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Neurological Complications of Childhood Malignancies

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Summary

Between Jan 1982 to Jun 1994, 154 children with malignant non-central nervous system tumors, excluding leukemias and lymphomas, were admitted and treated at the UKMC. Fifty-one (33%) of these cases suffered with 64 neurological complications during the course of their diseases. Nine cases suffered with multiple neurological complications. Nervous system metastasis was the most common neurological complication (n = 24; 15.6%), which was followed by nervous system infection (n = 17; 11%). Twelve (7.7%) cases had treatment related peripheral or cranial neuropathies. Seven (4.5%) cases had new onset of grand-mall seizures. One case had paraneoplastic syndrome, one case had panhypopituitarism secondary to whole brain radiation, and one case had Horner's syndrome secondary to tumor removal. Ten cases suffered with neurological sequelae secondary to neurological complications. Three of these cases suffered with developmental delay and mental retardation. Fifty-one patients with neurological complications were followed for 9 to 102 months. While 30 (19.7%) patients were alive, 20 (13%) patients died and one case was lost during the analysis of the results. Neuroblastoma/ganglioneuroblastoma has the highest rate for causing neurological complication.

In conclusion: neurological complications were seen on 33% of childhood solid malignant tumors. Nervous system metastasis had the worst prognosis and the most frequent neurological complication. Neurological complications did not increase the mortality rate, but one-third of surviving patients with neurological complications suffered with neurological sequelae.

Keywords: Children; malignant tumor; brain metastasis; neuropathy; seizures.

Introduction

The incidence of neurological complications from systemic cancer has been increasing because of improved survival of patients with cancer. As many as two thirds of all cancer patients develop some type of neurological problem during the course of their illness. These complications range in seriousness from relatively trivial to fatal. Neurological complications can be caused by direct involvement of metastatic tumor or by indirect causes related in some way to the systemic tumor or its treatment. Neurologic complications of systemic cancer are categorized as metastatic complications (brain metastases, metastatic epidural spinal cord compression, leptomeningeal metastases, metastases to peripheral nerves or nerve plexus) and non-metastatic complications (metabolic encephalopathies, neurological infections, cerebrovascular complications, paraneoplastic syndromes and treatment related complications) [17].

Although neurological complications of systemic cancer in adult population has been very well documented [4, 7, 17, 19], neurological complications of childhood solid malignant tumors have been rarely described [1] and most of the studies focused on brain metastases [2, 8, 29].

In this study, we retrospectively reviewed the 51 pediatric solid malign tumor cases with neurological complications, discussed the outcome and influence of the neurological complications on the survival.

Patients and Methods

Between Jan 1982 to Jun 1994, 242 children with solid malignant tumors, excluding leukemias and lymphomas, were admitted and treated at the UKMC. Among these 242 cases, 88 (36.6%) children had primary central nervous system (CNS) tumors and 154 cases (63.7%) had malignant non-CNS solid tumors.

Seventy-four of these 154 cases were male, 80 patients were female. The male : female ratio of 51 cases with neurological complications (complication group) was 25 : 26, and the male : female ratio of the non-complication group was 49 : 54. The ages of 154 cases ranged from 0 to 18 years. The mean age of complication group was 4.9 years and the mean age of non-complication group was 8.4 years.

Results

Among these 154 children with non-CNS solid malignant tumors, 51 (33%) cases suffered with 64 neuro-

Table 1. *Numbers and Types of Neurological Complication of 51 Cases*

Number and types of neurologic complications							
Tm. Path.	NSM	NSI	ME	CVC	PNPS	TRC	Total
Sarcomas	6	8	2	–	–	5	21
WT	2	2	1	–	–	1	6
NB-GNB	14	4	2	1	1	5	29
GCT	–	1	–	–	–	2	3
RB	–	1	–	–	–	–	1
HCC	1	1	–	–	–	1	3
MM	1	–	–	–	–	–	1
TC	–	–	–	–	–	–	–
Others	–	–	–	–	–	–	–
TOTAL	24	17	5	1	1	14	64

Tm. Path Tumor pathology; *NSM* Nervous System Metastasis; *NSI* Nervous System Infections; *ME* Metabolic Encephalopathy; *CVC* Cerebrovascular complications; *PNPS* Paraneoplastic syndrome; *TRC* Treatment related complications; *WT* Wilms' Tumor; *NB* Neuroblastoma; *GNB* Ganglioneuroblastoma; *GCT* germ cell tumor; *RB* Retinoblastoma; *HCC* Hepatocellular carcinoma; *MM* Malignant melanoma; *TC* Thyroid Carcinoma.

logical complications during the course of their disease (Table 1). Nine cases had multiple neurological complications (up to 3 complications per case) (Table 2). Five of 19 Wilms' tumors, 22 of 32 neuro/ganglioneuroblastomas, 17 of 49 sarcomas, 2 of 6 malignant liver tumors, 3 of 10 germ-cell tumors, 1 of 7 retinoblastomas, and 1 of two malignant melanomas caused neurological complications. None of the 9 cases with thyroid cancer caused neurological complication (Table 3). Among these childhood malignancies NBs had the highest rate for causing the neurological complication.

