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Research Article

Obstructive Aortic Arch Pathology and Infantile Hemangioma: Coincidence or PHACES Syndrome?

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Abstract

The objective of this article is to determine the prevalence of PHACES syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects, Eye anomalies, Supra-umbilical raphe and/or Sternal pit) in patients with obstructive aortic arch pathology (OAAP) in order to achieve more insight in the possible association between infantile hemangiomas (IH) and cardiovascular anomalies.

Pediatric patients diagnosed with OAAP between 1999 and 2013 in our tertiary referral center were included. A questionnaire on the presence of an IH and other symptoms fitting the diagnostic criteria of PHACES syndrome was created. Deceased patients were analyzed separately.

The questionnaire was sent to 266 patients with OAAP, of which 175 (66%) were returned. In 9 cases an IH was diagnosed. One child met the criteria of PHACES syndrome. This child demonstrated a segmental hemangioma and an atypical interrupted aortic arch with atresia of the left common carotid artery, which fits the complex vasculopathy seen in PHACES syndrome. The remainder (n=8) did not meet the PHACES criteria due to characteristics of IH or aortic arch. None of the deceased study objects fulfilled the PHACES syndrome criteria.

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In this retrospective cohort, one child met the PHACES criteria, indicating that PHACES syndrome in OAAP patients is rare. Due to limited cohort size this study was underpowered to provide evidence of an association between IH and obstructive aortic arch pathology.

Keywords: obstructive arch pathology, infantile hemangioma, PHACES, aortic coarctation

Introduction

In 1978, Pascual-Castroviejo was the first to report coinciding anomalies (including congenital heart disease) in patients with cervicofacial hemangiomas. In view of the rarity of this combination Schneeweiss et al (1982) suggested a new syndrome of congenital cardiac and peripheral vascular anomalies. This association was further defined by Frieden et al (1996), where the acronym PHACE was introduced, later extended to PHACES with the 'S' reflecting supra-umbilical raphe or sternal pit. This syndrome includes Posterior fossa malformations, segmental Hemangiomas of the head and neck, Arterial anomalies, Cardiac defects, Eye anomalies and aforementioned ventral closure defects. Segmental hemangioma of the face or neck is the PHACES syndrome hallmark (Metry et al 2009, Metry et al 2009, Metry et al 2006 and Wendelin et al 2004). Cardiac involvement appears in 21 – 67% of PHACES syndrome patients [Metry et al 2009, Metry et al 2006, Haggstrom et al 2010, Metry et al 2001 and Bayer et al 2013). Aortic arch anomalies are the main cardiovascular feature, in particular coarctation of the aorta (AC), which is also associated with an increased risk of arterial ischemic stroke (AIS) [Metry et al 2009, Metry et al 2006, Metry et al 2001, Rao et al 2008, Bronzetti et al 2004, Giardini et al 2010, Siegel et al 2012 and Heyer et al 2008). In contrast to the few hundred patients reported with PHACES, infantile hemangiomas (IH) and congenital heart diseases are much more frequently diagnosed in children. The overall incidence of IH is estimated to be around 4 – 10% (Kilcline et al 2008, Jacobs 1976 and Hoornweg et al 2012), while AC has a birth prevalence of approximately 0.032%-0.036% worldwide as reported by Van der Linde et al (2011).

The pathophysiology of PHACES syndrome remains to be elucidated. A recent post-mortem study of Chad et al (2012) emphasizes the concept that an arteriopathy is the underlying defect in PHACES syndrome, resulting in dysplasia of large to medium sized arteries. From an embryologic point of view, the observation that left heart valve is absent in PHACES coarctation as mentioned by Bayer et al (2013) is supportive of this hypothesis. However, this does not directly explain the presence of hemangiomas, which are neoplastic rather than dysplastic anomalies. It is hypothesized that a delay or disturbance in the shift of embryonic to fetal vasculature might cause a hypoxic environment. Hypoxia subsequently might serve as a stimulus of IH development (Metry et al 2009 and Leaute-Labreze 2011). Current research focuses on a genetic basis for the vascular anomalies in PHACES patients. It is most likely that PHACES syndrome has a multifactorial origin with both genetic and environmental causes. In the future, large databases such as the 'PHACE registry' (http://www.phaceregistry.com/StudyInfo.html) might be able to either definitely prove an association between the several congenital cardiovascular defects and PHACES and to eludicate its genetic or multifactorial origin.

