

Central Nervous System Metastases in Neuroblastoma

Radiologic, Clinical, and Biologic Features in 23 Patients

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BACKGROUND. Central nervous system (CNS) metastases rarely occur in patients with neuroblastoma, although recent reports suggest an increase in the rate. CNS recurrence may represent a different mechanism of spread than bone and bone marrow metastases and may be associated with unique genetic determinants. Further definition of the radiologic, clinical, and biologic features may provide clues to the predisposing factors and mechanisms of CNS dissemination.

METHODS. A retrospective analysis of all children ages 0–21 years with Stage IV neuroblastoma who were diagnosed at the Institut Curie and the Institut Gustave-Roussy between 1985 and 2000 was performed with direct review of medical records and magnetic resonance images, computed tomography scans, and iodine-123 or iodine-131 metaiodobenzylguanidine scintiscans (MIBG scans). When tumor tissue was available, genetic analysis was performed using comparative genomic hybridization (CGH).

RESULTS. Of 434 patients with Stage 4 disease, 23 children had the CNS as their site of first recurrence. The estimated risk of CNS recurrence was 8.0% at 3 years, with no significant change in risk over the 15-year period. Eleven patients had isolated CNS recurrences, and the remaining patients developed recurrences concomitantly in other sites. The sites of recurrences were parenchymal ($n = 8$ patients), parenchymal with meningeal ($n = 7$ patients), and meningeal alone ($n = 8$ patients). MIBG scans detected CNS lesions in only 43% of patients. Significant risk factors for CNS recurrence included lumbar puncture at diagnosis, ages 2–3 years, and *MYCN* gene amplification. Abnormalities that were identified using CGH, in addition to 2p24 amplification in 5/7, included gains of 17q and 18q and losses of 1p, 3p, 10q25-26, and 11q.

CONCLUSIONS. The risk of CNS recurrence in patients with neuroblastoma is 8% at 3 years after diagnosis and has not increased in the last 15 years. Because the CNS often is the sole site of recurrence, either it may be a sanctuary site, or the biologic determinants of CNS metastasis may be unique. Elucidation of risk factors and pathogenesis may allow prevention of this fatal event. *Cancer* 2003;98:155–65.

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Neuroblastoma is the most common extracranial tumor of childhood and is widely metastatic at the time of diagnosis in more than 50% of patients. Despite the high frequency of dissemination to the bones and bone marrow of the cranium in children both at presentation and recurrence, spread to the central nervous system (CNS) has been rare, including either brain parenchyma or leptomeningeal involvement. A recent report from the Children's Cancer Group (CCG) of metastatic sites in 567 patients with Stage IV disease who were diagnosed between 1989 and 1996 revealed that only 4 patients (0.7%) at diagnosis and 13 patients (2.2%) at recurrence had CNS involvement.¹ Recent reports have suggested that the incidence of CNS recurrence may be increasing and have confirmed that recurrence of neuroblastoma in the CNS is almost uniformly fatal.²⁻⁴ It is possible that different sites of CNS recurrence represent different mechanisms of spread, which eventually will be identified with unique genetic patterns. Further definition of the radiologic, clinical, and biologic features may provide clues to predisposing factors, mechanisms of CNS dissemination, and the reasons for the increasing incidence observed in some studies.

We undertook a review of CNS involvement in the 434 children with Stage 4 neuroblastoma who were diagnosed and treated at the Institute Curie and the Institute Gustave Roussy between January 1, 1985 and December 31, 2000, 225 of whom had developed recurrent disease. Twenty-three of those patients had CNS recurrence at the time of their first recurrence. The objective of this review was to define the clinical, radiologic, and prognostic characteristics of CNS recurrence in children with neuroblastoma who were treated with intensive chemotherapy and underwent hematopoietic stem cell transplantation (HSCT).

MATERIALS AND METHODS

A retrospective chart review included all 434 patients with Stage IV neuroblastoma who were diagnosed at the Institute Curie or the Institute Gustave Roussy between January 1, 1985 and December 31, 2000, including direct review of reports of all imaging studies, cerebrospinal fluids (CSF), pathology, and bone marrow specimens from the time of diagnosis and recurrence. For any patient who had a suggestion of involvement of the CNS either at diagnosis or first recurrence according to symptoms, scan reports, or clinical findings, the original radiologic studies were obtained and reviewed. Two patients were excluded due to CNS involvement that occurred after the time they first developed disease progression, because the mechanisms of spread and involvement may be different when there is further resistance.

Patients were treated on approved protocols that were either institutional or sponsored by the French Society of Pediatric Oncology. Induction therapy consisted of cisplatin, etoposide, cyclophosphamide, doxorubicin, and vincristine administered on the NB87 protocol.⁵ Patients who had incomplete responses received subsequent consolidation therapy with carboplatin. Patients without disease progression received high-dose chemotherapy regimens, which contained either melphalan, total body irradiation (TBI), and vincristine⁶ or melphalan and busulfan⁷, followed by HSCT.

Computed tomography (CT) scans ($n = 26$ patients) and/or magnetic resonance images (MRIs; $n = 16$ patients) at the time of diagnosis and recurrence were reviewed by the radiologists (D. C. and H. B.), and iodine-131 metaiodobenzylguanidine scintiscans (MIBG scans; $n = 16$ patients) were reviewed by nuclear medicine physicians (J. L. and V. E.). For each scan, data were recorded on techniques, tumor size, tumor numbers, anatomy, density/signal of the lesion(s), presence or absence of hemorrhage, and MIBG scan findings in the CNS and systemically. The scans at recurrence were done with 2.5 mm slices ($n = 5$ patients), 5-mm slices ($n = 14$ patients), or 10 mm slices ($n = 4$ patients), including 6 scans without contrast, 13 scans with contrast, and 4 scans with both noncontrast and contrast views.