Metastatic Complications

Nervous system metastasis was the most common neurological complication (n = 24) (Table 4) which was followed by nervous system infection (n = 17) (Table 5). Symptomatic (12 cases), and non-symptomatic (5 cases) spine metastases (total 17 cases; 11%) were characterized with epidural space and/or spinal column involvement. Eight cases had invasion of spinal epidural space by primary malignancies. While 4 of the 8 cases with spinal epidural invasion were primary spinal column sarcomas, 4 cases were NB-GNB. Symptomatic spinal column metastases were characterized with progressive neurological deficit, due to epidural spinal cord compression. Eight cases received laminectomy, gross total or subtotal tumor resection and spinal fusion operations. Among the 12 symptomatic cases, six of them were alive during their last follow-up. None of these 17 cases with spine metastases showed intradural or intramedullary invasion or metastases. Symptomatic (n = 10) and non-symptomatic (n = 2) cranial metastases were characterized with skull, dura mater and brain parenchyma involvement. Seven of these 10 symptomatic cranial metastases had single or multiple parenchymal lesions. Four of these 7 cases were treated with craniotomy and metastatic lesion(s) removal. Since they were in terminal stage, surgical interventions of the other 3 cases were declined by the families. Six of these 7 cases with brain metastases died due to relapse or progression of intracranial disease. Only one case who had neuroblastoma and single brain metastasis treated with chemotherapy and radiotherapy survived one year following diagno-

Table 2. *Pathology and Number of Patients with Multiple Neurological Complications*

Treatment related complications								
T. Pat	NSM	CVC	ME	Surgery	CT	XRT	NSI	T
HCC	brain metastasis				$B8^{th}$NNP-CPr			2
WT					PNP-Vr		VZ Inf.	2
NB	spine metastasis				$B8^{th}$NNP-CPr			2
NB	spine & skull metastasis						VZ Inf.	2
NB	skull metastasis				$B8^{th}$ NNP-CPr	PHP		3
ERMS	plexus invasion						HZ Inf	2
ERMS					PNP-Vr		HZ Inf	2
ES					PNP-Vr		HZ Inf	2
RMS					PNP-Vr		HZ Inf	2

T. Pat Tumor pathology; *NSM* Nervous System Metastasis; *inv* Invasion; *NSI* Nervous System Infections; *ME* Metabolic Encephalopathy; *CVC* Cerebrovascular complications; *CT* Chemotherapy; *XRT* Radiotherapy; *WT* Wilms' Tumor; *NB* Neuroblastoma; *HCC* Hepatocellular carcinoma; *ERMS* Embryonal Rhabdomyosarcoma; *ES* Ewing's sarcoma; *RMS* Rhabdomyosarcoma; *PNP-Vr* peripheral polyneuropathy-vincristine related; *HZ Inf* herpes zoster infection; *VZ Inf* Varicella zoster infections; *B 8^{th} NNP-CPr* Bilateral 8^{th} nerve neuropathy-cisplatinum related; *PHP* panhypopituitarism.

Table 3. *Histopathologic Diagnosis and Neurologic Complication Rates of 154 Cases*

Histopathologic diagnosis and complication rates of the solid tumors	Number of cases With complications and incidence	Number of cases without complications and incidence	Incidence and total number of cases according to 154 cases
WT 30%	5 cases 3.2%	14 cases 9%	19 cases 12.3%
NB-GNB 66.6%	22 cases 14.3%	10 cases 7.1%	32 cases 20.8%
S 34.7%	17 cases 11%	32 cases 20.8%	49 cases 31.8%
LC 33.3%	2 cases 1.3%	4 cases 2.6%	6 cases 3.7%
GCT 30%	3 cases 1.9%	7 cases 4.5%	10 cases 6.5%
RB 14.3%	1 case 0.6%	6 cases 3.7%	7 cases 4.5%
MM 50%	1 case 0.6%	1 case 0.6%	2 cases 1.3%
OM –	– –	20 cases 13%	20 cases 13%
TC –	– –	9 cases 5.7%	9 cases 5.7%
Total	51 cases 33%	103 cases 67%	154 cases 100%

WT Wilms' Tumor; *NB* Neuroblastoma; *GNB* Ganglioneuroblastoma; *S* Sarcomas (soft tissues and osseous); *LC* Liver cancers; *GCT* germ cell tumor; *RB* Retinoblastoma; *MM* Malignant melanoma; *OM* Other malignancies; *TC* Thyroid Carcinoma.

sis of intracranial lesion and the patient died with progression of primary disease. Histopathologic diagnoses were obtained in 4 cases. The other three cases were diagnosed with contrast enhanced axial CT scans of brain.

