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Structural Malformations of the Brain, Eye, and Pituitary Gland in PHACE Syndrome

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Abstract

PHACE syndrome is the association of segmental facial hemangiomas with congenital arterial, brain, cardiac, and ocular anomalies. Structural brain malformations affect 41–52% of PHACE patients and can be associated with focal neurologic deficits, developmental delays, and/or intellectual disability. To better characterize the spectrum of structural brain and other intracranial anomalies in PHACE syndrome, MRI scans of the head/neck were retrospectively reviewed in 55 patients from the PHACE Syndrome International Clinical Registry and Genetic Repository. All registry patients with a diagnosis of definite PHACE syndrome who had MRI scans of satisfactory quality were included. Of 55 patients, 34 (62%) demonstrated ≥1 non-vascular intracranial anomaly; structural brain malformations were present in 19 (35%). There was no difference in the prevalence of brain anomalies between genders. Brain anomalies were more likely in patients with S1 and/or S2 distribution of facial hemangioma. The most common structural brain defects were cerebellar hypoplasia (25%) and fourth ventricle abnormalities (13%). Dandy-Walker complex and malformations of cortical development were present in 9% and 7%, respectively. Extra-axial findings such as pituitary anomalies (18%) and intracranial hemangiomas (18%) were also observed. Six patients (11%) had anomalies of the globes or optic nerve/chiasm detectable on MRI. Brain malformations comprise a diverse group of structural developmental anomalies that are common in patients with PHACE syndrome. Along with brain malformations, numerous abnormalities of the pituitary, meninges, and globes were observed, highlighting the need for

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careful radiologic assessment of these structures in the neuroimaging workup for PHACE syndrome.

Keywords

PHACE syndrome; Brain malformations; Pituitary gland; Eye abnormalities; Magnetic resonance imaging

INTRODUCTION

PHACE syndrome is the association of segmental facial ***h***emangiomas with ***p***osterior fossa brain malformations, ***a***rterial anomalies, ***c***ardiac defects, and ***e***ye anomalies, with or without ventral developmental defects such as sternal clefting or supraumbilical raphe [Frieden, Reese, & Cohen, 1996]. The most common extracutaneous findings in PHACE syndrome are head/neck arterial anomalies (present in 91% of patients) and defects of the heart, aortic arch, and brachiocephalic vessels (41%) [Bayer et al., 2013; Haggstrom et al., 2010]. The frequency of structural brain anomalies in PHACE syndrome has been reported at 42–52% [Haggstrom et al., 2010; D. W. Metry et al., 2006]. The first brain malformations to be associated with facial hemangiomas were anomalies of the posterior fossa, though structural brain anomalies outside of this region have since been described [Grosso et al., 2004; Oza et al., 2008; Pascual-Castroviejo, 1978; Pascual-Castroviejo, Pascual-Pascual, Lopez-Gutierrez, Velazquez-Fragua, & Viano, 2007]. Due to the phenotypic diversity and relative rarity of PHACE syndrome, much is still unknown about the spectrum of anomalies associated with this disease. Data from the PHACE Syndrome International Clinical Registry and Genetic Repository has recently shed light on neurodevelopmental outcomes and cardiovascular anomalies in PHACE syndrome [Bayer et al., 2013; Brosig, Siegel, Haggstrom, Frieden, & Drolet, 2016; Tangtiphaiboontana et al., 2013]. With 55 total subjects, this is the largest study of brain and intracranial malformations in a PHACE cohort. This study builds upon preliminary phenotypic data in the literature by describing the spectrum of pituitary and ocular malformations detectible by MRI further characterizing the clinical and radiologic features of structural brain anomalies in PHACE syndrome.

MATERIALS AND METHODS

Patients

Patients included in the review were previously enrolled in the PHACE Syndrome International Clinical Registry and Genetic Repository housed at the Medical College of Wisconsin and Children’s Hospital of Wisconsin. The study has approval from the institutional review board at the Children’s Hospital of Wisconsin. All patients reviewed met consensus criteria for definite PHACE syndrome according to recent diagnostic guidelines [Garzon et al., 2016]. All patients enrolled in the registry that a) had MRI images acquired at the Children’s Hospital of Wisconsin and stored in the internal imaging database, or b) had MRI images from outside institutions available in compact disc format, were reviewed. Only patients without accessible MRI images were excluded. Some of the registry patients in this study were included as part of a previously published series [Hess et al., 2010].

