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Incidence of Pediatric Horner Syndrome and the Risk of Neuroblastoma: A Population-Based Study

Stephen J. Smith, BS¹, Nancy Diehl, BS², Jacqueline A. Leavitt, M.D.³, and Brian G. Mohny, M.D.³

¹Mayo Clinic College of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

²Mayo Clinic Division of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

³Mayo Clinic Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Abstract

Objective—To describe the incidence of pediatric Horner syndrome and the risk of occult malignancy in a population-based cohort.

Methods—The medical records of all pediatric patients (aged <19 years) residing in Olmsted County, Minnesota, who received diagnoses of Horner syndrome from January 1, 1969, through December 31, 2008, were retrospectively reviewed.

Results—Horner Syndrome was diagnosed in 20 pediatric patients during the 40-year period, yielding an age- and sex-adjusted incidence of 1.42 per 100 000 patients younger than 19 years of age (95% confidence interval [CI]: 0.80–2.04). Eleven of the 20 patients (55%) had a congenital onset, for a birth prevalence of 1 in 6250 (95% CI: 3333–10 000), while the remaining 9 (45%) had acquired syndromes. Seven of the 11 (63.6%) patients with congenital cases had a history of birth trauma, while the remaining 4 (36.4%) had no identifiable cause. Six of the 9 (66%) acquired cases occurred following surgery or trauma while the remaining 3 (33%) had no known etiology. None (95% CI: 0.0–16.8%) of the 20 patients were found to have a neuroblastoma or other malignancy during a mean following of 56.5 months (range, 0–256.9 months).

Conclusions—The incidence of pediatric Horner syndrome in this population was 1.42 per 100 000 patients younger than 19 years, with a birth prevalence of 1 in 6250 for those with congenital onset. Birth, surgical or other trauma occurred in 13 (65%) of the patients, while none of the 20 patients were found to have an underlying mass lesion, suggesting reappraisal of the current recommendation for extensive evaluations in these patients.

Horner syndrome, classically described as including miosis, ptosis, and anhidrosis, is caused by an interruption of the oculosympathetic tract and can occur anywhere along the three-neuron pathway between the hypothalamus and the orbit. Pupillary miosis and blepharoptosis are the clinical signs of the disease, though anhidrosis, iris heterochromia, and pupillary dilation lag may all be present concurrently.^{1–5} The causes of Horner syndrome in children have traditionally been classified as congenital or acquired.² The most common cause of congenital Horner syndrome is birth trauma,^{3,6,7} though vascular malformations^{3,8} and neoplasm⁶ have also been cited as underlying etiologies. Acquired

Corresponding Author: Brian G. Mohny, M.D., Mayo Clinic, Department of Ophthalmology, 200 First Street Southwest, Rochester, MN 55905, mohny@mayo.edu, Phone: 507-284-2233, FAX: 507-284-4612.

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causes of pediatric Horner syndrome include surgical intervention,^{4,5,9} trauma,^{3,4} neoplasm,^{4,6} infection,¹⁰ and vascular malformations.⁶

Idiopathic cases, whether congenital or acquired, are of special interest as they are currently believed to have the highest likelihood of a potentially fatal underlying pathology.^{3,4} The current recommended evaluation for pediatric Horner syndrome without a known surgical etiology includes urinary catecholamine testing and magnetic resonance imaging of the brain, neck, and chest.³ These recommendations are based on an evolution of thinking from published studies, all of which were conducted in large medical referral centers.^{3-5,11-14} The purpose of this study is to report the incidence, birth prevalence, and risk of occult neoplasia among a cohort of patients younger than 19 years with diagnosed Horner syndrome in Olmsted County, Minnesota, during a 40-year period.

Subjects and Methods

The medical records of all pediatric (aged <19 years) patients residing in Olmsted County who received diagnoses of Horner syndrome from January 1, 1969, through December 31, 2008, were retrospectively reviewed. Records of similarly-aged residents of Olmsted County with neuroblastoma were also reviewed to ascertain any cases with concurrent Horner syndrome. Potential cases of Horner syndrome 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.¹⁵ The racial distribution of Olmsted County residents in 1990 was 95.7% white, 3.0% Asian-American, 0.7% African-American, 0.3% American Indian, and 0.3% other. This semi-urban county (106 470 inhabitants in 1990) is relatively isolated from other urban areas, and virtually all medical care is provided to residents by the Mayo Clinic or the Olmsted Medical Group and their affiliated hospitals.

