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Orbital metastasis is associated with decreased survival in stage M neuroblastoma

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Abstract

Background—Approximately 30% of patients with metastatic (stage M) neuroblastoma present with periorbital ecchymosis from orbital osseous disease. Though locoregional disease is staged by imaging, the prognostic significance of metastatic site in stage M disease is unknown. We hypothesize that, compared to non-orbital metastasis, orbital metastasis is associated with decreased survival in patients with stage M neuroblastoma, and that periorbital ecchymosis reflects location and extent of orbital disease.

Procedure—Medical records and imaging from 222 patients with stage M neuroblastoma seen at St. Jude Children's Research Hospital between January 1995 and May 2009 were reviewed. Thirty-seven patients were <18 months of age at diagnosis and 185 were ≥18 months. Overall (OS) and 5-year survival (5YS) were compared for patients with and without orbital, calvarial and non-orbital osseous metastasis, and with and without periorbital ecchymosis (log-rank test).

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Conflicts of Interest
None.

Associations of periorbital ecchymosis with orbital metastasis location/extent were explored (fisher's exact test, t-test).

Results—In patients ≥ 18 months of age, only orbital metastasis was associated with decreased 5YS ($p=0.0323$) and OS ($p=0.0288$). In patients <18 months of age, neither orbital, calvarial or non-orbital bone metastasis was associated with OS or 5YS. Periorbital ecchymosis was associated with higher number of involved orbital bones ($p=0.0135$), but not location or survival.

Conclusions—In patients ≥ 18 months of age with stage M neuroblastoma, orbital metastatic disease is associated with decreased 5YS and OS. In future clinical trials, orbital disease may be useful as an imaging-based risk factor for sub-stratification of stage M neuroblastoma.

Keywords

neuroblastoma; orbit; metastasis; survival; stage M

Introduction

Neuroblastoma, an embryonal malignancy of the sympathetic nervous system, is the most common extra-cranial pediatric solid tumor, and accounts for $>7\%$ of all pediatric cancers. Approximately 50% of patients present with disseminated metastases, most frequently to bone.[1,2] Historically denoted Stage 4 disease by the International Neuroblastoma Staging System (INSS),[3] overall survival of disseminated neuroblastoma is as low as 22–27%, compared to up to 91% in those lacking distant metastasis or with stage 4S disease (<12 months of age with distant involvement limited to skin, liver and/or 10% marrow involvement).[4]

With the advent of the International Neuroblastoma Risk Group staging system (INRGSS) in 2008, staging of neuroblastoma shifted pre-treatment risk classification from a surgically-based (INSS) system to a radiology-based assessment of extent of disease. In the new staging system, locoregional tumors previously considered stages 1, 2 or 3 are stratified into stages L1 or L2 based on a set of image-defined risk factors (IDRFs).[5] Under the INRGSS, patients <18 months with distant involvement limited to the skin, liver or 10% bone marrow are considered Stage MS; those with metastasis at other sites are considered Stage M and high-risk if *MYCN* is amplified. [4] Patients ≥ 18 months of age with any metastasis are considered Stage M, with uniformly high risk regardless of *MYCN* status.[4]

Periorbital ecchymosis associated with orbital metastasis is observed in 28–33% of patients at diagnosis and is often the first clinical sign of disease. [6,7] Though orbital metastases frequently have extraosseous soft tissue components which result in proptosis and other ocular manifestations, the site of metastasis is to orbital bone.[8,9] Bone metastasis, a negative prognostic factor in neuroblastoma, is present in most patients with stage 4/M disease, [2,3,10] and in 1999 DuBois et al. reported a correlation between the presence of intracranial or orbital bone metastases and tumor *MYCN* amplification, a poor prognostic marker.[11] However, neither *MYCN* amplification nor Shimada classification alone definitively predict survival in patients >1 year old with stage 4/M disease, potentially due to still-undefined prognostic factors, [12–15] and there is currently no imaging-based sub-

stratification of risk for Stage M neuroblastoma. We hypothesize that in patients with stage M (metastatic) neuroblastoma, the prognosis for patients with orbital metastasis is less favorable than for patients with extra-orbital osseous or non-osseous metastasis, and that the presence of periorbital ecchymosis reflects location and extent of orbital metastasis. To test these hypotheses, we performed a retrospective review of imaging and clinical data in a large pediatric cohort at St. Jude Children's Research Hospital.