Most studies investigating PHACES phenomenon and the association with AC focused on patients that primarily had a (segmental) hemangioma. In sight of planning surgery for cardiac pathology, awareness of PHACES syndrome and its associated features is of in importance regarding for example, cerebral perfusion in PHACES patients. Because of the paucity of information from patients primarily diagnosed with AC, we performed a retrospective study in patients with obstructive aortic arch pathology (OAAP) in order to determine the prevalence of IH for the diagnosis PHACES syndrome in patients with aortic arch obstructions.

Methods

All pediatric patients referred to a tertiary referral centre for middle, south and east of the Netherlands between 1999 and 2013 were included. Patients were referred for diagnostic procedures or interventions (i.e. heart catherization and/or surgery) because of OAAP. OAAP was defined as AC, isolated hypoplastic aortic arch or interrupted aortic arch (IAA). A questionnaire focusing on presence of an infantile hemangioma and other symptoms in line with the diagnostic criteria of PHACES syndrome was constructed (available as online supplement). This survey including informed consent forms was sent to patients (aged > 16 years) or their parents (when aged < 16 years). Non-responders were reminded by mail one month later. When still not responding, they were reminded by telephone. We decided not to send questionnaires to parents of deceased children.

If in the questionnaire a (possible) hemangioma was reported, we asked parents or patients to send a photograph of the lesion. Following consent, medical charts were reviewed, or, when necessary, other institutions were asked for more detailed information about reported symptoms. The obtained data from the survey (age at diagnosis, location of a hemangioma, growth in time), photographs and medical chart reviews were analyzed anonymously. During a multidisciplinary meeting (two dermatologists, one plastic surgeon, one pediatric cardiologist and one pediatric hematologist, all members of the "Center of Congenital Vascular Anomalies Utrecht"; CAVU team) a diagnosis of hemangioma was confirmed or rejected. In addition it was discussed whether a subject met the criteria of PHACES syndrome in accordance with the criteria described by Metry et al (2009).

This study was judged as being not interventional by the ethics committee of the University Medical Center of Utrecht and thus did not require formal approval under Dutch law. All subjects provided informed consent for medical chart review and using information for research purposes.

Results

The database contained 286 children who were diagnosed with OAAP of which 90.9% had AC or an isolated hypoplastic aortic arch without intracardiac pathology. Twenty-six children (9.1%) had an IAA. Baseline patient characteristics are shown in table 1.

Table 1. Baseline Characteristics of All Patients

		All patients (n = 286) N (%)	Included patients (n = 164) N (%)	Deceased patients (n = 19) N (%)
Gender	Male	181 (63.3%)	108 (65.9%)	12 (63.2%)
Aortic arch obstruction	AC [a] Interruption	260 (90.9%) 26 (9.1%)	154 (93.9%) 10 (6.1%)	15 (79.0%) 4 (21.0%)
Complex disease [b]		164 (57.3%)	96 (58.5%)	17 (89.4%)
Aortic valve	Bicuspid Tricuspid (normal) Unknown	103 (36%) 171 (59.8%) 12 (4.2%)	67 (40.9%) 91 (55.5%) 6 (3.7%)	3 (15.8%) 10 (52.6%) 6 (31.6%)
Aberrant subclavian artery		10 (3.5%)	3 (1.8%)	5 (26.3%)

[a] Aortic Coarctation with or without hypoplasia of (segments) of the aortic arch or isolated hypoplastic aortic arch
[b] Complex disease is defined as coarctation in association with intracardiac pathology necessitating intervention[20]