Tumor tissue was obtained at the time of diagnosis from primary tumors or metastatic tissue and was frozen at -70°C or in liquid nitrogen. *MYCN* gene copy numbers were determined by Southern analysis, polymerase chain reaction analysis, or fluorescent in situ hybridization (FISH).⁸ Deletion 1p was determined by FISH and loss of heterozygosity. Comparative genomic hybridization (CGH) was performed according to the technique described by Kallioniemi et al. with minor modifications.^{9,10} For data analysis, DNA copy number changes for all individual patients were represented on ideogram charts. We chose upper (indicating gains) and lower (indicating loss) fluorescence ratio thresholds of 1.2 and 0.8, respectively. Amplifications were defined by a ratio > 1.5 in a subchromosomal region.

CNS recurrence rates were estimated by the Kaplan-Meier method¹¹ and were compared, according to clinical and biologic characteristics, with the log-rank test. Curves were calculated from the date of diagnosis of neuroblastoma. The endpoint was CNS recurrence as first site of disease progression; patients with the first event at other sites were censored at that time. Patients who did not develop recurrent disease were censored at the time of death or last follow-up.

TABLE 1
Characteristics of 434 Patients with Stage IV Neuroblastoma

Characteristic	No. of patients with Stage 4 neuroblastoma (%)
Median age (mos)	32.4 (—)
Median follow-up (mos)	100 (—)
Male gender	253 (58.3)
Cranial disease at diagnosis (bone or extradural)	239 (55.1)
Primary site abdominal	373 (85.9)
Lumbar puncture at diagnosis	39 (9.0)
High-dose therapy with HSCT	336 (77.4)
LDH > 750 iu/L	181/235 (77.0)
MYCN amplification	92/281 (32.7)
HVA/VMA > 2.0	119/351 (33.9)
Dopamine > 2500 mg/24 hr	227/346 (65.6)

HSCT: hematopoietic stem cell transplantation; LDH: lactate dehydrogenase; HVA/VMA: homovanillic acid/vanillylmandelic acid (urinary catecholamines).

RESULTS

Clinical Features

The patient characteristics for all 434 patients with Stage 4 disease (Table 1) were typical of children with high-risk neuroblastoma. Seventy-seven percent of patients were responsive to induction therapy and completed the planned high-dose myeloablative chemotherapy. The median follow-up for the entire group was 100 months (range, 1–180 months).

Disease progression occurred in 225 patients, including 23 patients with radiologically verified metastases to the CNS at first recurrence, with 1 patient who also had CNS disease at the time of diagnosis (Table 2). The original radiographs were unobtainable for review in 4 of those 23 patients but had been read previously by one of the authors (D. C.). In addition, pathologic or cytologic evidence of tumor in the CNS was available in three of those four patients. For all 23 patients, pathologic verification ($n = 5$ patients) or cytologic verification ($n = 8$ patients) of neuroblastoma in the CNS was obtained for 13 patients.

This constituted 23 of 434 patients, for a crude rate of 5.3% for all patients with Stage 4 neuroblastoma in this period, or 23 of 225 patients, for a rate of 10.2% for all recurrences. The estimated risk of CNS as the site of first recurrence according to the Kaplan-Meier method was 0.97% (95% confidence interval [95%CI], 0.03–1.91) at 6 months, 2.69% (95%CI, 1.02–4.36) at 12 months, 6.90% (95%CI, 3.98–9.82) at 24 months, and 8.04% (95%CI, 4.75–11.33) at 36 months. The estimated risk of CNS recurrence at 24 months after diagnosis for patients who were diagnosed during each 5-year period was not significantly different ($P > 0.8$): 1985–1989, 5.8%; 1990–1994, 7.9%; 1995–2000, 7.0%.

Only 1 patient had CNS disease at the time of diagnosis (Patient 8) (see below and Table 1), a child with an isolated lesion in the ventricle and choroid but with negative CSF cytology. He also had bone, bone marrow and lymph node metastases in the setting of a nonamplified *MYCN* adrenal primary tumor, with very high levels of lactate dehydrogenase and dopamine. He developed progressive disease in the meninges during induction chemotherapy after achieving a partial response of his ventricular tumor to radiotherapy and chemotherapy, and he died from progressive disease at 4 months. The remaining 22 patients developed CNS disease at the time of first recurrence, including 8 patients with recurrence in the brain only, 7 with both parenchymal and meningeal disease, and 7 with only meningeal involvement. Twelve of those 23 patients had recurrence that was confined to the CNS, without systemic recurrence. The median time to recurrence was significantly shorter for patients with CNS as the first site: 14 months compared with 18 months for the 202 patients who developed recurrent disease at other sites ($P < 0.05$).

Sixteen patients underwent HSCT prior to their CNS recurrence, and 7 patients did not undergo HSCT due to early disease progression. Those seven patients with early progression all developed recurrent disease in the meninges. One of these patients had ventricular disease at the time of diagnosis, and one patient developed concomitant parenchymal CNS recurrence. All but 1 of the patients with CNS involvement died prior to the cut-off date for analysis, with the exception of Patient 22, who developed a local meningeal recurrence and survived with a partial response to oral etoposide and local radiation at 265 + days. Subsequently, the patient died at 491 days after recurrence. The median survival after first recurrence was significantly shorter for patients with CNS as the first site of recurrence (2 months) compared with 6 months for the group of patients who had their first recurrence at other sites ($P < 0.0015$).

