Thomboembolism and Congenital Malformations

From Duane Syndrome to Thalidomide Embryopathy

Cameron F. Parsa, MD; Matthieu P. Robert, MD

Objective: To propose a pathophysiologic mechanism to unify a variety of disparate sporadic congenital malformations.

Methods: Inductive and deductive analyses to correlate malformation laterality with asymmetries in thoracic anatomy, critical analysis of malformations with female predominance, and concepts of hydrodynamic pressure gradients in vascular growth were applied to the ensuing development of guiding tissue scaffolds for cellular proliferation, differentiation, and apoptosis.

Results: Duane syndrome may develop following a focal vascular insult to the sixth nerve trunk with axonal degeneration, allowing for substitutive innervation from third nerve axons to the lateral rectus muscle. Causative fibrin clots may originate from the venous system and paradoxically migrate through physiological right-to-left shunts, or they may arise directly from the heart. Hence, the unilateral, left-sided, and female predominance of Duane syndrome results from the asymmetry in the thoracic anatomy and from thrombosis risk factors. Embolic occlusions may also alter local hemodynamic pressure gradients, leading to the compensatory enlargement and persistence of the fetal vasculature and may dysregulate tissue growth. Within the eye, this results in forms of Peters anomaly, unilateral congenital cataracts, and the morning glory disc anomaly, all in the vascular territory of the carotid arteries that also share a propensity for left-sided involvement in girls. Most aberrant misinnervation phenomena (eg, jaw-winking syndrome, crocodile tear syndrome, Brown syndrome, and congenital fibrosis syndrome) and, by extrapolation, the hypoplasia or dysgenesis of noncephalic anatomical structures (including limbs) may be similarly explained. Such malformations will occur more frequently under thrombogenic conditions, such as those induced by thalidomide.

Conclusions: Fibrin emboli and focal hypoperfusion may explain the development of many sporadic congenital malformations.


Author Affiliations: The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Dr Parsa); and Centre Hospitalier National d’Ophthalmologie des Quinze-Vingts, Paris (Dr Parsa), Service d’ophthalmologie, Hôpital Necker-Enfants Malades, Assistance Publique–Hôpitaux de Paris (Dr Robert), and Centre d’étude de la sensorimotoricité, Centre National de la Recherche Scientifique UMR 8194, Université Paris Descartes, Sorbonne Paris Cité (Dr Robert), France. Dr Parsa is now with the Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Although genetic mutations have been identified in a number of congenital abnormalities, many recognized malformations do not display typical patterns of Mendelian inheritance. Genetic mutations, systemic in nature, can be difficult to link to phenotypic conditions that appear focally, asymmetrically, and sporadically.

For editorial comment see page 522

Duane retraction syndrome has spurred much study and interest since its detailed clinical description in 1905.1 Brainstem autopsy reports and electromyographic studies of the extraocular muscles led to the deduction of a misinnervation mechanism in 1965.2 However, the underlying cause for Duane syndrome remains elusive. While intensive genetic research has led to reports of genetic mutations in a few familial occurrences of the syndrome, questions persist: Why is Duane syndrome generally sporadic, why is it predominantly unilateral and left sided, and why does it occur preponderantly in girls? Why is the lateral rectus muscle tight and fibrotic in its uninnervated portions rather than lax? Why does the substitutive innervation mainly arise from axons originally destined for the medial rectus muscle? Why, in the context of thalidomide embryopathy, does Duane syndrome occur with such time-specific exposures and yet in such an erratic fashion? By starting with these questions about this prototypical misinnervation syndrome and by using both inductive and deductive analyses, we shall propose a hypothesis that unifies the pathophysiology of Duane syndrome with a number of malformations that involve the eye and brain and that share these puzzling epidemiologic features. The underlying cause is
found to be applicable to a myriad of other congenital malformations.

NEUROANATOMY OF DUANE SYNDROME

Duane syndrome results from the deficient innervation from the sixth cranial nerve with an ensuing misdirection of third cranial nerve axonal fibers to the lateral rectus muscle. By making associations between apparently isolated published anatomical and electrophysiological findings, in 1965, Hoyt and Nachtigall initially deduced the need for axonal misdirection to explain the noted oculomotility features in this syndrome. Their essential hypothesis was validated first by necropsy findings, in 15 years later and, more recently, by magnetic resonance imaging studies, repeatedly confirmed and fully established. A century after its initial description, the understanding of the underlying cause for this misinnervation disorder remains enigmatic. Recent genetic hypotheses have invoked some basic disorder of axonal guidance and nuclear development, though manifesting essentially in the brainstem. Mutations have been reported in a few familial cases of this entity, with generally bilateral phenotypes, affecting both sexes equally, often also displaying other structural abnormalities, and accounting for, at most, 10% of all those presenting with ocular signs consistent with Duane syndrome. Yet, for the vast majority of affected individuals, Duane syndrome is an apparently isolated, sporadic, and often left-sided entity (about 70% of all unilateral cases) that affects females more frequently than males (about 60% of all cases).