As depicted in figure 1 (flowchart), 266 questionnaires were sent, with a response rate of 66% (n = 175). Because (parental) permission to use the data for research purposes was not obtained in 11 participants, 164 (62%) surveys were eventually analyzed. Baseline characteristics were comparable for the whole group (n=286) and only those who responded to the questionnaire (i.e. "included patients", n=164). In 23 cases (14%), patients or parents reported a possible IH. Eight of them were considered as true hemangiomas by the multidisciplinary team, based on patient history, photographs, chart review and, when available, histology reports. Characteristics of the 8 patients with a hemangioma (H01 – H08) are shown in table 2. No large (> 5cm in diameter) or segmental cervicofacial hemangiomas were diagnosed except for one patient (H09) who did not receive a questionnaire. This child was already known with PHACES syndrome, having a segmental hemangioma located mainly left sided in the periorbital and temporal region, with bilateral lesions retroauricular and a lesion of the soft palate. She had an atypical obstructed aortic arch (type C interruption) with agenesis of the left common carotid artery. During surgery a remarkable macroscopic aspect was noticed with perivascular scarring resembling like inflammatory alterations. When PHACES syndrome was suspected, further angiographic evaluation revealed hypoplasia of the left internal carotid and posterior communicating artery (major criteria) without symptoms of ischemia. In addition, the child had a sternal pit, which is also a major criterion.

