The article by Jeffery et al. on pages 159-67 of this issue of the Journal of AAPOS raises interesting points regarding pediatric Horner syndrome. On the basis of a retrospective review of 73 patients less than 18 years old seen over 10 years at two large referral centers, the authors provide a diagnostic paradigm emphasizing that seemingly idiopathic cases should be thoroughly investigated for the possible presence of malignancy, chiefly neuroblastoma. Their diagnostic workup would vary with the clinical profile and would include testing for urinary catecholamine breakdown products and imaging of the head, neck, chest, and abdomen.

Generally, an ideal diagnostic paradigm is highly sensitive and specific for the particular clinical situation, safe, convenient, and cost effective. For pediatric Horner syndrome, the usual evaluation variably includes a physical examination, ophthalmologic examination, urinary assay for catecholamine breakdown products, and imaging studies. Thoughtful acquisition of data in each component of this workup can help make the overall diagnostic paradigm approach the ideal above. Underlying the fear of missing or delaying the diagnosis of neuroblastoma is the observation that the age at diagnosis is the most important prognostic factor, with children less than 1 year old having the best prognosis. Evidence now suggests that this is so, at least in part, because some of the tumors detected in early life are biologically more benign and some are perhaps destined to spontaneously involute without treatment. This may have been the case in cases 20 and 21 of the authors' report. Early diagnosis, although very desirable, may sometimes detect tumors destined for spontaneous involution, a lesson now well learned from the Japanese studies on mass screening for neuroblastoma.1, 2

The physical evaluation should seek to exclude known causes of Horner syndrome and estimate the age of onset (inspection of old photographs is helpful). It should include palpation of the neck and abdomen for masses. Some so-called acquired cases of Horner syndrome may be congenital but undetected; the authors' cases 38 through 42 are possible examples.

The ophthalmologic examination should include pharmacologic testing of the pupils. Confirmation with cocaine testing should be considered because of the serious implications of this diagnosis and to exclude confounding disorders such as physiologic anisocoria. Also, some cases of congenital oculomotor palsy with aberrant reinnervation may resemble Horner syndrome.3 Hydroxyamphetamine testing is more difficult to interpret in children, but it can still be helpful. For example, a pupil that dilates well to hydroxyamphetamine after failing to dilate to cocaine is most likely a result of a central or preganglionic lesion irrespective of the patient's age. The presence of anhidrosis that involves the entire side of the head, the face, and the neck down to the clavicle or a history of thoracic or lower neck surgery or trauma further supports this localization. However, hydroxyamphetamine testing has two important caveats: (1) a fresh postganglionic Horner pupil (within a week of injury) may also dilate to hydroxyamphetamine, presumably before the stores of norepinephrine at the presynaptic terminals have been depleted, and (2) unlike adult Horner syndrome, failure of the pupil to dilate to hydroxyamphetamine does not definitively indicate a preganglionic lesion in a child because of the possible occurrence of transynaptic degeneration of postganglionic neurons after a preganglionic lesion.6 The frequency of transsynaptic degeneration in this setting is not known and further studies to elucidate this would be helpful. Despite these pitfalls, pharmacologic localization can sometimes reduce the need for near-total body imaging. Epinephrine 1% can be used as a substitute for hydroxyamphetamine, dilating the postganglionic Horner pupil as a result of denervation hypersensitivity.

Urinary catecholamine testing used to require a 24-hour urine collection and was therefore particularly difficult in infants. It has more recently become possible to assay for these products in random urinary samples collected either directly or from the infant's diaper.7 Given the test's high diagnostic sensitivity (96% when both vanillylmandelic acid and homovanillic acid are used) and specificity (more than 99%), it occupies a central role in screening for neuroblastoma.8, 9
Imaging in small children is inconvenient and expensive and requires anesthesia or sedation. Minimizing its unnecessary use is highly desirable. The approach to imaging in pediatric Horner syndrome is controversial. For a child with idiopathic acquired Horner syndrome, Jeffery et al. recommend physical examination, assay for urinary catecholamines, and neuroimaging of the head, neck, chest, and abdomen. Some authorities begin with a computed tomographic scan of the chest in this setting, perhaps on the basis of the premise that cervical lesions would be visible or palpable and abdominal lesions (e.g., adrenal neuroblastoma) are remote from the sympathetic pathway to the eye and would not generally be expected to cause Horner syndrome. However, the need to image other areas is supported by rare reports of the occurrence of Horner syndrome in children with tumors in the lower thoracic or abdominal regions (possibly because of a remote tumor effect or a multifocal tumor). Whether the possibility of this rare event justifies routine imaging below the upper thorax is unknown.

The study by Jeffery et al. and other related studies in the literature offer somewhat vague diagnostic approaches and leave some questions to be answered by future investigators. Should the components of the overall evaluation be obtained together or in a particular sequence, where the results of one test determine the necessity or extent of the subsequent test? For instance, it is unknown whether absence of visible or palpable masses in the neck and abdomen can substitute for imaging of these areas, especially in patients with negative workups and normal assay results for urinary catecholamines. Should urinary catecholamine testing precede imaging? Can its results help determine whether or how vigorous an imaging study to undertake? In children with idiopathic congenital Horner syndrome and a normal physical examination, Jeffery et al. recommend that a urinary test for catecholamines be obtained if the child is less than 5 years old, on the basis of the observation that the majority of cases of neuroblastoma occur before age 5 years. Subsequent imaging is recommended if “worsening of clinical signs” occurs and “needs to be made with consideration of the age of incidence of neuroblastoma, the urine assay results, and the physical examination.”

These recommendations are useful but vague, underscoring the need for further work in this area. Can an infant with normal urinary catecholamine levels who shows no worsening of the clinical signs over 1 year still harbor neuroblastoma? Should any further workup be performed? Should a 5-year-old child who has congenital Horner syndrome demonstrable in his infant photographs require a workup? Such a child may theoretically harbor neuroblastoma because it is currently unknown whether neuroblastoma tumors that become clinically apparent later in childhood are present and detectable in infancy. Does a 4-month-old infant with idiopathic congenital Horner syndrome and negative urinary catecholamine results require expedient neuroimaging? Because urinary catecholamines are positive in most (90% to 95%) but not all neuroblastomas, should the clinician be content with a negative urine test or should further imaging be entertained? If imaging is considered, is it necessary to image the head, neck, chest, and abdomen?

The article by Jeffery et al. is worthy of the clinician’s scrupulous reading. Given the limits of current knowledge, a diagnostic paradigm may still have to be somewhat vague, but spelling out some of the issues will hopefully highlight where our knowledge currently stands, paving the way for future studies addressing some of the above questions.

References