Imaging Analysis and Data Collection

Prior to analysis, a standardized data acquisition form was developed by a panel of two pediatric neuroradiologists (CPH, MM) and a geneticist (WBD). Forms were designed to record type, location, and severity of observed structural anomalies, in addition to patient demographic information. Particular attention was given to the detection of pituitary and ocular anomalies. Images underwent systematic review by an experienced pediatric neuroradiologist (MM), and findings were documented using the data acquisition form. Quality of analyzed images was variable, given that scans were acquired according to protocols at the patients' respective institutions. All scans were performed at field strength of at least 1.5T, and all scans were considered diagnostically sufficient to characterize anatomic abnormalities. When multiple MRI studies were available for a single patient, the earliest study was reviewed. Along with analysis of MRI images, patient medical records and registry intake forms stored onsite by the PHACE Syndrome International Clinical Registry and Genetic Repository were reviewed for pertinent clinical and demographic data. Clinical photographs were obtained from patient records and used to document the distribution of facial hemangiomas (S1/S2/S3/S4) [Haggstrom, Lammer, Schneider, Marcucio, & Frieden, 2006]. Fisher's exact tests were used to analyze data for associations between brain anomalies and hemangioma location/patient characteristics.

RESULTS

Of the 224 patients enrolled in the registry at the time of analysis, 55 patients had complete MRI images of the head and neck available for review (Table 1). Forty-three of the 55 analyzed patients were female (78%) and twelve were male (22%). The 3.6:1 female-to-male ratio in our study population reflects the previously reported female predominance in PHACE syndrome [D. W. Metry et al., 2008]. Most patients reported Caucasian (82%) or Hispanic (16%) ethnicity. Age at the time of MRI ranged from 1 day to 11.3 years. Median age at time of scan was 2 months, with an interquartile range of 1 to 5.5 months. The majority of patients (85%) were younger than 1 year.

Overall, 34/55 (62%) had at least one intracranial anomaly, defined by the presence of any brain structural abnormality, intracranial hemangioma, and/or abnormality of the meninges, pituitary gland, or optic nerves/chiasm (Table 2). Nineteen (35%) had structural brain abnormalities. There was no difference in the prevalence of brain or other intracranial anomalies between genders ($p=1.00$) or ethnicities ($p>0.80$).

Clinical photographs were available for review in 44 of the 55 study patients. Among these patients, intracranial anomalies were more common in those with hemangioma affecting the S1 segment ($p<0.01$). Patients with S1 and/or S2 hemangiomas were twice as likely to have structural brain anomalies as patients with S3 and/or S4 hemangiomas (36% vs. 18%), though this difference was not statistically significant. Structural brain anomalies were present in 52% of those with hemangiomas affecting S1 plus another segment, compared to only 10% in patients with S1 hemangioma alone.

Posterior Fossa Brain Malformations

Structural abnormalities of the hindbrain were observed in 15/55 patients (27%). The most common of these, and the most common structural brain anomaly overall, was cerebellar hypoplasia, which was seen in 14/55 patients (25%). The majority of these cases (79%) were unilateral (Figure 1a). Unilateral cerebellar hypoplasia (UCH) was associated with ipsilateral facial hemangioma in 10/11 patients (91%). The single patient who did not demonstrate this association had UCH with a medially-located nasal hemangioma.

Seven patients (13%) demonstrated abnormalities of the fourth ventricle, mainly enlargement and/or communication with the cisterna magna. Chiari I malformation was noted in a single patient. Dandy-Walker complex was observed in 5/55 patients (9%), only one of whom had classical-type Dandy-Walker malformation (Figure 1b). Additional brainstem and cerebellar abnormalities included vermian dysgenesis/agenesis (11%), brainstem hypoplasia (7%), and cerebellar germinal matrix hemorrhage/siderosis (2%). Severity and location of brainstem hypoplasia varied considerably, although the pons was hypoplastic in all four affected individuals. In two of these cases, the brainstem appeared developmentally hypoplastic and was associated with ipsilateral cerebellar hypoplasia. In the other two cases, tortuous vascular structures were noted immediately adjacent to the small brainstem segment, suggesting an acquired volume loss or “notching” effect from these vessels. Overall, patients with posterior fossa malformations were more likely to have S1 and S2 involvement of facial hemangioma (100% and 82%, respectively) than patients without these anomalies (64% and 30%).