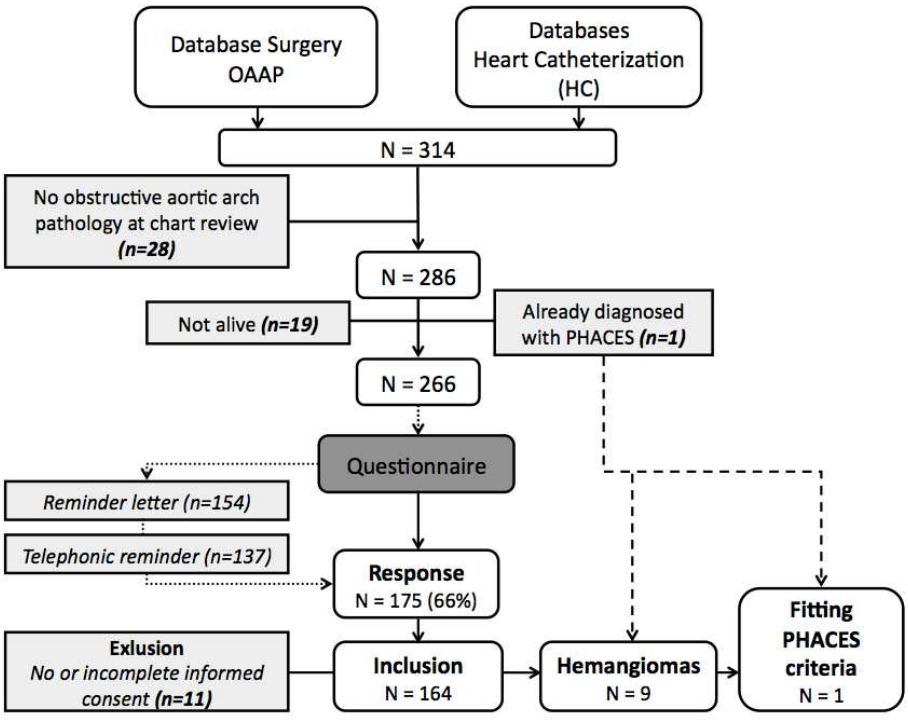

Fig. 1. Flowchart of Inclusion

Table 2. Characteristics of Hemangioma Patients

		Hemangioma [a]			Cardiovascular pathology			Other pathology	
H01	M	Left upper torso	Oval spot, +/- 1 cm in diameter Focal	No	Juxtaductal AC with long segment narrowing (15 mm)	BAV	None	None (no imaging)	ADHD
H02	F	Right side of scalp	1 cm Focal plaque	No	Ridge/kinking and mild constriction of isthmus (>0.4 of AAo) Right aortic arch	Mild valvular and subvalvular aortic stenosis, functional BAV	Dextrocardia with atrial situs inversus, multiple VSDs; abnormal IVC, bilateral SVC	None (no imaging)	Polysplenia with functional asplenia (heterotaxy)
H03	F	Left upper arm	4 - 5 cm Focal plaque	No	AC DAo	BAV, parachute like mitral valve	VSD	None (ultrasound only)	No
H04	M	Left thumb	1 x 2 cm Focal	No	Juxtaductal AC with hypoplastic transverse arch	BAV	VSD, PFO, LVH, subaortic stenosis	None (no imaging)	Inguinal hernia
H05	M	Right scapula	3 cm Focal	No	Hypoplastic transverse arch between LCA and arterial ligament (15 mm segment) with slightly hypoplastic LSA origin	Normal	Mild peripheral LPA stenosis	None (no imaging)	Recurrent respiratory tract infections Mild laryngomalacy
H06	M	Left lower back	3 - 4 mm Focal nodule	No	Severe AC with hypoplastic transverse arch	Stenotic BAV; parachute mitral valve with stenosis (Shone variant)	PFO, Mild subvalvular aortic obstruction (abortive Shone complex), Left SVC	None (ultrasound only)	No
H07	F	Left flank	1 x 0.5cm Focal	Surgical excision (PA: diagnosis confirmed)	AC DAo with hypoplastic transverse arch	Normal	VSD	None (no imaging)	ADHD
H08	M	Left thigh and toe (side unknown)	Thigh: 2 cm Toe: pinpoint, subcutaneous	No	AC DAo	BAV	PFO	None (no imaging)	No
H09	F	Face, mainly left side [b] Soft palate	Segmental / multifocal	Atenolol	IAA type C with (secundary) atresia left CCA	Normal	Bilateral SVC	Hypoplasia of left ICA and PCA Normal neurologic development at age 2 yrs	Sternal scar Genetics: Duplication 12q24.21

[a] In most cases determined by parental information in the absence of medical reportage
[b] Left temporal and periorbital, left auriculair helix. Bilateral retroauricular
[c] Hypoplastic aortic arch defined as diameter of isthmus < 40% of AAo, proximal transverse arch < 60% of AAo or distal transverse arch < 50% of AAo [34]. The term 'small' is used when no diameters were available or when not meeting the definition of hypoplasia.

ABBREVIATIONS: **AAo** Ascending Aorta; **AAR** Aortic Arch Reconstruction; **AC** Aortic Coarctation; **ADHD** Attention Deficit Disorder with Hyperactivity; **BAV** Bicuspid Aortic Valve; **CCA** Common Carotid Artery; **DAo** Descending Aorta; **EEA** End-to-End Anastomosis; **IAA** Interrupted Aortic Arch; **ICA** Internal Carotid Artery; **IVC** Inferior Vena Cava; **LPA** Left Pulmonary Artery; **LSA** Left Subclavian Artery; **LVH** Left Ventricle Hypertrophy; **PA** Pathology; **PCA** Posterior Communicating Artery; **PFO** Persistant Foramen Ovale; **SVC** Superior Vena Cava; **VSD** Ventricular Septal Defect

Seven other hemangioma patients had classical AC (discrete narrowing distal to the left subclavian artery (LSA)), with or without BAV (bicuspid aortic valve), not matching with the specific aortic arch anomalies in PHACES syndrome. One patient (H05) revealed a slightly atypical hypoplasia of the transverse arch with a hypoplastic origin of the LSA without other remarkable aortic arch pathology. A large or segmental hemangioma of the face, necessary for the diagnosis of PHACES syndrome, was not present in this child. No neurological or other symptoms leading to the suspicion of PHACES syndrome were reported in any of the eight participants.

