Pediatric Horner Syndrome: Etiologies and Roles of Imaging and Urine Studies to Detect Neuroblastoma and Other Responsible Mass Lesions

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• PURPOSE: To evaluate the frequency of etiologies of Horner syndrome in children and suggest an imaging and laboratory diagnostic protocol to evaluate for neuroblastoma and other lesions in a child presenting with Horner syndrome and no known cause.

• DESIGN: Retrospective chart and data review.

• METHODS: A retrospective review of all children seen at a large pediatric neuro-ophthalmology referral center with a diagnosis of Horner syndrome between 1993 and 2005 with particular attention to underlying etiologies and the results of imaging and urine catecholamine studies.

• RESULTS: Fifty-six children met criteria for Horner syndrome and further review. Twenty-eight children (50%) had no previously identified cause for Horner syndrome. Of these children, 24 (85.7%) had urine catecholamine metabolite studies, and all had negative results. Twenty (71.4%) had complete modern imaging of the brain, neck, and chest. Of the 18 children who had complete imaging and urine studies, responsible mass lesions were found in six (33%). Four had neuroblastoma, one had Ewing sarcoma, and the other had juvenile xanthogranuloma. Of all patients (diagnosis known and unknown), neoplasm was the etiology in 13 of 56 (23%) of patients.

• CONCLUSIONS: We confirm that Horner syndrome in a child of any age without a surgical history requires a complete examination to exclude a mass lesion. In such patients, we recommend brain, neck, and chest magnetic resonance imaging (MRI) with and without contrast as well as urinary catecholamine metabolite testing. However, imaging is more sensitive than urine testing in this setting. (Am J Ophthalmol 2006;142:651–659. © 2006 by Elsevier Inc. All rights reserved.)

Accepted for publication May 18, 2006.

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THE CLASSIC TRIAD OF HORNER SYNDROME, CONSISTing of ipsilateral miosis, mild upper eyelid ptosis, and facial anhidrosis, is caused by interruption of at least one of the three neurons in the oculosympathetic pathway.[1] In children, the etiologies of Horner syndrome have traditionally been subdivided into acquired and congenital causes. Acquired cases can be sequelae of head, neck, and chest surgery, but also can be caused by any neoplasm or infection affecting the oculosympathetic pathway.[1] Important identifiable *congenital* causes are birth trauma, neoplasm,[1] and carotid abnormalities.[2–4] The most common neoplasm presenting with Horner syndrome is a neuroblastoma, and, indeed, an isolated Horner syndrome is the first presenting symptom of neuroblastoma in 2% of cases.[5] However, often no etiology can be found, and in such instances the Horner syndrome is labeled idiopathic.

The best protocol for evaluating children with Horner syndrome of unknown etiology is not certain. Urine testing of catecholamine metabolites homovanillic acid (HVA) or vanillylmandelic acid (VMA) has been suggested as a useful screen for neuroblastomas because these tumors arise from undifferentiated sympathicoadrenal lineage cells.[6] Whether to image, and what imaging technique and protocol is best, have also not been established.

Previous authors of patient series have discussed Horner syndrome etiologies in children as well as the threat of neuroblastoma (Table 1).[7–12] Most did not focus specifically on the child presenting with no known etiology for their Horner syndrome. In addition, although some suggested urine tests and imaging in such patients, either the preferred tests were not specified or the suggested test

0002-9394/06/$32.00
doi:10.1016/j.ajo.2006.05.047
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TABLE 1. Previous Reviews of Horner Syndrome in Children and Their Recommendations for Work-up

Author (Year): Institution, Study Size	Recommended Protocol
Sauer[8] (1975): Case-Western, n = 7	"Our recommendations for the diagnostic evaluation of such a patient are as follows: Following thorough neurologic examination and examination of the structures of the head and neck, chest x-ray and cervical spine x-rays, a skull series with basal views should be performed as routine procedure. Because of the incidence of neural crest tumors in childhood, routine 24-hour urinary assays for catecholamines are indicated, especially if a cervical or pulmonary mass is present . . . Finally, because a variety of internal carotid artery lesions cause Horner's syndrome, cerebral angiography should be considered, especially if the earlier studies prove unrevealing."
Weinstein[9] (1980): Iowa, n = 11	Not mentioned.
Woodruff[10] (1988): Toronto, n = 10	"Except in cases precipitated by thoracic surgery, however, onset of the syndrome in childhood or at birth warrants investigation which should include chest radiograph, CT scanning of the head and neck, and 24-hour urinary catecholamine assay."
George[11] (1997): UCSF, n = 23	"In the present climate of cost effective medicine we have found that routine CT or MRI scanning of the neck and chest in isolated Horner's syndrome in infancy is unnecessary. Infants should therefore be examined for cervical or abdominal masses and involvement of other cranial nerves. If the Horner's syndrome is truly isolated then a urinary VMA level and follow up in conjunction with a pediatrician should detect any cases associated with neuroblastoma."
Jeffrey[12] (1997): Toronto & Wilmer, n = 73	"All children with acquired Horner syndrome not caused by surgical trauma or other known lesions involving the oculosympathethic pathway require a thorough systemic evaluation. In addition to the physical examination of the neck and abdomen, we recommend a urine assay for catecholamines (HVA and VMA) and neuroimaging of the head, neck, chest, and abdomen."