Other Structural Brain Malformations

Three patients (5%) had arachnoid cysts; pineal cyst and pericallosal lipoma (Figure 1c) were observed in one patient each. Malformations of cortical development were found in four subjects (7%). These included cortical dysplasia, polymicrogyria, and gray matter heterotopia (Figure 1d). Two patients had multiple cortical malformations. Agenesis/dysgenesis of the corpus callosum was seen in three patients (5%) (Figure 1c). Variants of the septum pellucidum (4 patients, 7%) were also observed, including both cavum septum pellucidum and cavum vergae. No cases of hydrocephalus were noted; however, two of the analyzed patients had ventricular shunts in place.

Isolated structural brain malformations were present in 10/55 (18%) of patients, and the majority of these (6/10) were cases of unilateral cerebellar hypoplasia. Two different structural brain malformations were noted in 4% and 3 or more structural brain malformations were found in 13% of the individuals (Table 3). Posterior fossa malformations such as fourth ventricle abnormalities, Dandy-Walker spectrum, cerebellar hypoplasia, and a/dysgenesis of the cerebellar vermis, were frequently seen together. Of the 8 patients with supratentorial brain malformations, 6 (75%) had accompanying posterior fossa malformations. Interestingly, one patient demonstrated multiple supratentorial lesions (cortical dysplasia, dysgenetic corpus collosum, and cavum septum pellucidum) in the absence of posterior fossa anomalies. The presence of structural brain anomalies was not associated with an increased frequency of non-brain intracranial anomalies (p=0.26).

Extra-Axial Anomalies

Dural ectasia in the region of Meckel's cave (trigeminal cistern) was the most common extra-axial finding, observed in 12/55 patients (22%) (Figure 1e). This was bilateral in 4 subjects and unilateral in 8; all of the latter were associated with ipsilateral facial hemangioma. Ten patients (18%) had intracranial hemangiomas visible on MRI. These were located predominately at the cerebellopontine angle and/or internal auditory canal. One patient with bilateral segmental facial hemangiomas had hemangiomas of the internal auditory canals bilaterally; all other cases of intracranial hemangioma were unilateral. In two patients, hemangioma extended from the fourth ventricle into the foramen of Luschka.

Pituitary Anomalies

Ten patients (18%) were found to have anomalies of the pituitary gland (Figure 1f). Three had pituitaries that appeared hypoplastic. Partially empty sella (2 patients), pituitary ectopia (1 patient) and absent pituitary stalk (1 patient) were also seen. Pituitary hypoplasia was characterized by small size of both the gland and surrounding bony sella, which distinguished this entity from partially empty sella, in which a small pituitary was observed within an enlarged sella. Rathke cleft cysts, all ≤3 millimeters in size, were observed in four subjects (7%). All patients with pituitary anomalies (10/10) had facial hemangioma involving the S1 segment. Hemangiomas affecting S2 (5/10), S3 (4/10), or S4 (2/10) segments were less common in these patients.

Eye Anomalies

Globe abnormalities were detected in 4 patients (7%) (Figure 1g). Only the globe ipsilateral to the hemangioma was affected. Two of these patients had posterior staphyloma and the other two had microphthalmia. One of the patients with microphthalmia also demonstrated choroidal hemorrhage and lens dislocation. Three patients had hypoplasia of the optic nerve(s) or chiasm. S1 segment was affected in 6/7 patients (86%) with eye anomalies; one patient had a large lower body hemangioma without the facial involvement typical of PHACE syndrome.