In most congenital misinnervation syndromes, it is difficult or impossible to distinguish cranial nerve dysgenesis caused by nuclear injury from cranial nerve dysgenesis caused by peripheral injury. Duane syndrome provides a notable exception to this analytic limitation. The absence of an associated ipsilateral horizontal gaze palsy or contralateral horizontal gaze-evoked nystagmus (as seen in a sixth nucleus syndrome), together with the histological evidence, points to the persistence of the third cranial nerve interneurons and cell groups of the paramedian tracts at the site of the sixth nerve nucleus in Duane syndrome. The insult therefore must be to the trunk of the sixth nerve, sparing the area of the nucleus itself (Figure 1A). A clue to the sort of insult responsible for such peripheral nerve injury can be found in benign recurrent sixth nerve palsies in childhood. Such cases are also isolated, sporadic, and predominantly left sided, and they occur more frequently in girls. Although considered benign, many cases nonetheless leave a residual sixth nerve paresis, indicating a degree of permanent axonal and substrate damage.

ETIOLOGY OF DUANE SYNDROME AND BENIGN RECURRENT SIXTH NERVE PALSY IN CHILDHOOD

We propose that an intrauterine process similar to that causing benign recurrent sixth nerve palsy in childhood could cause anterograde axonal degeneration with apoptosis and retrograde degeneration of the sixth nerve trunk. Such a process would result in secondary “hypoplasia” of the nerve cell bodies within the abducens nucleus. This sequence of events would allow for the persistence of the third nerve interneurons, which are necessary for the gaze direction of the contralateral eye, and the paramedian tract...
cells, which are involved in gaze stabilization. Prior to the complete connective tissue enshsheetment of the cranial nerves with neuromuscular contact, substitutive innervation from other cranial motor nerves can occur in the lateral rectus muscle. The enhanced neuronal input of fibers, which are responsible for both vergence and versional eye movements and which are originally destined for the medial rectus muscle, may predispose these axons over others to innervate the lateral rectus muscle, rescuing them from an otherwise physiologic pruning and elimination process. Once nerves are fully sheathed by connective tissue, however, migration and substitution of nerve axons are impeded, whereas axonal nerve regeneration can more easily occur when guided along already-developed collagen substrates. Wherever innervation is still deficient and there is a lack of neurotrophic factors, the differentiation of orbital mesenchyme will be altered in such a way as to produce a fibrotic, rather than muscular, tissue (Figure 1B). Depending on the extent of the initial insult to the sixth cranial nerve trunk and the degree of ensuing neuronal apoptosis with third nerve substitution, one then develops the various phenotypic variants that comprise the Duane retraction syndrome.

What differentiates the so-called benign sixth cranial nerve palsy of childhood from Duane syndrome is the timing of the insult, with additional processes of apoptosis and substitutive innervation occurring in utero. This begs the question: what might be the fundamental insult to the sixth nerve axons?

Clues exist: the unilateral, left-sided, and female predominance of both disorders. Consistently unilateral cephalic phenomena with a similar 2:1 left to right ratio have long been noted to occur secondary to emboli originating from the heart, a now rare occurrence in adults but one that remains the rule for fetal and perinatal strokes. Anatomical structures above the neck are notably symmetric, and this laterality of injury results from the asymmetry of the thoracic anatomy, with the heart being on the left side and with the left common carotid artery originating directly off the aortic arch (Figure 2) .