This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Group. Medical records were obtained for patients younger than 19 years who received diagnosis of Horner syndrome, Bernard-Horner syndrome, unspecified disorder of the autonomic nervous system, or oculosympathetic palsy during the 40-year period. All diagnoses 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.

Horner syndrome was defined in this study as miosis with or without ptosis and one or more of the following: (1) observed pupillary dilation lag, (2) iris heterochromia, (3) anhidrosis, or (4) a history of trauma to the oculosympathetic pathway.³ A diagnosis by an ophthalmologist, with or without a positive cocaine test, was considered sufficient for inclusion in the review. A positive cocaine test result was defined as an ophthalmologist-observed pupillary difference of 1 mm or more at 30 minutes following administration of cocaine eye drops (2.5%, 5%, or 10%) to both eyes. Patients' medical histories, including birth history, age at onset, initial symptoms, and affected side, were reviewed. Follow-up data were gathered for all patients when available, and any change at final follow-up was noted. The results of head, neck, and chest imaging, and catecholamine studies were included and analyzed to determine the incidence of underlying pathology.

The study cases were divided into two primary groups: congenital and acquired. To be considered as congenital, patients with Horner syndrome had to have their miosis/ptosis observed by a physician within the first 5 months of life. For late-manifesting syndromes, symptoms had to have been observed within the first 5 months of life as verified by the parent's history or a photograph. Acquired cases included those in which neither the patient's

parents nor a medical professional observed the syndrome within the first 5 months of life apart from known trauma to the oculosympathetic pathway.

To determine the incidence of pediatric Horner syndrome in Olmsted County, annual age- and sex-specific incidences rates were constructed using the age- and sex-specific population figures for the county from the US Census. Estimates from the State of Minnesota were used to aid with linear interpolation between census years. Birth prevalence for the congenital cases was calculated from the number of births occurring from December 31, 1969, through January 1, 2008, using annual birth incidence for this county. The 95% confidence intervals were calculated using assumptions based on the Poisson distribution.

Results

A total of 20 patients younger than 19 years received diagnoses of Horner Syndrome during the 40-year study, yielding an age- and sex-adjusted incidence of 1.42 per 100 000 patients younger than 19 years (Figure). Eleven of the 20 (55%) cases were congenital in onset, corresponding to a birth prevalence of 1 in 6,250 live births (95% CI: 3333 to 10 000). Table 1 contains summary information on the 20 patients, including age at diagnosis, birth history, etiology, evaluation, and final outcome.

Eleven patients were identified as having congenital Horner syndrome, with 7 cases (63.6%) due to birth trauma and 4 (36.4%) of unknown etiology. The median age at diagnosis for all 11 patients was 4.1 months (range, 1.7-119.8 months) with a mean follow up of 79.8 months (range, 0-256.9 months). Four of the seven cases first seen because of a difficult delivery were left-sided and 3 were on the right. Causes included shoulder dystocia (n=3), forceps delivery (n=2), neck traction (n=1), and molded head with ecchymosis (n=1). Two of the 7 patients had a brachial plexus injury, both resulting in paralysis of the left upper extremity. Miosis and ptosis were the two most common initial symptoms (n=5). Two of the patients were noted to have iris heterochromia, while anhidrosis was noted in 1 patient. Only 2 patients (cases 1 and 3) had a description of where in the oculosympathetic chain the interruption occurred (both preganglionic). Two of the 7 were noted to have a change on final examination; heterochromia was later discovered in one child and Horner syndrome resolved in a second child 6 months following traumatic birth.

Acquired Horner syndrome was diagnosed in 9 children, 6 (66%) of whom had a known etiology and 3 (33%) who were considered idiopathic. The median age at diagnosis for the 9 acquired cases was 10.2 months (range, 4.5-212.6 months) with a mean follow-up duration of 33.2 months (range, 0-186.2 months). Etiologies of the 6 acquired cases with known diagnosis were evenly divided between trauma (n=3) and surgical manipulation (n=3). Four of the patients had a right-sided syndrome and miosis and ptosis were present in all 6 cases. The Horner syndrome resolved in 1 patient, while 2 patients noted an improvement of their ptosis with time.

None (95% CI: 0.0-16.8%) of the 20 children were diagnosed with neuroblastoma or other occult neoplasm during a mean follow-up of 56.5 months (range, 0-256.9 months). A systemic evaluation including imaging and/or urine studies was performed on 4 of the 7 patients with idiopathic Horner syndrome and 2 of the 13 with a history of birth or acquired trauma; all of which were negative.

