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Incidence, Ocular Manifestations, and Survival in Children with Neuroblastoma: A Population-Based Study

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Abstract

Purpose—To determine the incidence, ophthalmic manifestations, and survival among children with neuroblastoma in a defined population.

Design—Population-based retrospective cohort.

Methods—The medical records of all pediatric (< 19 years) residents of Olmsted County, Minnesota diagnosed with neuroblastoma from January 1, 1969, through December 31, 2008, were retrospectively reviewed.

Results—Fourteen children were diagnosed with neuroblastoma as residents of Olmstead County, Minnesota, during the 40-year period, yielding an age- and gender-adjusted incidence of 11.8 (95% confidence interval [CI]: 5.6 -18.0) per million patients < 15 years of age. The calculated incidence for patients presenting before the age of 5 in this cohort was 1 in 5970 children (95% CI: 3920 – 12580 children). The mean age at diagnosis for the 14 study patients was 22.5 months (range, .4 - 42.6 months). Six (43%) of the 14 (95% CI: 18% -71%) had ocular manifestations, including orbital metastasis in 6 (100%), proptosis and ecchymosis in 4 (67%), ptosis in 2 (33%), and strabismus in 1 (17%). The Kaplan-Meier rate of survival for all 14 children was 57% at 1 year (95% CI: 36% – 90%) and 50% at 5 years (95% CI: 30% - 84%), while the 6 with eye findings had a survival rate of 17% at 9 months (95% CI: 3-100%).

Conclusions—The incidence of neuroblastoma in this population was 11.8 per million patients < 15 years, with ophthalmic involvement observed in 6 (43%) of the 14 study patients. Orbital metastasis in the 6 children in this cohort was associated with poor prognosis.

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Neuroblastoma is the most common extracranial solid tumor among children under the age of 5 years, with a published incidence for that age of approximately 1 in 7000 children.¹⁻⁴ Neuroblastic tumors are derived from primordial neural crest cells and ultimately populate the sympathetic ganglia, adrenal medulla, and other sites.⁴ Recent advancements in the understanding of tumor biology have aided in the diagnosis and medical management of this disease. However, cases of widespread metastasis, at times signaled by proptosis, ecchymosis, and other signs of orbital involvement, continue to have a poor prognosis.⁵ Ophthalmic manifestations are well documented and include proptosis,^{1,6,7} periorbital ecchymosis,^{1,6,7} Horner syndrome,⁸⁻¹¹ opsoclonus/myoclonus,¹² ocular motility defects,^{1,13} ptosis,¹³ and blindness.^{6,14}

Retrospective reviews conducted at large referral centers have found orbital metastasis in 10-20% of cases with neuroblastoma;^{1,6,7} however, there have been no population-based studies with which to compare these findings. The purposes of this study are to report the incidence and ophthalmic manifestations of neuroblastoma among a cohort of patients < 19 years diagnosed as residents of Olmsted County, Minnesota, over a defined 40-year period, and to calculate survival rates based on ophthalmic involvement.

Subjects and Methods

The medical records of all pediatric (< 19 years) patients residing in Olmsted County when diagnosed with neuroblastoma from January 1, 1969, through December 31, 2008, were retrospectively reviewed. Potential cases of neuroblastoma were identified using the resources of the Rochester Epidemiology Project, a medical record linkage system designed to capture data on any patient-physician encounter in Olmsted County, Minnesota.¹⁵ The racial distribution of Olmsted County residents in 1990 was 95.7% Caucasian, 3.0% Asian-American, 0.7% African-American, 0.3% each Native American and other. The population of this county (106,470 in 1990) is relatively isolated from other urban areas, and essentially all medical care is provided to residents by the Mayo Clinic or the Olmsted Medical Group and their affiliated hospitals.

