Bahrain Medical Bulletin, Vol. 20, No. 2, June 1998

Congenital Neuroblastoma. A Study of 34 Cases Treated Between 1986-1994 in U.K

Isam Haddadin, MD*, Annable Foot, MD*, Hiyam Shamon,MD*

Objective: To collect data on congenital neuroblastoma with respect to their presentation, investigations, treatment and outcome.

Method: The records of 34 neonates with neuroblastoma registered in UKCCSG between 1986-1994 were reviewed. The diagnosis was made by histological examination in 27 patients and elevated vanillymandelic acid (VMA), with ultrasonography (U/S) in 7 patients. Prenatal U/S diagnosis was done in 5 cases. Treatment was given according to Evans and International Neuroblastoma Staging System (INSS); Surgery for stages I & II. Surgery + chemotherapy for stages III & IV and for stage IV-s was varied according to the progression of the disease.

Results: The overall disease free survival for 34 neonates is 91% at 104 months post diagnosis. Three neonates died (2 with stage IV and 1 with stage IV-s). The remaining 6 patients have a residual damage due to the disease itself or due to side effect of the treatment.

Conclusion: The prognosis of congenital neuroblastoma is very good compared with that of older children. Therefore we need to define the high risk patients by doing some biological studies so as not to over-treat the good risk group and to minimize the side effect of the treatment.

Bahrain Med Bull 1998;20(2):38 - 40.

Malignant tumours are rare in the neonatal period (first 28 days of life). The reported incidence is 36.5 per million live birth[1]. Neuroblastoma is a malignant embryonal tumour that arises from the adrenal gland or any site containing autonomic nervous system fibers in the abdomen, thorax, cervical and pelvic region[2,3]. It is considered to be the most common malignant tumour in this age group. Neuroblastoma according to Evans and INSS is classified into five stages[4]. The prognosis gets progressively worse from stage I to stage IV with stage IV-s lying between them. Stage IV-s is defined as local stage I or II with liver, bone marrow and cutaneous metastases. Stage IV-s has sometimes spontaneous regression below the age of one year, while in other patients it may progress rapidly and the outcome is not good[5,6]. Regarding age, it is assumed that younger children have better outcome than older children[7].

Prenatal diagnosis of neuroblastoma by U/S was first reported by Fenart et al and Sones in 1983. Since then, there have been several additional case reports of prenatal U/S diagnosis during the third trimester of pregnancy[8]. This paper reviews the presentation and outcome of 34 neonates found to have neuroblastoma during 9 years period in United Kingdom.

METHODS

The records of 34 neonates (0-28 days) with neuroblastoma registered between 1986-1994 were reviewed from 13 centres in UK. Information obtained regarding the location of the primary tumour, metastatic disease, histology, catecholamine excretion, treatment modalities and outcome. The diagnosis was made by excisional biopsy of the primary tumour, skin nodules, liver metastases, finding at time of surgical exploration and after resection. Both elevated VMA in the urine and imaging of the primary tumour were considered as diagnostic tools. In a small proportion of patients serum ferritin and LDH, N-myc gene amplification were available.

The 34 neonates were divided into five groups according to Evans classification until 1992 and later on by INSS. We studied each group with respect to clinical presentation, management and outcome. The treatment was in the form of surgical resection of the primary tumour in stages I and II. Chemotherapy was used in stage III and IV in the form of vincristine and cyclophosphamide or in some cases modified OJEC (vincristine, carboplatin, VP16 and cyclophosphamide). Surgical resection of the primary tumour at diagnosis or later until tumour shrinkage following a few courses of chemotherapy. The management of stage IV-s varied from no chemotherapy and close follow up to surgical excision of the primary tumour, chemotherapy and radiotherapy for huge hepatomegaly.

RESULTS

The median age of the 34 neonates with congenital neuroblastoma at the time of diagnosis was 12 days (range: birth - 28 days). There were 18 males and 16 females with a male:female ratio of 1.1:1.0. The period of follow-up ranged from birth to 104 months with a median of 42 months. The patients were divided into five stages according to Evans and INSS Staging Systems. Stage I in 4 (11.8%) patients, Stage II in 5 (14.7%) patients, Stage III in 7 (20.6%)

* Paediatric Oncologist
P O Box 926119
Amman, Jordan

patients, Stage IV in 4 (11.8%) patients and Stage IV-s in 14 (41.1%) patients (Table 1).