Significant risk factors for CNS recurrence (Table 3) in the log rank analysis were age 2–3 years at diagnosis ($P < 0.0045$), *MYCN* gene amplification ($P < 0.0025$), LP at diagnosis ($P = 0.01$), and no HSCT ($P < 0.035$). Caution is necessary in interpretation of the potential risk of LP at the time of diagnosis, because LP was not mandated for all patients but was done for clinical indications, such as neurologic symptoms or for suspected invasion by bulky endocranial or paraspinal tumor deposits. Similarly, whether a patient underwent HSCT was influenced by response to induction; thus, patients with unresponsive disease did not undergo HSCT.

The signs and symptoms of CNS recurrence in-

TABLE 2
Patients with Central Nervous System Metastases from Stage 4 Neuroblastoma

Patient	Age (mos)	Gender	Yr of Dx	LP Dx	NMA	Del 1p	17q+	LDH (iu/L)	HSCT	Time Dx CNS to (mos)	MIBG CNS	Sites of CNS disease	Time CNS to death (mos)
1	23	M	1985	No	NA	NA	NA	NA	Yes	24	No	Single parietal hemorrhagic lesion with edema	9.8
2	31	F	1985	No	NA	NA	NA	NA	Yes	13	NA	Single hemorrhagic parietooccipital lesion	2.0
3	31	F	1986	No	NA	NA	NA	NA	Yes	11	+/-	Multiple frontal and occipital hemorrhagic with edema	13.8
4	20	F	1986	No	NA	NA	NA	NA	No	7	+/-	Diffuse leptomeningeal	0.9
5	3	M	1987	Yes	Yes	NA	NA	1769	No	7	No	Diffuse leptomeningeal	1.5
6	84	M	1987	No	NA	NA	NA	NA	Yes	25	NA	Extensive meningeal metastases (not seen on unenhanced MRI) with diffuse bone and bone marrow disease (sphenoid, spine)	5.9
7	16	F	1988	No	No	NA	NA	NA	Yes	14	NA	Large single hemorrhagic occipital mass with meningeal extension	1.6
8	11	M	1990	Yes	Yes	Yes	Yes	2146	No	0	NA	Intraventricular choroidal tumor at diagnosis with later meningeal extension	9.6
9	33	M	1990	No	No	No	NA	255	Yes	15	Yes	Chiasmatic suprasellar meningeal recurrence	13.0
10	11	M	1990	Yes	Yes	Yes	Yes	3874	No	5	NA	Diffuse nodular leptomeningeal metastases, including suprasellar mass	0.2
11	42	M	1990	No	Yes	No	No	2558	Yes	19	Yes	Single large temporal lesion with edema	5.6
12	31	M	1991	No	Yes	NA	NA	6790	Yes	22	Yes	Single large hemorrhagic parietal lesion with edema	1.1
13	65	M	1992	No	Yes	NA	NA	NA	Yes	14	Yes	Two large hemorrhagic frontal lesions with edema and later cystic lesions	6.0
14	30	F	1992	No	NA	NA	NA	NA	Yes	16	NA	Two frontal and one cerebellar hemorrhagic lesions with meningeal involvement	0.4
15	30	M	1992	Yes	No	No	Yes	978	Yes	30	Yes	Single cystic, classified occipital lesion	52.1
16	30	F	1994	Yes	No	No	NA	5148	No	4	No	Diffuse leptomeningeal disease with one parenchymal insular nodule	1.6
17	16	M	1994	No	Yes	Yes	No	8173	No	9	No	Diffuse leptomeningeal disease	1.4
18	26	M	1995	No	NA	NA	NA	600	Yes	15	No	Multiple nodular meningeal intracranial (including suprasellar) and spinal metastases; peripheral cerebellar nodule with edema	0.5
19	15	M	1998	No	Yes	Yes	Yes	8690	Yes	12	NA	Two cerebellar hemorrhagic lesions	0.2
20	26	F	1998	No	Yes	NA	NA	9300	Yes	16	No	Two temporal lesions with focal meningeal extension	5.8
21	28	F	1999	No	Yes	No	NA	10,600	Yes	12	No	Diffuse supratentorial meningeal disease with some parenchymal cortical nodules	0.9
22	28	M	1999	No	No	NA	NA	621	Yes	21	Yes	Single focal meningeal nodule at cerebellar-pontine angle with later diffuse meningeal spinal lesions	8.7
23	55	F	2000	No	No	No	NA	1359	No	6	No	Diffuse meningeal lesions with cortical nodules	0.1

Dx: diagnosis; mos: months; LP: lumbar puncture; NMA: N-MYC amplification; Del 1p: deletion of 1p; 17q+: 17q positive; LDH: lactate dehydrogenase; HSCT: hematopoietic stem cell transplantation; CNS: central nervous system; MIBG: iodine-131 or iodine-123 metaiodobenzylguanidine scintiscan; MIBG CNS: whether the MIBG scan visualized a CNS lesion at the time of recurrence (two patients had questionable results [+/-]); NA: data not available; MRI: magnetic resonance image.