All diagnosis were entered into the Rochester Epidemiology Project database and residency status was verified by specially-trained personnel. Children not living in Olmsted County at the time of their diagnosis were excluded. Neuroblastoma was defined in this study by clinical diagnosis, based on tumor biopsy results, catecholamine levels, and other systemic findings. Data collected included age at diagnosis, presenting symptoms, tumor staging, treatment received, ophthalmic involvement, and final outcome.

The cumulative probability of death was estimated using the Kaplan-Meier method.¹⁶ Continuous data were presented as a mean with the range. Categorical data were presented as counts and percentage. Annual age- and gender-specific incidences rates were constructed using the age- and gender-specific population figures for the county from the US Census. Estimates from the State of Minnesota were used to aid with linear interpolation of the 1970, 1980, 1990, and 2000 census years. The 95% confidence intervals were calculated with assumptions based on the Poisson distribution.

Results

A total of 14 patients < 19 years of age were diagnosed with neuroblastoma as residents of Olmsted County, Minnesota, during the 40-year study period, yielding an annual age- and gender-adjusted incidence of 11.8 cases per million children < 15 years of age. All 14 cases presented before the age of 5, leading to an age-adjusted incidence of 33.5 cases per million, or 1 per 5970 children < 5 years.

Clinical information, including age at diagnosis, presenting symptoms, ophthalmic site, tumor stage, and final outcome were recorded for all 14 patients (Table). The mean age at diagnosis for all 14 was 22.5 months (range, 0.4 – 42.6 months) and 8 (57%) were female. The adrenal gland was the primary site in 10 (72%) of the 14, 3 (21%) were in the abdomen, and 1 (7%) was located in both the mediastinum and thoracic spine. Eight (57%) of the 14 were diagnosed as stage IV, with 2 (14%) each of stage II, III, and IVS.

Ophthalmic involvement was noted in 6 (43%) (95% CI: 18% - 71%) of the 14 cases and was the presenting symptom in 2 (14%). Metastasis to the orbit was seen in all 6 cases with ocular involvement. There were 4 bilateral presentations and 1 each affecting the left and right orbit respectively. Proptosis and ecchymosis occurred in 4 (67%) of the 6 cases, ptosis was observed in 2 (33%), and 1 (17%) patient had strabismus. The 9-month survival in patients with orbital metastasis was 17% (95% CI: 3-100%) with an average age at diagnosis of 30.3 months (range, 21.5 – 42.6 months).

Seven of the 14 cases achieved clinical remission yielding a survival rate of 50% (95% CI: 30-84%) at 18 months (Figure 1). Survival was heavily age- and stage-dependent, and overall survival varied with the decade of the study, with markedly improved survival noted in cases presenting after 1980 (Figure 2). The 4 cases that presented before 1 year of age had a 100% 5-year survival, while the 10 cases presenting after their first birthday had a 5-year survival of only 30%. The 5-year survival for all 8 stage IV presentations was 13%. The mean survival for all 14 cases was 110.7 months (range, 3.1 – 454.6 months), while average survival for those with ocular involvement was only 5.6 months (range, 3.1 – 9.1 months).

Discussion

Neuroblastoma was diagnosed in 14 children or 11.8 per million patients less than 15 years of age as resident of Olmsted County, Minnesota, during the 40-year study period. Ocular involvement occurred in 6 (43%) with orbital metastasis observed in all 6 patients. The Kaplan-Meier rate of survival for all 14 children was 50% at 5-years and 0% at 1 year for the 6 children with orbital metastasis. None of the children had Horner syndrome or opsoclonus.