Metastasis or invasion of nerve plexus were seen in 3 cases. All of these cases had multiple neurological complications. The case with embryonal rhabdomyosarcoma (ERMS) originated from presacral region had unilateral lumbosacral plexus invasion, and the case with NB originated from presacral region had unilateral brachial plexus metastasis along with unilateral lumbosacral plexus invasion. The third case was primary C4 body osteosarcoma, and caused unilateral brachial plexus invasion. Among the 24 cases with nervous system metastases, 5 cases had cranial and spinal involvement, and 1 case had spinal, cranial and nerve plexus involvement.

Non-Metastatic Complications

Among the 17 cases with nervous system infection (Table 5), six of them had multiple neurological complications. Five cases had varicella zoster and 12 cases had herpes zoster infection during their chemotherapy. All cases improved with topical or i.v. acyclovir therapy.

Twelve cases had treatment related peripheral or cranial neuropathies (Table 6). Seven cases had vincristine related neuropathies. Six cases were improved following readjustment of vincristine dose. However one case never improved even after cessation of vincristine. Six cases had 8^{th} nerve neuropathy, secondary to cis-platinum chemotherapy, that was characterized with bilateral moderate to severe hearing loss. Following termination of cisplatinum treatment, only one case's hearing improved partially.

Seven cases had new onset of grand-mall seizures, due to hyponatremia, hypertension and brain metastasis (Table 7). One of these cases with multiple brain metastases died following status epilepticus. Seizures, controlled with antiepileptic medications, correction of fluid-electrolyte imbalance, and antihypertensive treatment. One case (1.9%) had paraneoplastic syndrome characterized with opsoclonus-myoclonus treated with cortisone and i.v. gamma globulin (Table 7). One case had iatrogenic Horner's syndrome secondary to tumor removal located in the upper mediastinum (Table 6).

Follow-up and Outcome

Among the 154 children, 103 cases did not have neurological complications and were followed for 17 to 75 months. Sixty-one (39.6%) patients were alive, 19 (12.3%) cases were lost and 23 (15%) patients died, during the analysis of results. Fifty-one patients had neurological complications and were followed for 9 to 102 months. While 30 (19.7%) patients were alive, 20 (13%) patients died and one case was lost during the analysis of the results (Table 8). Among the 24 cases who had nervous system metastases or invasion, 14 cases died and 12 of these cases survived less than a year after diagnosis. All cases with parenchymal brain metastases died due to neurological complication. Only 8 cases with nervous system metastasis were alive at the end of the follow-up period. Six of these cases had spinal column involvement, and 2 cases had skull metastases.

While the mean follow-up for 30 survivors who had

Table 4. *Outcome of the Neurologic Complication Characterized With Nervous System Metastasis*

Case # age, sex, loc., pathology	Type of metastasis	Treatment of complication	Outcome of complication	Outcome of the primary disease
1* 6, M, HCC	brain-parenchymal	craniotomy + CT + XRT	progressed	died 22 days after craniotomy
2 6, M, WT	brain + multiple skull metastases	CT + XRT	progressed	died 26 days after craniotomy
3 3, M, WT	brain parenchyma + T10 vertebra	CT + craniotomy	progressed	died 2 months after craniotomy
4 16, M, MM	brain parenchyma metastases	CT + craniotomy ×2	progressed	died 4 mos after 2nd craniotomy
5 8, M, LMAS	brain parenchymal	XRT + craniotomy	progressed	died 35 days after craniotomy
6* 16, M ERMS	lumbosacral plexus invasion	CT	improved	died
7 1, F, L4 MCS	L1–5 epidural inv + metastasis	CT + XRT + L1-laminectomy	improved	alive
8 9, M, C4 OS	brachial plexus inv. Epidural met	laminectomy ×2 + CT + XRT	progressed	died
9 7, F, L5 ES	epidural spinal cord compression.	CT + XRT + laminectomy	improved	alive for 82 months
10 14, M, L4–5 ES	L4–5 invasion and C6 epidural met.	CT + XRT	progressed	died 10 months after diagnosis
11 2, M, NB	spine mets T6	–	incidental finding	died
12 0, F, NB	spinal canal inv.	laminectomy + CT	improved	alive for 76 mos
13 3, M, GNB	skull + spine mets.	CT	progressed	died 18 months after diagnosis
14 2, M, NB	brain &skull mets.	CT	improved	died 12 months after diagnosis
15 1, F, NB	brain parenchyma	CT	progressed	died 7 months after diagnosis
16 2, M, GNB	spinal canal inv.	laminectomy + CT	improved	alive for 36 mos
17 6, F, GNB	thoracic spine metastases	CT	progressed	died 10 months after diagnosis
18* 1, F, NB	T spine and skull metastases	CT	improved	alive for 40 mos
19** 4, M, NB	skull metastases	CT + XRT	improved	alive for 60 mos
20 11, F, NB	skull + T-spine + plexus metastases	CT + XRT	progressed	died 7 months after diagnosis
21* 2, M, NB	spine metastases	CT	incidental finding	alive for 2 months
22 1, M, NB	skull&spine mets	CT	improved	alive for 23 mos
23 2, F, GNB	T-spine invasion	laminectomy + CT	improved	alive for 24 mos
24 1, F, NB	T-spine invasion	laminectomy + CT	improved	alive for 12 mos

