Online First

Association of Hearing Loss With PHACE Syndrome

Kelly J. Duffy, PhD; Christina Runge-Samuelson, PhD; Michelle L. Bayer, BS; David Friedland, MD, PhD; Cecille Sulman, MD; Robert Chun, MD; Joseph E. Kerschner, MD; Denise Metry, MD; Denise Adams, MD; Beth A. Drolet, MD

Background: PHACE syndrome describes a spectrum of anomalies associated with large facial infantile hemangiomas and characterized by posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. With improved recognition and imaging practices of infants with PHACE syndrome, additional associations have been identified. To our knowledge, the potential association of ipsilateral hearing loss and PHACE syndrome has not been previously emphasized.

Observations: We describe 6 patients, 4 with definite and 2 with probable PHACE syndrome, according to the new diagnostic criteria, and associated auditory deficiencies. One patient had isolated conductive hearing loss; 2 patients had isolated sensorineural hearing loss; 1 patient had mixed hearing loss (both conductive and sensorineural components); and 1 patient had hearing loss that was inconclusive at the time. Also, 1 patient had conductive loss and auditory neuropathy and auditory dysynchrony. Four of the 6 patients had magnetic resonance imaging features of lesions consistent with intracranial hemangiomas involving auditory structures. All 6 patients had facial hemangiomas in a nearly identical distribution ipsilateral to the ear with the hearing loss, with involvement of the proposed facial segments S1 and S3, the affected ear, the periauricular region, and the midoccipital area of the scalp.

Conclusions: There is an underrecognized risk of hearing loss in patients with PHACE syndrome, although the exact nature of such deficiencies can vary. Patients with PHACE syndrome who have cutaneous hemangiomas involving the ear should be evaluated for intracranial hemangiomas and monitored for hearing loss. Early detection and therapy of intracranial hemangiomas may slow or stop tumor growth, resultant hearing loss, and structural damage.


PHACE syndrome (Online Mendelian Inheritance in Man [OMIM] 606519) describes a spectrum of anomalies associated with large facial infantile hemangiomas (IHs): posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. With increased awareness of the syndrome and more comprehensive evaluations, additional associations, including otolaryngological, have been reported. While recent case reports have suggested a potential link between PHACE syndrome and hearing loss, this association has not been described in detail (to our knowledge). We describe 6 patients, 4 with definite and 2 with probable PHACE syndrome, according to the new diagnostic criteria, and auditory impairments and review prior reports with similar features.

REPORT OF CASES

CASE 1

A female infant presented with a large segmental IH involving the right side of the forehead, the right cheek, and the bottom lip, with extension to the right ear, the parietal and occipital scalp area, and the anterior aspect of the chest (Figure 1A). She met diagnostic criteria for definite PHACE syndrome according to magnetic resonance imaging (MRI) findings of a hypoplastic right cerebellum and magnetic resonance angiographic findings of a hypoplastic distal right internal carotid artery and a hypoplastic left posterior communicating artery. Magnetic resonance imaging of the nasopharynx showed considerable impingement of the right eustachian tube by a lesion that showed imaging features consistent with an IH (Figure 2).

Author Affiliations are listed at the end of this article.
Repeated otoacoustic emissions testing from newborn screening through 6 months of age showed no otoacoustic emissions from the right ear. Tympanometry performed at 6 months showed a right-sided reduction in tympanic membrane mobility with negative middle ear pressure. Air and bone conduction auditory brainstem response testing using click stimuli at 10 months of age indicated a right-sided, conductive hearing loss. These results were consistent with right middle ear dysfunction.

**CASE 2**

A female infant presented for evaluation of a large IH that extended over the left side of her face and involved the upper and lower eyelids, the lateral aspect of the upper lip, the preauricular skin, the left ear, and the parietal region of the scalp. She met diagnostic criteria for definite PHACE syndrome according to MRI findings of a Dandy-Walker malformation and magnetic resonance angiographic findings of right internal carotid artery stenosis. An echocardiogram also showed a small, muscular ventricular septal defect and patent foramen ovale.

