Posterior fossa and arterial abnormalities in patients with facial capillary haemangioma: presumed incomplete phenotypic expression of PHACES syndrome

Abstract We report on the neuroradiological studies performed on three infants with capillary haemangioma (CH) of the head and neck with associated posterior fossa and arterial abnormalities. Posterior fossa malformations were represented by cerebellar hemispheric and vermian hypoplasia and cerebellar cortical dysgenesis, whereas arterial anomalies included bilateral agenesis, kinking, and looping of the internal carotid arteries. One patient had marked exophthalmos due to intraorbital CH. We suggest that these patients had an incomplete phenotypic expression of PHACES syndrome, a vascular phakomatosis characterised by the variable association of posterior fossa malformations, CH, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and sternal and mediastinal defects. Evidence suggests that PHACES syndrome is not a random association but a true phakomatosis; further studies are awaited to shed light on a possible genetic background. The phenotypic spectrum is broad and still largely unexplored, and precise diagnostic criteria have not yet been identified. A causal teratogenic influence, possibly related to anomalous expression of vascular growth factors and their modulators, is suggested to occur between gestational weeks 3 and 5.5.

Introduction Capillary haemangioma (CH) is the most common tumour of infancy, occurring in up to 12% of infants of European descent in the 1st year of life [1], and usually involving the head and neck with marked predominance in girls [2]. These lesions are superficial, red, lobulated, or deeper, blue-red masses that generally grow and recede spontaneously; only 20%–30% of haemangiomas are present at birth, whereas nearly all are evident by 9 months of age and 98% recede within 9 years of age [2]. There is no known genetic predisposition, but girls are affected more often than boys are.

Although CHs are usually isolated, their possible association with craniocervical arterial anomalies was reported by Pascual-Castroviejo as early as 1978 [3]; subsequently, concurrent abnormalities of the posterior cranial fossa, heart, aortic arch, and eye were added to the picture, and such terms as “3C syndrome” [4], “cutaneous haemangioma-vascular complex syndrome” [5], and “PHACE syndrome” [6] were introduced to describe such non-random association. The acronym PHACE has recently gained greater popularity, probably because it easily recalls the major features of this neurocutaneous syndrome: Posterior fossa malformations, Haemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities. The acronym has subsequently been expanded to “PHACES” in order to include midline sternal and ven- tral defects, which may be associated in a minority of patients [6, 7]. We now report on three infants with CH and associated posterior fossa and arterial abnormalities, discuss the kaleidoscopic manifestations of PHACES syndrome with special focus on the head and neck, and provide insight into the embryological timing and target of the underlying teratogenic event.
Table 1 Clinical and neuroradiological features (F female, M male, CT computed tomography, MRI magnetic resonance imaging, MRA magnetic resonance angiography)

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Reason for referral</th>
<th>Neuroradiological exams at presentation</th>
<th>Posterior fossa malformations</th>
<th>Haemangioma</th>
<th>Arterial anomalies</th>
<th>Cardiac defects</th>
<th>Eye anomalies</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Cardiorespiratory distress, cyanosis</td>
<td>CT, MRI, MRA</td>
<td>Hypoplastic right cerebellar hemisphere, absent inferior vermis, cerebellar cortical dysgenesis</td>
<td>Right pinna</td>
<td>Bilateral agenesis of internal carotids</td>
<td>Tricuspid atresia</td>
<td>None</td>
<td>Died from cardiopulmonary arrest at age of 18 months</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Extracranial haemangioma</td>
<td>MRI, MRA</td>
<td>Hypoplastic left cerebellar hemisphere, absent inferior vermis</td>
<td>Left orbitofacial</td>
<td>Kinking and looping of internal carotids</td>
<td>None</td>
<td>Exophthalmos</td>
<td>Alive and neurologically normal at age of 24 months</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Extracranial haemangioma</td>
<td>CT</td>
<td>Hypoplastic right cerebellar hemisphere, absent inferior vermis</td>
<td>Right orbitofacial</td>
<td>None</td>
<td>None</td>
<td>Exophthalmos</td>
<td>Lost</td>
</tr>
</tbody>
</table>

Materials and methods

We studied three infants with CH of the head and neck who had associated central nervous system and arterial abnormalities. There were two girls and one boy aged less than 1 month at presentation, and 1.5 to 4 months at the time of the initial neuroradiological study. Clinical and neuroradiological data from these patients were evaluated retrospectively, and are summarised in Table 1. One patient (case 1) presented with severe neonatal cardiopulmonary distress and cyanosis, and a small CH of the right pinna, whereas two (cases 2 and 3) elicited medical attention because of large, partly bulky, partly plaque-like agglomerations of reddish cutaneous papules that involved the soft tissues of the face and scalp without strict dermatomal distribution, but with prevailing development on one side of the midline and intraorbital extension. Neurological examination was normal, and family histories were unremarkable in all cases.

Neuroradiological studies included computerised tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) in two cases (Figs. 1 and 2) and contrast-enhanced CT alone in the third (Fig. 3). In case 1, CT was performed in the aftermath of cardiac catheterisation to exclude brain sequelae to the procedure, and revealed intracranial abnormalities that were subsequently studied by MRI and MRA. In cases 2 and 3, CT and MRI were initially used to assess the cutaneous CH, and revealed the presence of concurrent intracranial abnormalities; MRA was also performed in one of these cases (case 2).

Results

The CT and MRI imaging features of the facial lesions were consistent with those of CHs, namely a solid mass that was isodense to muscle on unenhanced CT, showed increased signal intensity on T2-weighted images as well as diffuse and intense contrast enhancement both on CT (Fig. 3) and MRI, and contained prominent intralesional flow voids (Fig. 3).

All patients displayed hypoplasia of the cerebellar hemisphere homolateral to the external CH associated with abnormal inferior vermis (Figs. 1–3). Concurrent cerebellar cortical dysgenesis involving the nodulus, right flocculus, and right cerebellar hemisphere was found in one patient (Fig. 1).

Abnormalities of craniocervical arteries were identified in two cases; one patient had bilateral kinking and looping of the internal carotid arteries (Fig. 2), whereas case 1 displayed bilateral agenesis of the internal carotid arteries, which was differentiated from hypoplasia or secondary occlusion by means of CT, showing absence of both carotid canals in the petrous bones; a markedly enlarged basilar trunk supplied the anterior intracranial circulation via enlarged posterior communicating arteries, and the left posterior cerebral artery was dilated and tortuous (Fig. 1).

Cardiac malformations were restricted to tricuspid atresia in case 1; congenital ocular abnormalities were not found, and the only remarkable ocular finding was represented by exophthalmos due to mass effect exerted by the intraorbital CH in two cases (Fig. 3). No sternal or medioventral defects were found either.

Patient 1 died from cardiopulmonary arrest at the age of 18 months, whereas patient 2 is alive and neurologically normal at 24 months of age. Patient 3 was lost at follow-up.