DISCUSSION

This study is the most comprehensive review of non-vascular intracranial anomalies in PHACE syndrome to date. Structural brain malformations have been associated with focal neurologic deficits, headache, speech delay, and poor neurodevelopmental outcomes in PHACE patients, and thus have the potential to significantly impact quality of life [Brosig et al., 2016; Martin et al., 2015; Tangtiphaiboontana et al., 2013; Yu et al., 2016]. Structural brain anomalies were identified in 35% of patients with PHACE syndrome, lower than previously reported rates of 42%–52% [Haggstrom et al., 2010; D. W. Metry et al., 2006]. In our study, anomalies that did not involve the brain parenchyma (e.g., pituitary malformations, intracranial hemangiomas) were not classified as "brain anomalies," which may account for this difference. Nearly two-thirds of patients had some type of non-vascular intracranial anomaly.

The most common malformation observed in this study was cerebellar hypoplasia, and the majority of cases were unilateral. Ipsilateral facial hemangioma was present in 10/11 cases of UCH. A similar association between unilateral arterial anomalies and ipsilateral facial hemangiomas has previously been described in PHACE syndrome [Hess et al., 2010; Heyer et al., 2008]. UCH is a common finding in PHACE, as evidenced by the 20% of patients affected in the present study as well as prior reports [Hess et al., 2010; Oza et al., 2008]. UCH is most often asymptomatic, but it can manifest clinically with speech or other developmental delays, hypotonia, ataxia, abnormal ocular movements, seizures, or headaches [Benbir et al., 2011]. Cognitive deficits are more common when the cerebellar vermis is affected [Poretti et al., 2010]. Clinicians should be aware of these neurologic symptoms when caring for patients with PHACE syndrome, especially those with documented UCH or other posterior fossa brain malformations. It is important to note, however, that most PHACE patients with structural brain anomalies will have normal neurologic examinations during infancy [D. Metry et al., 2009].

UCH has been reported in genetic disorders such as Prader-Willi syndrome, osteogenesis imperfecta, and neurofibromatosis type 1; it has also been seen following unilateral cerebellar ischemic injury, or as an isolated finding with no associated syndrome [Benbir et al., 2011; Harbord, Finn, Hall-Craggs, Brett, & Baraitser, 1989; Poretti, Boltshauser, & Doherty, 2014; Tabarki, Al-Malki, & Al-Ghamdi, 2007; Titomanlio et al., 2006]. In most of these reported cases, arterial anomalies were observed in conjunction with UCH. In PHACE syndrome, UCH is almost always associated with anomalies of the ipsilateral internal carotid artery or persistent embryonic carotid-vertebrobasilar connections [Poretti, Boltshauser, & Doherty, 2014]. This fact, together with the well-established association between prenatal hypoxic-ischemic insult and UCH, suggests that abnormal arterial development in PHACE may cause hypoxia in utero, resulting in underdevelopment of the cerebellum [Poretti, Prayer, & Boltshauser, 2009]. Hess et al. postulated that disruption of one of the paired dorsal longitudinal arteries, which during development supply the cerebellum separately before fusing to form the basilar artery, could account for the unilaterality of cerebellar hypoplasia commonly seen in PHACE syndrome [Hess et al., 2010]. The primitive internal carotid arteries transiently supply the dorsal longitudinal arteries starting around day 28 of development, and also serve as embryologic precursors to large portions of the anterior and posterior circulations [Padget, 1948]. It follows that anomalies of proximal arteries such as the primitive ICA might result in bilateral cerebellar anomalies or more global defects in the developing brain.

In the present study, 7% of patients demonstrated malformations of cortical development (MCD). MCD are clinically heterogeneous, with associated symptoms ranging from mild behavioral disturbances and intellectual disability to intractable epilepsy [Guerrini & Dobyns, 2014]. Radiologically, MCD that are unilateral, localized (versus diffuse), and not associated with other brain malformations tend to carry a better prognosis [Guerrini & Dobyns, 2014]. In our study, all MCD were localized, and only one patient had bilateral MCD. However, additional structural brain anomalies accompanied MCD in all of these cases.