CT = computed tomography; MRI = magnetic resonance imaging; VMA = vanillylmandelic acid; HVA = homovanillic acid.

modality (e.g., chest x-rays) is outdated. Two articles[11,12] published in 1997 from recognized experts gave different recommendations. George and associates[11] recommended urine VMA screening without imaging. Jeffrey and associates[12] suggested HVA and VMA screening as well as imaging of the head, neck, chest, and abdomen.

The purposes of this investigation are to (1) evaluate the frequencies of etiologies of Horner syndrome seen by the Children's Hospital of Philadelphia Neuro-ophthalmology service and (2) suggest an imaging and laboratory diagnostic protocol in a child with Horner syndrome and no known cause. Our analysis will help to answer two important clinical questions: "If a Horner syndrome is present in a child, and the cause is unknown, (1) what is an appropriate work-up?" and (2) "What is the chance of a mass or neoplasm?"

METHODS

• **PATIENT ASCERTAINMENT AND CLINICAL REVIEW:** Approval from the Children's Hospital of Philadelphia Institutional Review Board was obtained for this study. The Neuro-ophthalmologic examination records, imaging reports, and pertinent laboratory data were reviewed for all children with a diagnosis of Horner syndrome seen by the Children's Hospital of Philadelphia Neuro-ophthalmology service from July 1993 through July 2005. For the purposes of this study, Horner syndrome was defined as unilateral miosis with or without ipsilateral ptosis and one of the following: (1) obvious pupillary dilation lag in the dark, (2) a positive cocaine test, (3) iris heterochromia, (4) ipsilateral facial anhidrosis, or (5) an obvious cause for oculosympathetic pathway interruption such as neck surgery. A positive cocaine test was defined as a difference in pupil size of more than 1 mm at 30 minutes after instillation of 4% or 10% cocaine drops at zero and five minutes into both eyes. Only children presenting to the Children's Hospital of Philadelphia before age 18 years with at least partial evaluation of the Horner syndrome were included in this study; patients without any examination were excluded. The age at presentation was recorded, and the clinical history and examination and test results were reviewed.

• **LABORATORY TESTING AND IMAGING:** The results of HVA and VMA urine studies were documented. Tests were performed using standard methodology in national reference laboratories using high-pressure liquid chro-

TABLE 2. Characteristics and Examination Findings of Pediatric Horner Syndrome Patients Seen at the Children's Hospital of Philadelphia Between 1993 and 2005 Subdivided into Initial *Diagnosis Unknown* vs *Diagnosis Known* at Presentation

	Diagnosis Unknown	Diagnosis Known	Total
Patient characteristics			
Number – n (%)	28 (50.0%)	28 (50.0%)	56 (100.0%)
Age – Mean (range)	2.04 (0.12–8.83)	7.40 (0.27–17.90)	4.86 (0.12–17.90)
Left (* = 1 bilateral)	12 (42.9%)	15* (53.6%)	27* (48.2%)
Male	15 (53.6%)	10 (35.7%)	25 (44.7%)
Examination findings			
Anhidrosis	7 (25.0%)	3 (10.7%)	10 (35.7%)
Dilation lag	19 (67.9%)	16 (57.1%)	35 (62.5%)
Iris heterochromia	5 (17.9%)	2 (7.1%)	7 (12.5%)

matography from a random urine sample ("spot") in almost all cases. The results were expressed as a ratio to urine creatinine, thereby avoiding the need for timed urine collections. Laboratory assay ranges were calculated from normative data from patients of a similar age. All available imaging reports were reviewed. The imaging modality (for example, magnetic resonance imaging without contrast, computed tomography with contrast), study findings, and study impressions were recorded for all scans of the brain, neck, chest, or abdomen.

• **PATIENT ANALYSIS:** The patients were divided into categories of *diagnosis known* and *diagnosis unknown* based on their initial presentation. Patients characterized as *diagnosis known* were patients seen with a known etiology for Horner syndrome such as neck surgery or known neuroblastoma compressing the oculosympathetic pathway. Patients characterized as *diagnosis unknown* had no prior diagnosis or intervention that would have been an obvious cause for Horner syndrome. It is important to note that patients in the *diagnosis unknown* group may have had an etiology found on subsequent testing. The original diagnosis and etiology of the Horner syndrome was reviewed, verified, and documented. The latest Neuro-ophthalmology follow up was also reviewed. All patients with a documented lesion (all patients in the *diagnosis known* group and a subset of patients in the *diagnosis unknown* group who had an etiology established) were classified as first order, second order, or third order based on the presumed neuron involved in the lesion anatomically. Hydroxyamphetamine testing was not performed on the majority of patients because of the possibility of a false positive from transsynaptic degeneration in congenital cases[9] and an overall relatively high false-negative rate and lack of specificity.[13,14] Therefore, the localization was clinical. Patients with no known cause elucidated for the Horner syndrome were classified as idiopathic.