Neuroblastoma accounts for 8% to 10% of all childhood cancers, with a gender-and race-adjusted published incidence of 9.8 annual cases per children < 15 years.¹⁷ Prior studies of incidence are lower than that reported in this study; however, our findings are within the upper range reported by the Surveillance, Epidemiology and End Results Program (SEER) of the United States National Cancer Institute, which recorded incidence rates ranging from 7/10⁶ to 12.6/10⁶ in developed countries.^{3,18} In addition, our results are similar to the 11.1/10⁶ obtained in a comprehensive review of all cases of neuroblastoma in Denmark from 1943-1980.¹⁹ Most cases of neuroblastoma present by the age of 5 and it is rare to see the disease present after the age of 10.⁴ Current reports have estimated that 1 in 7000 children < 5 years will be diagnosed with neuroblastoma.¹⁻⁴ The calculated incidence for patients presenting before the age of 5 in this cohort was 1 in 5970 children (95% CI: 3,920 – 12,580 children).

Nearly half (43%) of the patients in this series manifested orbital metastasis, which is significantly higher than the 10-20% orbital metastasis currently reported in literature.^{1,6,7} Five (83%) of the 6 patients were diagnosed in the first 12 years of the study and none presented during the last 20 years. These 5 cases all presented with advanced stage disease, which may explain the increased occurrence of ocular metastasis. However, Musarella et al⁷ reviewed 405 cases from 1919 through approximately 1980 and observed ocular involvement in only 80 (19.8%). More recently, Belgaumi et al⁶ reviewed cases from

1971-1994 and observed ocular involvement in 47 (10.4%) of 450 cases; however, their study only included cases that presented with ophthalmic involvement. Orbital involvement was the presenting sign in only 2 (14%) of the 14 cases during this study. It is likely that their overall percentage of ocular involvement would have been higher had they recorded ophthalmic involvement observed after diagnosis. Survival in this group was 0% at 12 months, owing largely to the advanced stage of disease that defines orbital metastasis.²⁰

Orbital metastatic neuroblastoma, presenting with proptosis and periorbital ecchymosis, is considered one of the classic signs of neuroblastoma in children.^{4,6} In this cohort, proptosis and ecchymosis were the two most frequent ocular manifestations of neuroblastoma, each observed in 4 (67%) of the 6 cases. This result is slightly higher than the published range of 38% to 60% for this finding in cases of ophthalmic involvement^{6,7,13} and may be due in part to the number of cases (5) that presented in advanced stage during the first decade of the study.

Horner syndrome and opsoclonus are infrequent manifestations of neuroblastic tumor mass effect on the sympathetic innervation of the eye.^{9-11,21} Horner syndrome is associated with localized neuroblastoma and consequently demonstrates markedly better survival rates than those seen in cases of orbital metastasis.⁷ The absence of Horner syndrome in this cohort is consistent with the findings of Weinstein et al²¹ and Wilhelm et al,²² who found no underlying mass lesion among their patients with pediatric Horner syndrome, and Jeffrey et al¹¹ who found only 3 (4.1%) of 73 cases due to a neuroblastoma. Despite the frequent association of Horner syndrome and neuroblastoma in the literature,^{8-10,23} Musarella et al⁷ and Jaffe et al²⁴ have concluded that as few as 3.5-13% of children with neuroblastoma have an associated Horner syndrome, while only 2.2% present with Horner syndrome as the initial symptom. Although rare, the gravity of pediatric Horner syndrome due to neuroblastoma understates the importance of a careful work-up to preclude an underlying mass lesion. Presentations of idiopathic pediatric Horner syndrome warrant a thorough physical exam, including palpation of the neck, abdomen, and axilla, and spot urine testing of homovanillic acid (HVA) and vanillylmandelic acid (VMA).¹⁰ Further investigation, including imaging, should be based on physical findings (including acquired or increasing iris heterochromia), and the relative incidence of neuroblastoma by age.¹¹

Opsoclonus-myoclonus, a well-documented but rare sign of neuroblastoma, was also not observed in this cohort.^{7,12,25} Musarella et al⁷ observed opsoclonus in only 9 (2.2%) of 405 cases. Belgaumi et al,⁶ describing a cohort of 450 patients, and others,^{13,14,26} did not observe this paraneoplastic symptom. A population-based study of opsoclonus-myoclonus in the United Kingdom over a two-year period found an incidence of 0.18 cases per million total population per year.²⁵ Only 4 of the 15 cases of opsoclonus-myoclonus were observed to have an underlying neuroblastoma. Given the small sample size of this study, it is not surprising that opsoclonus-myoclonus was not observed in this cohort.