Of 286 patients with obstructive aortic arch disease, 19 patients deceased. Details of these children are summarized in table 3. None of the children had a hemangioma mentioned in their medical records or correspondence (including autopsy reports). Most children (9/19; 47%) had typical coarctation located distally of the LSA or did not have unusual characteristics of the coarctation mentioned (4/19; 21%). Two children (D10 and D15) had a coarctation proximal of the LSA and 4 children (D07, D11, D13, D14) had a type B interruption of the arch (between LCA and LSA), the most common type of IAA [20]. One child (D04) had a double aortic arch (minor criterion). None of the children had a right aortic arch. Ten patients (53%) died within the first 3 months of life, almost all due to circulatory failure as a consequence of their complex cardiac condition.

Table 3. Characteristics of Deceased Patients

			Cardiovascular pathology		Other pathology	Death		IH	Comments
D01	M	HLHS	Unknown	LPA stenosis	Factor VII deficiency	12 years	Circulatory insufficiency / cardiac (presumably secondary to sepsis, embolisms, myocarditis, coronary ischemia)	No	
D02	M	Juxtaductal AC with small transverse arch	Normal	TGA, VSD, ASD, DORV, coronary anomaly	Hemorrhage adrenal gland, testicular hydrocele	2 months	Circulatory insufficiency / cardiac	No	
D03	F	AC Dao wit small transverse arch	Small mitral valve	ASD I, PDA	Multiple dysmorphic features (incl. down slanted eyes, low set ears, long fingers, four finger line)	4 months	Pneumonia	No	Genetics: triploidy chromosome 15 (unbalanced translocation chr. 4 – 15)
D04	F	Juxtaductal AC Double aortic arch	Normal	PFO	Prematurity (33 weeks) Bilateral subependymal hemorrhage	Unknown (> 7 months)	Unknown	No	Pathology report: ductal tissue in whole AC segment, no fibrosis or necrosis as seen in PHACES vasculopathy {Chad 2012; Bayer in press}
D05	M	AC	Normal	ccTGA, VSD, DORV, PA aneurysm and stenosis, PH	Recurrent atelectase, hypermobility, palatoschisis with facial dysmorphism (suspicion of Pierre	10 years	Perioperative cardiac failure	No	Genetically excluded Marfan or Ehler Danlos disease

					Robin sequence)				
D06	M	Juxtaductal AC Overriding aorta	Dysplasia of mitral valve	VSD, ASD II, partial APVR	Bilateral choroideal coloboma, webbed neck, cysts in plexus choroidius, mega-cisterna magna, vermal hypoplasia (Dandy Walker variant), bronchial malacy, hepatosplenomegaly, biliary anomaly	4 ½ months	PH and bronchopneumonia	No (autopsy report)	Genetics: suspicion of cerebellar-craniofacial-cardiac (3C) or Joubert's syndrome
D07	F	IAA type B	Normal	Malalignment VSD, subaortic stenosis	None	4 days	During cardiac surgery (hemorrhage and myocardial infarction)	No	
D08	F	Juxtaductal AC Aberrant RSA	Normal	AVSD	Trisomy 21	6 months	Unknown (most likely due to pneumonia)	No derma-tologic abnormalities	
D09	M	Juxtaductal AC	Normal	None	Multiple dysmorphic features (incl. micrognathia, small fontanel, microcephaly, microphtalmia, palatoschisis, clinodactyly), aphakia left eye, possible neuronal migration disorder	15 days	E. coli meningitis (with secondary epilepsy and ischemic and ventricular abnormalities on brain MRI)	No	Parental consanguinity Genetics: suspicion of Smith-Lemli-Opitz or Cerebro-oculo-facio-skeletal syndrome
D10	M	AC proximal of origin LSA	Cleft mitral valve	HLHS (forme fruste), AVSD	Bilateral cheilognathoschisis, testicular hydrocele, hemiparesis due to cerebral infarct [b] (large medial cerebral artery right infarct with hemorrhagic component)	3 months	Untreatable cardiac condition	No	No MRA brain imaging
D11	M	IAA type B Aberrant origin of the RSA	BAV	VSD, subaortic stenosis	Prematurity (35 weeks), inguinal hernia with testicular hydrocele, small airway disease	2 ¼ years	Unknown (most likely cardiac failure due to chordal rupture of mitral valve)	No	