Table 1. **Main presentation of the 34 patients**

Stage	*%*	*1 site*	*Presentation*
Stage I = 4	11.8	Adrenal (3) Spine (1)	Mass
Stage II = 5	14.7	Adrenal (2) Spine (3)	Mass LL weakness
Stage III = 7	20.6	Adrenal (1) Spine (5) Thorax (1)	LL weakness Mass
Stage IV = 4	11.8	Adrenal (3) Thorax (1)	Mass Hydrops
Stage IV-s = 14	41.1	Adrenal (12) Liver (1) Skin (1)	Mass Hepatomegaly Nodules
Total = 34	100.0		

The main presenting symptoms were abdominal mass that was discovered on routine physical examination by a paediatrician as seen in Stages I and II, while in Stage II a palpable abdominal mass with lower limb weakness was the mode of presentation. The more severe symptoms such as respiratory distress due to abdominal distension and hydrops fetails were present in Stage IV. Hepatomegaly with abdominal distension was a prominent sign with or without skin nodules in Stage IV-s (Table 1).

The site of the primary tumour was in the adrenal gland in 21 (62%) neonates, spine at neck, thorax and abdomen in 11 (32%) neonates and one in the liver with another involving the skin. The metastases in stage IV was to the liver, bone, lung, brain, bone marrow and skin (Table 1). The prognostic factors that were considered in the patients were: serum ferritin (in 8 patients), LDH (in 5 patients), N-myc gene amplification (in 6 patients) and 4 showed increased copies of gene amplification from 1 to 5. Urinary catecholamines (VMA) was measured in 32 patients and the level was elevated in 25 (78%) patients as shown in Table 2.

Table 2. **Laboratory investigations in the 34 neonates**

	Done	*Elevated**
Serum Ferritin	8	6
LDH	5	4
VMA	32	25
N/myc	6	4

* *Ferritin > 200 ng/ml, LDH > 400 U/L, Urine VMA > 10 ug mol/d, N-myc gene 1-5 copies*

A pre-natal diagnosis by ultrasonography was performed on 5 patients (2 in Stage I, 2 in Stage IV and 1 in Stage III). Tissue diagnosis was made either by biopsy obtained, after surgical resection of the primary tumour or post mortem examination on 27 patients. The diagnosis by ultrasonography and elevated VMA was made on 7 patients, mainly of the Stage IV-s, the details of which are shown in Table 3.

Table 3. **Basis of diagnosis and stages**

Stage		Histology	U/S + VMA
Stage	I = 4	3	1
Stage	II = 5	5	-
Stage	III = 7	7	-
Stage	IV = 4	3	1
Stage	IV-s = 14	9	5

Surgical resection of the primary tumour was the main treatment in Stages I and II. A combination of chemotherapy and surgical resection in both Stages III and IV - one newborn baby died shortly of renal failure after the start of chemotherapy (Cyclophosphamide and Vincristine) and another one born dead and the post mortem examination revealed disseminated neuroblastoma in multiple organs. An autologuos bone marrow transplantation (BMT) was performed on one patient (Stage IV) 15 months after the diagnosis and a follow-up at 31 months post BMT showed no recurrence of the disease. In Stage IV-s the treatment was varied from one hospital to another. Some used Cyclophosphamide alone or with Vincristine where others used a modified OJEC based on the severity and progress of the disease[9]. Radiotherapy for severe hepatomegaly was used in one patient and no treatment given to 5 patients as there was no progress of the disease (Table 4). One newborn died during surgery for the insertion of central venous catheter.