During the period of development, there is no evidence to implicate either calcific or cholesterol emboli as a source of focal ischemic injury. Dissolvable fibrin emboli, on the other hand, may occur, particularly in patients with maternal or inborn prothrombotic conditions, such as the not uncommon factor V Leiden genetic mutation. Higher estrogen levels, a higher predisposition to inflammation and other factors, further predispose girls to thrombus formation and embolic risks. Fibrin clots can originate directly from the arterial system or from cardiac chambers if malformations exist there; however, they generally form on the venous side of the circulatory system. Although large clots may occasionally produce recognizable symptoms of a pulmonary embolus in children and adults, most venous clots are filtered and uneventfully rapidly dissolved within the pulmonary circulatory bed. In utero, however, such clots enter into the arterial circulation via ductus arteriosus and the foramen ovale. Postnatally, this may still occur when cardiac abnormalities with right-to-left shunts persist. When they enter the arterial circulation, most small fibrin emboli remain clinically silent, unless they cause significant ischemia before their rapid dissolution. By contrast, events affecting the trunk of the sixth cranial nerve are somewhat distinctive: significant ischemia from small emboli may easily ensue, and the resulting phenomena are phenotypically visible and, therefore, tend to attract immediate attention.

On this basis, the majority of cases of Duane syndrome may arise from paradoxical fibrin emboli, initially forming in the venous circulation of predisposed embryos, then passing via right-to-left cardiac shunts into the arterial circulation, and finally lodging into the vasa nervosum of the sixth cranial nerve. These lodged emboli precipitate dysregulated apoptosis, with substitutive misinnervation sequelae. The occurrence of similar events later in utero, after nerve sheaths (epineurium and perineurium) to target organs have been established, or perinatally, would give rise to a congenital sixth nerve palsy without aberrant innervation. However, a congenital sixth nerve palsy manifests less frequently because axonal regrowth can occur when the substrate of a guiding sheath scaffolding remains, as is the rule for postnatal microvascular ischemic sixth nerve palsies. Thus, as opposed to Duane syndrome, congenital sixth nerve palsies are rare and transitory. If a right-to-left shunt persists postnatally (or if another thrombogenic cardiac malformation exists), there may develop a so-called benign sixth nerve palsy of childhood. When associated with pain, this pathophysiology could also explain instances of so-called sixth nerve ophthalmoplegic migraine. This pathophysiologic mechanism gains support from the genetic associations with Duane syndrome that are known to be coupled with abnormal vasculature. A minority of Duane syndrome cases, often nonsolated and bilateral and affecting both sexes equally, may appear as genetically transmitted, with a few families found to exhibit various genetic mutations presumed to be respon-
sible for systemic defects in neuronal guidance. Three genes have been implicated.

Mutations in the CHN1 gene were reported in 10 families with Duane syndrome, mainly type 2 and mainly bilateral, but with considerable intrafamilial variability. Some individuals exhibited, instead (or in addition), hypoplasia of the superior oblique muscle, Brown syndrome, hypoplasia of the oculomotor nerve, vertical strabismus, hypoplasia, and vascular dysgenesis of the optic disc. The extraocular phenotype in these families remains to be fully described.

Dominant mutations reported in the SALL4 gene have been associated with a large range of overlapping phenotypes, including acro-renal-ocular syndrome or Okihiro syndrome (Duane syndrome, most often bilateral, with radial ray anomaly, often renal anomalies and occasionally hearing anomalies), Holt-Oram syndrome (radial bone and/or thumb defects and cardiac malformations), syndromes initially diagnosed as thalidomide embryopathy, and IVIC syndrome (Okihiro syndrome with thrombocytopenia).

Recessive mutations in the HOXA1 gene have also been described in a few families with Duane syndrome. While either horizontal gape palsy or Duane syndrome was initially thought to be a sine qua non of this phenotype, additional severe brainstem maldevelopment features may be present: cardiac and cerebrovascular malformations are now recognized to be the hallmark of these mutations. Recent studies on a mouse model indicate that HOXA1 is required for patterning of the great arteries and cardiac outflow tract.

Genetic mutations linked to Duane syndrome and associated conditions may predispose to thromboembolism. Microtubules, for example, are necessary for proper platelet function to avoid abnormal fibrin clot formation. Although the focal and sporadic effect of emboli causing hypoperfusion should be emphasized, many molecular cues noted to be responsible for axonal guidance are also involved in vascular growth, as well as the growth of other tubular structures such as nephrons. Other mutations that cause systemic inhibition of angiogenesis are known to produce a different constellation of findings, with pathognomonic vascular findings visible at the level of the optic disc.