Discussion

Pediatric Horner syndrome was diagnosed in 20 patients, or 1.42 per 100 000 patients, younger than 19 years of age who were residents of Olmsted County during the 40-year study period. Among this heterogeneous group, 11 cases (55%) were diagnosed with

congenital Horner syndrome, resulting in a birth prevalence of 1 in 6250, while the remaining 9 (45%) had an acquired onset. Birth, surgical, or other trauma accounted for 13 (65%) of the patients while none were found to harbor an occult malignancy.

We are unaware of any prior population-based studies in English on either the incidence or prevalence of pediatric Horner syndrome. Weinstein et al⁵ estimated that no more than 5% of cases of Horner syndrome could be labeled congenital, though it was not clear whether they referred to all cases of Horner syndrome or just pediatric Horner syndrome. No statistics were given to support their claim. This population-based study recorded 9 (45%) of 20 cases as acquired, while 11 (55%) of the 20 cases were labeled congenital. Jeffery and coauthors,⁴ describing a referral-based cohort, identified 31 (42%) of 73 as having a congenital onset, similar to the findings of this study.

Table 2 lists recent reports of pediatric Horner syndrome, including the year of publication, number of patients, common causes, and recommended evaluation. In this study, birth trauma, including forceps delivery, was a common cause of congenital Horner syndrome (63.6%), which has been reported in prior studies.^{4,5,12,13} Brachial plexus injury was recorded in 2 (10%) of the 20 study cases. Sauer and Levingohn¹⁴ found one case of brachial plexus injury among 7 cases (14.3%), and Jeffery et al⁴ recorded 3 cases in 73 (4.1%). Increased obstetric awareness of the complications of limb manipulation during birth is felt to have contributed to the decline in brachial plexus injury over time.^{3,14,16} The mean duration of follow-up for all patients with Horner syndrome secondary to birth trauma was 85.6 months (range, 7.6-190.9 months), during which time no other etiology was uncovered.

Six (30%) of the study patients had acquired Horner syndrome as a result of either surgical manipulation (n=3) or trauma (n=3). This finding is similar to that of other studies.^{4,13} Two of the patient's showed improvement of their symptoms with time, while 1 patient had complete resolution following trauma. None of these 6 patients were found to have an underlying pathology after a mean follow-up of 45.7 months (range, 0-186.2 months). This finding concurs with that of other studies and suggests that additional work-up in a patient with a history of surgical or other obvious trauma to the oculosympathetic pathway is unnecessary.^{3,4,12}

Recent literature has emphasized distinguishing idiopathic Horner syndrome from cases in which the underlying cause is known.^{3,4} In this study, the 7 (35%) patients with idiopathic Horner syndrome (4 congenital and 3 acquired) were followed up for a mean of 5 years (range, 0-256.9 months), and no underlying pathology was detected. The absence of an underlying pathology in this small cohort is in contrast to the findings of Jeffery et al⁴ who found that 6 of 11 (55%) cases of idiopathic acquired Horner syndrome had a potentially fatal underlying disease (2 with neuroblastoma), and Mahoney et al³ who found an underlying mass lesion in 6 of 28 (21%) idiopathic manifestations. However, both of these studies included all children evaluated at large medical referral centers.

Neuroblastoma is the most common occult malignancy to be associated with pediatric Horner syndrome.^{3,4,12,14,17} With an incidence of approximately 1 in 7000 children younger than 5 years,¹⁸⁻²¹ neuroblastoma is the most common extracranial solid tumor among children younger than 5 years, and rarely appears in children older than 10 years.²¹ The absence of neuroblastoma underlying Horner syndrome in this study prompted a review of the Olmsted County medical records of the 21 pediatric patients with diagnoses of neuroblastoma during the same 40-year period, and none were found to have a concurrent Horner syndrome. This finding is consistent with those of Weinstein et al⁵ and Wilhelm et al²² who found no underlying mass lesion among their patients with pediatric Horner

syndrome, and Jeffery et al⁴ who found only 3 (4.1%) of 73 cases (2 acquired idiopathic and 1 congenital) due to a neuroblastoma. Despite the frequent association of Horner syndrome and neuroblastoma in the literature,^{3,11-14,17} Musarella et al²³ and Jaffe et al²⁴ have concluded that as few as 3.5% to 13% of children with neuroblastoma have associated Horner syndrome, while in only 2.2%, Horner syndrome is the initial symptom. Extrapolating from the incidence of neuroblastoma in patients younger than 5 years, we found that neuroblastoma concurrent with Horner syndrome would have a projected incidence of 1 in 54 000 to 200 000 pediatric patients, while 1 in 318 200 would initially manifest Horner syndrome.