Methods

Following approval by our institutional review board, a retrospective search of the electronic medical record yielded 334 patients evaluated for a diagnosis of primary or relapsed neuroblastoma at our institution between January, 1995 and May, 2009. Sites and dates of disease involvement as recorded in the medical record were reviewed. Patients ≥ 18 months of age with evidence of distant metastasis according to INRGSS criteria were defined as having Stage M (high-risk) metastatic disease. Patients <18 months of age with stage M disease by INRGSS criteria were stratified into high-risk (*MYCN* amplified) and low/intermediate risk (*MYCN* non-amplified) groups.[4,5] Dates of initial diagnosis of neuroblastoma and sites of disease were reviewed. Dates of death were recorded when applicable. Osseous and orbital metastases were classified as occurring at diagnosis (defined as within 30 days of diagnosis of neuroblastoma), during treatment (defined as 30–365 days after diagnosis) or at recurrence/progression (>365 days after diagnosis). At a minimum, all patients with Stage M disease underwent surgical resection and received similar cytotoxic chemotherapy. Patients with stage M disease who were ≥ 18 months of age at diagnosis or <18 months with high-risk disease received induction chemotherapy, consolidation with high-dose chemotherapy followed by autologous stem cell transplant, radiation therapy to the primary tumor bed and 6 courses of cis-retinoic acid. Only five children received anti-GD2 immunotherapy, as this retrospective study included patients diagnosed prior to publication of the randomized trial which demonstrated a survival benefit of anti-GD2 immunotherapy in high-risk neuroblastoma.[16] Imaging studies for subjects with documented orbital, calvarial or CNS metastases, and those with documented widespread osseous disease without specific metastasis location reported, were reviewed by a board-certified pediatric neuroradiologist with certificate of added qualification (JHH) for clarification of site. The imaging of all patients <18 months of age was reviewed for determination of focal osseous metastasis (stage M) versus meta-iodobenzylguanidine (MIBG)-negative marrow involvement by aspirate (stage MS). For patients with orbital metastasis and adequate cross-sectional imaging, lesions were localized to the right or left greater or lesser sphenoid wings; sphenoid body; pterygoid; ethmoid/lacrimal; frontal; maxilla; zygoma. Though extra-orbital, temporal bone or clivus metastases were also recorded due to the association between skull base trauma and periorbital ecchymosis,[17] to exclude metastasis at these sites as contributory to periorbital ecchymosis. Each bone was evaluated for the presence or absence of metastasis, and the total number of involved bones recorded. Clinical notes were reviewed for presence or absence of periorbital ecchymosis at the time of imaging.

Statistical Analysis

For groups with more than 30 subjects, the log-rank test was employed to investigate differences in overall survival (OS) from initial diagnosis of neuroblastoma between subjects with orbital metastasis with vs. without periorbital ecchymosis; subjects with vs. without bone metastasis; subjects with vs. without calvarial metastasis; and subjects with orbital or non-orbital bone metastases based on timing of metastasis (at diagnosis, during treatment, at recurrence and overall). The exact log-rank test was used to compare OS in groups with fewer than 30 and at least 5 subjects. Differences in 5-year survival (5YS) were investigated by Fisher's exact test and chi-square test dependent on sample size in groups. OS and 5YS were not compared for groups with fewer than 5 subjects. No statistical adjustment for treatment was performed, as treatment is based on stage and all subjects were Stage M.[4] The Cox regression model was used to explore the association between age at neuroblastoma diagnosis and time to death. All the above analyses were performed separately for subjects less than 18 months with and without *MYCN* amplification (high and low/intermediate risk respectively), and subjects at least 18 months old.