The two most important clinical factors for predicting outcomes in neuroblastoma are the stage of the disease and age at diagnosis.^{2-4,7,27,28} According to the International Neuroblastoma Staging System, orbital involvement is a sign of stage IV disease.²⁰ In this study, 8 (57%) of 14 cases presented as stage IV, and their 5-year survival was 13%. Published reports of 3- or 5- year survival rates in patients with stage IV disease show significant improvement in outcomes in recent years, reflecting improved efficacy of treatment regimens.²⁹ Survival rates for patients diagnosed with stage IV disease after 1 year of age range from 2.5% mid-century³⁰ to 16% in the 1980s³ and 38% in the 1990s.³¹ In this cohort, only 2 patients were diagnosed with stage IV disease after 1985, explaining in part the lower than expected survival in these patients.

The 4 cases in this study that presented before their first birthday had a 5-year survival of 100%, while the 10 diagnosed after 1 year had a 5-year survival of 30%. Comparative data from the SEER program reports a 5-year survival of 90.2% for those diagnosed at less than 1 year, while only 66.1% of those diagnosed between the ages of 1 through 4 years achieved a 5-year survival.¹⁷ It is likely that a larger sample size would have yielded results closer to those in other published reports.

There are several limitations to the findings in this study. First, the small sample size makes it difficult to calculate accurate incidence rates with which to compare to other studies. However, the extended duration of the study, the accuracy of residency status analysis made possible by the Rochester Epidemiology Project, and the relatively infrequent occurrence of Olmsted County residents seeking medical care in other urban centers allows for an accurate calculation from this population. The small sample size also decreases the likelihood of identifying relatively infrequent ophthalmic manifestations of neuroblastoma such as Horner syndrome and opsoclonus-myoclonus. However, these signs are infrequently noted in patients with neuroblastoma.^{6,13,21,22,25,26} Finally, the largely Caucasian patient population of Olmsted County (95.7%) best translates to semiurban, white populations in the United States and thereby may limit the generalizability of calculated incidence and survival rates to more diverse populations. Statistics from the Pediatric Oncology Group (POG) indicate that neuroblastoma is 9.5% more common among African-Americans patients, which suggest that a more diverse patient population may have had a higher incidence of neuroblastoma.⁴

Neuroblastoma was diagnosed in 11.8 per million children < 15 years in this population, with a mean 5-year survival of 50.0%. Ocular involvement, consisting solely of orbital metastasis, was observed in 6 (43%) of the 14 cases, with a mean survival of 4.4 months (range, 3.1 – 9.1). Proptosis and ecchymosis, seen in 4 (67%) of the 6 cases, were the most common signs of orbital involvement, and were the presenting sign of neuroblastoma in 2 (14%) of the 14 cases. The Kaplan-Meier survival rate for the entire cohort was 50% at 5 years (95% CI: 30-84%) while none of the 6 patients with ocular involvement survived.