TABLE 3
Prognostic Characteristics for Central Nervous System Recurrence in 434 Patients with Stage 4 Neuroblastoma according to the International Neuroblastoma Staging System

Characteristic	No. of patients	No. with CNS recurrence	CNS recurrence (%)			P value ^a
			6 mos	12 mos	24 mos	
Gender						
Male	253	14	0.8	2.3	7.1	NS (0.83)
Female	181	9	1.2	3.3	6.6	—
Age (yrs)						
≤ 1	62	3	3.5	5.5	5.5	< 0.0045
≤ 2	88	5	0.0	4.2	7.7	—
≤ 3	89	11	1.2	4.2	17.2	—
> 3	195	4	0.5	0.5	2.2	—
Other cranial disease (bone or extradural)						
No	195	6	1.1	1.1	3.7	NS, trend (~0.06)
Yes	239	17	0.9	4	9.6	—
Primary site						
Abdominal	373	21	0.8	2.9	7.3	NS (> 0.25)
Nonabdominal	51	1	2.0	2.0	2.0	—
LP at diagnosis						
No	395	18	0.3	1.9	6.4	0.01
Yes	39	5	7.7	10.6	10.6	—
HSCT						
No	98	7	5.2	10.1	10.1	< 0.035
Yes	336	16	0.0	1.1	6.0	—
LDH ^b (iu/L)						
< 750	54	3	0.0	0.0	7.5	NS (> 0.51)
> 750	181	12	2.4	5.3	8.6	—
MYCN amplification ^b						
No	189	6	1.1	1.1	3.3	< 0.0025
Yes	92	10	2.3	8.2	16.6	—
HVA/VMA ^b ratio						
≤ 2	232	11	0.9	1.9	5.8	NS (0.3)
> 2	119	9	1.8	6.5	12.0	—
Dopamine ^b (mg/24 hr)						
≤ 2500	119	4	0.9	2.8	4.0	NS (> 0.14)
> 2500	227	15	1.4	3.2	9.5	—

INSS: International Neuroblastoma Staging System; CNS: central nervous system; NS: not significant; LP: lumbar puncture; HSCT: hematopoietic stem cell transplantation; LDH: lactate dehydrogenase; HVA/VMA: homovanillic acid/vanillylmandelic acid (urinary catecholamines).

^a Log rank test: The prognosis was worse for patients older than 2 years but younger than 3 years and was better for patients older than 3 years. Patients younger than 2 years were intermediate (did not differ significantly either from patients ages 2–3 years or from patients older than 3 years).

^b The comparisons for LDH, urinary catecholamines, and MYCN may be less reliable due to the higher percentage of missing values (20% for catecholamines, 35% for MYCN, and 46% for LDH).

cluded (in order of frequency) nausea and emesis, depressed consciousness, motor weakness or paralysis, headaches, extremity or back pain, fever, cranial nerve signs, and seizures (Table 4). Headaches were seen only in patients who had a brain parenchymal component to their CNS recurrence, whereas fever and extremity or back pain were more frequent in patients with a meningeal component. Patients with pure meningeal recurrence, compared with isolated parenchymal recurrence, tended to be younger at the time of diagnosis and to have a shorter time to recurrence. Eight of 12 patients who underwent LP at the time they developed recurrent disease had positive

CSF cytology. One patient had negative CSF cytology and no radiologic evidence of meningeal disease. Three patients who had radiologically confirmed meningeal disease had negative CSF cytology: Two of those patients had focal disease, one in the optic chiasm and one at the cerebellopontine angle, and the third patient had diffuse but nodular meningeal involvement.

Radiologic Features

Fifteen patients had lesions that involved brain parenchyma (Table 5, Figs. 1–5), including 11 lesions that apparently had spread to the brain directly and, thus,

TABLE 4
Clinical Features of Patients with Central Nervous System Involvement

Characteristic	All patients (n = 23 patients)	Site(s) of involvement		
		Brain only (n = 8 patients)	Brain and meninges (n = 7 patients)	Meninges only (n = 8 patients)
Median age (mos)	28	31	28	23
Time to recurrence (mos)				
Median	13.9	16.4	13.2	12.0
Range	3.6–29.7	6.1–29.7	3.6–16.4	5.2–21.1
Clinical symptoms (no. of patients)				
Headaches	10	5	5	0
Nausea and emesis	14	6	5	3
Seizures	5	3	1	1
Motor weakness or paralysis	11	4	1	6
Limb/back pain	8	1	4	3
Change in consciousness	12	3	5	4
Cranial nerve symptoms	6	2	1	3
Fever	6	1	2	3
Other metastases at recurrence	11	3	3	5
Other cranial disease at recurrence (bone/dural)	5	3	0	2
Positive CSF cytology	8/12	0/1	2/3	6/8
Positive biopsy	5/5	—	—	—
Death	22	8	7	7 ^a

CSF: cerebrospinal fluid.

^a One patient, who survived for > 265 days with disease after receiving radiation to a large, focal, meningeal lesion and oral etoposide, died after the cut-off date (at 491 days).

were surrounded by parenchyma (Fig. 1), 1 lesion that was located in the ventricle (Fig. 3), and 3 lesions in which involvement appeared to develop from the extension of a meningeal lesion (Fig. 5a). The majority of patients ($n = 12$ patients) with parenchymal involvement had only supratentorial lesions. Of the 15 patients who had leptomeningeal extension (Figs. 2–5), 14 had lesions that were identifiable radiologically, and the other patient had documented positive CSF cytology; however, because the MRI for this patient was done without contrast injection, the meningeal involvement was not seen clearly. The incidence of spinal meningeal metastases cannot be delineated reliably, because only three patients had MRI studies of the whole spine.

The lesions ranged in size from 2 mm to 65 mm. Hemorrhage was seen in 8 of 15 patients who had parenchymal lesions, whereas calcifications were seen in only 1 patient. One patient (Patient 15) had a cystic pattern at recurrence (Fig. 1), whereas another patient (Patient 13) had two parenchymal hemorrhagic locations that led to cystic masses on a radiograph that was taken 3 weeks later. Edema around parenchymal lesions was observed in only six patients.