The Wilcoxon rank sum test was used to investigate the association between periorbital ecchymosis and age at diagnosis of neuroblastoma and between periorbital ecchymosis and age at orbital metastasis. Fisher's exact test was employed to investigate the difference in lesion location between patients with and without documented periorbital ecchymosis. T-test was used to compare number of involved orbital bones between patients with and without documented periorbital ecchymosis. Significance was assumed when p value <0.05. Exact log-rank tests were performed in StatXact version 10.1. All other statistical tests were performed in SAS software 9.3.

Results

Of 334 subjects, 222 had metastatic (stage M) neuroblastoma. Age, gender and INRGSS staging of the overall cohort, and of the < and ≥ 18 month sub-groups, are summarized in Table I. Nine children with biopsy-confirmed metastatic neuroblastoma, all ≥ 18 months of age, had a diagnosis of ganglioneuroblastoma at the primary tumor site. Sites of primary tumor in subjects with stage M neuroblastoma are outlined in Table II.

Bone, calvarial, and orbit metastasis and survival in stage M neuroblastoma

Associations of bone metastasis, orbital metastasis and periorbital ecchymosis with 5YS and OS in children with neuroblastoma and Stage M disease are summarized in Table III. Associations between time to development of orbital and non-orbital bone metastasis and survival are summarized in Table IV. Fifty-six subjects had orbital metastases documented in the medical record and reported on computed tomography (CT), magnetic resonance imaging (MRI), MIBG and/or ^{99m}Tc-MDP bone scan. All subjects with orbital metastasis (n=56) also had extra-orbital bone metastases, which were contemporaneous with (38 at diagnosis, 6 at recurrence) or preceded orbital metastasis (n=12) in all cases. Orbital metastasis was strongly associated with the presence of calvarial metastasis (p<.0001); 48 of 80 subjects (60%) with calvarial metastasis also had orbital metastasis.

<18 months of age

Both 5YS ($p=0.0024$) and OS ($p=0.017$) were significantly lower for subjects <18 months of age with tumor *MYCN* amplification (high-risk, $n=19$) compared to those without ($n=17$). *MYCN* status was unknown for one subject. Neither orbital, calvarial nor non-orbital bone metastasis influenced OS or 5YS, regardless of *MYCN* status (Table III).

18 months of age

In subjects 18 months of age with stage M disease, the presence of orbital metastasis was associated with significantly decreased 5YS ($p=0.0323$) and OS ($p=0.0288$) [Table III, Figure 1]. 5YS rate was similar when orbital metastases were first present at diagnosis (29%) or at recurrence (27%); 5YS when diagnosed during treatment was 0. Statistical comparison was precluded by sample size <5 in the during treatment group.

An association between calvarial metastasis and decreased 5YS ($p=0.0439$) was not significant once orbital metastasis was taken into account, and there was no association between calvarial metastasis and OS (0.0947). Neither presence nor timing of non-orbital bone metastases was associated with 5YS or OS [Table III, Table IV].

Age and Survival

OS ($p<0.0001$) and 5YS ($p=0.0006$) were significantly decreased for patients 18 months compared to patients <18 months of age [Table III, Table IV].

For subjects 18 months of age with stage M disease without orbital metastasis, survival was negatively associated with age at diagnosis; in this group, the risk of death increased by 6.1% for each one year increase in age at neuroblastoma diagnosis (hazard ratio 1.061, $p=0.0404$). There was no such association in subjects 18 months with orbital metastasis ($p=0.8334$), for whom both 5YS and OS were poor.

For subjects <18 months of age with stage M neuroblastoma, there was no association between age at initial diagnosis and survival in subjects with ($p=0.1118$) or without ($p=0.8819$) orbital metastases.

