Group Proposes Diagnostic Criteria for PHACES

BY KERRI WACHTER

PHILADELPHIA — An expert group has proposed consensus diagnostic criteria for PHACES syndrome that call for full neurologic and cerebrovascular, ophthalmologic, and cardiologic work-ups to be performed on infants with hemangiomas who are at risk for the syndrome.

"Basically we're recommending a work-up of all three organ systems for any patient who has large facial hemangioma, no matter where it's located," said Dr. Denise Metry, first author of a poster on the criteria presented at the annual meeting of the Society for Pediatric Dermatology.

The neurocutaneous PHACES—**p**osterior fossa anomalies, **h**emangioma, **a**rterial abnormalities, **c**ardiac and aortic arch defects, **e**ye abnormalities, and **s**ternal cleft anomalies—syndrome affects a subgroup of patients with infantile hemangiomas.

The syndrome involves structural anomalies of the brain, cerebral vasculature, aorta, eyes, and the chest wall. The most common features are brain and cerebral vasculature abnormalities, so neurologic and cognitive impairments are among the most common morbidities.

Often, patients with hemangiomas on the upper part of the face tend to be more at risk for brain and eye abnormalities, while infants with hemangiomas on the lower part of the face are more likely to be at risk for cardiac issues or airway involvement. These are not, however, hard and fast rules. "I had a patient [with] a mandibular segment hemangioma, who had brain involvement," said Dr. Metry, highlighting the need for the criteria.

The proposed criteria for PHACES syndrome include a facial hemangioma larger than 5 cm in diameter plus one major criterion or two minor criteria. The major and minor criteria are categorized by organ system: cerebrovascular, structural brain, cardiovascular, ocular, and ventral or midline. (See table.)

Possible PHACES syndrome criteria include a facial hemangioma larger than 5 cm in diameter and one minor criterion, a hemangioma of the neck or upper torso plus one major or two minor criteria, or no hemangioma plus two major criteria.

"We're hoping that the criteria gain widespread acceptance," said Dr. Metry, who is chief of the Texas Children's Dermatology Clinic in Houston.

Formal guidelines have been lacking for the care of infants with this disorder, though it is generally recommended that infants with large hemangiomas of the face or scalp undergo head, neck, and chest imaging, along with ophthalmologic and skin examinations.

Likewise, there have been no standardized criteria for the diagnosis of PHACES syndrome.

The development of these criteria followed standard consensus methodology, based on a review of published clinical data and the combined experience of a multidisciplinary expert panel that included pediatric dermatologists, neuroradiologists, pediatric oncologists, geneticists, pediatric cardiologists, ophthalmologists, and representatives from patient support groups.

The expert panel reviewed published, peer-reviewed medical literature obtained by querying the Medline and PubMed databases.

After the panel put together and reviewed an initial draft, key features were discussed and a basic consensus statement was drafted during an executive session at the PHACE syndrome research conference and workshop in 2008.

During the conference, diagnostic criteria were circulated to the attendees for discussion and revision. After the conference, the expert panel resolved all conflicting recommendations via e-mail and teleconferencing.

In creating the major and minor criteria, the panel members determined the relative frequencies of each criterion in the literature and existing registries.

"While these diagnostic criteria will continue to evolve as new research findings are incorporated, the establishment of guidelines will enhance clinical care by improving screening, detection, and awareness of this neurocutaneous disorder," Dr. Metry and her associates wrote. ■

Major and Minor Criteria for PHACES Syndrome

Organ system	Major criteria	Minor criteria
Cerebrovascular	Anomaly of a major cerebral artery Dysplasia of a large cerebral artery Arterial stenosis or occlusion with or without moyamoya collaterals Absence of moderate-severe hyperplasia of a large cerebral artery Aberrant origin or course of a large cerebral artery Persistent trigeminal artery Saccular aneurysm of any cerebral artery	Persistent embryonic artery other than trigeminal artery Proatlantal intersegmental artery (types 1 and 2) Primitive hypoglossal artery Primitive otic artery
Structural brain	Posterior fossa anomaly Dandy-Walker complex or unilateral/bilateral cerebral hypoplasia/dysplasia Neuronal migration disorder	Enhancing extra-axial lesion consistent with intracranial hemangioma Midline anomaly
Cardiovascular	Aortic arch anomaly Coarctation of the aorta Dysplasia Aneurysm Aberrant origin of the subclavian artery with/without a vascular ring	Ventricular septal defect Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomaly Morning glory syndrome Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormality Microphthalmia Sclerocornea Coloboma Cataract
Ventral or Midline	Sternal defect Sternal cleft Supraumbilical raphe	Hypopituitarism Ectopic thyroid

Source: Dr. Metry

FDA Announces Six Steps to Speed Enforcement Efforts

BY MARY ELLEN SCHNEIDER

The Food and Drug Administration is vowing to get tougher and act faster when it comes to protecting public health.

Over the past several years, the FDA's enforcement activities have declined significantly, and those enforcement actions taken have been hamstrung by delays, mostly due to internal red tape, said Dr. Margaret A. Hamburg, the agency's new commissioner.

"The pathways to enforcement action can be too long and arduous when the public's health is in jeopardy," Dr. Hamburg said at a Food and Drug Law Institute conference in August. "We're fixing these pathways to improve the effectiveness of our enforcement system," she said.

Dr. Hamburg outlined six steps to streamline the way the FDA handles enforcement across all regulated areas—drugs, devices, and food.

For example, in cases where agency officials deem that public health is at risk, the FDA is prepared to take enforcement action before issuing a formal warning letter. Agency officials will also work with other regulators—state, local, and international—to figure out who can act fastest in a public health emergency.

The FDA also plans to change some of its internal processes. The agency will establish a 15-day deadline for industry to respond once a significant problem is identified during an inspection. The agency will also aim to get warning letters out the door more quickly by limiting review to significant legal issues.

Prompt follow-up on warning letters and other enforcement actions is also part of Dr. Hamburg's plan.

The Food and Drug Administration will move more quickly in assessing corrective actions that are taken by industry after a warning letter is issued or a major product recall occurs. And in an effort to motivate industry to act quickly, the FDA is developing a formal warning letter "close-out" process.

Once the FDA has confirmed that a firm has fully corrected its violations, the agency will issue a "close-out" notice and post theinformation on the FDA Web site.

"What we want to create is really a standard of practice that is a little bit different than what's been happening in recent years, where we commit to being as transparent as possible about our expectations and industry commits to working in as responsive a way as possible to address our concerns," Dr. Hamburg said. ■