Six of 16 patients who had positive MIBG scans at diagnosis and then had scans performed at the time of CNS recurrence had definite visualization of the lesion

by MIBG uptake (Figs. 2, 4), whereas 8 patients clearly had negative results. Two additional patients had uptake seen in the head in the region of the lesion; however, because those patients had numerous other skull lesions, the uptake in the parenchymal CNS lesion was uncertain.

Genetic Features

The patients who had CNS metastases tended to have very unfavorable genetic features. A greater proportion of patients who had tumors that exhibited *MYCN* amplification developed CNS recurrence ($P < 0.0025$). Cryopreserved primary tumor tissue was available from 7 of 23 patients with CNS metastasis for CGH analysis (Table 2) (Patients 8, 10, 11, 15, 16, 17, 19, and 20). Five of those patients (Patients 8, 10, 17, 19, and 20) had amplification at 2p24 (*MYCN*), deletion at 1p, and gains at 17q. Other aberrations in these 5 patients included 2 patients (Patients 8 and 10) with $-11q23-25$, 2 patients (Patients 10 and 19) with $-10q25-26$ and $+18q$, and 1 patient (Patient 17) with $-3p21-25$ and -14 . One patient (Patient 15) who had nonamplified *MYCN* had normal 1p but had $+17q$ and $-11q$ as well as $-3p21-25$, $+6p$, -15 , and $+18$. The seventh patient (Patient 11) had no genetic imbalances in his malignancy and no *MYCN* amplification, although it

TABLE 5
Radiologic Characteristics

Characteristic	No. of patients
Anatomy	
Parenchymal only	8/23
Meningeal only	7/23
Parenchymal and meningeal	7/23
Ventricular/choroid (at diagnosis)	1/23
Location	
Supratentorial only	13/23
Infratentorial only	3/23
Supragentorial and infratentorial	7/23
Pattern of parenchymal metastases	
Single/multiple	7/8
Supratentorial/infratentorial/both	12/1/2
Size of largest lesion (mm)	
Range	10–65
Median	29
Cystic pattern	1
Calcification	1
Hemorrhage	8
Edema	6
Pattern of meningeal metastases	
Diffuse/focal	9/7 ^a
Linear/nodular	5/5 ^a
Optic chiasm	3
MIBG scan	
Positive	6
Negative	8
Doubtful ^a	2

MIBG scan: iodine-123 or iodine-131 metaiodobenzylguanidine scintiscan.

^a These patients (Patients 3 and 4) had MIBG positive lesions, but it could not be determined whether these were skull or brain parenchyma by MIBG because of multiple other known skull lesions.

was verified histologically that the sample contained tumor cells.

DISCUSSION

In the current study, we have reported a 3-year estimated risk of 8.0% for CNS metastasis in children with Stage 4 neuroblastoma. The current results did not appear to show the trend toward increasing risk over the past 15 years that has been suggested in other reports.^{2,3} We can compare only crude percentages in our study with other studies, which do not provide Kaplan–Meier estimates; and we have restricted such comparisons to studies that reported a denominator of patients with Stage 4 disease (Table 6). The crude percentage was 5.3% in the current series of patients with CNS metastasis, compared with the previous study covering the period 1982–1987 at the Institute Gustave Roussy, which reported 7 of 258 patients (3%) with CNS metastases. There is a wide range in the literature, from 2.3%, in the large CCG study of 567 children with Stage 4 neuroblastoma,¹ to 16%, in the single-institution report from Pittsburgh,³ and even as

high as 25% (3 of 12 high-risk patients), in a small series from Spain.⁴ The crude overall incidence in previous series of patients with CNS metastasis was 50 of 1315 patients (3.8%), slightly lower compared with our study.^{1–4,12–15} However, because the rate of CNS recurrence is dependent on the length of follow-up, and none of the previous reports provided Kaplan–Meier estimates of recurrence over time, the crude percentage may underestimate the actual risk, which is reported here as 8% at 3 years.

Almost all reported CNS metastases have occurred at the time of recurrence rather than at diagnosis. It is possible that more intensive systemic therapy has succeeded in ablating systemic areas of microscopic disease, thus permitting the emergence of a *sanctuary* recurrence. It is also possible that intensive chemotherapy leads to further genetic evolution of the tumors, with a change in metastatic potential. Tumor samples from the time of diagnosis were examined in 16 patients and showed a predominance of genetic changes connoting very high-risk disease. *MYCN* amplification was correlated significantly with CNS recurrence, as in the report of DuBois et al.,¹ which differs from the report of Kramer et al.,² who found that only 4 of 11 children had *MYCN*-amplified tumors, the usual percentage in a Stage 4 high-risk population. Seven patients had detailed studies of their tumor genetics by CGH and demonstrated, in addition to 2p24 amplification, multiple poor prognostic changes, such as gain of 17q and losses of 1p and 11q. One tumor without *MYCN* amplification (Patient 15) corresponded to Type 2 of Lastowska et al.¹⁶ Without tumor samples from recurrence, it is not possible to determine whether further changes or evolution occurred. In the future, cryopreservation of tumors in these patients at the time of metastasis may permit genetic comparisons with original tumor tissue.