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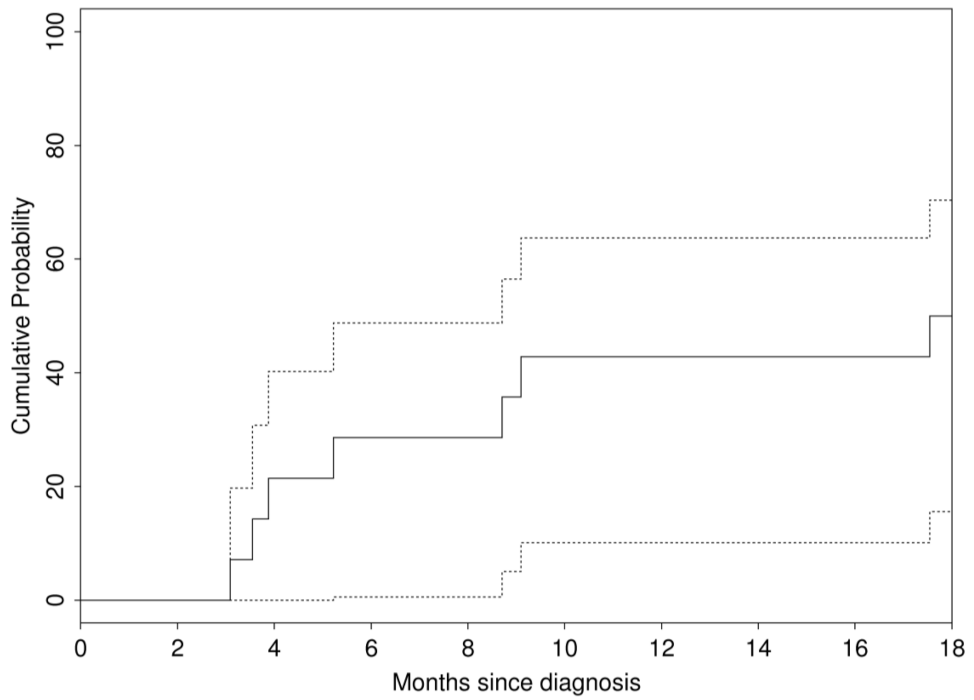


Figure 1. Kaplan-Meier cumulative probability of survival in pediatric patients diagnosed with Neuroblastoma in Olmsted County, MN, 1969-2008.

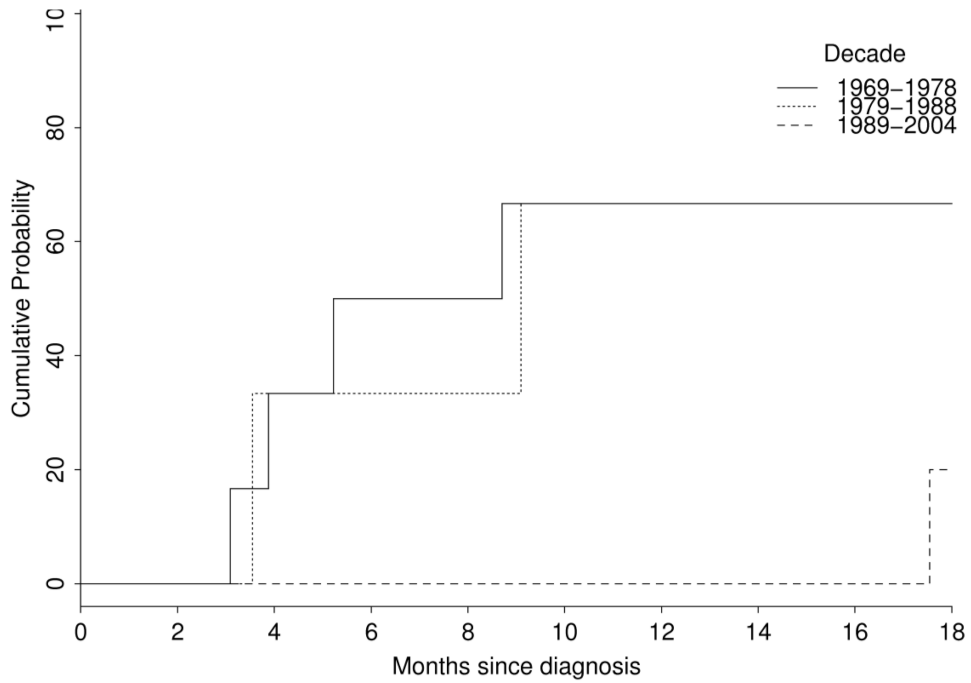


Figure 2. Kaplan-Meier cumulative probability of survival by decade of diagnosis in pediatric patients diagnosed with Neuroblastoma in Olmsted County, MN, 1969-2008.