MCD result from defects in neuron or glial cell apoptosis/proliferation, neuronal migration, or postmigrational development [Barkovich, Guerrini, Kuzniecky, Jackson, & Dobyns, 2012]. A number of causative genetic variants have been identified for MCD, most of which are thought to impair at least one of these processes [Barkovich et al., 2012; Poretti, Boltshauser, & Huisman, 2014]. Several MCD, including polymicrogyria, gray matter heterotopia, and cortical dysplasia, in addition to agenesis/dysgenesis of the corpus callosum, have well-described ischemic etiologies [Barth & van der Harten, 1985; Poretti et al., 2009; Weinstein, Goldstein, & Barkovich, 2003]. In PHACE syndrome, such malformations could theoretically result from the same hypoxic environment in utero that predisposes to anomalies of the posterior fossa. As previously suggested, post-zygotic mutations might also explain the segmental hemangiomas and regional congenital anomalies characteristic of PHACE [D. W. Metry et al., 2006; Sullivan et al., 2013].

Dural ectasia of Meckel's cave was the second most common intracranial anomaly observed after cerebellar hypoplasia. Meckel's cave, also referred to as the trigeminal cistern, is a cerebrospinal fluid-filled arachnoid pouch that protrudes from the posterior fossa and houses the trigeminal ganglion. Lesions of this space, including neoplasms, vascular malformations, aneurysms, and dural ectasia, cause it to appear prominent on MRI [Beck & Menezes, 1987; Majoie, Verbeeten, Dol, & Peeters, 1995]. Dural ectasia of Meckel's cave may represent an incidental finding in the general population, and has not previously been considered a typical structural anomaly in PHACE syndrome. "Prominent" Meckel's cave associated with PHACE syndrome has been described in only two case reports [Judd, Chapman, Koch, & Shea, 2007; Rosmaninho, Machado, Bastos-Leite, & Selores, 2011]. In one of these cases, the lesion was thought to be extension of periorbital hemangioma along the trigeminal nerve [Judd et al., 2007]. The frequency of this finding in our study suggests that dural ectasia of Meckel's cave may be more common in PHACE syndrome than the current literature suggests.

Particular attention was paid to pituitary anomalies in this study, as no comprehensive review of pituitary anomalies in PHACE syndrome has been published to date. Pituitary hypoplasia, a subtle radiologic finding that has rarely been reported in PHACE, was observed in 5% of our patients [Poindexter, Metry, Barkovich, & Frieden, 2007]. These results suggest that hypoplastic pituitary gland may be under-reported in PHACE syndrome, although further studies may be needed to confirm the true incidence and significance of this finding. Other pituitary abnormalities included Rathke cleft cyst and partially empty sella turcica; one patient demonstrated both absent infundibular stalk as well as ectopic pituitary. Collectively, these results reflect the spectrum of PHACE-associated pituitary anomalies previously described in case reports. No cases of empty sella or absent pituitary were found in our study population; however, these findings have been reported in PHACE syndrome [Denzer, Denzer, Lennerz, Bode, & Wabitsch, 2012; Lasky, Sandu, & Balashanmugan, 2004].

The clinical importance of a diminutive or malformed pituitary in PHACE syndrome is unclear. To assess for hypopituitarism, correlation with history, physical examination, and/or endocrine lab values is recommended when incidental pituitary malformations are discovered on MRI. Endocrine dysfunction is seen in PHACE syndrome, both in the

presence and absence of pituitary anomalies, though it is considered an uncommon manifestation of the disease [Altin et al., 2012; Poindexter et al., 2007]. Hypothyroidism, growth hormone deficiency, adrenal insufficiency, and hypogonadotropic hypogonadism have all been described [Denzer et al., 2012; Lasky et al., 2004; Merheb, Hourani, Zantout, & Azar, 2010; Poindexter et al., 2007]. Endocrinopathy may result from pituitary insufficiency or from hypofunction elsewhere in the hormonal axis, such as at the hypothalamus or target endocrine organs [Poindexter et al., 2007]. Review of clinical records revealed no documented hypopituitarism in patients with pituitary gland anomalies in our study. However, given the young age of these patients at the time of MRI (median age=1.5 months), continued follow-up is necessary to assess for future development of hypopituitarism.

