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# Do infants with stage IV-S neuroblastoma need treatment?

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SUMMARY This study reports the results of treatment in 31 infants under age 12 months with stage IV-S neuroblastoma diagnosed between 1976 and 1979. All had small or undetected primary tumours associated with disease in one or more of the following sites: liver, skin, or marrow. The primary site was left adrenal (in 16), right adrenal (in 6), and other areas included paravertebral, mediastinum, and pelvis (in 5); in 3 the primary site could not be found. Distant disease was found in the liver (in 29), marrow (in 16), and skin (in 8). Other sites affected were pancreas, pleura, peritoneum, and regional nodes. Treatment varied according to the clinical course of the disease; most patients had very little. In 19 the primary tumour was resected, in 21 the liver was irradiated with a median dose of 450 rad, and 15 received chemotherapy in courses varying between 1 month and 1 year. Nine patients had resection of the primary tumour as their only treatment and all survive; a total of 16 patients had sites of disease which regressed spontaneously. Four of 31 patients died in the first 2 months despite vigorous measures, all from some complication of the disease or its treatment. The projected 2-year survival rate is 87%. Children with this 'special' pattern of widespread neuroblastoma fare well with little or no treatment unless early complications develop. In this study none died of late progression of their disease.

The staging system proposed for neuroblastoma by Evans *et al.* divided patients with disseminated disease into two subgroups termed stages IV and IV-S, S for 'special'.[1] The IV-S patients had primary tumours* that were stage I or II and involvement of the liver, skin, bone marrow (or a combination of these), without roentgenographic evidence of bone metastases. It was found that such children had a better survival rate than patients with stage IV—77% compared with 6%.[2] Subsequently it was shown that most patients were infants in the first months of life, that the majority survived with minimal treatment, and that a large percentage had evidence of spontaneous regression.[3] All three papers dealt with retrospective analyses of patients collected over a period of two decades. Since the concept was first suggested that there existed a special disease pattern with a good prognosis, we have had the opportunity to collect information on several such patients prospectively from our own experience and from colleagues. The IV-S character of these patients was established at the time of diagnosis, and the clinical course and treatment form the basis of this report.

* The term primary tumour is used to describe a neoplasm in one of the common sites of origin for neuroblastoma—that is, the adrenal gland, the sympathetic ganglia, the organs of Zuckerkandl, etc. 'Distant disease' or similar terms are used to designate neuroblastoma in other sites. It is not meant to imply that these children necessarily have primary tumours and metastases according to the usual pattern. In fact, we believe that the multiple tumours actually represent multifocal primary neoplasms.

## Clinical data

Since January 1976, 31 patients have been seen in 19 institutions (Apendix gives names of collaborating investigators and their institutions). The age of diagnosis ranged from the newborn period to 11 months with a median age of 2 months; 22 (71%) of 31 were 3 months of age or younger. Seventeen were girls and 14 boys; the female to male ratio was 1·2. The primary sites of involvement are shown in Table 1. Two patients had what appeared to be 2 primary tumours, in the adrenal and paravertebral regions and in the posterior mediastinum. The sites of disseminated disease are also listed in Table 1. The liver was affected in 29, the marrow in 16, and the skin in 8. Other sites of involvement not in the original classification of IV-S disease were: pancreas

Table 1 *Site of local and distant disease in 31 infants with stage IV-S neuroblastoma*

| *Local site* | | *Other organs affected* | |
|---|---|---|---|
| Left adrenal | 16 | Liver | 29 |
| Right adrenal | 6 | Marrow | 16 |
| Right paravertebral | 2 | Skin | 8 |
| Mediastinum | 2 (+2*) | Pancreas | 1 |
| Pelvis | 1 | Peritoneum | 1 |
| Unknown | 3 | Pleura | 1 |
| | | Regional nodes | 2 |

*2 patients had 2 primary tumours.