Table 1
Historical and clinical characteristics of 14 patients < 19 years diagnosed with Neuroblastoma in Olmsted County, MN, 1969-2008

Case No. (year at diagnosis)	Age at diag. (mon)	Gender	Presenting symptoms	Primary site	Ophthalmic site/manifestations	Ophthalmic complications	Treatment	F/U duration (months)	Final outcome	Stage
1 (1969)	42.6	F	Bilateral periorbital ecchymosis	R adrenal	Bilateral orbits/painful proptosis	Scleral hemorrhage	Chemotherapy	5.2	Pt deceased	IV
2 (1970)	21.5	M	Decreased appetite, listless, afebrile, hematuria	L adrenal	Right orbit/Prosis, right subconjunctival hemorrhage secondary to right temporal mass	Sluggish pupillary response	Radiation and chemotherapy	3.1	Pt Deceased	IV
3 (1971)	16.5	F	Fever, rhinorrhea, cough, swollen L inguinal nodes	L adrenal	None	None	Resection, L adrenal and L inguinal nodes	309.6	Remission	IV
4 (1971)	4.6	F	Fever, vomiting, palpated RUQ mass	R adrenal	None	None	Resection, R adrenal mass and L supraclavicular mass	454.6	Remission	IVS
5 (1976)	29.7	F	Listless, purpura, thrombocytopenia, anemia	L adrenal	Bilateral orbits/Right proptosis, with ecchymosis and ptosis. Bilateral temporal tumor nodules	Difficulty depressing and abducting the right eye	Resection of L adrenal, L metastatic lymph nodes, L nephrectomy. Radiation and chemotherapy	3.9	Pt deceased	IV
6 (1977)	34.8	F	Irritability, dehydration, fever, lethargy	L adrenal	Bilateral orbits/Left proptosis with inward and medial displacement of the left globe. Bilateral metastasis	Left esotropia with III, IV, and VI nerve palsies	Resection of L adrenal, L kidney, and L peri-aortic lymph nodes. Radiation and chemotherapy	8.7	Pt deceased	IV
7 (1981)	24.5	M	Fatigue, fever, poor appetite, swollen L testicle	L adrenal	Left orbit/Left proptosis and ecchymosis	None	Radiation and chemotherapy	3.5	Pt deceased	IV
8 (1987)	29.5	M	Bilateral periorbital ecchymosis, tender abdomen, ataxic gait	R abdomen	Bilateral orbits/Bilateral periorbital ecchymosis. Left eye swelling with hemorrhage.	None	Resection of R abdominal mass and peri-aortic lymph nodes	9.1	Pt deceased	IV
9 (1988)	37.9	M	Hydronephrosis, noted abdominal mass	R abdomen	None	None	Resection of abdominal mass. chemotherapy	245.4	Remission	III
10 (1990)	36.2	F	Decreased appetite, irritability, palpable LUQ mass.	Abdomen	None	None	Chemotherapy	17.5	Pt deceased	IV
11 (1993)	31.3	F	Ataxia, irritability, fever, urinary incontinence	R adrenal	None	None	Resection of R adrenal tumor. Chemotherapy	142.1	Remission	III
12 (1997)	4.9	M	6 wk history of cough, nasal congestion. Chest x-ray showed mass	Mediastinum, thoracic spine	None	None	Resection of epidural tumor and mediastinal mass.	144.0	Remission	II
13 (1997)	.6	M	Irritability, vomiting, diarrhea	L adrenal	None	None	Resection of L adrenal tumor	142.9	Remission	II
14 (2004)	.4	F	Pre-natal ultrasound	R adrenal	None	None	Resection of R adrenal tumor. Chemotherapy	60.6	Remission	IVS