Case # Case number; *Loc* location. *M* male; *F* female; *HCC* hepatocellular carcinoma; *CT* chemotherapy; *XRT* radiotherapy; *WT* Wilms'tumor; *MM* malignant melanoma; *ERMS* embryonal rhabdomyosarcoma; *LMAS* left mandible angiosarcoma; *OS* osteogenic sarcoma; *ES* Ewing's sarcoma; *NB* neuroblastoma; *GNB* ganglioneuroblastoma; *MCS* mesenchymal chondrosarcoma; *CT* chemotherapy; *XRT* radiotherapy; *T spine thoracic spine mos* months; *inv* invasion; number of asterisks stands for the number of multiple neurological complications

neurological complications was 51 months (ranged from 4 to 95 months); the mean follow-up for 61 survivors without neurological complications was 42 months (ranged from 14 months to 56 months). Neurological complication rate of the patients with the advanced staged of disease was higher than the patients whose diseases were in early stages. The mean age in complication group (4.9 years) is significantly less than the mean age in non-complication group (8.4 years) ($p = 0.0012$).

Among the 30 cases who survived with neurological complications, 10 cases suffered with neurological sequelae related to primary disease or therapy. Three of these cases had neurological sequelae characterized with developmental delay and mental retardation (Table 9).

Discussion

Neurologic complications were seen 33% of the children with non-CNS solid malign tumors. Multiple

Table 5. *Outcome of the Neurological Complication Characterized with Nervous System Infection*

Age, sex, pathology case no	Type of infection	Treatment of infection	Outcome of complication	Outcome of the primary disease
1, F, HB, 1	varicella zoster	acyclovir iv	improved	alive for 52 months
2, F, RB, 2	chicken pox	acyclovir iv	improved	died 72 months after diagnosis
5/12, F, GCT(EST) 3	varicella zoster	acyclovir iv	improved	alive for 105 months
3, F, WT, 4	herpes zoster	acyclovir iv + top.	improved	alive for 5 months
2, F, WT, 5*	chicken pox	IgG iv	improved	alive for 15 months
16, M, ERMS, 6*	herpes zoster	acyclovir iv	improved	died 63 months after diagnosis
2, M, ERMS, 7	herpes zoster + chicken pox	acyclovir iv + IgG iv	improved	alive for 67 months
4, F, ERMS, 8,	varicella zoster	acyclovir iv	improved	alive for 103 months
4, M, RMS, 9	herpes stomatitis	acyclovir iv	improved	lost FU
1, F, ERMS, 10	herpes stomatitis	acyclovir iv	improved	alive for 48 months
6, M, ERMS, 11*	herpes zoster	acyclovir iv	improved	alive for 24 months
6, F, ES, 12*	herpes zoster	acyclovir iv	improved	died 36 months after diagnosis
3, M, RMS, 13*	herpes zoster ×2 + chicken pox	acyclovir iv + IgG iv	improved	alive for 24 months
2, M, GNB, 14	herpes zoster	acyclovir iv	improved	died 14 months after diagnosis
1, F, NB, 15*	herpes zoster	acyclovir iv	improved	alive for 40 months
1, M, NB, 16	herpes zoster	acyclovir iv	improved	died 24 months after diagnosis
3, F, GNB, 17	herpes simplex	acyclovir iv	improved	alive for 84 months

HB Hepatoblastoma; *FU* follow-up; *GCT(EDS)* Germ-cell Tumor (Endodermal sinus tumor); *i.v.* intravenous; number of asterisks stands for the number of multiple neurological complications; *IgG* immune globulin G; *iv* intravenous.