Table 2 *Type of treatment of the primary tumour and distant disease in 31 infants*

| *Primary tumour* | | *Distant disease* | |
|---|---|---|---|
| Initial removal | 16 | Liver, radiation therapy | 11 |
| Subsequent removal | 3 | Chemotherapy | 6 |
| Radiation therapy | 6 | Radiation + chemotherapy | 6 |
| None (3 unknown) | 6 | None | 6 |
| | | Marrow, chemotherapy | 8 |
| | | None | 8 |
| | | Skin, removal | 2 |
| | | Chemotherapy | 2 |
| | | None | 4 |
| | | Serosa, none | 1 |
| | | Pleura, chemotherapy | 1 |
| | | Pancreas, chemotherapy | 1 |

1, peritoneum 1, and pleura 1. Two patients had regional lymph node involvement. It is evident from the foregoing that many (21 of 31) patients were affected in more than one distant site: 16 had two sites, 3 had three, 1 had four, and 1 had five: liver, marrow, skin, pancreas (unbiopsied), and pleura.

Treatment varied according to the clinical course of the disease and the therapeutic philosophy of the physician. Most patients had little, if any, treatment (Table 2). The primary tumour was excised at diagnosis in 16 patients, and in an additional 5 some months after onset. Radiation to the primary tumour was given in 6 patients with doses of irradiation ranging from 400 to 700 rad. No treatment was given to the primary tumours of 4 patients because the site was unknown in 3, and 1 died before treatment could be given; the tumour will be removed electively in the remaining 2 some time in the future.

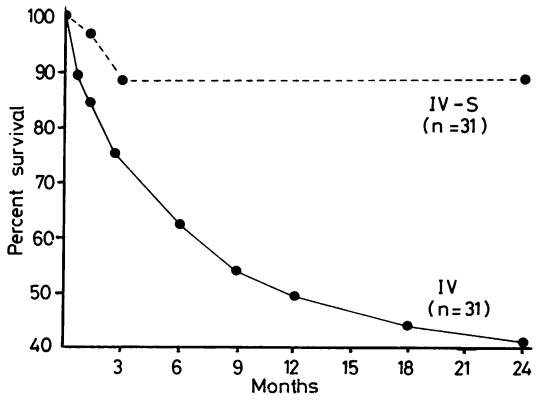


Figure *Survival of infants with disseminated neuroblastoma diagnosed during the first year of life.*

Disease in the liver was irradiated in 11, and chemotherapy was given to 6. Six patients were given combined chemo- and irradiation therapy, and 6 received no treatment. The dose to the liver ranged from 200 to 1200 rad with a median of 450. Of the 6 patients treated with chemotherapy, cyclophosphamide was used in 4, cyclophosphamide with vincristine in 1, and cyclophosphamide, vincristine, plus imidazole carboxamide in 1. The duration of chemotherapy varied between 1 month and 1 year. Half of the patients with marrow disease received chemotherapy and half had no treatment. The skin lesions were excised in 2 patients, treated with chemotherapy in 2, and 4 had no treatment. The patient with a presumed pancreatic nodule and the pleural foci responded to two 10-day courses of cyclophosphamide, the serosal lesion was not treated.

Nine patients had no treatment other than removal of the primary tumour, and all survived. These 9 had disease in the liver only (3), liver, marrow, and serosa (1), liver and marrow (1), liver and skin (2), and skin only (2). There were 6 additional patients who showed evidence of spontaneous regression of at least one tumour site, all 6 had disease in the marrow and 1 had skin lesions too. In all, these 15 patients had 19 sites of disease which were untreated and regressed spontaneously (Table 2).

The 31 patients of this report have been followed up for between 2 and 40 months. Four have died, 8 are alive with regressing disease from 2 to 12 months from the time of diagnosis, and 19 are alive without evidence of disease 9 to 40 months after onset. By life table analysis, the survival rate at 2 years is 87%. All 4 deaths occurred in the first 2 months despite vigorous treatment, 1 with renal failure, 1 of infection, and 2 with respiratory failure. Some area of disease progressed and required initiation of treatment or change of regimen in 5 additional patients and all are alive; 3 are disease-free at 40, 36, and 24 months, and 2 still have discernible disease at 12 and 17 months.