RESULTS

FIFTY-SEVEN PEDIATRIC PATIENTS FULFILLED CRITERIA FOR Horner syndrome between 1993 and 2005 and were entered for further review. One six-year-old patient with a positive cocaine test and signs of Horner syndrome noted in infant photos was lost to follow-up and was not included in this study. Patient characteristics are included in Table 2. One patient was diagnosed with bilateral oculosympathetic pareses.[15] Half of the patients had no previously established or readily identifiable etiology at presentation and were labeled *diagnosis unknown*. This cohort presented at a younger age (mean 2.04 vs 7.50 years) and on clinical examination more frequently had striking features of Horner syndrome such as iris heterochromia (17.9% compared with 7.1%) compared with the *diagnosis known* group. There were only minor differences in gender distribution or side of lesion in the two subgroups.

The majority of patients in the *diagnosis unknown* group were evaluated with the following general protocol: (1) the neck and chest were palpated for masses; (2) if a Horner syndrome was suspected, but no obvious dilation lag or heterochromia was present (clinical confirmation), a cocaine test was performed (pharmacologic confirmation); (3) if the Horner syndrome was clinically or pharmacologically confirmed, imaging and urine testing were ordered. MRI with and without contrast of the head, neck, and upper chest was preferred. Urine VMA and HVA testing were performed on a random urine collection. Biopsies and surgical interventions were performed as appropriate when imaging disclosed a mass lesion; (4) if the cocaine test was equivocal or negative, clinical observation and follow-up in three or 12 months, respectively, were recommended.

Most patients in the *diagnosis unknown* group had cocaine testing to verify Horner syndrome. Among 28 patients, 23 (82.1%) had cocaine testing performed, with 20 having greater than 1-mm difference in anisocoria at 30 minutes or longer after instillation. The other three patients had equivocal cocaine testing with 1-mm anisocoria 30 min-

TABLE 3. Studies Performed and Etiologies Found in Pediatric Horner Syndrome Patients Seen at the Children's Hospital of Philadelphia Between 1993 and 2005 in a *Diagnosis Unknown* at Presentation Subgroup

#	Urine	Head	Neck	Chest	Etiology	Description
1	*	MRI	MRI/MRA	MRI	Idiopathic	No urine studies
2	**	MRI	MRI/MRA	MRI	Idiopathic	Any imaging studies
3	**	MRI	MRI	X-ray	Idiopathic	
4	**	MRI	MRI	*	Idiopathic	
5	Yes	MRI	MRI/MRA	*	Idiopathic	Yes urine studies
6	Yes	MRI	MRI	*	Idiopathic	Incomplete imaging
7	Yes	MRI	*	X-ray	Idiopathic	
8	Yes	***	MRI	*	Idiopathic	
9	Yes	***	X-Ray	X-ray	Idiopathic	
10	Yes	****	MRI	MRI	Reactive Submandibular Lymphadenopathy	Yes urine studies Incomplete imaging Dx found
11	Yes	MRI	MRI	MRI	Idiopathic	Yes urine studies
12	Yes	MRI	MRI	MRI	Idiopathic	Complete imaging
13	Yes	MRI	MRI	MRI	Idiopathic	
14	Yes	MRI	MRI	MRI	Idiopathic	
15	Yes	MRI	MRI	MRI	Idiopathic	
16	Yes	MRI	MRI	MRI	Idiopathic	
17	Yes	MRI	MRI	MRI	Idiopathic	
18	Yes	MRI	MRI	MRI	Idiopathic	
19	Yes	MRI	MRI	MRI	Idiopathic	
20	Yes	MRI	MRI	MRI	Idiopathic	
21	Yes	CT	MRI	MRI	Idiopathic	
22	Yes	MRI	MRI	CT	Idiopathic	
23	Yes	MRI	MRI	MRI	Neuroblastoma	Yes urine studies
24	Yes	MRI	MRI	MRI	Neuroblastoma	Complete imaging
25	Yes	MRI	MRI	MRI	Neuroblastoma	Dx found
26	Yes	MRI	MRI	MRI	Neuroblastoma	
27	Yes	MRI	MRI	MRI	Juvenile Xanthogranuloma	
28	Yes	CT	CT	CT	Ewing Sarcoma	

CT = computed tomography; MRI = magnetic resonance imaging.
Patients in gray box were considered as having a "complete" work-up.
* = test was not ordered; ** = ordered by physician but not obtained by patient; *** = limited study; **** = not needed.

utes after cocaine drops. One patient had hydroxyamphetamine testing alone with a positive test result. The remaining four patients had a presentation that did not require cocaine testing for diagnosis because of obvious miosis with anisocoria greater in the dark, dilation lag, and ptosis.

Urine catecholamine testing (VMA and HVA) was performed in 24 of these 28 patients (75%) and was normal for age in all cases. Twenty (71.4%) had complete modern imaging of the brain, neck, and chest. Imaging was performed to some degree in the remaining eight patients, but was felt to be incomplete because one or more parts were omitted or imaged with an x-ray only. Tests were not completed because of insurance issues in some cases, one child woke up in the middle of the MRI study before all portions could be completed, and some patients and parents refused.

