in neonates*	*% Incidence in neonates*	*Mortality* from malignancy (No (%))*	*Long term survivors (No (%))*
Neuroblastoma	404	48	11·9	11*(23)	21†(44)
Retinoblastoma	148	17	11·5	4 (24)	13 (76)
Wilms' tumour	293	4	1·3	0*(0)	3 (75)
Liver tumour	56	1	1·8	1 (100)	0 (0)
Leukaemia	1609	8	0·5	8 (100)	0 (0)
Central nervous system tumour	917	9	1·0	8 (89)	1 (11)
Sarcoma	623	12	1·9	10 (83)	2 (17)
Miscellaneous tumours	1240	3	0·2	0 (0)	3 (100)
Total	5290	102	1·9	42 (41)	43 (42)

*Excluding 16 neonates with neuroblastoma in situ, one neonate with Wilms' tumour who died of unrelated medical problems, and one child with neuroblastoma who died at age 11 from a motor traffic accident.
†Including the child with neuroblastoma who died, free of disease, at age 11 from a motor traffic accident.

tumour in our series (48 cases) and represented 12% of all neuroblastomas seen. The boy:girl ratio was 2:1. Sixteen neonates had unsuspected neuroblastoma in situ within the adrenal glands that were discovered at autopsy after their deaths from unrelated medical problems. Thirty two patients presented with overt neuroblastoma. Fourteen patients had adrenal primary tumours, of which five were bilateral. Seven patients had cervical tumours, eight had thoracoabdominal paraspinal tumours, and three had pelvic neuroblastomas. Two of the seven patients with cervical neuroblastoma presented with unilateral congenital Horner's syndrome. Three of the eight patients with thoracoabdominal paraspinal neuroblastoma had extradural extension of tumour into the spine. The prognosis was dependent on the stage of the disease. Death resulting from tumour occurred in none of the 16 patients with neuroblastoma in situ, in one of the 11 with stage I/II disease, in neither of the two with stage III disease, in four of the five with stage IV disease, and in six of the 14 with stage IV-S disease. Fifty five per cent of patients received treatment, which consisted of surgery or radiochemotherapy, or both. All of the 21 survivors received one or more treatment modalities. Of these 21 patients (median follow up 13 years, range 6–30 years), one boy had developed multifocal papillary carcinoma of the thyroid gland induced by radiation 18 years later, and another girl had died, in remission, of a motor traffic accident 10 years later.

Retinoblastoma, the next most common neonatal tumour, was diagnosed in 17 babies. Thirteen patients had bilateral tumours, while four had unilateral disease. Four patients were diagnosed at elective examinations of the eyes under anaesthesia performed because of a family history of retinoblastoma. The remaining 13 patients presented with strabismus, leucocoria, or heterochromia iridis. Treatment consisted of enucleation or radiochemotherapy, or both. Thirteen of the patients were long term survivors of retinoblastoma (median survival 6 years, range 2–35 years), and so far none have developed second malignancies.

Wilms' tumour was found in four patients. In two cases the mothers had colon and renal cell carcinoma, respectively. The two patients with bilateral disease presented at birth with bilateral abdominal masses. One patient died at 11 hours of age of hyaline membrane disease. The other patient had a left total and a right partial nephrectomy, abdominal irradiation, and chemotherapy. He was alive and free of disease at 12 years. The other two patients with unilateral stage I Wilms' tumours presented at weeks 3 and 4, with an abdominal mass and with haematuria, respectively. Both had surgery only and were free of disease at 14 and 10 years, respectively. All four cases of Wilms' tumour had favourable histology, but one of the patients with bilateral disease had focal dysplastic changes in the renal parenchyma.

One patient presented at birth with a fetal hepatoblastoma. He was treated with surgical resection, chemotherapy, and irradiation but died of brain metastases one year later.

The clinical information on eight neonates with leukaemia is shown in Table 2. Three patients had acute myelogenous leukaemia, one acute lymphoblastic leukaemia, and four acute undifferentiated leukaemia. All patients presented with anaemia, thrombocytopenia, high white blood cell counts, and organomegaly. One patient (case 8 in Table 2) also had meningeal leukaemia and leukaemic iritis, with leukaemic cells in the anterior chambers of his eyes at presentation. Four babies had leukaemic infiltration of the skin and two had testicular leukaemia at diagnosis. All eight died of their disease. The four who received no chemotherapy

Table 2 *Clinical information on neonates with leukaemia*

Case No	*Sex*	*Presenting age*	*Diagnosis*	*Treatment*	*Outcome*
1	M	3 days	Acute undifferentiated leukaemia	None	Died, 1 month
2	M	Birth	Acute lymphoblastic leukaemia	Pred, VCR, Asp	Died, 15 months
3	F	Birth	Acute undifferentiated leukaemia	VCR, Cyclo, 6MP, Ara C	Died, 4 months
4	M	Birth	Acute myelogenous leukaemia (Down's syndrome with ventricular septal defect)	6MP, MTX	Died, 23 months
5	M	27 days	Acute myelogenous leukaemia	None	Died, 5 months
6	F	26 days	Acute myelogenous leukaemia	None	Died, 1 month
7	M	3 days	Acute undifferentiated leukaemia	None	Died, 35 days
8	M	Birth	Acute undifferentiated leukaemia	Pred, VCR, 6MP, MTX	Died, 24 months