## Discussion

Early reports of stage IV-S disease were subject to criticism because each was a retrospective review of patients seen over a period of decades. Unconscious bias could colour such analyses in that only the

patients who survived or had unusually protracted courses were identified, and those who died early were grouped with the stage IV children and thus were masked from the reviewer. These problems were largely avoided in these 31 patients. Information on them was collected for a relatively brief period by one observer and the IV-S designation was agreed at the time of diagnosis before the long-term clinical course had become manifest.

Another doubt expressed concerning the 'natural history' of such patients is that the age rather than the pattern of disease *per se* is the more important factor. Certainly infants with stage IV disease fare better than older children with similarly advanced disease. This is documented by the data reported by Breslow and McCann[2] who found survival of stage IV patients under 1 year of age to be 27% compared with 5% for those older than 1 year. Finklestein *et al.*[4] reported a 50% survival in 13 stage IV infants diagnosed between 1971 and 1975. These two groups are combined and their survival experience compared with the 31 IV-S patients described here. At 2 years the survival is 42% compared with 87%.

Stage IV is rare in infants, there being merely 18 among the 136 patients with metastatic (non IV-S) tumour reported by Breslow and McCann.[2] During the period of this study one of us has treated or been consulted about 7 infants with stage IV tumours, 5 of whom are dead. Their ages ranged from newborn to 11 months. Four mimicked IV-S disease, having liver or skin lesions, but they were clearly stage IV in that there was *x*-ray evidence of bone metastases. Three of these 4 died soon after diagnosis (1 to 5 months), and 1 is alive with disease. One of the other 3 'classic' stage IV patients is alive in clinical remission 5 months after diagnosis and the other 2 died of progressive disease.

Whether the disseminated foci in these patients represent metatastic involvement or multicentric primary tumours (a special form of neurocristopathy) is unknown and is discussed at greater length elsewhere.[5]

Not all the IV-S patients fare well. Nine of the 31 patients here reported had continued growth or spread of disease after initial treatment and 4 died. Six of the 9 were 1 month of age at diagnosis, and the very young infant seems vulnerable to the mechanical complications caused by a greatly enlarged liver. Such complications are raised diaphragms leading to respiratory problems, compression of the inferior vena cava and renal vasculature with resultant kidney failure, gastric compression or hepatic dysfunction with secondary haemorrhagic problems resulting from compression of liver lobules by tumour growth. It is striking that none of the children developed icterus until late in the course of the disease despite massive hepatomegaly often being present at diagnosis or soon after. It is also clear that these children differ from the usual picture of late stage IV disease where emaciation, bone pain, proptosis, and other tumour masses become evident at scattered sites. The 4 children who died from hepatic involvement were vigorously treated to reverse the mechanical problems described above, but nonetheless died from the complication of hepatic tumour size or its treatment rather than from the spread of cancer. All 4 who died did so in the first 2 months. It appears characteristic of the syndrome that the tumour grows rapidly in some patients before it undergoes spontaneous regression. If tumour growth can be arrested during this initial phase late recurrences leading to death are rare.

The 5 patients with progressive disease that did respond to treatment were all 1-month old when first seen and were apparently still in the first phase of the disease (before the natural regression). Two each developed a single skull lesion below a tumour in the scalp; both responded to treatment.

The most striking aspect of this group of patients however, is not that 9 of 31 had some form of progressive disease, but that 15 had spontaneous regression of neuroblastoma at at least one site, most often marrow (8) or liver (6). The marrow infiltration was not heavy in the 6 preparations reviewed but were undoubtedly tumour clumps; they were not activated lymphocytes which must be differentiated from isolated tumour cells.[6]

So far in this group of patients there have been no late relapses, although many have been followed only for a short period.* Such late relapses have been reported, both recurrent primary disease and bone metastases;[7–9] this is a rare phenomenon and we have not met it.