Periorbital ecchymosis

All subjects with periorbital ecchymosis had orbital metastasis. Of 56 subjects with orbital metastasis, 13 (23.2%) had documented periorbital ecchymosis; ecchymosis status was unknown for one subject. Patients with ecchymosis were significantly younger (2.39 ± 1.43 years) than those without ecchymosis (5.05 ± 3.98 years) ($p=0.0103$). Because correlating periorbital ecchymosis with metastasis site required precise lesion localization, eight patients diagnosed with orbital metastasis only by MIBG without adequate cross-sectional imaging were excluded from this sub-analysis. The imaging examinations of 48 children were evaluable and included 26 CT scans, 20 MRI scans, and two MIBG studies which proved adequate for disease localization without additional cross-sectional imaging. MIBG acquired within two days of CT was used to assist in lesion localization in one patient. The sphenoid body was most frequently involved (42/48 evaluable subjects), followed by the greater sphenoid wing ($n=40$), frontal bone ($n=33$), lesser sphenoid wing ($n=28$), maxilla ($n=26$),

zygoma (n=25), pterygoid process (n=17) and ethmoidal/lacrima region (n=16). Patients with ecchymosis had a greater number of involved orbital bones (p=0.0135) [Figure 2]. Periorbital ecchymosis was not associated with orbital lesion location. In subjects 18 months, ecchymosis did not influence 5YS or OS. There were too few subjects <18 months with periorbital ecchymosis for statistical comparison of survival [Table III].

Discussion

Despite overall improvement in outcomes in neuroblastoma, the prognosis for children with metastatic (stage M) disease remains poor. Refinement of risk stratification in patients with low and intermediate-risk neuroblastoma according to biologic and imaging-based risk factors has facilitated the successful implementation of risk-stratified therapies, but remains elusive in high-risk, metastatic (stage M) neuroblastoma.[4,10] Though several potential biologic markers for sub-stratification of risk in stage M neuroblastoma have been identified, their precise relationship to disease progression remains unclear.[4,18,19] Patterns of metastasis may provide insight into biologic mechanisms of disease progression, and provide a basis for imaging-based risk stratification in high-risk, stage M neuroblastoma. [10,20,21]

Bone metastasis is associated with poor prognosis in neuroblastoma, and is present in most children with stage M disease.[2,3,10] In this study, we found that while extra-orbital bone metastasis conferred no additional risk in children 18 months of age with stage M (high-risk) disease, the presence of orbital bone metastasis was associated with decreased overall and 5-year survival post-diagnosis of neuroblastoma. There was no such association in children <18 months of age with either high-risk (*MYCN* amplified) or low/intermediate risk (*MYCN* non-amplified) stage M neuroblastoma, in whom prognosis is more favorable overall (Table III, Table IV).[4] This finding may be of use in imaging-based sub-stratification of risk for patients 18 months old with stage M disease.

Identifying patterns of metastasis may also contribute to our understanding of how molecular changes lead to progression of metastatic neuroblastoma. Metastatic neuroblastoma cells undergo continuous molecular changes that optimize their ability to survive, [1,22] and can differ significantly in their propensity for osseous metastasis despite *MYCN* status. [23] Neuroblastoma cells metastatic to bone down-regulate the expression of cell adhesion molecules, and upregulate genes normally expressed by bone marrow cells, thereby evading detection by the immune system. [24] We found that regardless of patient age, orbital metastasis occurred at the same time or after, but never before, extra-orbital osseous metastasis, implying a unidirectional sequence of events. This could indicate that additional abnormalities are required for spread of tumor to certain sites. Comparison of genomic/structural anomalies between primary tumor and site-specific metastases may contribute to our understanding of how accumulated abnormalities, in conjunction with site-specific microenvironments, contribute to progressive dissemination of disease. The study of orbital metastasis may be particularly helpful in this regard, given its late onset and frequently superficial location, facilitating biopsy.

The cause of periorbital ecchymosis in neuroblastoma remains elusive. We found no association between location of orbital metastasis and ecchymosis. Subjects with periorbital ecchymosis had a greater number of involved orbital bones ($p=0.0135$) and were younger than those without ecchymosis ($p=0.0103$), suggesting that immaturity of periorbital vessels and/or degree of anatomic disruption may contribute to the development of ecchymosis. There was no independent association between the presence of periorbital ecchymosis and survival, despite the presence of orbital metastasis in all patients with ecchymosis. This could be in part because some patients with orbital metastasis were without ecchymosis, lowering the survival rate in the “no ecchymosis” group, and in part due to the small number of patients with ecchymosis, limiting our ability to detect a significant difference in survival.