Table 6. *Outcome of the Treatment Related Neurological Complications*

Age, sex, path. and case no	Type of neurol. complication	Treatment of complication	Outcome of complication	Outcome of primary disease
6, M, HCC, 1*	B8thNN-CPr	CT stopped	not changed	died in 22 days
2, F, WT, 2*	PNP-VCr	VC dose decreased	improved	alive for 15 months
8, F, DG, 3	B8thNN-CPr	CT stopped	not changed	alive for 84 months
14, M, ECC + DG, 4	PNP-VCr	VC dose decreased	not changed	died in 2 months
12, M, ERMS, 5	B8thNN-CPr	CT stopped	not changed	alive for 60 months
6, M, ERMS, 6*	PNP-VCr	VC dose decreased	improved	alive for 24 months
6, F, ES, 7*	PNP-VCr	VC dose decreased	not changed	died in 2 months
3, M, RMS, 8*	PNP-VCr	VC dose decreased	improved	alive for 24 months
16, F, RMS, 9	PNP-VCr	VC dose decreased	not changed	alive for 36 months
2, M, NB, 10*	B8th NN-CPr	CT stopped	not changed	alive for 2 months
1, F, GNB, 11	B8th NN-CPr	CT stopped	partially improved	alive for 110 months
4, M, NB, 12**	B8th NN-CPr + Skull mets + XRTr PHP	CT stopped	sequel	alive for 60 months
2, F, NB, 13	SR-CBH Synd.	–	sequel	alive for 38 months

ECC + DG Embryonal Cell Carcinoma + dysgerminoma; *PNP-VCr* Peripheral neuropathy vincristine related; *B 8th NN-CPr* Bilateral 8th nerve neuropathy cisplatinum related; *CT* Chemotherapy; *VC* Vincristine; *XRTrPHP* Radiotherapy related panhypopituitarism; *SR-CBH Synd* Surgery related Claude-Bernard Horner's Syndrome; number of asterisks stands for number of neurological complications.

neurological complication rate was 5.9%. While the rate of neurological complications of the pediatric solid malign tumors was reported 31% by Arush *et al.* [1], the neurological complication rates of pediatric NB and sarcomas were found 68% [28] and 26.5% [13], respectively. Although among the adult population frequency of neurological complications of the carcinoma of cervix, the lung cancer and gastrointestinal

Table 7. *Outcome of the Other Neurological Complications*

Age, sex, pathology case no	Type of neurologic complication	Treatment of complication	Outcome of complication	Outcome of primary disease
3, F, WT, 1	CPrME + Seiz. + HN	intubated + CWEI	improved	sequel
13, F, LMS, 2	CPrME + Seiz. + HN	CP St + CWEI	improved	alive for 19 mos.
1.5, F, RMS, 3	CPrME + Seiz. + HN	CP St + CWEI	improved	alive for 76 mos.
1/2, M, NB, 4	CPrME + Seiz. + HN	CP St + CWEI	improved	alive for 100 mos.
0, M, NB, 5	HTNrStroke + Seiz.	–	sequel	alive for 15 mos.
1, F, NB	multiple brain metastases + Seiz.	chemotherapy	died with status epilepticus	died 7 months after diagnosis
1, M, NB, 6	PNS	IgG iv + steroid	sequel	alive for 36 mos.

CPrME Cisplatinum related metabolic encephalopathy; *Seiz* seizure; *HN* hyponatremia; *CWEI* correction of water-electrolyte imbalance; *CP St* cisplatinum stopped; *mos* months, *HTNrStroke* Hypertension related stroke; *PNS* Paraneoplastic syndrome.

Table 8. *Outcome of 154 Cases with Solid Malignant Tumors*

	Without	Neurologic	Complications		With	Neurologic	Complications	
Pathol.	died	lost F-U	alive	MFU-ms	died	lost F-U	alive	mFU-ms
Sarcoma	12	5	15	43	5	1	11	49
HCC	1	2	1	14	1	–	1	52
WT	2	–	12	56	3	–	2	21
GCT	2	1	6	24	1	–	2	95
NB-GNB	4	–	6	49	8	–	14	50
RB	–	–	6	49	1	–	–	0
Others	2	8	9	46	1	–	–	4
TC	–	3	6	53	–	–	–	–
Total	23	19	61	42	20	1	30	51
%	14.9%	12.3%	39.6		13%	0.6%	19.5%	

Lost F-U Lost follow-up; *MFU-ms* mean follow up-months.

