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COMMENTARY

PHACES Syndrome: From the Brain to the Face via the Neural Crest Cells

As the neural tube closes, a set of specialized cells develops along its dorsal crests. Under the influence of specific proteins (RhoB, Slug, and N-cadherin), these cells detach from the neural crests just before the closure of the neural tube and begin to migrate extensively and populate 3 main regions: trunk, heart, and cranium.[1] These pluripotential cells come to rest and accumulate in these different locations in a process related not only to existing and developing physical barriers but to the presence of specific proteins (fibronectin, laminin, tenascin, and others). While some proteins promote migration, others such as ephrins impede it. When the neural crest cells (NCC) populate the cranium, they either give rise to neurons and glia or extend extracranially following patterns of expression under the control of HOX genes.[1,2] After migrating, NCC come to rest along the course of the pharyngeal arches (the locations of these arches are determined by the rhombomeres, which are, in turn, controlled by HOX genes). Specific NCC populate the arches as follows: NCC from the second and fourth rhombomeres go to the first and second pharyngeal arches, NCC from the sixth rhombomere stream into the third and fourth arches, while those from the fifth rhombomere probably do not contribute to any arches.[1,2]

As mentioned before, these migrations are under the control of specific HOX genes; for example, NCC from the fourth rhombomere express HOXB1 and HOXB2 and end up in the second arch. Complex environmental, biochemical, and physical relationships cause the NCC to differentiate into specific mesenchyme and other tissues at these sites.[3] NCC in the first arch give origin to the mandibular (including the malleus and incus) and maxillary processes that correspond to segments 1 and 2 in the Haggstrom classification of the location for facial hemangiomas, respectively.[4] NCC ending up in the second arch give rise to the frontonasal process, which corresponds to segment 2 in the Haggstrom scheme.[4]

Now here comes a most interesting aspect: NCC also migrate intracranially and differentiate into diverse tissues. In the mesencephalon and prosencephalon, they give rise to dura, arachnoid, and pia (at least in animals).[1-4] In the rhombencephalon, they generate neurons, glia, and cranial nerve glial cells; and in the spinal cord, they are involved in the formation of all ganglia and their associated glia.[1-4] As we all know, the rhombencephalon gives rise to most posterior fossa structures. Thus, it is highly conceivable that abnormal NCC give rise to synchronous intra- and extracranial lesions and that these lesions will be at similar levels as established by the rhombomeres. NCC from rhombomeres 1–7 form the myelencephalon and metencephalon; specifically, rhombomeres 1–3 give rise to the latter and therefore to the pons and cerebellum.[5] NCC from rhombomeres 2, 4, and 6 fill arches 1–3, and as previously mentioned, arches 1 and 2 give origin to the mandible and maxilla.[5] This may explain why patients with posterior fossa malformations, segmental hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sternal or ventral defects (PHACES) syndrome have simultaneous anomalies of the face ("beard hemangiomas") and Dandy-Walker–type malformations.

In my personal experience with a similar (albeit more common) disease, patients with Sturge-Weber syndrome who have cutaneous hemangiomas involving the lower face always have pial angiomas on the surface of the cerebellar hemispheres. Patients with this neurocutaneous disorder who have facial angiomas involving Haggstrom segments 1, 2, and 4 always have pial lesions in the occipital and parietal lobes, and those with bilateral facial lesions also have bilateral intracranial lesions. It seems that in this syndrome, abnormal NCC result in formation of similar venous lesions: facial and leptomeningeal angiomas in the same metameres. Curiously, since NCC may serve also as neuronal and glial precursors, both PHACES and Sturge-Weber syndrome may have anomalies of neuronal migration and cortical organization.

Another aspect that I find intriguing is the following: We know that by the time NCC disperse, many blood vessels have already invaded the mesenchyme of the face.[6] Although it is possible that in some manner, NCC help to establish the presence of arteries and veins, it is more probable that NCC have an effect on already-formed blood vessels by cell-to-cell signaling. During blood vessel formation, the mesoderm contributes to the formation of the tunica media, while the NCC directly produce endothelium. Once NCC are grafted to blood vessels, they too give rise to parasympathetic cells that regulate their peristalsis and dilation.[6] Hemangiomas are dilated vascular spaces that resemble veins. More important, hemangiomas are devoid of nerves, and their absence is essential in telling them apart from other vascular lesions.[7] The development of vascular smooth muscle may also be dependent on NCC migration.[8] Thus, abnormal NCC may give rise to hemangiomas or vascular lesions that contain deficient walls (lack of smooth muscle) such as aneurysms (a lesion also seen in PHACES).

I will now speculate in an attempt to put all of this information together as it pertains to PHACES syndrome and other neurocutaneous vascular disorders. It is possible that alterations in the number and/or quality of NCC lead to blood vessels that cannot regulate their lumen size or intrinsic pressure, leading to dilation and formation of ectatic vascular networks as seen in hemangiomas. Different microenvironmental factors may then result in the formation of angiomas in the face, pia, or cisterns as in PHACES and Sturge-Weber syndromes. Lack of neural regulation of the intracranial large arteries may lead to dolichoectasia, which, in turn, may lead to alterations of blood flow, which, in combination with a deficient wall, result in aneurysms; again features of PHACES syndrome. Underexpression of NCC may result in agenesis of arteries, while anomalous expression may result in stenoses. Furthermore, these anomalous NCC may produce abnormal neurons and glia, leading to cerebellar, vermian, and pontine malformations seen as variations of the Dandy-Walker spectrum in PHACES syndrome. Additionally, these abnormal glial cells and neurons may result in cortical and callosal dysplasias also seen in PHACES syndrome.

As I have mentioned before, NCC also contribute to the formation of all 3 meningeal layers, and a malformation involving them may lead to arachnoid cyst development as seen

in patients with PHACES syndrome. Because NCC belong to 1 family, if those related to cranial formation are abnormal, those related to cardiac and trunk formation may be abnormal too and lead to cardiac and sternal defects seen in PHACES syndrome.[9] NCC contribute to the formation of the cardiac septum and the trunks of the great vessels, and patients with PHACES syndrome often have tetralogy of Fallot, anomalous origin of the aorta, a common brachiocephalic trunk, aortic coarctation, and other anomalies of the great vessels.[10] Although a matter of controversy, it seems too that cranial and trunk NCC have the potential to generate bone and cartilage, and this could explain the skull base, facial (clefting), and sternal anomalies seen in the syndrome.[9] Finally, NCC contribute to the formation of the eye at the optic vesicle stage, explaining many of this organ's malformations found in the PHACES syndrome.[1-4]

It seems that we are beginning to understand the relationship between skin and central nervous system lesions in patients with some of the so-called vascular phakomatosis (or vascular metameric syndromes). It is possible that abnormalities of NCC play an important role in the development of these disorders. If we understand what NCC do and where they go, we will know where and what to look for in our imaging studies. Abnormalities of NCC are probably at least partly responsible for the development of the metameric vascular neurocutaneous syndromes, including Sturge-Weber, PHACES, Cobb, craniofacial and spinal arteriovenous syndromes, as well as retinal and optic nerve/chiasm arteriovenous malformations.[11]

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