The clinical presentation and timing of CNS recurrence in our series was similar to other reports, with symptoms referable to the location and nature of the lesion. Headache, nausea, and emesis were associated with parenchymal disease; whereas patients with meningeal disease presented more often with pain, fever, or motor signs. We found a slightly greater proportion of patients with meningeal involvement (65%) compared with what is reported in the literature (47%),^{1–4,12–15} and this value might have been even greater if routine spinal MRI studies had been performed. The time to CNS recurrence in the literature ranged from 2 months to 34 months, with median similar to the 14 months reported here. The median survival after CNS metastasis was extremely short in our patients, despite therapy, commensurate with previous reports.^{2–4,13} Patients with meningeal recur-

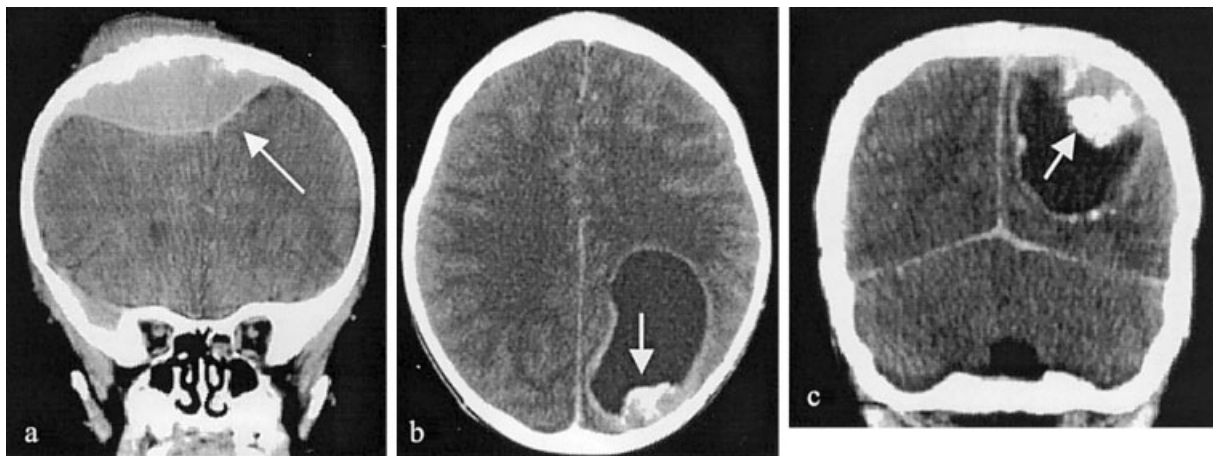


FIGURE 1. Images from Patient 15, a male age 2 years with headaches and emesis 2 years after undergoing hematopoietic stem cell transplantation. The patient had a single supratentorial central nervous system (CNS) parenchymal metastasis from neuroblastoma and concomitant bone and bone marrow recurrence. (a) A postcontrast computed tomography (CT) scan at the time of diagnosis (coronal view) showing skull metastasis with extradural involvement (arrow). (b–c) CNS recurrence seen on a postcontrast CT scan in axial (b) and coronal (c) views. A parenchymal parietooccipital mass is seen with a cystic component and a solid calcified (arrow) component without bone involvement.

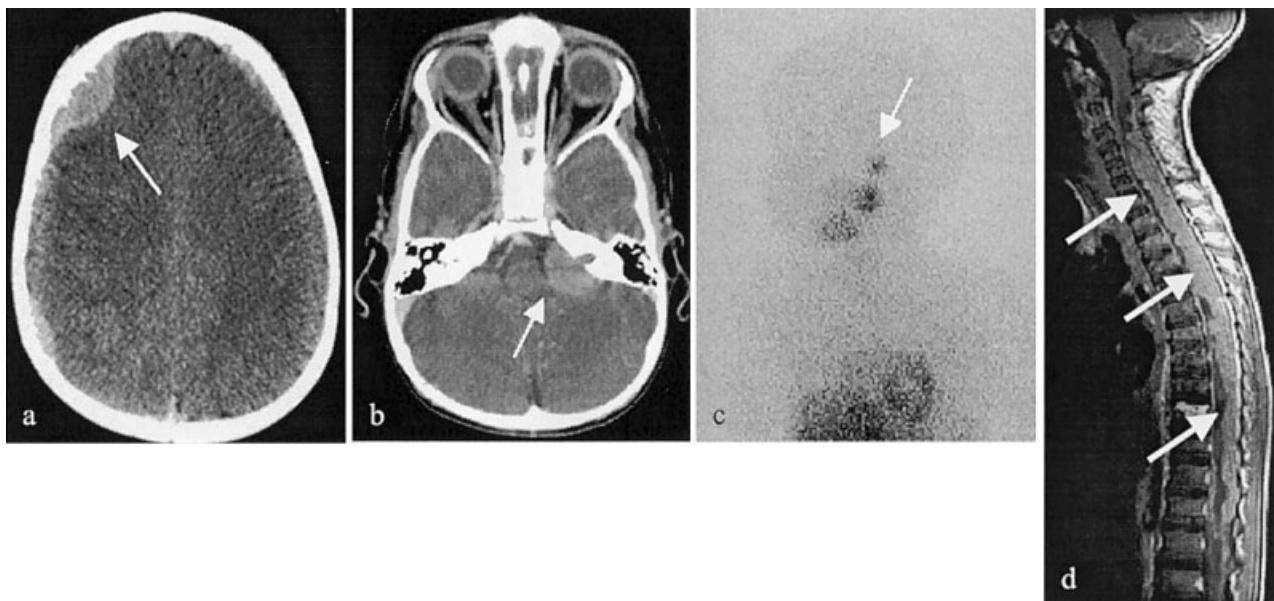


FIGURE 2. Images from Patient 22, a male age 2 years with isolated central nervous system (CNS) meningeal metastasis 16 months after undergoing hematopoietic stem cell transplantation. (a) A postcontrast computed tomography (CT) scan at the time of diagnosis (axial view) showing skull metastasis with extradural involvement (arrow). (b) CNS recurrence seen on a postcontrast CT scan (axial view). A noncalcified leptomenigeal mass without bone involvement is located in the pontocerebellar angle. (c) CNS recurrence seen on an iodine-123 metaiodobenzylguanidine scintiscan (lateral view). Left pontocerebellar uptake (arrow) corresponds to the leptomenigeal location. (d) CNS progression is seen 11 months later on a postcontrast, T1-weighted, sagittal magnetic resonance image that shows diffuse leptomenigeal involvement (arrows).