This retrospective study has several limitations. Patients did not receive routine ophthalmologic screening, nor was periorbital ecchymosis recorded in the medical record consistently, potentially affecting the relationship with survival. Exclusion of eight patients without cross-sectional imaging from the sub-analysis of orbital lesion location vs. ecchymosis may have decreased our statistical power to detect such an association. Additionally, adjustments for treatment or primary tumor site were not independently evaluated, although all patients had stage M neuroblastoma and received similar treatment. However, due to the change in the staging system from INSS to INRGSS during the period reviewed by this study, some subjects between 12 and 18 months who may have been treated as high-risk under the INSS were considered as low-risk for this study, potentially altering survival calculations for the <18 month age group in an unpredictable way. We did not correlate survival and orbital vs. non-orbital bone metastasis with genomic data or with overall extent of disease, as these were outside the scope of this study, but these would be worthwhile future endeavors. Finally, the results of this single-center, retrospective study are subject to the inherent limitations of this approach, and should be validated by larger multicenter trials prior to their incorporation into clinical staging guidelines.

In conclusion, orbital metastases occur contemporaneously with or after extra-orbital bone metastases in neuroblastoma, and are independently associated with decreased 5-year and overall survival in children 18 months of age with stage M disease. Orbital metastasis may be useful as an imaging-derived risk factor for sub-stratification of stage M neuroblastoma. Future investigation may clarify the relationship between site-specific metastasis and the accumulation of genomic/structural chromosomal abnormalities in neuroblastoma.

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Abbreviation key

5YS	5-year survival
99m Tc-MDP	technetium 99m-methylene diphosphate

CI	confidence interval
CT	computed tomography
IDRF	Image-defined risk factor
INRGSS	Interntional Neuroblastoma Risk Group Staging System
INSS	International Neuroblastoma Staging System
MIBG	metaiodobenzylguanidine
MRI	magnetic resonance imaging
NCAM	neural cell adhesion molecule
OS	Overall survival
STIR	short tau inversion recovery
T1WI	T1-weighted image
TP53	tumor protein 53

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Figure 1.

Overall survival is decreased in subjects 18 months of age with Stage M neuroblastoma with (red line) orbital metastasis compared to those without (blue line) orbital metastasis ($p=0.0288$).

Figure 2.

Coronal STIR (a) and axial T1WI +contrast (b) MR images show extensive orbital osseous metastasis in a one-year-old child with widespread osseous metastasis by MIBG (c) and periorbital ecchymosis at initial diagnosis with neuroblastoma. In a 9-year-old child with newly diagnosed neuroblastoma, also widely metastatic to bone by MIBG (d), coronal STIR (e) and axial T1WI +contrast (f) show a similar distribution, though fewer number, of orbital osseous metastases; there was no documented periorbital ecchymosis. (F=frontal; Z=zygoma; M=maxilla; GrW=greater wing of sphenoid; Bdy=body of sphenoid; E=ethmoid; T=temporal. * = inflammatory sinus mucosal thickening.)

Table 1

Characteristics of the overall cohort and <18 month & 18 month subgroups.

All Stage M		<18 months			18 months	
		All	MYCN Amp	MYCN Non-amp	MYCN Unknown	All
Number		222	37	19	17	185
Gender						
Female		84(38%)	19(51%)	8(42%)	11(65%)	65 (35%)
Male		138(62%)	18(49%)	11(58%)	6(35%)	120 (65%)
Age (years)						
mean(sd)		4.13(3.26)	0.88(0.46)	1.13(0.33)	0.64(0.43)	4.78(3.19)
(min, max)		(0.01, 19.39)	(0.01, 1.47)	(0.01, 1.47)	(0.02, 1.28)	(1.51, 19.39)
					n/a	

Table II

Primary Tumor Site in Stage M Disease.