The patient passed a neonatal hearing screen in her right ear but was referred for further audiometric testing owing to abnormal results in her left ear. At 3 months of age, otoacoustic emissions results showed normal cochlear function in the right ear and absent cochlear function in the left ear; middle ear function was normal in both ears. Auditory brainstem response testing was conducted at this time, and responses to click stimuli and 250- and 1000-Hz tone-burst stimuli revealed moderate hearing loss in the left ear. Magnetic resonance imaging at 3 months of age did not show intracranial extension of the IH or involvement of internal auditory structures, although computed tomography at 11 months of age demonstrated a prominent enhancing region within an expanded left internal auditory canal, a large cochlear aperture, and prominence of the labyrinthine facial canal proximally. A dedicated internal auditory canal MRI has
not been performed to evaluate the enhancing region; however, the combined results of tympanometry, otoacoustic emissions testing, and auditory brainstem response testing suggested sensorineural hearing loss in the left ear.

**COMMENT**

In 1996, Frieden et al. introduced the PHACE acronym to describe the association of a large, cervicofacial hemangioma with the following extracutaneous complications: posterior fossa brain malformations, hemangiomas, arterial cerebrovascular anomalies, cardiovascular anomalies, and eye anomalies. PHACE syndrome is uncommon but not rare, with well over 300 cases reported in the literature. While the exact prevalence of the syndrome is unknown, a recent prospective study using standardizing screening protocols and strict diagnostic criteria for the syndrome demonstrated a 31% incidence among infants with facial IHs larger than 22 cm². Such efforts will positively affect future PHACE studies because more complete evaluations of at-risk patients are being performed and extracutaneous anomalies otherwise common to the normal population (so-called normal variants) are now excluded from the criteria for definitive diagnosis.

We describe 6 patients, 4 with definite and 2 with probable PHACE syndrome, according to the new diagnostic criteria, with associated hearing loss (Table). The hearing loss was ipsilateral to the cutaneous IH in all cases. The IH distribution was nearly identical in all cases, involving the proposed facial segments S1 and S3, as described by Haggstrom et al. with additional extension to most of the ear and the periauricular and midoccipital region in a circular pattern on the scalp (Figure 1). This latter region is not a previously characterized segment according to the original description by Hagstrom and colleagues, nor does it correspond to any known representative embryologic fields. Infantile hemangiomas occurring in this distribution with ear involvement are particularly vulnerable to ulceration of the superior helical rim, as was observed in our group and others, although the exact reason for such susceptibility is unknown.

In at least 4 of these 6 patients, enhancing intracranial lesions that were consistent with IHs involving auditory structures were seen on MRI and were present on the same side as the hearing loss. A 2002 review by Poetke et al. showed a 12% incidence of intracranial IHs among patients with PHACE syndrome. Viswanathan et al. later emphasized the need for careful identification of true intracranial IHs, which can be distinguished by their unique natural history, response to therapy, and pattern of central nervous system involvement, to avoid misclassification and improper management. Their study also supported observations by other authors that intracranial IHs tend to localize in or adjacent to the internal auditory canal and cerebellopontine angle ipsilateral to the cervicofacial IHs.

The nature of hearing loss observed in our patients varied. Conductive hearing loss was definitively observed in 3 patients. In 2 of these 3 patients, the conductive hearing loss was unilateral and could be directly attributable to occlusion of the eustachian tube by the IH. In the third patient (case 6), the conductive hearing loss was thought to be attributable to a middle ear effusion because (1) the conductive hearing loss was bilateral, (2) there was no occlusion of the external ear canal, and (3) MRI did not reveal occlusion of the eustachian tube. Sensorineural hearing loss was definitively observed in another 3 patients, 2 of whom had unilateral hearing loss. The etiology of unilateral sensorineural hearing loss in children is multifactorial and includes genetic defects that affect sensory and neural function and anatomical and developmental abnormalities. Defects may manifest at any point along the auditory pathway, from the cochlea to the central nervous system. Two of our patients (cases 4 and 5) had unilateral sensorineural hearing loss that could be directly attributable to the IH affecting cranial nerve VIII in the internal auditory canal (Figure 3). The other patient (case 2) did not have any quality images at 3 months of age to definitively address involvement of the IH or its association with any internal auditory structures, and computed tomograms at 11 months of age were only suggestive of a possible intracranial IH; therefore, the exact cause of her sensorineural hearing loss could not be verified.