rence had a particularly short survival, especially patients with extensive diffuse involvement, who had a median survival of 0.9 months. DuBois et al. also observed this shortened survival, reporting that four patients with meningeal disease at diagnosis all died in

< 6 months. CNS recurrence was an isolated event in half of our patients, similar to other reports.¹

We found a significantly greater proportion of CNS metastases in the group that underwent LP compared with the group that did not undergo LP, similar

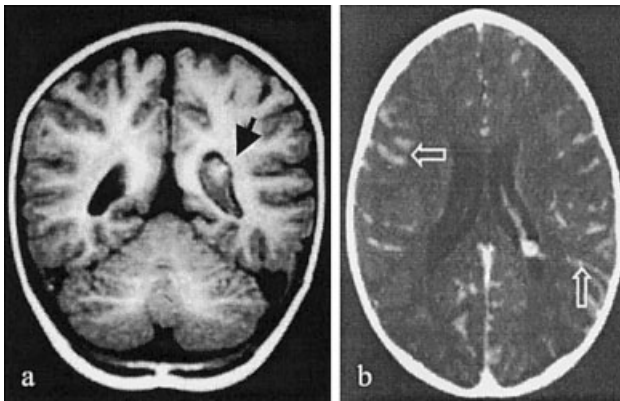


FIGURE 3. Images from Patient 8, a male age 1 year with intraventricular involvement at diagnosis and rapid meningeal progression on induction. (a) At diagnosis, a postcontrast, T1-weighted, coronal magnetic resonance image showed a left intraventricular heterogeneous mass (arrow). (b) Central nervous system (CNS) progression 5 months later seen on a postcontrast computed tomography scan (axial view). The scan shows a residual intraventricular mass, probably calcified, and diffuse leptomeningeal involvement (arrows).

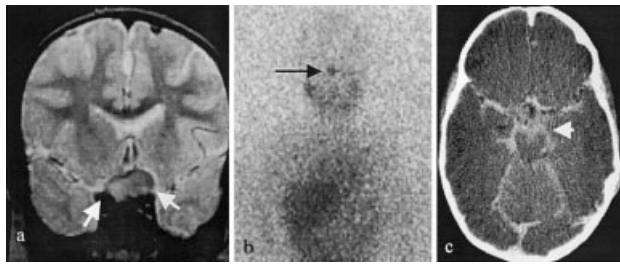


FIGURE 4. Images from Patient 9, a male age 4 years at 3 months off therapy, with acute visual loss and isolated meningeal metastases. (a) A T2-weighted, coronal magnetic resonance view shows a suprasellar mass with intermediate signal (arrows), consistent with a leptomeningeal location. (b) An iodine-123 metaiodobenzylguanidine scintiscan (anterior view) shows suprasellar uptake (arrow). (c) central nervous system progression 1 year later seen on a postcontrast computed tomography scan (axial view). Diffuse leptomeningeal involvement is seen with a predominant interpeduncular location (arrows).

to the report of Kramer et al.² However, LP was not a routinely required evaluation and was used only for patients with suspicion of parameningeal or meningeal involvement. In the report by Blatt et al., none of the patients with CNS recurrence underwent LP at diagnosis, despite the high incidence of CNS disease.³ It is difficult to determine whether contamination of CNS by circulating tumor cells in blood at the time of diagnosis leads to later CNS recurrence. Other authors previously reported a lack of evidence for direct penetration of the CNS from dural locations and the fact that the CSF appears to be the major conduit of tumor cell spread in the neuraxis.¹³ A meningeal or ventricular surface origin of the parenchymal locations

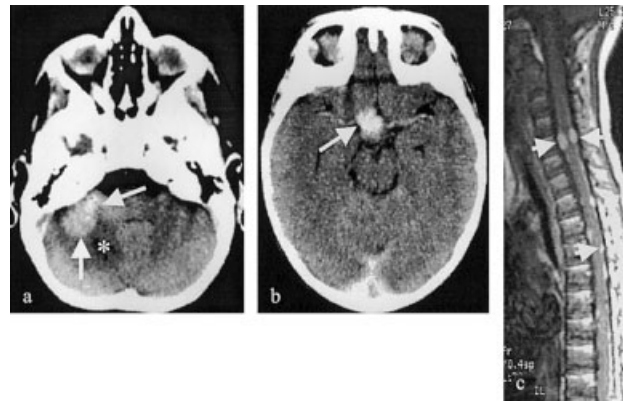


FIGURE 5. Images from Patient 18, a male age 3 years with mydriasis and hemianopsia from multifocal leptomeningeal recurrence and without other sites of recurrence. (a) A postcontrast computed tomography (CT) scan (axial view) shows a right cerebellar parenchymal mass (arrows) with peripheral edema (asterisk). (b) A postcontrast CT scan (axial view) shows a suprasellar mass (arrow), consistent with a leptomeningeal location. (c) A postcontrast, T1-weighted, sagittal magnetic resonance view shows multifocal, nodular, leptomeningeal involvement (arrows).

and/or focal microinvasion adjacent to Virchow-Robin spaces were suggested on the basis of pathologic comparisons.¹³