A total of 10 patients (Table 3, numbers one to 10) had partial but incomplete imaging and urine testing. Within this group, one was found to have reactive submandibular lymphadenopathy as a cause of the Horner syndrome. The others were labeled as "idiopathic."

The remaining 18 patients (Table 3, numbers 11 to 28) in the *diagnosis unknown* cohort had complete head, neck, and chest imaging and urine testing. All 18 had negative urine testing. Six of the 18 (33%) had a mass identified by imaging that was confirmed histopathologically: four (22%) had neuroblastoma, one had juvenile xanthogranuloma, and one had Ewing sarcoma. The remaining 12 of 18 (67%) were labeled "idiopathic." The four patients with neuroblastoma had radioactive iodine-131-meta-iodobenzylguanidine (MIBG) scanning performed. The MIBG tracer radioisotope is taken up by neuroblastoma cells and can be seen on special scanning. All four of these patients'

TABLE 4. Etiologies of Horner Syndrome in Patients Younger Than age 18 Years Seen at the Children's Hospital of Philadelphia Between 1993 and 2005

	Initial Diagnosis Unknown	Initial Diagnosis Known	Total
1st			
Neoplasm		5 (17.9%)	5 (8.9%)
Lymphoma		1 (3.6%)	1 (1.8%)
Craniopharyngioma		1 (3.6%)	1 (1.8%)
Astrocytoma		1 (3.6%)	1 (1.8%)
Gliomatosis		1 (3.6%)	1 (1.8%)
Medulloepithelioma		1 (3.6%)	1 (1.8%)
Trauma		3 (10.7%)	3 (5.4%)
Vertical dissection		1 (3.6%)	1 (1.8%)
Motor vehicle accident with cerebral damage		2 (7.1%)	2 (3.6%)
Infection		2 (7.1%)	2 (3.6%)
Medullary abscess		1 (3.6%)	1 (1.8%)
Septic emboli		1 (3.6%)	1 (1.8%)
Klippel-Feil		1 (3.6%)	1 (1.8%)
2nd			
Neoplasm	5 (17.9%)	3 (10.7%)	8 (14.2%)
Neuroblastoma	4 (14.3%)	1 (3.6%)	5 (8.9%)
Neurofibroma		1 (3.6%)	1 (1.8%)
Schwannoma		1 (3.6%)	1 (1.8%)
Ewing sarcoma	1 (3.6%)		1 (1.8%)
Surgery		7 (25.0%)	7 (12.5%)
Chest surgery		3 (10.7%)	3 (5.4%)
Neck surgery		4 (14.3%)	4 (7.2%)
Infection		3 (10.7%)	3 (5.4%)
Mediastinitis		1 (3.6%)	1 (1.8%)
Pneumonia with pneumomediastinum		1 (3.6%)	1 (1.8%)
Retropharyngeal abscess secondary to brachial cleft cyst		1 (3.6%)	1 (1.8%)
Other	2 (7.2%)		
Reactive cervical lymphadenopathy	1 (3.6%)		
Juvenile xanthogranuloma	1 (3.6%)		
3rd			
Carotid malformation		2 (7.1%)	2 (3.6%)
Birth-related injury		1 (3.6%)	1 (1.8%)
Autonomic dysregulation		1 (3.6%)	1 (1.8%)
All neoplasms	5 (17.9%)	8 (28.6%)	13 (23.2%)
Idiopathic (etiology not found)	21 (75.0%)	0 (0.0%)	21 (37.5%)
Total	28 (100%)	28 (100%)	56 (100%)

1st = 1st-order neuron; 2nd = 2nd-order neuron; 3rd = 3rd-order neuron.

Patients were divided into categories of *diagnosis unknown* and *diagnosis known* based on initial presentation. After evaluation, etiologies were found in 7 of 28 patients in the *diagnosis unknown* category. Etiologies are subclassified according to the neuron involved.

studies were suggestive of localized neuroblastoma without metastases. To our knowledge, no patients who had a negative MRI had an MIBG scan. Six of the 28 patients with an unknown diagnosis in this study had an abdominal computed tomography or ultrasound to investigate the possibility of a remote abdominal neuroblastoma,[5,11,16] but none were identified. The case details of the six children who were found to have a mass are detailed as follows.

• **PATIENT 23:** A six-month-old girl was evaluated for ptosis and anisocoria. The parents thought the eyelid abnormality had been present since at least two weeks of age, and maybe since birth. MRI showed a right lung apical mass. Stage 2A (International Neuroblastoma Staging System[17]) neuroblastoma was resected. After 15 months, no recurrence has been noted, and the Horner syndrome has persisted.

• **PATIENT 24:** A six-month-old boy was evaluated for anisocoria and ptosis. He had been born via vacuum extraction that resulted in a right occipital hematoma. At 4.5 months of age, his parents noticed right eyelid "swelling." MRI revealed a cervical lymph node. Repeat MRI three months later showed an increase in size of the lymph node, which was removed surgically and found to be neuroblastoma, Stage 3 intermediate risk. He was treated with chemotherapy, and after two years has had no recurrences. The Horner syndrome has persisted.