Table 9. *Neurologic Sequelae of the Patients*

Age-sex-pathology	Location-grade	Type of neurologic complication	Type and reason of neurological sequela	Length of follow-up
7, F, ES	L5 pedicle	epidural spinal cord compression	RLEW, neurogenic bladder	82 months
12, M, ERMS	R nasolabial area	cisplatinum related 8th nerve neuropathy	bilateral hearing impairment	60 months
16, F, RMS	R forearm	cisplatinum related 8th nerve neuropathy	bilateral hearing impairment	36 months
3, F, WT	R kidney	cisplatinum related seizures	development delay and MR (IQ = 60)	44 months
8, F, DG	ovary	cisplatinum related 8th nerve neuropathy	bilateral hearing impairment	84 months
2, F, NB	left Upper mediastinum, A	latrogenic left Horner's Syndrome	myosis, ptosis, enophthalmus	38 months
1, M, NB	suprarenal, A	paraneoplastic syndrome (ataxic gait and opsoclonus)	speech delay, wide-based ataxic gait	36 months
0, M, NB	suprarenal, congenital C	hypertension related multiple cerebral infarcts	seizures, cortical blindness, cerebral palsy, MR	15 months
4, M, NB	suprarenal, D	skull metastases cisplatinum related 8th nerve neuropathy	panhypopituitarism, bil. hearing loss, bil. cataract + MR	60 months
1, F, NB	posterior mediastinum, D	Thoracic spinal canal invasion	neurogenic bladder	40 months

MR Mental retardation; *bil* bilateral.

cancers were reported consecutively 8% [24], 40% [16], and 4% [3], and most of those studies were focused on brain metastases. Clauston *et al.* [4] reported 45.2% of incidence of nervous system metastasis and found the cerebral metastasis as the most common neurological diagnosis (15.9%; 135 of 851 patients). In our study and the others revealed that the metastatic complications were more frequent than non-metastatic complications.

In this study, 12 cases had cranial metastases, and 7 of them had parenchymal brain metastases. The incidence of parenchymal brain metastasis was 4.5%, that varied between 2% to 13% in different series [5, 8, 29]. Although, the prognosis was poor and brain metastasis was the leading cause of death, we recommended aggressive treatment (surgery, radiation therapy and chemotherapy) for pediatric intracranial parenchymal metastases [27].

In this study incidence of spinal metastasis was 11% ($n = 17$ cases). Symptomatic epidural spinal cord compression was seen 7.7% of cases ($n = 12$), and 6 of them were alive during their last follow-up visit. However, Klein *et al.* [12] found the incidence of metastatic epidural spinal cord compression lower than adult series which occurred in approximately 3% of all children with malignant solid tumors. In this study the incidence of metastatic spinal cord compression (7.7%) was higher than previous report (3%) [12]. In our study half of the cases that caused spinal cord compression were dumbbell neuroblastomas. that invade the spinal epidural space through neural foraminae. If we exclude those cases, our incidence for metastatic spinal cord compression would be 3.7%.

In this study and the others [9, 18] indicated that the children with NB and useful motor function, chemotherapy worked rapidly and neurological improvement obtained without surgery. Surgical decompression should be reserved for children with NB who have very rapid neurological deterioration or complete loss of motor function.

However, sarcomas either soft tissue or bony, does not respond as rapidly or dramatically to chemotherapy and radiation therapy as does NB [12]. Combined treatment consisting of chemotherapy, radiotherapy and surgery should be the treatment of choice for the primary spinal column sarcomas and/or spinal epidural metastases [12, 25, 26].

Brachial plexus metastasis or invasion is a rare complication and treatment is usually palliative. In adult series, incidence was reported 0.43% to 0.71% [10] and differential diagnosis from a radiation plexopathy could be difficult. Epidural tumor involvement was seen in more than 50% of patients. In our study, the incidence of nerve plexus metastasis was 1.9% and 2 of these cases had epidural spinal cord compression. All 3 cases were in terminal stage and died short after the diagnosis of plexus metastasis.

Nervous system infection was encountered in 17 (11%) cases. All cases were benign viral skin infections, such as herpes zoster, herpes simplex or varicella zoster, and improved with topical and/or systemic antiviral therapy. In one case the site of primary malignant neoplasm showed correlation with the dermatomal presentation of varicella zoster infection [20]. That was the case with varicella zoster infection involved left L1 nerve root distribution, which was the first clinical symptom of the patient's left adrenal gland NB. Since these benign nervous system infections is usually seen in immune-compromised patients, all of these infections were seen during chemotherapy, that showed the effectiveness of chemotherapy. Among these 17 cases, although, 5 cases died and one case was lost during follow-up, 11 cases were alive for 5 to 103 months. Presence of benign viral skin infection, may indicate better prognosis and longer survival rate.

Thirteen (8.4%) cases had treatment related neurological complications. One case had postoperative sequel as Horner's syndrome following the removal of upper mediastinal stage I NB. We have encountered 12 cases with chemotherapy-related peripheral or VIII. Nerve neuropathy. Vincristine related peripheral neuropathy improved following decreasing vincristine dose or interruption of vincristine chemotherapy; however, cis-platinum related VIII. Nerve neuropathy, did not improve following cessation of cis-platinum chemotherapy. Cis-platinum related VIII. Nerve neuropathy is characterized with permanent high frequency hearing impairment due to cochlear hair loss. It is dose related, exacerbated with radiation therapy has worse prognosis in children [14]. One case with vincristine related-neuropathy, had also family history of Charcot-Marie-Tooth Disease, which was described as a triggering factor for producing chemotherapy related peripheral neuropathy [15].