Some conclusions regarding treatment can be drawn from this review. Treatment should be directed to life-threatening complications such as respiratory or renal problems resulting from an enlarged liver. This can generally be accomplished by radiation therapy through across-table opposing lateral ports angled slightly (about 15°) above the horizontal to avoid the spine, kidneys, and ovaries in the girls. The dose of 450 rad (150 rad midplane per day × 3) has been found to be effective. Stressing the point that treatment is used to initiate normal spontaneous regression are the facts that (1) the dose used is hardly in the range usually considered curative, and (2) not all the liver need be included in the beam in order to achieve the total tumour regression in the liver. A large Silastic patch may be inserted in the abdominal wall if the radiation

*Since submitting this paper one patient developed bone metastases 14 months after diagnosis and died at 16 months.

response is not prompt and may provide decompression while awaiting the expected liver regression, which can take 2 to 3 weeks to occur.[10] If still further treatment is needed, we prescribe low-dose oral cyclophosphamide 5 mg/kg a day for 5 days and then interrupt treatment for 2 to 3 weeks to allow liver regression to take place. This can be repeated if no effect is seen but we do not give additional treatment once regression has been initiated. Sometimes it is difficult to decide whether treatment is indicated in an infant with hepatomegaly causing discomfort and other problems. The potential late deleterious effect of chemo- and radiotherapy remains to be defined in these very young patients and must be weighed against the gains obtained by hastening the regression. Indications for treatment other than life threatening complications could be hypertension, inadequate oral intake, vomiting, or other associated problems requiring prolonged time in hospital.

It is our practice to remove the primary tumour at some time during the course because it is known that it may grow despite regression of distant disease. Treatment of the primary tumour can be postponed if the liver size suggests that the surgery could be complicated until the clinical course has stabilised and partial regression taken place.

It is evident from the above that we believe these patients should be treated only when vital function is threatened by local tumour growth and that otherwise they probably require no treatment. Indeed it may well be that treatment is detrimental in disrupting normal host defences against infection and possibly to tumour growth itself in this extraordinary clinical setting. It is also evident from the clinical course of these 31 children and others described previously that there is a special group of patients with disseminated neuroblastoma who have an excellent survival expectancy but who require individual attention and careful management by experienced personnel.

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**Appendix** *Investigators and institutions contributing patients to the review*

| *Investigator* | *Institution* |
|---|---|
| A J Altman | University of Connecticut, Farmington, CT |
| E Baum | Children's Memorial Hospital, Chicago, IL |
| M L Brecher | Rosewell Park Memorial Institute, Buffalo, NY |
| R L Chard | Children's Orthopedic Hospital, Seattle, WA |
| A E Evans | Children's Hospital of Philadelphia, Phila., PA |
| S Gross | Rainbow Babies Hospital, Cleveland, OH |
| E I Hatch | Egleston Hospital, Atlanta, GA |
| R M Heyn | University of Michigan, Ann Arbor, MI |
| G R Honig | Children's Memorial Hospital, Chicago, IL |
| J J Hutter | University of Arizona, Tucson, AZ |
| P H Kelker | Children's Clinic, Los Alamos, NM |
| S Kisker | University of Iowa Hospital, Iowa City, IO |
| D M Komp | University of Virginia, Charlottesville, VA |
| S S Rinsler | The Health Place, 73 Broadway, Rensselaer, NY |
| D G Tubergan | Denver children's Hospital, Denver, CO |
| A Sitarz | Babies Hospital, New York, NY |
| N Shah | Geisinger Clinic, Danville, PA |
| S Siegel | Children's Hospital of Los Angeles, Los Angeles, CA |
| L A Somers | St. Christopher's Hospital, Philadelphia, PA |
| R Wimmer | St. Christopher's Hospital, Philadelphia, PA |
| J A Wolff | Babies Hospital, New York, NY |
| H Zusman | Tulane University, New Orleans, LA |