• **PATIENT 25:** A three-year-old boy was evaluated for new anisocoria and ptosis. Imaging revealed a right apical lung mass. Neuroblastoma, unfavorable histology, was resected. Three local recurrences at ages four, five, and seven were treated with resection, chemotherapy, and radiation, respectively.

• **PATIENT 26:** A five-month-old girl was seen for ptosis for one week. Anisocoria was noted on examination, but cocaine testing was equivocal (1-mm difference). The child was followed conservatively. At six months of age, the parents noticed anhidrosis ipsilateral to the miosis. At seven months of age, the patient was treated for an "infected lymph node in the neck." At eight months of age, pupillary dilation lag was noted and a neck mass was palpated. MRI confirmed a large mass arising from the right posterior mediastinum extending into the right lung apex and soft tissues of the neck. Surgery revealed Stage 2 neuroblastoma, and she was treated with chemotherapy. There has been no recurrence after five years.

• **PATIENT 27:** A 15-month-old girl was evaluated for three months of ptosis and miosis. At age three months, she developed yellow skin lesions, proven by biopsy to be juvenile xanthogranulomas. MRI of the neck revealed a 10 × 18 mm enhancing mass between the left common carotid artery and thyroid gland. Radiographically, the lesion was felt to be consistent with a neuroblastoma, but surgery revealed a xanthogranuloma. She was treated at another institution and lost to follow-up.

• **PATIENT 28:** A three-year-old boy was seen for new right miosis and anhidrosis of several months' duration. The parents also noticed dilated neck veins and right axillary itchiness. An axillary mass and nodules in the neck were palpated, and computed tomography scanning revealed a 7.5 cm × 6 cm × 5.8 cm mass extending from the lung apex superiorly into the posterior cervical triangle and inferiorly to the origin of the main bronchus. Surgical resection revealed a Ewing sarcoma, and he was treated with chemotherapy and radiation. He remains well after three years, and the Horner syndrome has persisted.

Thus, an etiology for Horner syndrome, was found in seven of the 28 patients in the *diagnosis unknown* cohort. All diagnoses were found on imaging. The diagnoses of these patients is summarized in (Table 4).

The distribution of diagnoses in the *known* group is also listed in Table 4. One quarter were the result of neck or chest surgery, and 28.6% were associated with a known neoplasm, one of which was a neuroblastoma. The child with the neuroblastoma also did not have elevation of catecholamine metabolites on urine testing. One patient presented with Erb palsy, but ultimately was found to have multiple congenital abnormalities and agenesis of the carotid artery ipsilateral to the lesion. One had a difficult forceps and vacuum delivery remarkable for traction on the neck and direct ocular trauma. The child was delivered via cesarean section after labor trial with forceps and developed Horner syndrome and VIIth nerve palsy in the setting of multiple skull fractures. This patient's Horner syndrome was thought most likely secondary to interruption of the third-order neuron. In addition, a child with neurofibromatosis had Horner syndrome noted at birth. She was found to have ipsilateral paraspinal neurofibromas at the neural foramina at C4 to C5 and C5 to C6, slightly higher than would be expected to cause Horner syndrome, but no other etiology was found. In the patients with first-order Horner syndrome, most had other neurologic signs and symptoms, such as hemiparesis and altered mental status, to suggest a central nervous system lesion.

DISCUSSION

A STRIKING NUMBER (6/18 [33%]) OF CHILDREN PRESENTING with Horner syndrome without a known etiology, but who subsequently had a complete workup including urine screening and head, neck, and chest imaging were found to have a responsible mass. Of these six children, four had a neuroblastoma found on MRI imaging despite the absence of elevated urine catecholamines.

• **CLASSIFICATION OF PATIENTS:** The separation into *diagnosis known* and *diagnosis unknown* groups at presentation in our study helps to determine the frequency of neoplasm specifically in two different clinical scenarios. Previous studies have focused on the difference between *congenital* cases and *acquired* cases of Horner syndrome.[11,12] Unfortunately, this distinction is less useful for generating a prognosis for a patient when no diagnosis is known. By looking only at the data from the *diagnosis unknown* at presentation cohort and excluding data from patients in the *diagnosis known* group, we can accurately provide prognostic data for our patients. In addition, it is sometimes difficult for parents to recognize the subtle findings of Horner syndrome and to pinpoint when they first occurred. *Congenital* cases are certainly less frequently a result of a neoplasm such as a neuroblastoma, but there are exceptions. For instance, our study revealed two cases of congenital Horner syndrome (that is, children born with ptosis

and miosis) that were caused by masses (one neuroblastoma and one neurofibroma).