We observed mental status changes in 6 (3.7%) cases, who had new onset of seizures related to 3 different types of encephalopathies. One of these cases with NB had multiple brain metastases and died with status epilepticus. Four cases had metabolic encephalopathies secondary to hyponatremia, which was the

result of cis-platinum chemotherapy. All 4 cases responded to correction of hyponatremia and water electrolyte imbalance [Table 7]. Metabolic factors are common reasons for seizures in cancer patients. High dose of cis-platinum, disturbs the fluid and electrolyte balance, and encephalopathy with confusion and seizures can occur [14]. The sixth case with NB had multiple cerebral infarcts secondary to hypertensive encephalopathy, which caused the neurological sequel.

Mental status changes (MSC) occurred in 11% (89 of 815) of the children with cancer [6]. Sixty percent of the patients with MSC, suffered with seizures, which was 6.5% of the total group of cancer patients [6]. The encephalopathy range was 27% of children with MSC which corresponds 3% (24 of 815) of all children with systemic cancer. The encephalopathy rarely had a single etiology and was usually due to multiple factors, such as vital organ failure, electrolyte imbalance, side effects of treatment, analgesic medication and infection [6].

We have seen two cases with intracerebral hemorrhage, the histopathologic diagnoses of these cases were angiosarcoma and WT metastases, respectively. Both of these cases were characterized with parenchymal brain metastases with metastatic tumor hemorrhage. The most common cause of intraparenchymal brain hemorrhage in cancer patients is the hemorrhage of parenchymal metastasis [22]. During the course of NB, cerebral hemorrhage due to thrombocytopenia or hypertension, was relatively a frequent cause of acute neurological compromise in children [11, 22]. We have 5 cases of NB with hypertension and one of these cases had hypertension related multiple cerebral infarctions. We have one case with the opsoclonus-polymyoclonus syndrome [Table 7]. Although his stage I NB cured by tumor removal, he suffered with neurological sequelae. Approximately 2% of children with NB opsoclonus-myoclonus syndrome occurs [23]. Although this condition is associated with persistent neurological sequelae, the limited tumor indicates a favorable prognosis.

Among these 51 cases with neurological complications 10 cases suffered with neurological sequelae due to neurological complications. NB had highest rate (50%; $n = 5$) among the solid malign tumors that caused neurological sequelae. Among these 10 cases only 3 of them showed neuropsychological abnormalities, mental and developmental delay. Two cases had the neuropsychologic sequelae due to primary malignant disease. These were hypertension related multiple cerebral infarcts of the NB case and developmental delay with IQ < 60 of the WT case. Only one case with NB had mental retardation and panhypopituitarism, due to cranial radiation. Panhypopituitarism have been reported as many as 50% of long-term survivors of brain tumor patients following cranial radiation [21]. Also, neuropsychologic and neurological abnormalities have been reported in patients treated with cranial radiation and chemotherapy [21]. However neuropsychologic deficits and CT and MRI abnormalities does not correlate clearly

In conclusion: Neurologic complication rate of the pediatric solid malign tumors is 33%. Metastatic complications were seen more frequently than non-metastatic complications, and had the most dismal prognosis. Although neurological complication rate of the patients with the advanced staged of disease was higher than the patients whose diseases were early stages, there were to difference of the sex between the complication and non-complication groups. Besides, no difference in survival was found between the complication and non-complication groups.

Almost one-third ($n = 10$) of the surviving patients with neurological complication suffered with neurological sequelae. Among the ten cases with neurological sequelae, 3 cases had mental retardation and developmental delay. Most of the permanent neurological deficits were related to treatment and they could be prevented.

References

1. Arush MW-B, Stein M, Perez-Nachum M, Dale J, Babilsky H, Zelnik N, Kuten A (1995) Neurologic complications in pediatric solid tumors. Oncology 52: 89–92
2. Baram ZT, van Tassel P, Jaffe N (1988) Brain metastases in osteosarcoma: incidence, clinical and neuroradiological findings and management options. J Neurooncol 6: 47–52
3. Cascino TL, Leavengood JM, Kemeny N, Posnwer JB (1983) Brain metastases from colon cancer. J Neurooncol 1: 203–209
4. Clouston PD, De Angelis LM, Posner JB (1992) The spectrum of neurological disease in patients with systemic cancer. Ann Neurol 31: 268–273
5. Deutsch M, Albo V, Wollman MR (1982) Radiotherapy for cerebral metastases in children. Int J Radiat Oncol Biol Phys 8: 1441–1446
6. DiMario Jr. FJ, Packer RJ (1990) Acute mental status changes in children with systemic cancer. Pediatrics 85: 353–360
7. Gilbert MR, Grossman SA (1986) Incidence and nature of neurological problems in patients with solid tumors. Am J Med 81: 951–954
8. Graus F, Walker RW, Allen JC (1983) Brain metastases in children. J Pediatr 103: 558–561
9. Hayes FA, Green AA, O'Connor DM (1989) Chemotherapeutic management of epidural neuroblastoma. Med Ped Oncol 17: 6–8