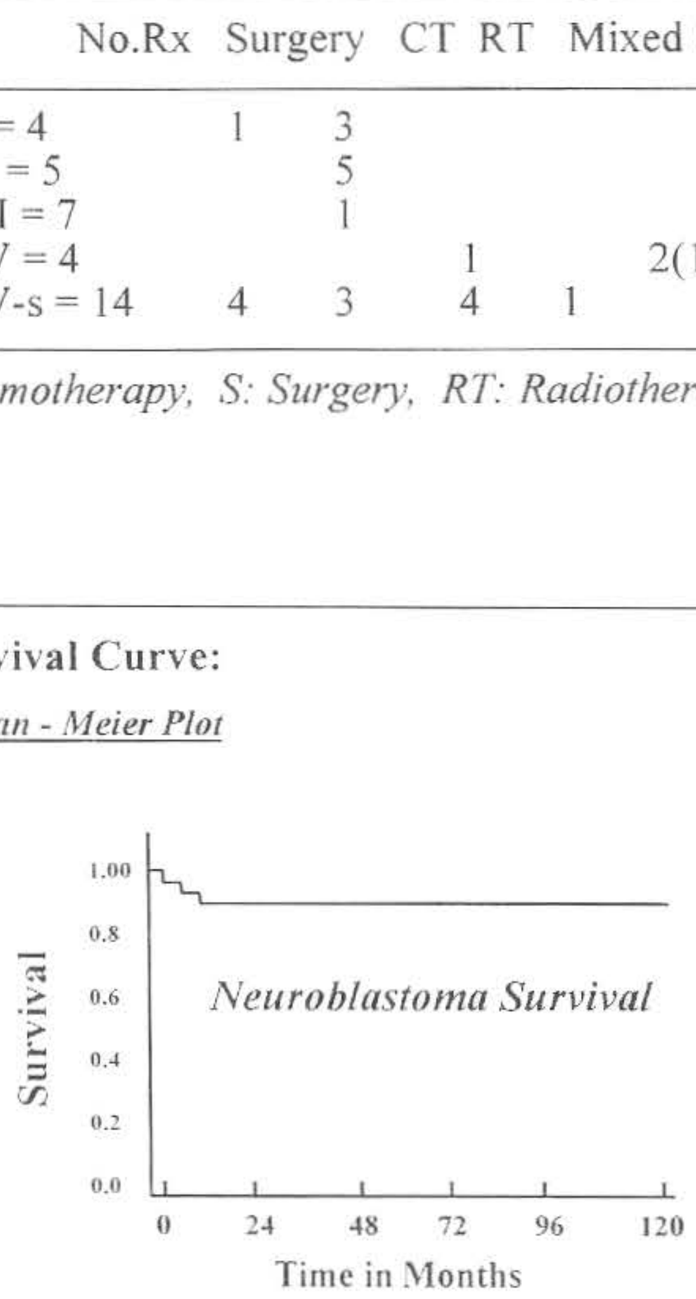
Table 4. **Treatment of the 34 patients**

Stage	No.Rx	Surgery	CT	RT	Mixed S + CT
Stage I = 4	1	3			
Stage II = 5		5			
Stage III = 7		1			6
Stage IV = 4			1		2(1 ABMT)
Stage IV-s = 14	4	3	4	1	1

CT: Chemotherapy, S: Surgery, RT: Radiotherapy

Survival Curve:

Kaplan - Meier Plot



The long term sequelae of the disease itself, surgery and side effects of chemotherapy were seen in 6 patients (4 lower limbs weakness, 1 high tone deafness and 1 scoliosis). The survival curve showed 91% at 104 months post diagnosis.

DISCUSSION

Neonatal cancer accounts for about 2% of paediatric cancer and neuroblastoma comprising 47% of these[10]. As the incidence of malignant tumours in the neonatal period is low, data will be very scant. Few centres collected data about neonatal cancer. For example, St.Jude research hospital found 19 out of 34 neonates had neuroblastoma between 1962-1988[1]. Also, the Italian Cooperative Group on Neuroblastoma registered 183 cases under 1 year of age over 10 years period, with only 14 (7%) cases in the neonatal period[7]. In UK the review of all cases during 9 years period (1986-1994) showed that the most frequent anatomical site of the primary tumour is the adrenal gland, 21 (62%) cases and the main presenting sign is abdominal mass followed by spinal site, 11 (32%) cases, with no difference in the survival between the two mentioned sites. However, paraspinal or intraspinal extension of the tumour did not worsen the prognosis although it left some residual damage[11].

Age is considered the most important prognostic factor and it is inversely proportional to the survival rate[12]. Many series have documented that children below the age of one year have better survival than older ones[7]. In our series the survival curve showed 91% at 104 months post diagnosis. This also supports the fact that neuroblastoma is virtually congenital and that the difference in age at diagnosis reflects the difference in growth rate of the tumour, thus age may be a measure of the probability of micrometastases in addition to the clinical extent or stage of the disease[13].