• **URINE STUDIES:** It has previously been suggested that urine studies alone are sufficient in the evaluation to exclude neuroblastoma in infants.[11] Urine testing may have been presumed adequate because 90% to 95% of children with neuroblastoma have been reported to have elevations in urinary catecholamines.[6]

It is surprising but unclear why none of the patients with newly diagnosed neuroblastomas in our series had elevated levels of urinary catecholamines. It is possible but uncertain whether the more modern use of VMA and HVA analysis in spot or random urine collections is relatively insensitive compared with 24-hour urine collections performed in previous studies. However, we have found outpatient 24-hour collections to be virtually impractical in young children, particularly those in diapers. Most parents prefer the spot urine collection.

It is also possible that the tumors detected in our cohort were relatively small. The majority of apical thoracic and cervical neuroblastomas, those responsible for causing Horner syndrome, are localized tumors arising in infants and younger children with favorable biology and outcome.[18,19] It is widely accepted that the magnitude of urine catecholamine elevations correlates with tumor "bulk" in neuroblastoma; that is, elevations are more pronounced in patients with larger tumors or widely metastatic disease.[6,19] In fact, urine catecholamine levels track with disease burden enough to be considered a reasonable assessment of treatment response and relapse surveillance for this disease.

Perhaps because Horner syndrome develops in such patients from subtle compression of the oculosympathetic pathway by a relatively small neuroblastoma before a palpable mass is noticed, these children may have presented earlier in their course before the urinary catecholamines became measurably elevated. Indeed, localized tumors are often associated with normal urine studies.[20] In a report of 144 patients with Stage 1 or 2 neuroblastoma, fewer than 40% had elevated urinary VMA or HVA greater than two standard deviations.[21] Ostensibly, the majority of these children with abnormal urine tests presented with signs or symptoms attributable to mass effects, rather than oculosympathetic pathway interruption. Thus although the usefulness of urine catecholamine studies in neuroblastoma screening or a neuroblastoma examination is not in question, our study demonstrates urine studies alone are certainly not adequate to rule out neuroblastoma in a child presenting with Horner syndrome.

• **EVIDENCE FOR A CAUSE IN IDIOPATHIC CASES:** Seventy-five percent of our patients (21 of 28) with no initial diagnosis for Horner syndrome had no etiology found. This number is within the rather large range reported or extrapolated from other reviews.[7–12] Many causes have been suggested in these cases, ranging from microvascular malformations in the carotid plexus to regressed, differentiated, or otherwise undetected neuroblastomas. Indeed, multiple large-scale urine screening studies for neuroblastoma during infancy that demonstrated an increased detection of neuroblastic tumors[22] suggested the majority of those additional tumors detected are asymptomatic at diagnosis, low grade in their biologic features, and prone to regression.[22–25] With no clinical sign or symptom of disease, it is impossible to determine the frequency of clinically silent, regressing neuroblastomas that do not secrete urinary catecholamines. Our patients reviewed with neuroblastoma and no elevation in urinary VMA or HVA suggest that a small and early-stage neuroblastoma in the cervical region can certainly interrupt the oculosympathetic system and not lead to elevations in measurable urinary catecholamines. It is also possible that some idiopathic Horner syndrome cases are due to congenital neuroblastomas that have spontaneously regressed by the time imaging and urine testing are performed.

One limitation of our study is that some of the patients (10 of 28) did not have a "complete" examination to exclude a neuroblastoma or other mass lesion and were labeled as "idiopathic." However, all of these patients had some combination of urine testing and imaging, albeit incomplete, and most were followed without any neoplasm identified. Another limitation inherent in a study such as this is referral bias. However, although bias could easily influence the distribution of etiologies in the *diagnosis known* group, there should have been no or little effect on the *diagnosis unknown* group—as these patients' ultimate diagnoses had no influence on whether they were referred or not.

• **BIRTH TRAUMA:** No patient in our study had Horner syndrome from brachial plexus injury at birth. This most likely reflects increased awareness and prevention of arm pulling by obstetricians, who have been noting a gradual decrease in the rate of brachial plexus injury as a result of delivery.[26–28] As mentioned previously, this may also be a consequence of a referral bias, because birth trauma is an easily recognized entity whose benign course is known in the obstetric community. Still, many patients ultimately considered idiopathic cases in our review had a history of forceps or vacuum delivery, although one case was believed to be Horner syndrome from forceps-related birth trauma. Prior reviews have suggested that if a history of birth trauma is elicited, urine screening and imaging are not necessary.[12] The infrequent incidence of birth trauma–related Horner syndrome in our review would argue against this approach. Instead, our finding of a patient with a history of birth trauma and Horner syndrome from cervical neuroblastoma underscores the importance of full screening in all patients with purported delivery-related Horner syndrome.

Addendum. After the final version of this paper was submitted, we saw one infant with birth trauma leading to brachial plexus injury and Horner syndrome.

• **IMAGING:** MRI is preferable to computed tomography scan in these circumstances because the resolution for assessing paravertebral structures, including encroachment through the neural foramina, is superior in our experience. In addition, many children with idiopathic Horner syndrome are infants and using MRI spares these young tissues radiation exposure that would be received during computed tomography scanning. Should a neoplasm be identified, subsequent studies would preferably use the same modality, further sparing additional radiation exposures to these vulnerable tissues.