The evolution of the recommended evaluation for pediatric Horner syndrome is shown in Table 2. Recently, Mahoney and coauthors³ recommended urine catecholamine testing and magnetic imaging of the brain, neck, and chest for all patients with pediatric Horner syndrome in whom there was no history of pertinent surgery. However, positive physical examination findings led to further investigations in 2 of their 6 (33%) patients with unknown etiologies.³ Although we have a small sample size, the relatively uncommon occurrence of neuroblastoma causing Horner syndrome in this population-based study combined with the extremely low extrapolated incidence of concurrent Horner syndrome and neuroblastoma suggests that the current recommendation be reconsidered. Patients with Horner syndrome with a history of birth, surgical, or other trauma should be evaluated with a thorough physical examination, including palpation of the neck, abdomen, and axilla, and close follow-up monitoring. For idiopathic cases, a physical exam and spot urine testing of homovanillic acid and vanillylmandelic acid are warranted.^{3,25} However, because urine catecholamine studies have been normal in a few patients with neuroblastoma,^{3,26} further investigation, including imaging, should be based on physical findings (including acquired or increasing iris heterochromia), and the relative incidence of neuroblastoma by age.^{4,12}

There are several weaknesses to the findings in this study. First, the small sample size makes it difficult to understand completely the various etiologic factors and to extrapolate meaningful recommendations for evaluating children with Horner syndrome. In fact, the confidence interval for the occurrence of neuroblastoma as a cause for Horner syndrome in this study was as high as 16.8%. However, other studies have reported minimal correlation between neuroblastoma and pediatric Horner syndrome.^{4,5,18,22-24} The relatively high number of occult malignancies among patients with Horner syndrome in some studies can be explained, at least in part, by referral bias.^{3,4,11-14} Another potential weakness of this study is that some patients may have sought care outside Olmsted County, thereby underestimating the incidence of Horner syndrome. However, the population of Olmsted County is relatively isolated from other populations and outside evaluations are uncommon. The homogenous patient population of Olmsted County may also affect the calculated incidence rate of both neuroblastoma and Horner syndrome. Statistics from the Pediatric Oncology Group indicate that neuroblastoma is 9.5% more common among African-Americans patients, which suggests that a more diverse patient population may have identified cases of Horner syndrome due to neuroblastoma.²¹ However, there are currently no studies to indicate that race plays a role in the incidence of Horner syndrome. Finally, more subtle forms of Horner syndrome may have gone unnoticed by parents and physicians and thus were not included in this study. Mild cases due to an underlying neuroblastoma should have been detected as the tumor progressed, however, and are likely to have been identified in our review of neuroblastoma cases during the same 40-year period.

This population-based study found that pediatric Horner syndrome occurs in approximately 1.42 in 100 000 patients younger than 19 years, with a birth prevalence of 1 per 6250 live births for those with congenital onset. Two-thirds of the study patients had a history of birth, surgical, or other trauma, and neuroblastoma was not detected in any of the patients. These

findings suggest that extensive imaging can be appropriately reserved for selected idiopathic cases of pediatric Horner syndrome.

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1. . Incidence of Horner syndrome by age at diagnosis in 20 pediatric patients (aged <19 years) who received diagnoses of Horner syndrome in Olmsted County, Minnesota, from 1969 to 2008

Table 1
Historical and Clinical Characteristics of Patient With Diagnoses of Horner Syndrome, 1969–2008