THROMBOEMBOLIC PHENOMENA AND OTHER ACQUIRED AND CONGENITAL ANOMALIES

Postnatally, paradoxical or cardiogenic fibrin emboli have been incriminated in a wide spectrum of transient neurologic phenomena, including ischemic attack, monophasic seizure, or migraine with aura. The higher incidence of Bell palsy in females, especially during pregnancy (a particularly thrombogenic diathesis), can be explained by a similar process. Enigmatic fleeting localized corporal symptoms (e.g., coughing fits, or limb or abdominal cramps) may also result from transient postnatal emboli. After birth, ischemia of already-formed and slowly-changing tissues can be far better endured and tolerated than in utero. A link exists between the 2 environments during gestation, when thromboembolic events in the mother have the potential to affect placental and fetal growth, a fact already being recognized and successfully treated in those with antiphospholipid syndrome.

The pathophysiologic mechanism described for Duane syndrome and transient sixth nerve palsies could be inferred only from its obvious features of ocular misalignment. The particular vulnerability of the sixth cranial nerve to focal ischemia, moreover, derives from its small-caliber, fine feeding vessels and its lack of an alternate blood supply. However, what occurs when the fibrin emboli in utero pass through the arterial circulation and do not end up embedded within the vasa nervosum of the peripheral portion of the sixth cranial nerve trunk?

Other Cranial Nerves and Misinnervation Syndromes

A number of other congenital disorders exhibit a similar unilateral, left-sided, and female predominance. These include congenital ptosis, with or without Marcus-Gunn jaw-winking aberrant innervations, and congenital facial palsy, among others. The cranial nerves involved are all vascularized in their peripheral portions by the ipsilateral internal carotid artery, which points to a similar embolic causal mechanism.

A subset of Brown syndrome, predominantly seen in females, may represent another misinnervation disorder resulting from injury to the fourth cranial nerve, which receives its blood supply principally from the basilar arterial system.

In some instances, Duane syndrome, Brown syndrome, and congenital ptosis with jaw winking occur with ipsilateral aberrant tearing (“crocodile tears”), a frequently overlooked phenomenon. The auditory latencies of patients with these conditions may be altered, which points to a more proximal fascicular involvement within the brainstem. In this area, anatomical structures are supplied by vessels originating from the midline basilar artery. When so associated, these syndromic entities do not exhibit laterality, and frequently are bilateral. It is likely that instances of congenital third nerve palsy and third nerve misinnervation share a similar pathogenesis.

Congenital fibrosis of the extraocular muscles can occasionally present with stereotypical phenotypes within families, for which different dominant and recessive genetic mutations have been described. More often, though, it appears sporadically. Sporadic cases, particularly when associated with aberrant innervation phenomena such as Marcus-Gunn jaw winking, may also result from a thromboembolic mechanism.

The possibility of ischemic events in the pathogenesis of the Möbius syndrome (an oromandibular limb hypogenesis syndrome), commonly associated with both Duane syndrome and aberrant tearing, has long been corroborated by both imaging and necropsy results revealing secondary brainstem calcifications, leading to the concept of a “subclavian artery supply disruption sequence.” The ischemic insult involves various cranial nerve nuclei that contain the cell bodies, including the surrounding tissue substrate, so that axonal re-growth may not always be possible. Usually developing later than Duane syndrome, when nerve sheaths to tar-
get organs may have already been established, substitu-
tive misinnervation less commonly occurs.

The apparent paradox of a vascular disruption caus-
ing such focal manifestations can be understood either
by supposing a zone of vascular vulnerability with the
fetal brainstem or by invoking transient focal ischemia
resulting from an embolic mechanism affecting the brain-
stem directly.

Prenatal Thromboembolism: A Unifying Hypothesis
for Craniofacial Malformations

Several other disparate cephalic disorders show a left-
sided predominance (Table). Because these may be dis-
orders of vascular origin, the possibility of a thrombo-
embolic embryogenesis similar to Duane syndrome should
not be ignored. This hypothesis may elucidate congen-
tal malformations, from cases of optic nerve hypoplasia
long suspected of having a vascular etiology to cases
with more significant losses of tissue resulting in poren-
cephalic cavities (sometimes mislabeled as "arachnoid
cysts"), for which an association with prothrombotic fac-
tors is now well established and which predominate in
the territory of the left carotid artery.