Future studies should clarify whether or not more sensitive functional imaging techniques, such as 123I-MIBG or positron emission tomography scintigraphy, will identify occult lesions not detectable by standard anatomic imaging. In patients with Horner syndrome, at this time we prefer MRI over MIBG scanning because the clinician knows precisely where to look for a lesion—along the oculosympathetic pathway. MIBG scanning is better for screening for neuroblastoma and metastases anywhere in the body when the location is unknown, as one would when evaluating a child with opsoclonus or known neuroblastoma.

Most Horner syndromes from central nervous system lesions will be accompanied by other neurologic signs and symptoms. In addition, in our *diagnosis unknown* group, no patient with an isolated Horner syndrome was found to have a central nervous system lesion. However, because first-order Horner syndromes are relatively common, at this time we are unwilling to eliminate brain imaging in our protocol.

Noncervical (abdominal) neuroblastoma was the attributed cause of Horner syndrome in three publications.[5,11,16] No such cases were found in our study, although not all patients underwent abdominal imaging. It is possible that a responsible small cervical metastasis was missed in the three published patients, and the lesion would have been detected with modern MRI. Because of the rarity of the association of abdominal neuroblastoma and Horner syndrome, and because additional abdominal imaging requires a longer period for the child in the MRI machine, at this time we are not recommending abdominal imaging. However, in the examination room the abdomen, along with the neck, upper chest, and axilla, should be palpated for masses. In addition, the urine VMA and HVA testing may offer some screening for nonvisualized abdominal neuroblastomas.

At this time, we do not advocate formal contrast angiography or MRI angiography of the neck and circle of Willis to screen for carotid malformations. The routine MRI through the neck offer views of the carotid artery. Additional studies would require more scanning and time in the magnet for a sedated child.

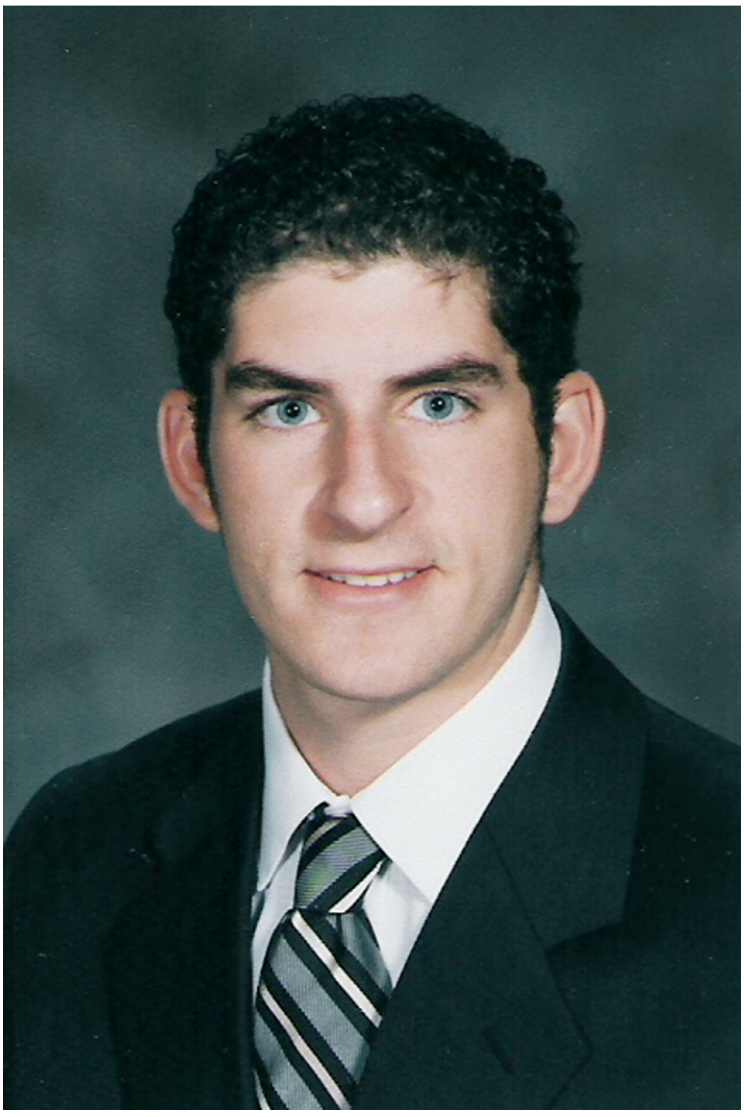
• **A RECOMMENDED PROTOCOL:** Our data confirm that a child presenting with Horner syndrome without a known diagnosis requires imaging studies to investigate the cause and exclude underlying neoplastic processes such as neuroblastoma. Our results demonstrate that urine testing alone is inadequate, because urine screening does not rule out neuroblastoma, and other types of mass lesions also may be found.