A number of congenital syndromes are associated with hypoplasia or structural malformations of the pituitary gland [Fard, Wu-Chen, Man, & Miller, 2010; Guran et al., 2011; Kelberman & Dattani, 2007; Voutetakis, Sertedaki, & Dacou-Voutetakis, 2016]. Many cases have been linked to mutations in developmental genes responsible for the formation and patterning of the pituitary gland and other midline structures (e.g., HESX1, PROP1, POU1F1, GLI2, and others) [Kelberman & Dattani, 2007]. Interestingly, several reports have described pituitary malformations (especially hypoplasia) co-occurring with unilateral agenesis of the internal carotid artery [Lamine et al., 2012; Savasta et al., 2012; Shulman & Martinez, 1996]. Two potential mechanisms for this association have been proposed, namely vascular insufficiency and neural crest cell defects. The vascular theory suggests that decreased perfusion to the developing pituitary gland results in hypoplasia or other structural anomalies [Inamo & Harada, 2003]. Because neural crest cells give rise to both carotid vascular smooth muscle cells and the neurohypophysis, impaired neural crest cell migration or differentiation might also cause this phenotype [Blustajn et al., 1999; Triulzi et al., 1994]. As previously discussed, prenatal vascular insult and mutations in developmental genes have also been suggested as possible etiologies for PHACE syndrome. Unlike the patients in our study, all cases of pituitary hypoplasia with concomitant unilateral ICA agenesis presented with hypopituitarism, with structural pituitary and arterial anomalies discovered subsequently on MRI.

In addition, a number of structural eye anomalies were detectable on MRI, including staphyloma, dysmorphic appearance of the globe, and optic nerve/chiasm hypoplasia. One patient had additional findings of choroidal hemorrhage and lens dislocation associated with phthisis bulbi. Ocular anomalies are present in approximately 10% of PHACE patients [D. Metry et al., 2009]. The most frequently reported anomalies are microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory disc anomalies, although staphyloma, coloboma, congenital cataracts, iris hypoplasia, and retinal vascular anomalies can also be seen [D. Metry et al., 2009]. The majority of these defects are discovered by clinical ophthalmic examination, which is more sensitive than MRI for this purpose [Roy, Davagnanam, & Evanson, 2012]. Our results suggest that MRI, which is routinely performed for detection and monitoring of brain and arterial anomalies in PHACE syndrome, may serve as a useful adjunct to ophthalmoscopy in diagnosing anomalies of the eye in these patients.

In general, the constellation of intracranial anomalies observed in PHACE differs from that of other vascular anomaly syndromes. Sturge-Weber, for example, can present with both neurologic (focal deficits, seizures) and ocular findings (glaucoma, visual field defects) in conjunction with a facial vascular anomaly (capillary malformation). However, MRI typically demonstrates leptomeningeal capillary-venous malformations as opposed to developmental anomalies of the brain parenchyma as seen in PHACE. There is some neuroradiologic overlap between PHACE and *PIK3CA*-related spectrum (PROS) [Keppler-Noreuil et al., 2015]. A number of supratentorial lesions associated with PHACE, including cortical dysplasia, polymicrogyria, and septum pellucidum anomalies have also been reported in PROS [Conway et al., 2007]. However, the posterior fossa malformations associated with PROS (cerebellar tonsillar herniation, asymmetric cerebellar overgrowth) were starkly different than those seen in PHACE.

The present study highlights the frequency and diversity of structural brain and other intracranial anomalies in PHACE syndrome. Malformations of the eye and pituitary were detected, suggesting the utility of MRI in characterizing these anomalies as well. Additional studies are needed to correlate malformations with long-term clinical outcomes. The multi-institutional and retrospective nature of this study posed several limitations. Because MRI images were obtained using different protocols and field strengths, image quality was variable. All scans considered diagnostically unsatisfactory by the reading neuroradiologist were excluded in an attempt to mitigate this inconsistency. In addition, MRIs were reviewed by only one neuroradiologist; review of scans by another neuroradiologist would have added weight to our conclusions.

Of the individuals in this study, 28 have had copy number variant analysis and 20 have had whole exome sequencing [Siegel et al., 2013]. To date, a shared copy number variant or causative genetic mutation have not been identified. Further study is needed to elucidate the pathogenesis of PHACE syndrome on the associated brain anomalies.