A nonneuronal cerebral vascular anatomical vari-
tion, persistent primitive trigeminal artery, heretofore in-
explicably found more frequently on the left side and in fe-
males, can now be understood. It is known that
vascular occlusions may cause the persistence of fetal ves-
sels. The occasional postnatal persistence of this ar-
tery, which normally joins the carotid and vertebrobasili-
ar circulations in the fetus, can be explained by in utero
embolic events involving the internal carotid artery and
necessitating vertebrobasilar blood flow to fill the ca-
rotid circulation distally. Described as one of the most
frequent carotid-to-vertebrobasilar fetal arteries to per-
sist, its off-midline position makes it more easily recog-
nizable on imaging.

Persistent embryonic or fetal vasculature (such as the
trigeminal artery) may occur frequently and serves to pre-
vent ischemia in the face of upstream vascular occlu-
sion. Within the eye, however, which must become trans-
lucent for its unique purposes, the persistence of such
blood vessels with subsequent fibrous proliferation post-
natally also has negative consequences. The major cause
of unilateral congenital cataracts, what was formerly re-
ferred to as persistent hyperplastic posterior vitreous, re-
sults from persistent fetal vasculature (PFV) as empha-
sized by Goldberg. In one bilateral case, such vascular
Persistence was presumed secondary to thrombi gener-
ated intraocularly in the setting of protein S defi-
cency and, later, in another bilateral case with severe
protein C deficiency, such thrombi were confirmed.

Nonetheless, although it is known to generally be uni-
ilateral, a review of published series of PFV cataracts also
reveals a heretofore unappreciated 2:1 left-sided and fe-
male predominance, again in similar ratios to Duane
syndrome, consistent with emboli of venous and car-
diac origin rather than local arterial thrombus forma-
tion. Persistent fetal vasculature within the eye is thus
also always associated with microphthalmia. The wide-
range of manifestations of ocular PFV, as listed by Gold-
berg and described as ischemic in etiology, can now be
understood to be caused by thrombi or emboli lodged
at various points within the rich anterior ciliary and hya-
loid vascular system, diminishing blood flow down-
stream. The resulting increase in pressure upstream,
in turn, causes alternative collateral vessels to enlarge or
fetal vascular pathways to persist (PFV).

Ischemia has been proposed as the pathophysologi-
ical mechanism in some cases of Peters anomaly, an-
other entity associated with PFV, which could result either
from migrating emboli or from thrombus formation by the
limbus or the major arterial circle of the iris. More post-
eriorly in the hyaloid artery, emboli would cause PFV
within the lens and congenital cataracts; further poste-
rior, near the level of the retina, this vasooclusion would
produce posterior PFV. In the morning glory anomaly
(more frequent in girls, nearly always unilateral, and more
often left sided), a wide, funnel-shaped excavation and
distal nerve results from the loss of retaining structural
laminar tissue support. An associated lack of Kuhnt in-
termediary tissue can lead to retinal detachments,
whereas persistence of the glial tuft (remnants of the hya-
loid vessels/Bergmeister papilla) and cilioretinal ves-
sels, including arteriovenous malformations within the
retina, corresponds to a form of PFV secondary to an
embolus with hypoperfusion occurring specifically at the
very level of the developing lamina scleralis, much as a
prenatal version of a central retinal artery occlusion. In
addition to thrombophilic tendencies, anatomical differ-
ences in the optic disc among ethnic groups (including
differences in the diameter of the optic disc) may ac-
count for the differing prevalences of such prelaminar
embolic capture. It is not surprising that the morning glory
disk anomaly can be associated with recognized fea-
tures of PFV. Emboli in the short posterior ciliary
arteries can conceivably also produce posterior staph-
atomatous thinning of the sclera and occasionally anom-
aliess of differentiation leading to smooth muscle and adi-

Table. List of Sporadic Congenital Malformations
Hypothetically Resulting From In Utero Thromboembolism
in the Carotid Territory

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Left-Sided Cases Among Unilateral Cases, %</th>
<th>Female Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duane syndrome19</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Congenital ptosis56</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>Jaw-winking phenomenon65</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Congenital facial palsy92</td>
<td>77</td>
<td>54</td>
</tr>
<tr>
<td>Ocular and cerebral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral congenital</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>cataracts13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning glory anomaly92</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Optic nerve hypoplasia45</td>
<td>Unknown</td>
<td>54</td>
</tr>
<tr>
<td>Persistent trigeminal artery94</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Porencephalic cavities96</td>
<td>75</td>
<td>58</td>
</tr>
</tbody>
</table>