Pred=Prednisone, VCR=Vincristine, Asp=L-Asparaginase, Cyclo=Cyclophosphamide, 6MP=Mercaptopurine, MTX=Methotrexate, Ara C=Cytosine arabinoside.

died one to five months after diagnosis, and the four who received chemotherapy died four to 24 months after diagnosis.

Nine infants had malignant tumours that arose from the central nervous system (Table 3). The most common presenting feature was a rapidly enlarging head. Roughly half of the babies also developed vomiting or seizures. Most of the patients presented in the era before computed tomography and the diagnosis was made with ventriculography, arteriography, or air encephalography. Astrocytoma was the most common disease, all three cases being high grade tumours. There were two cases of primitive neuroectodermal tumour, one of medulloblastoma, one of ependymoma, and two of myxofibrosarcoma. The prognosis was poor, and only one patient remained alive beyond 2 years. Three patients had no treatment and died shortly after diagnosis. Five patients had radiotherapy or chemotherapy, or both, because their tumour could not be completely resected, and all five died of disease progression or complications of treatment. The patient who was alive, free of disease, and neurologically normal at 30 months after diagnosis had total resection of his frontoparietal myxofibrosarcoma, radiotherapy, and chemotherapy.

Twelve infants presented with soft tissue sarcomas in the neonatal period (Table 4). Eight patients had rhabdomyosarcoma, three had undifferentiated sarcoma, and one had leiomyosarcoma. Ten of the 12 babies died of their disease. The two long term survivors included a patient with leiomyosarcoma of the colon and a patient with an undifferentiated sarcoma of the orbit. It is of interest that both were cured by surgery alone.

The miscellaneous group comprised three patients.

Table 3 *Clinical information on the nine neonates with brain tumours*

Case No	*Sex*	*Presenting age*	*Presenting features*	*Diagnosis*	*Treatment*	*Outcome*
1	F	Birth	Hydrocephalus, seizures	Cerebellar and cerebral primitive neuroectodermal tumour	Ventriculoperitoneal shunt	Died, 11 days
2	F	Birth	Large head	Left cerebral anaplastic astrocytoma	None	Died, 1 day
3	F	27 days	Hydrocephalus, vomiting	Ependymoma of fourth ventricle	Torkildsen shunt, partial resection	Died, 3½ months
4	M	20 days	Hydrocephalus, exophthalmus, seizures	Right cerebral astrocytoma	None	Died during air encephalogram
5	M	14 days	Large head, strabismus	Left frontal anaplastic astrocytoma	Surgery, chemotherapy	Died, 8 months
6	M	27 days	Vomiting large head	Cerebellar medulloblastoma	Partial resection, radiotherapy	Died, 2 months, of meningitis
7	F	27 days	Large head, hydrocephalus	Pineal primitive neuroectodermal tumour	Subtotal resection, ventriculoperitoneal shunt radiotherapy, intrathecal chemotherapy	Died, 4½ months
8	F	Birth	Occipital mass, vomiting	Posterior fossa myxofibrosarcoma	Subtotal resection, radiotherapy, chemotherapy	Died, 15 months
9	M	Birth	Left frontoparietal mass	Left temporoparietal myxofibrosarcoma	Total resection, radiotherapy, chemotherapy	Alive, 2½ years

Table 4 *Clinical information on 12 infants presenting with soft tissue sarcomas in the neonatal period*

Case No	*Sex*	*Presenting age*	*Site*	*Diagnosis*	*Treatment*	*Outcome*
1	M	Birth	Colon	Leiomyosarcoma	Resection, colostomy	Alive at 13 years
2	M	Birth	Axilla	Embryonal rhabdomyosarcoma	Resection, radiotherapy	Died, 6 months, of metastases
3	F	Birth	Vagina	Rhabdomyosarcoma	Resection	Died, 16 months, of recurrence
4	M	Birth	Tongue	Rhabdomyosarcoma	Resection, irradiation using Tantalum implant	Died, 2½ years, of metastases
5	F	Birth	Vagina	Sarcoma botryoides	Resection	Died, 1 year, of recurrence
6	F	Birth	Axilla	Undifferentiated sarcoma	Resection, radiotherapy, chemotherapy	Died, 3 months, of metastases
7	F	Birth	Foot	Alveolar rhabdomyosarcoma	Amputation, chemotherapy, radiotherapy	Died, 12 months, of metastases
8	F	5 days	Ulnar arca	Aveolar rhabdomyosarcoma	Resection, radiotherapy	Died, 3 months, of metastases
9	M	7 days	Scalp and neck	Undifferentiated sarcoma	None	Died, 11 months, of metastases
10	M	14 days	Neck	Alveolar rhabdomyosarcoma	Resection	Died, 1 month, of metastases
11	M	14 days	Orbit and eyebrow	Undifferentiated sarcoma	Orbital exenteration	Alive, 18 years
12	M	28 days	Intradural spinal mass at T10-L2	Rhabdomyosarcoma	Resection	Died, 6 months, of disease