One of our patients (case 6) was uniquely diagnosed as having bilateral auditory neuropathy and auditory dyssynchrony, which is characterized by the presence of cochlear microphonics and absent or asynchronized neural response during auditory brainstem response testing. There are multiple potential localized and systemic causes of auditory neuropathy/auditory dyssynchrony. Localized causes, including absent or deficit auditory nerves, auditory nerve myelination, and abnormal labyrinthine structures, are usually unilateral and were excluded in our patient after careful review of MRIs of the auditory pathways showed normal structures and myelination. The bilateral nature of our patient’s auditory neuropathy/auditory dyssynchrony suggests a systemic pathogenesis, and the 2 greatest risk factors known for this type of auditory deficiency are perinatal hypoxia and hyperbilirubinemia. Review of our patient’s birth records indicated that she was exposed to both factors. While this may be independent from her PHACE syndrome, it is also plausible that a combination of congenital PHACE anomalies with maternal preeclampsia (per birth records) contributed to an environment of global hypoxia resulting in auditory neuropathy/auditory dyssynchrony.

While prior case reports of PHACE syndrome have suggested a potential link with hearing loss, to our knowledge this association has not been examined in detail nor previously emphasized. Two recent, independent reviews by Hartemink et al. and Rudnick et al. recognized the potential impact of otologic abnormalities and vascular anomalies of the head and neck on otologic development, suggesting that such findings may be more prevalent in patients with PHACE syndrome. Three previously reported cases of PHACE syndrome noted the presence of conductive hearing loss, and 2 other reports mentioned the presence of sensorineural...
<table>
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<tr>
<th>Patient No./Sex</th>
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<th>Facial IH Distribution</th>
<th>Auditory-Related MRI Findings</th>
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<td>1/F</td>
<td>Definite PHACE: Large facial IH Hypoplastic right cerebellum Hypoplastic distal right internal carotid artery Hypoplastic left posterior communicating artery MRI enhancement consistent with intracranial IH</td>
<td>S1 and S3 (right)</td>
<td>Significant impingement of the right eustachian tube by a lesion with imaging features consistent with IH</td>
<td>Passed (left) Failed (right)</td>
<td>Birth to 6 mo: Absent OAEs (right) 6 mo: Reduced tympanic membrane mobility with negative middle ear pressure (right) 10 mo: Air and bone conduction ABR indicative of middle ear dysfunction (right)</td>
<td>Conductive hearing loss (right)</td>
</tr>
<tr>
<td>2/F</td>
<td>Definite PHACE: Large facial IH Dandy-Walker malformation Right internal carotid artery stenosis Ventricular septal defect</td>
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<td>None to date</td>
<td>Referred (left) Passed (right)</td>
<td>3 mo: Absent OAEs (left); middle ear function normal (left) 3 mo: ABR revealed moderate hearing loss (left)</td>
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<td>4/M</td>
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<td>5/F</td>
<td>Probable PHACE: Large facial IH MRI enhancement consistent with intracranial IH</td>
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<td>Conductive and sensorineural hearing loss (left)</td>
</tr>
<tr>
<td>6/F</td>
<td>Definite PHACE: Large facial IH Bilateral optic nerve hypoplasia Narrowing of right internal carotid artery Left-sided aortic arch Aberrant origin of right subclavian artery Tortuosity of both vertebral arteries with a dominant left vertebral artery</td>
<td>S1 and S3 (right)</td>
<td>None to date</td>
<td>Passed (left) Passed (right)</td>
<td>24 mo: Reduced tympanic membrane mobility (right) 33 mo: Present OAEs and absent middle ear muscle reflexes (bilateral) 33 mo: Normal ABR</td>
<td>Bilateral conductive hearing loss and bilateral auditory neuropathy and auditory dyssynchrony</td>
</tr>
</tbody>
</table>

Abbreviations: ABR, auditory brainstem response; IH, infantile hemangioma; MRI, magnetic resonance imaging; OAEs, otoacoustic emissions.
hearing loss. Other case reports of PHACE syndrome have described patients with clinical presentations similar to ours: one with a large facial IH in association with “hemangiomatous” tympanic membrane involvement and conductive hearing loss, and another with an intracranial IH involving the internal auditory canal and/or cerebellopontine angle but without mention of auditory status.

