Incidence of Pediatric Horner Syndrome and the Risk of Neuroblastoma

A Population-Based Study

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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 of the 20 patients (95% CI, 0.0%-16.8%) were found to have a neuroblastoma or other malignancy during a mean follow-up 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 a congenital onset. Birth, surgical, or other trauma occurred in 13 (65%) of the patients, while none were found to have an underlying mass lesion, suggesting a need for reappraising current recommendations 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 3-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. The causes of Horner syndrome in children have traditionally been classified as congenital or acquired. The most common cause of congenital Horner syndrome is birth trauma, though vascular malformations and neoplasm have also been cited as underlying etiologies. Acquired causes of pediatric Horner syndrome include surgical intervention, trauma, neoplasm, infection, and vascular malformations.

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. 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. These recommendations are based on an evolution of thinking from published studies, all of which were conducted in large medical referral centers. 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.

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Methods: The medical records of all pediatric patients (aged <19 years) 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. The racial distribution of Olmsted County residents in 1990 was 93.7% white, 3.0% Asian American, 0.7% African American, 0.3% American Indian, and 0.3% other. This semiurban county (106,470 inhabitants in 1990) is relatively isolated from other urban areas, and virtually all medical care is provided to residents by Mayo Clinic or Olmsted Medical Group and their affiliated hospitals.

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

Horner syndrome was defined in this study as miosis with or without ptosis and 1 or more of the following: (1) observed pupillary dilation lag, (2) iridocorneal heterochromia, (3) anhidrosis, or without ptosis and 1 or more of the following: (1) observed pupillary dilation lag, (2) iridocorneal heterochromia, (3) anhidrosis, or (4) a history of trauma to the oculosympathetic pathway. A diagnosis by an ophthalmologist, without or without a positive cocaine test result, was considered sufficient for inclusion in the review. A positive cocaine test result was defined as an ophthalmologist-observed pupillary dilatory response 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 incidence of underlying pathology.

The study cases were divided into 2 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 be 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 incidence rates were calculated 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% confidence interval, 3333-10,000). 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 7 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 2 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 1 child and Horner syndrome resolved in a second child 6 months following a 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 diagnoses 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.

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None (95% confidence interval, 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 these results were negative.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Diagnosis, mo</th>
<th>Birth History</th>
<th>Birth Weight, g</th>
<th>Affected Eye</th>
<th>Etiology</th>
<th>Manifesting Signs</th>
<th>Workup a</th>
<th>Follow-up Duration, mo</th>
<th>Final Eye Report Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>119.8</td>
<td>Cesarean section, neck traction</td>
<td>U OD</td>
<td>Birth trauma (preganglionic)</td>
<td>Miosis, dilation lag</td>
<td>None</td>
<td>144.1</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>L shoulder dystocia, L brachial plexus injury, L upper extremity paralysis</td>
<td>4880 OS</td>
<td>Birth trauma</td>
<td>Miosis, ptosis, anhidrosis</td>
<td>None</td>
<td>190.9</td>
<td>Symptoms cleared</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.8</td>
<td>Forceps delivery</td>
<td>3880 OD</td>
<td>Birth trauma (preganglionic)</td>
<td>Miosis, upside-down ptosis</td>
<td>None</td>
<td>137.9</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>Forceps delivery</td>
<td>2500 OD</td>
<td>Birth trauma</td>
<td>Miosis, ptosis, iris heterochromia</td>
<td>None</td>
<td>18.7</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>Severe L shoulder dystocia, L brachial plexus injury, Erb palsy</td>
<td>5005 OS</td>
<td>Birth trauma</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>9.4</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.1</td>
<td>L shoulder dystocia, broken L clavicle, bruised L occiput, molded head, L eyelid swelling</td>
<td>3450 OS</td>
<td>Birth trauma</td>
<td>Miosis, ptosis</td>
<td>Head CT</td>
<td>7.6</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.9</td>
<td>Maternal herpes infection, cesarean section</td>
<td>3090 OS</td>
<td>Birth trauma</td>
<td>Miosis, ptosis</td>
<td>Urine studies</td>
<td>90.4</td>
<td>Developed iris heterochromia</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>4065 OD</td>
<td>Idiopathic</td>
<td>Miosis, ptosis</td>
<td>CT and MRI of head, neck, and thorax</td>
<td>0</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5.3</td>
<td>NA</td>
<td>2807 OS</td>
<td>Idiopathic</td>
<td>Miosis, ptosis</td>
<td>MRI of head</td>
<td>9.6</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>21.4</td>
<td>Maternal herpes infection, cesarean section</td>
<td>3600 OD</td>
<td>Idiopathic</td>
<td>Miosis, dilation lag</td>
<td>None</td>
<td>29.5</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3.3</td>
<td>NA</td>
<td>U OD</td>
<td>Idiopathic</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>256.9</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>87.5</td>
<td>Adoption, no birth history</td>
<td>U OD</td>
<td>Trauma; child fell on board with nails sticking out</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>0</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>43.2</td>
<td>NA</td>
<td>U OD</td>
<td>Trauma; table pulled on anterior neck and chest and chest</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>9.0</td>
<td>Symptoms cleared</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>10.2</td>
<td>NA</td>
<td>3288 OS</td>
<td>Posterolateral thoracotomy to repair ventricular septal defects</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>186.2</td>
<td>Ptosis improved</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>212.6</td>
<td>NA</td>
<td>3458 OS</td>
<td>Trauma; skull fracture</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>0</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5.8</td>
<td>NA</td>
<td>2700 OD</td>
<td>Bilateral, bidirectional superior caval pulmonary anastomosis</td>
<td>Miosis, ptosis, anhidrosis</td>
<td>None</td>
<td>15.9</td>
<td>Ptosis improved</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>9.2</td>
<td>NA</td>
<td>U OD</td>
<td>Cardiac surgery for tricuspid atresia</td>
<td>Miosis, ptosis</td>
<td>None</td>
<td>62.8</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>7.4</td>
<td>Maternal HPV, uncomplicated delivery</td>
<td>3600 OD</td>
<td>Idiopathic</td>
<td>Miosis, positive cocaine test result</td>
<td>Urine studies, chest radiography</td>
<td>54.5</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>4.5</td>
<td>NA</td>
<td>2610 OD</td>
<td>Idiopathic</td>
<td>Miosis, upside-down ptosis</td>
<td>Urine studies, chest radiography, MRI refused</td>
<td>0</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>4.6</td>
<td>NA</td>
<td>3390 OD</td>
<td>Idiopathic</td>
<td>Miosis, dilation lag</td>
<td>None</td>
<td>7.5</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