D12	M	HLHS	Stenotic BAV	(prenatally?) Closed foramen ovale	Prematurity (31 + 5/7 weeks), ischemic cerebral lesions, potentially prenatally developed secondary to congenital heart disease	4 days	Severe and untreatable cardiac condition	No (autopsy report)	No abnormalities found during brain autopsy except for old and recent hypoxic lesions in cerebrum
D13	M	IAA type B Arteria lusoria	Doming and thickening of aortic valve	VSD, subaortic stenosis, DORV	Tracheomalacy, horseshoe kidney with hydronephrosis, costovertebral anomalies, multiple dysmorphic features (retro/micrognathia, long fingers, sandal gap, hypospadia)	6 months	Unknown (during hospitalization after cardiac procedures)	No	Genetics: suspicion of osteo-vertebral chondrodysplasia
D14	M	IAA type B Arteria lusoria	BAV	VSD, ASD, LVOTO, PA stenosis, PDA,	22q11 deletion syndrome, recurrent SVC syndrome/thrombotic events, cerebral (periventricular) hemorrhage (most likely due to venous infarction), urethral stricture, developmental delay, auto-immune enteropathy	1 year and 8 months	Pulmonary detoriation, cutaneousGVHD and suspicion of pulmonary fungal infection after stem cell transplantation	No derma-tologic abnor ma-lities	
D15	M	HLHS Arteria lusoria	Small aortic and mitral valve	ASD, left SVC, PDA	Hypoplasia of pons and vermis, partial agenesis of corpus callosum, unilateral hydronephrosis, dysplastic kidney with cyst, Pierre Robin sequence, bilateral conductive hearing loss, multiple skeletal deformities (scoliosis, abnormal rib position, abnormal ossification	2 months	Severe respiratory obstructive incident	No	

					pubic bone, rockerbottom feet, digital abnormalities), multiple other dysmorphic features (inguinal hernia, tracheomalacy)				
D16	M	AC with hypoplastic transverse arch	Normal	VSD	Necrotizing enterocolitis	2 months	Bowel perforation secondary to necrotizing enterocolitis	No	
D17	F	HLHS	Mitral valve hypoplasia	Dextro/mesocardia, VSD, ASD, partial APVR (Scimitar syndrome), hypoplasia RPA, left SVC, MAPCAs	Hypoplasia right lung with lung sequestering (Scimitar syndrome), PH	5 weeks	Circulatory and respiratory failure due to progressive PH	No	
D18	F	AC distal of LSA with small transverse arch	Normal	Mesocardia, VSD, ASD, complete APVR (Scimitar syndrome), agenesis LPA, hypoplasia RPA, MAPCA, PDA	Omphalocele, PH, hypoplasia right lung with lung sequestering (Scimitar syndrome), male chromosomal pattern (XY) with female phenotype	7 days	Untreatable cardiac condition	No	
D19	F	AC DAo with small arch	Small aortic valve	TGA, VSD, OFO, DORV	Necrotizing enterocolitis, multiple ischemic cerebral lesions on MRI [b]	2 months	Progressive circulatory insufficiency	No	

[a] Hypoplastic aortic arch defined as diameter of isthmus < 40% of AAo, proximal transverse arch < 60% of AAo or distal transverse arch < 50% of AAo [34]. The term 'small' is used when no diameters were available or when not meeting the definition of hypoplasia.
[b] Considered to be consequence of cardiovascular condition and/or surgical procedure