CONCLUSION

We conducted a retrospective MRI review of 55 patients to better characterize the spectrum of intracranial anomalies in PHACE syndrome. Brain malformations were present in 35%, and included a variety of lesions both within and outside the posterior fossa. Abnormalities of the pituitary gland and globes were also observed, highlighting the need for careful radiologic assessment of these structures during neuroimaging for PHACE. Better understanding of the wide range of brain malformations seen in PHACE syndrome may offer clues into its etiopathogenesis and aid in the diagnosis and clinical management of this uncommon disease.

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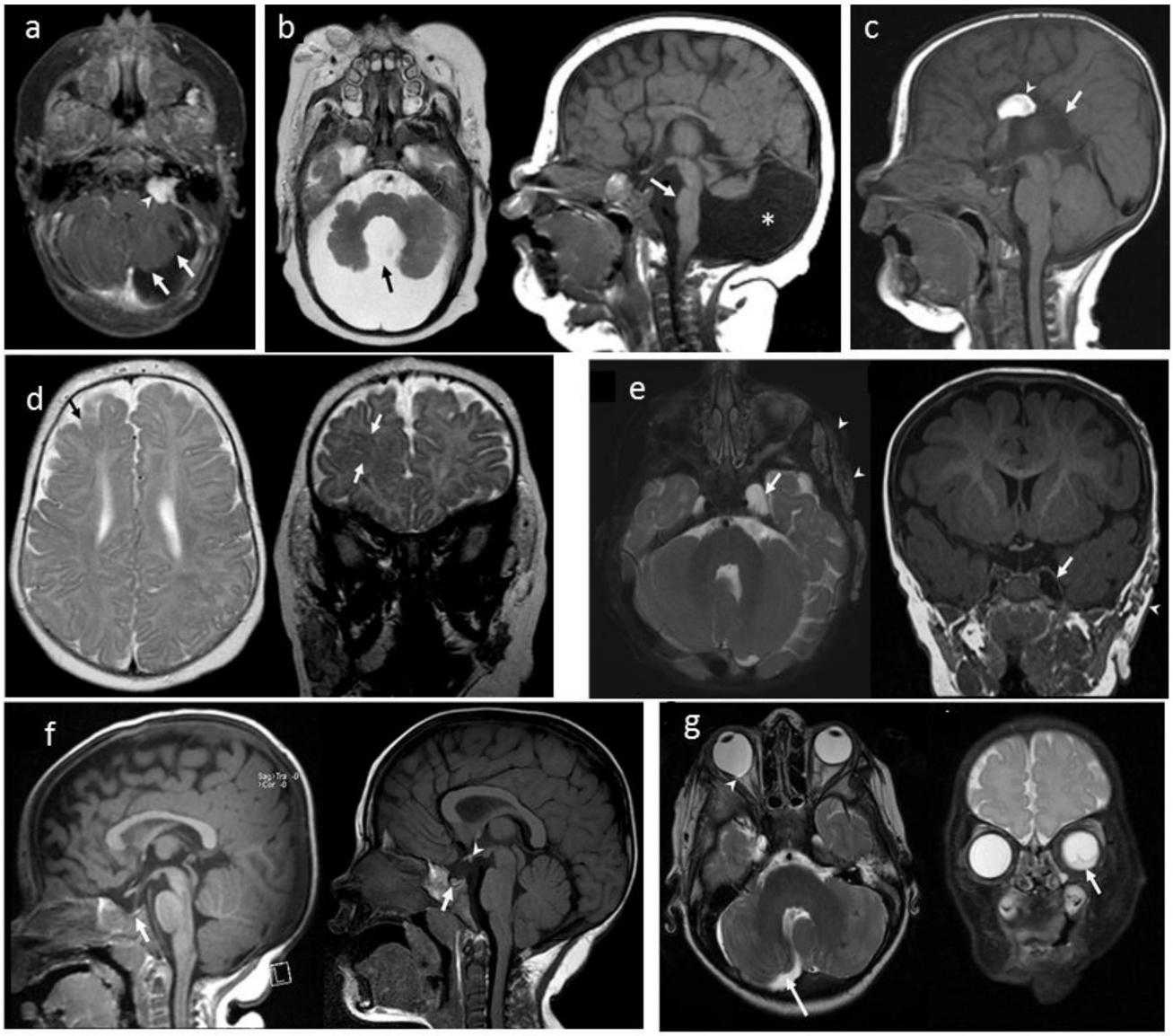