	Overall	<18 months	18 months
Abdomen	8	1	7
Adrenal	153	25	128
Celiac axis	4	n/a	4
Mediastinum/Thorax	12	2	10
Neck	4	1	3
Paraspinal/paraaortic	9	3	6
Retroperitoneal	24	4	20
Pelvis	3	1	2
NOS	5	n/a	5
Total	222	37	185

Table III

Survival by orbital vs. non-orbital bone metastasis, calvarial metastasis and ecchymosis in Stage M subjects.

	Subjects		5-year Survival		Overall Survival
	n=	%	rate (%)	P=	P=
Stage M, <18 Months, All:					
<hr/>					
Non-orbital Bone Metastasis					
	Present	16	43%	63%	0.1832
	Absent	11	30%	91%	0.4282
Calvarial Metastasis					
	Present	13	35%	77%	0.7106
	Absent	24	65%	67%	0.1927
Orbital Metastasis					
	Present	10	27%	60%	0.4417
	Absent	27	73%	74%	0.8336
Ecchymosis					
	Present	4	11%	50%	**
	Absent	33	89%	73%	**
<hr/>					
<18 Months, MYC/Non-amplified (Low/intermediate risk):					
<hr/>					
Non-orbital Bone Metastasis					
	Present	6	35%	100%	1
	Absent	8	47%	88%	0.1668
Calvarial Metastasis					
	Present	6	35%	100%	1
	Absent	11	65%	91%	0.1094
Orbital Metastasis					
	Present	3	18%	100%	**
	Absent	14	82%	93%	**
Ecchymosis					
	Present	1	6%	100%	**
	Absent	16	94%	94%	**

	Subjects		5-year Survival		Overall Survival	
	n=	%	rate (%)	P=	P=	
<hr/>						
<u><18 Months,MYCNamplified (High-risk):</u>						
<hr/>						
Non-orbital Bone Metastasis						
	19		47%			
Present	10	53%	40%	**	**	
Absent	2	11%	100%			
Calvarial Metastasis						
Present	7	37%	57%	0.65	0.36	
Absent	12	63%	42%			
Orbital Metastasis						
Present	7	37%	43%	1.00	0.98	
Absent	12	63%	50%			
Ecchymosis						
Present	3	16%	33%	**	**	
Absent	16	84%	50%			
<hr/>						
<u>Stage M, 18 Months (all High-risk):</u>						
<hr/>						
Non-orbital Bone Metastasis						
Present	124	67%	41%	0.06	0.48	
Absent	15	8%	67%			
Calvarial Metastasis						
Present	67	36%	30%	0.04	0.09	
Absent	118	64%	45%			
Orbital Metastasis						
Present	46	25%	26%	0.03	0.03	
Absent	139	75%	44%			
Ecchymosis						
Present	9	5%	33%	1	0.82	
Absent	176	95%	40%			

** n<5, no statistical analysis/comparison

Table IV

Survival by timing of orbital vs. non-orbital bone metastasis in Stage M subjects.

All <18 months:				MYCN non-amplified (Low/Intermediate-risk):				MYCN amplified (High-risk):				>18 Months (High-risk):			
n=	%	5YS rate (%)**	n=	%	5YS rate (%)**	n=	%	5YS rate (%)**	n=	%	5YS rate (%)	5YS P=	OS P=		
Non-orbital Bone Metastasis															
37		70%	17		94%	19		47%	185		39%				
At Diagnosis															
14	38%	71%	6	35%	100%	8	42%	50%	105	57%	44%	0.2	0.06		
30–365 days post-diagnosis															
0	0%	n/a	0	0%	n/a	0	0%	n/a	7	4%	14%				
>365 days post-diagnosis															
2	5%	0%	0	0%	n/a	2	11%	0%	11	6%	27%				
Orbital Metastasis															
At Diagnosis															
10	27%	60%	3	18%	100%	7	37%	43%	28	15%	29%	1	0.71		
30–365 days post-diagnosis															
0	0%	n/a	0	0%	n/a	0	0%	n/a	3	2%	0%	**	**		
>365 days post-diagnosis															
0	0%	n/a	0	0%	n/a	0	0%	n/a	15	8%	27%				

** No statistical comparison; <5 subjects in comparison group