10. Jaeckle KA (1991) Nerve plexus metastases. Neurol Clin 9: 857–866
11. Kellie SJ, Hayes FA, Bowman LC, Kovnar FH, Langston J, Jenkins III JJ, Pao WJ, Ducos R, Green AA (1991) Primary extracranial neuroblastoma with central nervous system metastases. Characterization by clinicopathologic findings and neuroimaging. Cancer 68: 1999–2006
12. Klein SL, Sanford RA, Muhlbauer MS (1991) Pediatric spinal epidural metastases. J Neurosurg 76: 70–75
13. Kramer ED, Lewis O, Raney B, Womer R, Packer RJ (1989) Neurologic complications in children with soft tissue and osseous sarcoma. Cancer 64: 2600–2603
14. McDonald DR (1991) Neurologic complications of chemotherapy. Neurol Clin 9: 955–967
15. Neumann Y, Toren A, Rechavi G, Seifried B, Shoham NG, Mandel M, Kenet G, Sharon N, Sadeh M, Navon R (1996) Vincristine treatment triggering the expression of asymptomatic Charcot-Marie-Tooth Disease. Med Ped Oncol 26: 280–283
16. Newman S, Hansen H (1974) Frequency, diagnosis, and treatment of brain metastases in 247 consecutive patients with bronchogenic carcinoma. Cancer 33: 492–496
17. Patchell RA (1991) Neurologic complications of systemic cancer. Neurol Clin 9: 817–1035
18. Plantaz D, Rubie H, Michon J, Mechinaud F, Coze C, Chastagner P, Frappaz D, Gigaud M, Passagia JG, Hartman O (1996) The treatment of neuroblastoma with intraspinal extension with chemotherapy followed by surgical removal of residual disease. A prospective study of 42 patients-results of the NBL 90 study of the French Society of Pediatric Oncology. Cancer 78: 311–319
19. Posner JB (1978) The role of neurologist in the management of cancer. Am J Med 65: 4–6
20. Pruitt AA (1991) Central nervous system infections in cancer patients. Neurol Clin 9: 867–888
21. Ried HL, Jaffe N (1994) Radiation-induced changes in long-term survivors of childhood cancer after treatment with radiation therapy. Sem Roentgenol XXIX: 6–14
22. Rogers LR (1991) Cerebrovascular complications in cancer patients. Neurol Clin 9: 889–899
23. Russo C, Cohn SL, Petruzzi MJ, de Alarcon PA (1997) Long-term neurological outcome in children with opsoclonus-myoclonus associated with neuroblastoma. A report from pediatric oncology group. Med Ped Oncol 29: 284–288
24. Saphner T, Gallion HH, Van Nagell JR, Kryscio R, Patchell RA (1989) Neurologic complications of cervical cancer. A review of 2261 cases. Cancer 64: 1147–1151
25. Sundaresan N, Rosen G, Huvos AG, Krol G (1988) Combined treatment of osteosarcoma of the spine. Neurosurgery 23: 714–719
26. Taşdemiroğlu E, Bagatur E, Ayan I, Darendeliler E, Patchell RA (1996) Primary spinal column sarcomas. Acta Neurochir (Wien) 138: 1261–1266
27. Taşdemiroğlu E, Patchell RA (1997) Cerebral metastases in childhood malignancies. Acta Neurochir (Wien) 139: 182–187
28. Taşdemiroğlu E, Ayan I, Kebudi R (1998) Extracranial neuroblastomas and neurological complications. Child's Nerv Syst 14: 713–718
29. Vannucci RC, Baten M (1974) Cerebral metastatic disease in childhood. Neurology 24: 981–985

Comment

The topic addressed by the paper is quite interesting because – as the author state – this type of study has been frequently carried out in adults whereas few information are available. in the pediatric population. The series of patients considered is large and the amount of data collected sufficient to provide a good representation of the problem. We think the results could have been schematized in a more clear way. For example, it could be suggested to subdivide the material in various subsets of complications: those related to the tumor behavior and those related to the treatment, both chemotherapic and radiotherapic. In fact, to subdivide the complications simply in metastatic and non-metastatic does not provide a useful information for the clinician. Certain complications are known to depend on the treatment rather than on the disease. As these complications could be, at least partly avoided, it would be useful to separate them from those unavoidable complications related to the aggressviness of a specific tumor. In such a way, it could be more easy for the reader to evaluate the actual relationship between a given tumor and a given neurological complication

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