ABBREVIATIONS: AAo Ascending Aorta; **AAR** Aortic Arch Reconstruction; **AC** Aortic Coarctation; **APVR** Anomalous Pulmonary Venous Return; **ASD** Atrial Septal Defect; **AVSD** Atrioventricular Septal Defect; **BAV** Bicuspid Aortic Valve; **DAo** Descending Aorta; **DORV** Double Outlet Right Ventricle; **EEA** End-to-End Anastomosis; **GVHD** Graft-Versus-Host-Disease; **HLHS** Hypoplastic Left Heart Syndrome; **IAA** Interrupted Aortic Arch; **IVC** Inferior Vena Cava; **LPA** Left Pulmonary Artery; **LSA** Left Subclavian Artery; **LVOTO** Left Ventricular Outlet Tract Obstruction; **MAPCA** Major Aortopulmonary Collateral artery; **PDA** Persistent Ductus Arteriosus; **PFO** Persistant Foramen Ovale; **PH** Pulmonary Hypertension; **RPA** Right Pulmonary Artery; **RSA** Right Subclavian Artery; **SVC** Superior Vena Cava; **(cc)TGA** (congenital corrected) Transposition of Great Arteries; **VA** Vertebral Artery; **VSD** Ventricular Septal Defect

Discussion

AC is a relatively common congenital abnormality. Within the PHACES spectrum, AC and IAA account for 45% of the cardiovascular anomalies as mentioned by Bayer et al (2013). As IH, the hallmark of PHACES syndrome, is highly prevalent in the healthy population, the appearance of IH in our study population of OAAP patients could also be by normal distribution. This study demonstrates that PHACES syndrome is uncommon in patients with OAAP.

IH and PHACES Prevalence

A recent prospective study among the Dutch population by Hoornweg et al (2012), showed an IH prevalence of 9.9% in newborns (0 – 16 months of age). The relatively low prevalence we found (5.5%) is most likely due to recall bias, lack of registration in medical records by physicians of these benign lesions or misdiagnoses because of the retrospective nature of assessment.

In contrast, the actual prevalence of PHACES syndrome is unknown. A frequency of 2.3% in children with IH was reported by Metry, et al (2006). In the same study, PHACES was diagnosed in 20% of IH patients with the segmental facial type (approximately 10% of all IH), which is a characteristic feature and main criterion for definite diagnosis of PHACES. Given an IH prevalence of 9.9% in the Dutch population, the prevalence of PHACES is suggested to be as high as 1:500 children. One fifth of all PHACES patients are affected by AC or IAA [10], suggesting that approximately 1 per 2500 children has PHACES with aortic arch obstruction. As the birth prevalence of AC is also around 1:2000-3000 (Van der Linde et al 2011, EUROCAT Central Registry and Website Database 2013), this would suggest that a large proportion of, if not all, AC patients could be diagnosed with PHACES.

We only found one AC patient (0.6%) with an already diagnosed PHACES syndrome in the studied cohort. This is substantially less than expected as suggested by Metry et al (2006). It should be recognized though that the cohort studied by Metry et al (2006) only concerned IH patients in tertiary dermatology centers, which may have caused selection bias that resulted in the observed high prevalence of PHACES in IH patients.

The prevalence we found here is also lower than reported by Prada et al (2010) in which 4 cervicofacial hemangiomas were shown with segmental distribution or ulceration in a cohort of 63 subjects (6.3%). We diagnosed only one child with a similar hemangioma in our cohort (0.6%). There's no direct explanation for this remarkable difference in prevalence, but it might be partially explained by Prada et al using an outdated broad definition of Frieden et al (1996). This inclusive case definition consists of facial hemangioma plus 1 or more extracutaneous features. In contrast, we used the current diagnostic criteria as proposed by Metry et al (2009) in a consensus statement. This statement stratifies patients into 2 categories: [1] PHACES syndrome or [2] possible PHACES syndrome and uses major and minor criteria for the diagnosis.

A strong relationship between the occurrence of aortic arch obstruction and segmental IH, has been hypothesized by others (Metry et al 2009 and Bronzetti et al 2004). Despite the fact that our single PHACES case accounts for 11% of the identified hemangiomas in AC patients, which is much higher than the 2.3% of 'general' IH patients as reported by Metry et al (2006), our limited cohort size makes it difficult to draw definite conclusions.