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

a All examination results were negative.
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 6,250, 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 al. 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 of 20 cases (45%) as acquired, while 11 of the 20 cases (55%) were labeled congenital. Jeffery and coauthors, describing a referral-based cohort, identified 31 of 73 (42%) cases as having a congenital onset, similar to the findings of this study.

Table 2 lists published articles on 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 syn-
drome (63.6%), which has been reported in prior studies.\textsuperscript{4,5,12,13} Brachial plexus injury was recorded in 2 of the 20 (10%) study cases. Sauer and Levingohn\textsuperscript{44} found 1 case of brachial plexus injury among 7 cases (14.3%), and Jeffery et al\textsuperscript{41} recorded 3 cases in 73 patients (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.\textsuperscript{3,4,14,16} 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.\textsuperscript{4,13} Two of the patients 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 workup in a patient with a history of surgical or other obvious trauma to the oculosympathetic pathway is unnecessary.\textsuperscript{3,11,12}

Recent literature has emphasized distinguishing idiopathic Horner syndrome from cases in which the underlying cause is known.\textsuperscript{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 contrasts with the findings of Jeffery et al,\textsuperscript{4} 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 al,\textsuperscript{3} 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.\textsuperscript{3,4,12,14,17} With an incidence of approximately 1 in 7000 children younger than 5 years,\textsuperscript{16,21} neuroblastoma is the most common extracranial solid tumor among children younger than 5 years and rarely appears in children older than 10 years.\textsuperscript{21} The absence of neuroblastoma underlying Horner syndrome in this study prompted a review of the Olmstead 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 al\textsuperscript{22} and Wilhelm et al,\textsuperscript{23} who found no underlying mass lesion among their patients with pediatric Horner syndrome, and Jeffery et al,\textsuperscript{4} who found only 3 of 73 (4.1%) cases (2 acquired idiopathic and 1 congenital) due to a neuroblastoma. Despite the frequent association of Horner syndrome and neuroblastoma in the literature,\textsuperscript{3,11,12,17} Musarella et al\textsuperscript{23} and Jaffe et al\textsuperscript{24} 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 coauthors\textsuperscript{3} 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 without known etiologies.\textsuperscript{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 examination and spot urine testing of homovanillic acid and vanillylmandelic acid are warranted.\textsuperscript{2,3} However, because urine catecholamine study results have been normal in a few patients with neuroblastoma,\textsuperscript{2,26} further investigation, including imaging, should be based on physical findings (including acquired or increasing iris heterochromia) and the relative incidence of neuroblastoma by age.\textsuperscript{1,12}

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 of Horner syndrome in this study was as high as 16.8%. However, other studies have reported minimal correlation between neuroblastoma and pediatric Horner syndrome.\textsuperscript{3,4,10,16,22-26} 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.\textsuperscript{3,4,11,14} Another potential weakness of this study is that some patients may have sought care outside Olnmsted County, thereby underestimating the incidence of Horner syndrome. However, the population of Olnmsted County is relatively isolated from other populations, and outside evaluations are uncommon. The homogenous patient population of Olnmsted 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 American patients, which suggests that a more diverse patient population may have identified cases of Horner syndrome due to neuroblastoma.\textsuperscript{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 6,250 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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REFERENCES