Figure 1.

a) Axial T1 post contrast fat saturated image showing hypoplasia of the left cerebellum (arrows) and a large hemangioma in the region of left internal auditory canal (arrowhead). Small hemangioma is also seen in the left masticator space, b) Axial T2 (left panel) and sagittal T1 (right panel) weighted images showing Dandy-Walker spectrum malformation with absence of vermis (black arrow), hypoplasia of the cerebellar hemisphere, and large posterior fossa cyst (white asterisk). Mild hypoplasia of the brainstem (white arrow) is also noted, c) Sagittal T1 weighted image of the brain in the midline showing dysgenesis of the corpus callosum (arrow) and a pericallosal lipoma (arrowhead), d) Axial (left panel) and coronal (right panel) T2 weighted images of the brain show malformation of cortical development (polymicrogyria) in the right frontal lobe. e) Axial T2 (left panel) and coronal T1 (right panel) show dural ectasia in the form of enlargement of the left Meckel's cave (arrows). Large hemangioma is seen in the left temporal region (arrowheads). Ipsilateral

cerebellar hypoplasia is also noted (left panel), f) Pituitary malformations in two different patients. Sagittal T1 weighted image showing hypoplasia of the bony sella and pituitary gland (left panel, arrow). Sagittal T1 weighted image showing ectopic posterior pituitary bright spot (right panel, arrowhead) and hypoplasia of the pituitary gland (arrow). Pituitary stalk is also absent, g) Ocular abnormalities in two children with PHACE syndrome. Axial T2 weighted image showing staphyloma involving the right globe (left panel, arrowhead) and mild hypoplasia of the ipsilateral cerebellum (left panel, arrow). Coronal T2 weighted image showing subchoroidal hemorrhage in the left globe (right panel, arrow).

Table 1

Patient Demographics

	N (%)
Gender	
Female	43 (78)
Male	12 (22)
Age at Scan	
<1mo	10 (18)
1–6 mo	31 (56)
7–12 mo	6 (11)
>12 mo	8 (15)
Ethnicity *	
Caucasian	45 (82)
Hispanic	9 (16)
African-American	1 (2)
Asian	1 (2)

* One patient reported both Caucasian and African-American ethnicity.

Table 2

Structural Anomalies Observed

	N (%)
Any intracranial anomaly	34 (62)
Any structural brain defect	19 (35)
Posterior fossa defect	15 (27)
Cerebellar hypoplasia	14 (25)
Abnormal fourth ventricle	7 (13)
Dandy Walker spectrum	5 (9)
A/dysgenesis of vermis	6 (11)
Cerebellar germinal matrix hemorrhage/siderosis	1 (2)
Brainstem hypoplasia	4 (7)
Malformation of cortical development	4 (7)
Polymicrogyria	2 (4)
Cortical dysplasia	1 (2)
Gray matter heterotopia	2 (4)
A/dysgenesis of corpus callosum	3 (5)
Abnormal septum pallucidum	4 (7)
White matter changes	1 (2)
Arachnoid cyst	3 (5)
Dural ectasia of Meckel’s cave	12 (22)
Intracranial hemangioma	10 (18)
Pituitary anomalies	10 (18)
Pituitary hypoplasia	3 (5)
Empty sella	0 (0)
Partially empty sella	2 (4)
Absent pituitary stalk	1 (2)
Ectopic pituitary	1 (2)
Rathke’s cleft cyst	4 (7)
Optic nerve/chiasm hypoplasia	3 (5)
Globe abnormalities	4 (7)
Staphyloma	2 (4)

Table 3

Number of brain anomalies per individual

	N (%)
Number brain or intracranial anomalies	21 (38)
1 structural brain anomaly	10 (18)
2 structural brain anomalies	2 (4)
≥3 structural brain anomalies	7 (13)
1 non-brain intracranial anomaly	15 (27)
2 non-brain intracranial anomalies	7 (13)
≥3 non-brain intracranial anomalies	3 (5)
≥1 structural brain anomaly + ≥1 non-brain intracranial anomaly	11 (20)