The first patient had a malignant schwannoma of the humeral area. He was alive and free of disease at 3 years after excision only. The second patient presented at birth with a large presacral mass. This was completely removed, and histology showed a benign sacrococcygeal teratoma with a malignant focus of embryonal carcinoma. She had adjuvant chemotherapy and was alive and free of disease at 21 months. The third patient had a testicular endodermal sinus tumour, which was resected, and was alive and free of disease at 43 years.

Discussion

Tumour masses are fairly common findings in the neonatal period but are rarely malignant. In our series malignant neonatal tumours comprised only 2% of all childhood malignancies. The exact prevalence is difficult to determine, but in the United States it is reported to be in the region of 1 per 27 000 births.[2] In an average size maternity hospital one such patient would be born every nine years. Any experience in this must be gathered over a period of years from a large neonatal referral centre.

Forty one per cent of the tumours were evident on the first day of life, but 17% were only found at autopsy as an incidental finding. Thus the true prevalence may well be higher than the figures quoted, bearing in mind that many neonatal deaths do not undergo postmortem examination. Unlike other series, we found a male predominance, with a sex prevalence of 1·7:1. This was similar to but even more pronounced than the male predominance of 1·2:1 in all paediatric cancers.[4] Prenatal factors may play a part and affect one sex more than the other.

Like others,[5] we found no evidence of heredity in congenital malignancies, with the exception of four cases of familial retinoblastoma. Miller reported that certain childhood cancers were associated with congenital anomalies.[6] One might expect that this association would be more pronounced in congenital neoplasia. We only found one case of leukaemia associated with Down's syndrome and ventricular septal defect, a well known association.[7] Five patients with neuroblastoma had congenital heart disease, and one with neuroblastoma had multiple congenital abnormalities. There have been isolated reports describing the transplacental metastatic spread of cancer cells from mother to fetus in malignant melanoma,[8] leukaemia,[9] and choriocarcinoma.[10] We found no such instances in our series. We previously reported one baby with congenital neuroblastoma who had clumps of tumour cells in the fetal but not the maternal vascular channels of the placenta.[11] There was no evidence of transplacental spread of cancer from the child to the mother in this or in other reports.[12] Two mothers with recently diagnosed malignancies, colon and renal cell carcinoma, respectively, both gave birth to babies with congenital Wilms' tumour. We found no previous reports of similar associations and there was no evidence of maternal exposure to drugs or carcinogens that could have accounted for either the maternal or the neonatal tumours. Similarly, there was no history of maternal ingestion of alcohol or hydantoin anticonvulsants[13 14] in any

of our cases of neonatal neuroblastoma or Wilms' tumour.

The treatment of neonatal cancer poses major management problems. Some lesions, like hemangioendothelioma of the liver, are of borderline malignant potential, while others, like neuroblastoma, may sometimes undergo spontaneous regression.[15] In the acute clinical setting the biological behaviour of the tumour is often unpredictable and the management of the patient can be controversial. This controversy is particularly common in cases of congenital neuroblastoma where death can occur from complications related to either treatment or disease.[16]

The use of chemotherapy in neonates is associated with a higher incidence of immediate complications, especially infections,[17] and chemotherapy can potentially affect the child's subsequent development. Radiotherapy, especially to immature tissues such as brain, lung, liver, kidney, and bone, can lead to major handicaps in survivors.[18] The review of our 43 long term survivors has not shown severe physical or mental disabilities. Irradiation is also implicated in the development of second malignancies.[19] Patients of all ages are at risk, but there is no evidence that younger children and neonates are especially vulnerable.[18] They are, however, at risk for many more years than adults who received similar treatment. Li and coworkers calculated that there is a 12% cumulative probability of developing a second cancer in an irradiated field in patients of all ages who survived five years or more after their first cancer.[19] So far, in 43 long term survivors of neonatal cancer we have documented only one case of thyroid carcinoma, which developed in an irradiated field. In patients with hereditary retinoblastoma who have a predisposing genetic risk for cancer the computed risk of second malignancies is considerable.[20]

We conclude that although neonatal malignancy is rare, a large percentage of the patients can be successfully treated and cured with little impairment to future well being. As the management of these patients poses great demands on both the parents and the physicians any proposed treatment and the risks should be thoroughly discussed with the parents before it is implemented.

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