It is our recommendation that children with suspected Horner syndrome undergo a general physical examination and palpation of the neck, axilla, and abdomen. If Horner syndrome is then clinically or pharmacologically confirmed, MRI of the head, neck, and chest with and without contrast, in addition to random urine studies for HVA and VMA, should be ordered. Although we found no positive urine studies and published data suggest it may not be as sensitive a test as was previously thought, the test is inexpensive and easy to administer in children and should not be skipped. We recommend quantitative VMA and HVA by high-performance liquid chromatography because of the simplicity and noninvasive nature of such a test. Spot urine testing as mentioned earlier is more practical than 24-hour collections in this age group. The subsequent discovery of a neuroblastoma or other mass lesion demands a consultation with a pediatric oncologist.

REFERENCES

1. Liu GT, Volpe NJ, Galetta SL. Neuro-ophthalmology: diagnosis and management. Philadelphia: WB Saunders, 2001: 442–454.
2. Gupta M, Dinakaran S, Chan TK. Congenital Horner syndrome and hemiplegia secondary to carotid dissection. J Pediatr Ophthalmol Strab 2005;42:122–124.
3. Singh RR, Thomas AA, Barry MC, et al. Traumatic pseudoaneurysm of the internal carotid artery presenting with oculosympathetic palsy. Ir J Med Sci 2004;173:162–163.
4. Starr BE, Shubert RA, Baumann B. A child with isolated Horner's syndrome after blunt neck trauma. J Emerg Med 2004;26:425–427.
5. Musarella M, Chan HSL, DeBoer G, et al. Ocular involvement in neuroblastoma: prognostic implications. Ophthalmology 1984;91:936–940.
6. LaBrosse EH, Com-Nougue C, Zucker JM, et al. Urinary excretion of 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylacetic acid by 288 patients with neuroblastoma and related neural crest tumors. Cancer Res 1980;40:1995–2002.
7. Giles CL, Henderson JW. Horner's syndrome: an analysis of 216 cases. Am J Ophthalmol 1958;46:289–296.
8. Sauer C, Levinsohn MW. Horner's syndrome in childhood. Neurology 1976;26:216–220.
9. Weinstein JM, Zweifel TJ, Thompson HS. Congenital Horner's syndrome. Arch Ophthalmol 1980;98:1074–1078.

10. Woodruff G, Buncic JR, Morin JD. Horner's syndrome in children. J Pediatr Ophthalmol Strab 1988;25:40–44.
11. George NDL, Gonzalez G, Hoyt CS. Does Horner's syndrome in infancy require investigation? Br J Ophthalmol 1998;82:51–54.
12. Jeffery AR, Ellis FJ, Repka MX, et al. Pediatric Horner syndrome. J AAPOS 1998;2:159–167.
13. Maloney WF, Younge BR, Moyer NJ. Evaluation of the causes and accuracy of pharmacologic localization in Horner's syndrome. Am J Ophthalmol 1980;90:394–402.
14. Van der Wiel HL, Van Gijn J. Localization of Horner's syndrome. Use and limitations of the hydroxyamphetamine test. J Neurol Sci 1986;59:229–235.
15. Smith SA, Smith SE. Bilateral Horner's syndrome: detection and occurrence. J Neurol Neurosurg Psychiatr 1999;66:48–51.
16. Gibbs J, Appleton RE, Martin J, et al. Congenital Horner syndrome associated with non-cervical neuroblastoma. Dev Med Child Neurol 1992;34:642–644.
17. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–1477.
18. Adams GA, Shochat SJ, Smith EI, et al. Thoracic neuroblastoma: a Pediatric Oncology Group Study. J Pediatr Surg 1993;28:372–377.
19. Weinstein JL, Katzensteinc HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. Oncologist 2003;8:278–292.
20. Fritsch P, Kerbl R, Lackner H, et al. "Wait and see" strategy in localized neuroblastoma in infants: an option not only for cases detected by mass screening. Pediatr Blood Cancer 2004;43:679–682.
21. De Bernardi B, Conte M, Mancini A, et al. Localized resectable neuroblastoma: results of the second study of the Italian Cooperative Group for Neuroblastoma. J Clin Oncol 1995;13:884–893.
22. Yamamoto K, Hayashi Y, Hanada R, et al. Mass screening and age-specific incidence of neuroblastoma in Saitama Prefecture, Japan. J Clin Oncol 1995;13:2033–2038.
23. Woods WG, Gao RN, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. N Engl J Med 2002;346:1041–1046.
24. Ijiri R, Tanaka Y, Kato K, et al. Clinicopathologic study of mass-screened neuroblastoma with special emphasis on untreated observed cases: a possible histologic clue to tumor regression. Am J Surg Pathol 2000;24:807–815.
25. Yamamoto K, Hanada R, Kikuchi A, et al. Spontaneous regression of localized neuroblastoma detected by mass screening. J Clin Oncol 1998;16:1265–1269.
26. Jennett RJ, Tarby TJ, Kreinick CJ. Brachial plexus palsy: an old problem revisited. Am J Obstet Gynecol 1992;166:1673–1676.
27. Bennet GC, Harrold AJ. Prognosis and early management of birth injuries to the brachial plexus. Br Med J 1976;1:1520–1521.
28. Specht EE. Brachial plexus palsy in the newborn. Incidence and prognosis. Clin Ortho 1975;110:32–34.



Biosketch

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Biosketch

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