The radiologic features varied from single, large, parenchymal lesions to diffuse meningeal involvement. There was not a close association of intraparenchymal CNS disease with skull lesions, suggesting that these were blood-borne metastases. This is supported by the observation that CNS lesions are extremely rare at diagnosis, occurring later in the course of the disease. The radiologic pattern of parenchymal lesions has been described previously as cystic¹⁷ or hemorrhagic without edema.^{13,18} Cystic lesions were seen in two patients in our series (Patients 13 and 15). Imaging follow-up studies in Patient 13 suggested that the cystic pattern was the consequence of previous hemorrhagic necrosis, although others have presented evidence that it may be the result of disruption of the blood-brain barrier with plasma protein exudation.¹⁹ If the cystic pattern is isolated and in the absence of MIBG uptake, differentiation from other cystic brain neoplasms or infectious diseases may be impossible, rendering neurosurgical biopsy necessary.¹⁷ Edema was observed in < 50% of our patients with parenchymal lesions, mostly around the largest lesions (Fig. 5a). The exact incidence of hemorrhagic or calcified lesions was difficult to ascertain in this retrospective study, because not all patients had CT scans with precontrast examination. Hemorrhage was proven radiologically in \approx 50% of our patients with parenchymal lesions. Calcifications were seen rarely. Supratentorial

TABLE 6
Literature Review of Incidence of Central Nervous System Metastases in Children with High-Risk Stage 4 Neuroblastoma

Reference	Organization	Yrs	Median follow-up (mos)	Time to CNS recurrence (mos)	No. with CNS recurrence	No. with Stage IV disease	Crude % ^a
Kramer et al. ²	MSKCC	1980–1998	26	5–32	11	251	4.3
Shaw and Eden ¹⁴	ENGS	1982–1989	NA	13–29	10	NA ^b	NA
DuBois et al. ¹	CCG	1991–1996	25 ^c	2–15	13	567	2.3
Blatt et al. ³	Pittsburgh	1978–1993	NA	11–30	7	43	16.3
Astigarraga et al. ⁴	Hospital de Cruces	1987–1990	NA	9–16	3 ^d	12	25.0
Bouffet et al. ¹⁵	Centre Leon Bernard	1987–1995	NA	9–17	3	160	1.8
Rohrlich et al. ¹²	Gustave-Roussy	1982–1987	NA	8–29	7	122	5.7
Kellie et al. ¹³	St. Jude's	1978–1989	NA	2–34	6 ^d	160	3.8

CNS: central nervous system; MSKCC: Memorial Sloan-Kettering Cancer Center; ENGS: European Neuroblastoma Study Group; CCG: Children's Cancer Group; NA: data not available.

^a Crude %: [the number of patients with CNS metastases at first recurrence ÷ number of patients with Stage IV disease at the time of diagnosis] × 100.

^b There were 950 patients with neuroblastoma of all stages; the number of patients with Stage 4 neuroblastoma was not provided.

^c Unpublished data provided by the CCG.

^d Patients in these reports were excluded when the CNS was not the first site of recurrence.

lesions, as reported previously, are more common than infratentorial involvement.

The radiologic pattern of meningeal metastasis has been reported sporadically.^{3,13} We observed nonspecific, diffuse or localized, linear or nodular meningeal enhancement. It is noteworthy that three patients had a suprasellar/optic chiasm nodular location that was observed without simultaneous sphenoidal bone involvement. This particular location also was observed in one patient from the series by Blatt and colleagues.³ The meninges were involved primarily and solely in only three patients, whereas other patients developed meningeal disease in combination with parenchymal lesions or other metastases. An intraventricular location appears to be exceptional: It was observed at diagnosis in only one patient in our series (Fig. 3) and has not been reported previously.

It is interesting to note that MIBG scans were not always a reliable means of detecting CNS metastasis, because they were negative in over half of the patients. This was due in part to difficulty in discriminating CNS lesions from skull lesions without SPECT images and in part to some patients with meningeal disease without bulky lesions. However, there were 5 patients with positive tumor uptake of MIBG systemically who had CNS tumors that were not visualized, despite the fact that each of these patients had at least 1 CNS nodular lesion measuring > 1 cm in greatest dimension. Although it is possible to speculate that MIBG does not cross the blood-brain barrier, multiple studies both in rat brain²⁰ and after diagnostic²¹ and therapeutic doses in humans have demonstrated physiologic uptake of MIBG in the cerebellum as well as in basal nuclei and the thalamus.^{22,23} There are rare re-

ports of uptake in other CNS neuroendocrine lesions: one in a metastatic medullary thyroid carcinoma²⁴ and one in an intracerebral retinoblastoma.²⁵ Because neuroimaging is not performed routinely in patients with metastatic recurrence from neuroblastoma, because false negative MIBG scans appear to be common for patients with CNS lesions, and because clinically asymptomatic patients have been described previously,³ the incidence of CNS metastases may be underestimated.

In conclusion, CNS metastasis in patients with neuroblastoma is rare at diagnosis but occurs most commonly in the first 18 months after diagnosis, with an estimated 3-year risk of 8%. The rate of CNS disease has not appeared to change in the past 15 years, the time in which myeloablative therapy has been standard. Half of the patients who develop recurrent CNS disease have isolated parenchymal metastases. Predictive features at the time of diagnosis for CNS recurrence are ages 2–3 years, tumor *MYCN* amplification, and LP at diagnosis (although it is not known whether LP has any cause or effect on presentation). MIBG scan is not a reliable indicator of CNS disease, and other modalities should be used to rule out CNS metastasis. Further investigation of tumor genetics may elucidate the propensity of some of these tumors to metastasize to the CNS, and the use of drugs with CNS penetration may help prevent such growth.

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