Patient No.	Age at Diagnosis, mo	Birth history	Birth Weight g	Affected Eye	Etiology	Manifesting Signs	Work-up *	Duration, mo	Final Eye Reported Outcome
1	119.8	Cesarean-section, neck traction	U	OD	Birth trauma (preganglionic)	Miosis, dilation lag	None	144.1	No change
2	1.7	L shoulder dystocia, L brachial plexus injury, L upper extremity paralysis	4880	OS	Birth trauma	Miosis, ptosis, anhidrosis	None	190.9	Symptoms cleared
3	3.8	Forceps delivery	3880	OD	Birth trauma (preganglionic)	Miosis, upside down ptosis	None	137.9	No change
4	5.0	Forceps delivery	2500	OD	Birth trauma	Miosis, ptosis, iris heterochromia	None	18.7	No change
5	2.1	Severe L shoulder dystocia, L brachial plexus injury, Erbs palsy	5005	OS	Birth trauma	Miosis, ptosis	None	9.4	No change
6	4.1	L shoulder dystocia, broken L clavicle	3450	OS	Birth trauma	Miosis, ptosis	Head CT	7.6	No change
7	1.9	Bruised L occiput, molded head, L lid swelling	3090	OS	Birth trauma	Miosis, ptosis	Urine studies	90.4	Developed Iris heterochromia
8	13.6	NA	4065	OD	Idiopathic	Miosis, ptosis	CT & MRI of head	0	No change
9	5.3	NA	2807	OS	Idiopathic	Miosis, ptosis	MRI of head, neck, and thorax	9.6	No change
10	21.4	Maternal Herpes infection, Cesarean section	3600	OD	Idiopathic	Miosis, dilation lag	None	29.5	No change
11	3.3	NA	U	OD	Idiopathic	Miosis, ptosis	None	256.9	No change
12	87.5	Adoption, no birth history	U	OD	Trauma. Child fell on board with nails sticking out	Miosis, ptosis	None	0	No change
13	43.2	NA	U	OD	Trauma. Table pulled on anterior neck and chest	Miosis, ptosis	None	9.0	Symptoms cleared
14	10.2	NA	3288	OS	Posterolateral thoracotomy to repair ventricular septal defects	Miosis, ptosis	None	186.2	Ptosis improved
15	212.6	NA	3458	OS	Trauma. Skull fracture	Miosis, ptosis	None	0	No change
16	5.8	NA	2700	OD	Bilateral, bidirectional superior caval pulmonary anastomosis	Miosis, ptosis, anhidrosis	None	15.9	Ptosis improved

Patient No.	Age at Diagnosis, mo	Birth history	Birth Weight g	Affected Eye	Etiology	Manifesting Signs	Work-up *	Duration, mo	Final Eye Reported Outcome
17	9.2	NA	U	OD	Cardiac surgery for tricuspid atresia.	Miosis, ptosis	None	62.8	No change
18	7.4	Maternal HPV, uncomplicated delivery	3600	OD	Idiopathic	Miosis, positive cocaine test result	Urine studies. Chest radiography	54.5	No change
19	4.5	NA	2610	OD	Idiopathic	Miosis, upside down ptosis	Urine studies. Chest radiography. MRI refused.	0	No change
20	4.6	NA	3390	OD	Idiopathic	Miosis, dilation lag	None	7.5	No change

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; HPV, human papillomavirus; L, left; NA, not applicable; U = Unknown

• = all examinations were negative

Table 2

Studies of pediatric Horner syndrome and recommended evaluation.

Author (year)	No. of Patients	Etiology (%)				Recommended work-up
		Birth trauma	Surgery/trauma	Neuroblastoma/mass lesion	Other	
Giles and Henderson, ^{1,3} 1958	32	12 (37%)	15 (47%)	4 (13%)	1 (3%)	Emphasis on obtaining an accurate history.
Saur and Levingohn, ¹⁴ 1975	7	1 (14%)	0 (0%)	5 (72%)	1 (14%)	A thorough neurologic exam, including examination of the head and neck, and radiography of the chest, cervical spine, and skull, should be performed routinely, with 24-hour urinary assays, especially in cases of a known cervical or pulmonary mass.
Weinstein et al., ⁵ 1980	11	5 (46%)	2 (18%)	0 (0%)	4 (36%)	No recommendation
Woodruff et al., ¹¹ 1988	10	0 (0%)	2 (20%)	2 (20%)	6 (60%)	Except in cases associated with surgical manipulation, congenital and acquired onset warrants chest radiography, CT of the head and neck, and 24-hour urinary assays.
Jeffery et al., ⁴ 1998	73	16 (22%)	32 (44%)	6 (8%)	19 (26%)	Children with acquired Horner syndrome without a known mass lesion or surgical trauma should undergo physical examination of the neck and abdomen with neuroimaging of the head, neck, chest, and abdomen in addition to urine assays.
George et al., ¹² 1998	23	4 (17%)	0 (0%)	3 (13%)	16 (70%)	Infants should be examined for cervical or abdominal masses and involvement of other cranial nerves. In truly isolated manifestations, a urinary VMA level and follow up in conjunction with a pediatrician should detect any cases associated with neuroblastoma. Further investigation is warranted if the Horner's syndrome is acquired or associated with other signs such as increasing heterochromia.
Mahoney et al., ³ 2006	56	1 (2%)	10 (18%)	13 (23%)	32 (57%)	Brain, neck, and chest magnetic resonance imaging (MRI) with and without contrast and urinary assays are recommended in all cases of pediatric Horner syndrome without a surgical history.
Total (%)	212	39 (18%)	61 (29%)	33 (16%)	79 (37%)	