Disease stage at presentation also is considered an important factor, since stage I & II after surgical resection have excellent prognosis while for stage IV-s the survival is also good even without treatment in some cases. The disease may progress to stage IV and the analysis of some biological factors such as DNA contents and N-myc gene amplification may identify these risk groups[14-16]. The five years survival of stage IV neuroblastoma above the age of 1 year is about 20% and below the age of one year is 60%. The latter figure is approximately similar to stage IV in our series (2 died out of 4). This means that the age and stage at diagnosis are still important influencing factors on the survival. Urinary Catecholamine (VMA) is important for the diagnosis and follow up. 7 cases were diagnosed according to elevated VMA and U/S findings. it is not necessary to have 24 hr urine collection to measure VMA as some authors concluded that spot urine collection is sufficient to diagnose neuroblastoma[2]. VMA is a measure of tumour activity and in most of our neonates the catecholamine follow-up levels returned to normal after treatment. Serum ferritin, LDH and N-myc gene are elevated in the majority of cases but were done only in few cases. The finding of a solid or cystic suprarenal mass by prenatal U/S is suggestive of congenital neuroblastoma, although adrenal abscess or cyst and renal anomalies are included in the differential diagnosis[17]. We diagnosed 5 cases by U/S antenatally and more cases could have been detected if the test was asked for before birth. This will encourage the diagnosis of congenital neuroblastoma antenatally in order to permit planned delivery and prompt neonatal treatment.

CONCLUSION

We conclude from this review that the prognosis is verygood in congenital neuroblastoma compared with that of the older children and the treatment modalities mainly depend on the initial clinical presentation and the progression of their disease. Therefore, this raises the need to define the high risk patients by doing some biological studies so as not to over treat the good risk group and minimise the side effect of the treatment.

REFERENCES

1. Crom DB, Wiliams JA, Green AA, et al. Malignancy in the neonate, Med Pediatr Oncol 1989;17:101-4.
2. Lowis SP, Draft AW. Neuroblastoma in 1993. Current Paediatrics 1993;3:114-21.
3. Candito M, Thyss A, Albertini M, et al. Methylated Catecholamine Metabolites for Diagnosis of Neuroblastoma. Med Pediatr Oncol 1992;20:215-20.
4. Carlsen NLT, Christensen IJ, Schroeder H, et al. Prognostic value of different staging systems in Neuroblastoma and completeness of tumor excision. Arch Dis Child 1986;61:832-42.
5. Wilson PCG, Coppes MJ, Solh H, et al. Neuroblastoma stage 4-s: A heterogenous disease. Med Pediatr Oncol 1991;19:467-72.
6. Haas DBA, Ablin AR, Miller C, et al. Complete pathologic maturation and regression of stage 4-s Neuroblastoma without treatment. Cancer1988; 62:818-25.
7. De Bernard B, Di Tullio MT, Di Montezemolo LC, et al. Neuroblastoma under one year of age. Contrib Oncol 1990;41:118-28.
8. Ho PTC, Estroff JA, Kozakewish H, et al. Prenatal detection of Neuroblastoma: A ten year experience from the Dana Farber Cancer Institute & Children's Hospital. Pediatrics 1993;92:358-63.
9. Shorter NA, Davidoff AM, Evans AE, et al. The role of surgery in the management of stage 4 Neuroblastoma: A single institution study. Med Pediatr Oncol 1995;24:287-91.
10. Campell AN, Chan HSL, O'brien A, et al. Malignant tumours in the neonate. Arch Dis Child 1987;62:19-23.
11. Munro FD, Carachi R, Fyfe AHB. Congenital Neuroblastoma presenting with paraplegia. Arch Dis Child 1991;66:1246-7.
12. Stephenson SR, Cook BA, Mease AD, et al. The prognostic significance of age and pattern of Metastases in stage 4-s Neuroblastoma. Cancer 1986;58:372-5.
13. Carlsen NLT, Christensen IBJ, Schroder H, et al. Prognostic factors in Neuroblastoma treated in Demark from 1943-1980. Cancer 1986;58:2726-35.
14. Hayashi Y, Inaba T, Hanada R, et al. Similar chromosomal patterns and lack of N-myc Gene amplification in localised stage 4-s Neuroblastomas in infants. Med Pediatr Oncol 1989;17:111-5.
15. Suarez A, Hartmann O, Vassal G, et al. Treatment of stage 4-s neuroblastoma: A study of 34 cases treated between 1982-1987. Med Pediatr Oncol 1991;19:473-7.
16. Ohnume N, Takahahi H, Kaneko M, et al. Treatment combined with bone marrow transplantation for advanced Neuroblastoma: An analysis of patients who were pretreated intensively with the protocol of the study group of Japan. Med Pediatr Oncol 1995;24:181-7.
17. Martinez-Mora J, Castellvi A, Coroleu W, et al. Cystic adrenal neuroblastoma: A prenatal diagnosis by ultrasonography. Med Pediatr Oncol 1995;24:109-15.