Diagnostic Considerations

Except for the child with already diagnosed PHACES syndrome (H09), no patients fitted the diagnostic criteria for "definite" diagnosis of PHACES based on the hemangioma characteristics.
However, two patients with IH (H01 and H05) may be diagnosed with "possible" PHACES for having a hemangioma on the upper torso, as stated in the diagnostic criteria by Metry et al (2009). The possibility of PHACES syndrome in children with nonfacial hemangiomas is based on case reports of children with large segmental hemangiomas of the upper trunk or arm with or without minor facial involvement (Metry et al 2006 and Nabatian et al 2011). Our two 'possible PHACES' cases however exhibited a small (< 5 cm in diameter), non-segmental hemangioma and thus were not suspected for PHACES syndrome by our CAVU expert team. The data suggest that occurrence of IH in this cohort (except for H09) seems to be coincidental rather than related with OAAP.

The aortic abnormalities found in PHACES patients represent a distinctive morphologic entity with unusually complex and unpredictable anatomic involvement. Whereas the "classical" coarctation involves a discrete part of the proximal descending (juxtaductal) segment of the aorta, the coarctation observed in PHACES syndrome has been described to consist of a long-segment narrowing of the transverse arch with unusual dilation and aneurysm formation of adjacent arch segments (Metry et al 2006, Metry et al 2001, Rao et al 2008, Bronzetti et al 2004). These arch anomalies are often associated with abnormalities of the brachiocephalic vessels (dilation, tortuosity, and aberrant subclavian artery origin) and aortic arch sidedness as written by Metry et al (2009) and Bronzetti et al (2004).

The prevalence of BAV is as high as 50-80% in the "classic" coarctation. In PHACES syndrome however no aortic or mitral valve pathology is seen in PHACES syndrome (Metry et al 2009 and Beekman et al 2008). A recent study of 150 PHACES cases by Bayer et al (2013), showed that left heart valve pathology (BAV in particular) was completely absent in all of the 28 coarctation patients.

Our child with PHACES syndrome revealed such unusual anatomy (interruption between innominate and left common carotid artery with absence of the left carotid artery). No unusual dilation, aneurysm formation or abnormalities of the brachiocephalic vessels, in particular aberrant origin of the right subclavian artery, were observed in the other IH patients. Despite the slightly atypical aortic arch (long segment hypoplasia of arch and hypoplastic origin of LSA) in H05, this child was not considered to have PHACES. In addition, the aortic arch in the other "possible" PHACES subject (H01) did neither correspond with the bizarre arch anatomy seen in PHACES syndrome.

Deceased Patients

Another explanation for the low PHACES prevalence in our study might be that potential PHACES patients died early in life due to complications of cardio- or cerebrovascular anomalies. Therefore, we investigated the available data of deceased OAAP patients.

No hemangiomas were mentioned in medical records or autopsy reports of these children.

The diagnosis of PHACES could be deliberated in some deceased children based on certain aortic arch anomalies (e.g. double aortic arch or aberrant subclavian artery), neurologic sequelae or dysmorphic features (such as micrognathia or schizis). For all these there were arguments against this diagnosis, for example the presence of (cardiac) abnormalities which are unknown in PHACES, being diagnosed with or being suspected for another syndrome (e.g. 22q11 deletion syndrome). Unfortunately, no definite answers can be given due to lack of angiographic imaging, missing data and unreliable documentation of possible hemangiomas.

Conclusion

In this retrospective cohort of 164 OAAP patients, one child met the PHACES criteria, indicating that PHACES syndrome is rare in OAAP patients. Due to limited cohort size this study was underpowered to provide final proof of an association between IH and obstructive aortic arch pathology.

List of abbreviations

AC Aortic Coarctation

BAV Bicuspid Aortic Valve

IAA Interrupted Aortic Arch

IH Infantile Hemangioma

LSA Left Subclavian Artery

PHACES Acronym for Posterior fossa malformations, Hemangioma, Arterial anomalies, Cardiac defects, Eye anomalies, Supraumbilical raphe and/or Sternal pit

OAAP Obstructive Aortic Arch Pathology

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