These prior and current cases indicate a likely underrecognized role for intracranial IH in hearing loss among patients with PHACE syndrome, given their proximity to and involvement with auditory structures. Importantly, because IHs are generally subtle or non-evident at birth and proliferate during the first 6 to 18 months of life, patients at risk for hearing loss may pass their initial newborn hearing screen but go on to develop problems later in infancy. In contrast to conductive hearing loss, sensorineural hearing loss is generally irreversible; although in cases of a space-occupying mass such as an IH, it may still be possible to preserve function or to prevent further damage with early lesion detection and therapeutic intervention. We therefore recommend that patients with PHACE syndrome with large, at-risk IHs of the face, scalp, and ears be closely monitored for potential auditory deficiencies, including audiological objective testing with tympanometry and auditory brainstem response, even if they pass their newborn hearing screen. These patients should undergo additional audiomeric evaluation at 6 to 9 months of age and again at 12 to 18 months of age, depending on the progression of the IH and the child’s development. Furthermore, the family should be counseled, and the pediatrician vigilant, in looking for delays or plateaus in language development over the first several years of life. Any delays should prompt referral for speech-language, audiological, and otolaryngological evaluation.

In conclusion, with the involvement of multidisciplinary clinical teams in the diagnosis, management, and study of PHACE syndrome, previously unrecognized manifestations of PHACE syndrome continue to be elucidated. Our cases show that hearing loss is a true potential association, which has probably been underdiagnosed previously but is likely to become more apparent with improved recognition of at-risk patients and screening practices. Hearing loss in association with PHACE syndrome can be conductive or sensorineural in nature and affect various auditory structures but is often directly attributable to an intracranial IH involving auditory structures. Infants at particular risk for PHACE syndrome–associated hearing impairments tend to have large IHs that extend over the head and neck in an S1 and S3 distribution, with additional ipsilateral ear and scalp involvement. Although many children with PHACE syndrome pass their initial newborn hearing screen, it is important that complete audiological assessment and testing be completed routinely for all at-risk children. Early evaluation and diagnosis can provide opportunity for more timely intervention and treatment of potential intracranial IH-associated hearing deficits.

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Author Affiliations: Departments of Pediatric Dermatology (Dr Duffy), Otolaryngology and Communication Sciences (Dr Runge-Samuelson), and Otolaryngology and Communication Sciences (Dr Friedland), Medical College of Wisconsin (Ms Bayer), and Division of Pediatric Otolaryngology, Department of Otolaryngology and Communication Sciences (Drs Sulman, Chun, and Kerschner), and Department of Dermatology and Pediatric Dermatology (Dr Drolet), Medical College of Wisconsin, Children’s Hospital of Wisconsin, Milwaukee; Departments of Dermatology and Pediatrics, Texas Children’s Hospital and Baylor College of Medicine, Houston (Dr Metry); and Departments of Pediatrics and Oncology, Cincinnati Children’s Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio (Dr Adams).

Correspondence: Beth A. Drolet, MD, Department of Dermatology, Medical College of Wisconsin, 9000 W Wisconsin Ave, Milwaukee, WI 53226 (drolet@mcw.edu).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Duffy, Runge-Samuelson, Bayer, Kerschner, Adams, and Drolet. Acquisition of data: Duffy, Runge-Samuelson, Bayer, Kerschner, Metry, Adams, and Drolet. Analysis and interpretation of data: Duffy, Runge-Samuelson, Bayer, Friedland, Sulman, Chun, Kerschner, Adams, and Drolet. Drafting of the manuscript: Duffy, Runge-Samuelson, Bayer, Kerschner, and Drolet.
cal revision of the manuscript for important intellectual content: Duffy, Runge-Samuelson, Bayer, Friedland, Chun, Sulman, Kerschner, Metry, Adams, and Drolet. Administrative, technical, or material support: Duffy, Runge-Samuelson, Friedland, Kerschner, and Drolet. Study supervision: Duffy, Kerschner, Adams, and Drolet. Specialty knowledge: Sulman.

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REFERENCES


Correction

Error in Text. In the Practice Gap by Stratman titled “Overscreening and Underscreening for Melanoma,” published in the October issue of the Archives (2010;146[10]:1102), the second sentence of the first paragraph, “This occurs not just in free skin cancer screenings, as described in the article by Andruenos et al, but also in dermatologist offices for patients seeking or being encouraged to seek full-body screening,” should have read: “This occurs not just in free skin cancer screenings, but also in dermatologist offices for patients seeking or being encouraged to seek full-body screening, as described in the article by Andruenos et al.”

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