4 With series references indicating their left-sided and female
predominance.
remnants known as Bergmeister papilla, as well as pre-
produce arteriovenous communications that are visible
malformations exist. Hence, embolic phenomenon may
likely frequent when other emboli-induced congenital
bogenic process. Thus, vascular anomalies are also more
a primary focal inflammatory or other focal arterial throm-
sions affecting bony and cartilaginous mesenchyme may
be part of Poland-Möbius syndrome, and Duane syn-
theroblasts could accumulate in small limb arteries and trig-
ters also noted the presence of vascular anomalies but
scribed these to be the cause of the noted defects, rather
than the physiologic effects of adaptive collateral vessel
enlargement upstream in response to embolic vascular
occlusive phenomena downstream.113 Hunter114 pro-
vided evidence that inherited thrombophilies were pres-
ent in a large number of those with limb reduction mal-
formations, whereas others115 have felt that vascular
occurrences of uncertain or various etiologies could be
responsible for a wide variety of congenital anomalies.

Unsurprisingly, limb defects are often seen in asso-
ciation with misinnervation syndromes or with persist-
ence of fetal vasculature.116 When they occur with Duane
syndrome, they may sometimes be given eponyms such as
Okiiro, Wildervank syndrome, etc.117 Some of these investiga-
tors also noted the presence of vascular anomalies but
scribed these to be the cause of the noted defects, rather
than the physiologic effects of adaptive collateral vessel
enlargement upstream in response to embolic vascular
occlusive phenomena downstream.113 Hunter114 pro-
vided evidence that inherited thrombophilies were pres-
ent in a large number of those with limb reduction mal-
formations, whereas others115 have felt that vascular
occurrences of uncertain or various etiologies could be
responsible for a wide variety of congenital anomalies.

Thalidomide Embryopathy

Among various congenital defects, including skeletal and
limb malformations, Möbius syndrome, and Duane syn-
drome, aberrant tearing and other substitutive misinnerv-
ations syndromes have frequently been associated with
thalidomide use, specifically during the third to sixth week
postfertilization.117,118 Despite numerous studies, the long-
sought-after teratogenic mechanism and highly erratic
effect of this medication remained elusive.123 Suspect-
ing a vascular origin, Petter124 believed that altered eryth-
roblasts could accumulate in small limb arteries and trig-

Vascular occlusions may also affect other end-
organs, such as the extraocular muscles, to produce hy-
poplasia. Via intrauterine transsaccadic degeneration, this
would lead to a secondary loss of motor neurons to un-
derlie muscle hypoplasia (without fibrosis) with corre-
sponding cranial nerve hypoplasia, as documented in cases
of congenital superior oblique palsy.108 Vascular occlu-
sions affecting bony and cartilaginous mesenchyme may
give rise to bony defects and encephalocoeles. Wherever
tissue scaffold has already been established, but hypoper-
fusion and relative ischemia occurs later during tissue
differentiation, rather than apoptosis, amphiopotentia-
tial cells and tissues may undergo diverted differentiation
because of insufficient metabolic nutrients to form choris-
tomas. Readily visible within PFV cataracts,65 they are also
present in some instances of morning glory anomaly and
posterior staphylomas, including hemifacial microso-
mia106 in the region of the external carotid artery, and can
be noted elsewhere in the body.

Nonencephalic Thromboembolism

Not all fibrin emboli emerging from the heart go through
the carotid circulation or end cephalically. What would
result from thromboemboli that migrate through other
vessels? Radial ray and similar skeletal syndromes, skin
defects,110 lung aplasia, fistulas, hernias, and forms of
arthrogryposis can result from in utero thromboembolic-
induced transient focal hypoperfusion or ischemia while
developmental tissue processes are active and engaged.
Thrombus formation had been invoked in the patho-
physiology of some congenital limb defects by Hoyme,
Van Allen, and colleagues.111,112 Some of these investiga-
tors also noted the presence of vascular anomalies but
scribed these to be the cause of the noted defects, rather
than the physiologic effects of adaptive collateral vessel
enlargement upstream in response to embolic vascular
occlusive phenomena downstream.113 Hunter114 pro-
vided evidence that inherited thrombophilies were pres-
ent in a large number of those with limb reduction mal-
formations, whereas others115 have felt that vascular
occurrences of uncertain or various etiologies could be
responsible for a wide variety of congenital anomalies.

Unsurprisingly, limb defects are often seen in asso-
ciation with misinnervation syndromes or with persist-
ence of fetal vasculature.116 When they occur with Duane
syndrome, they may sometimes be given eponyms such as
Okiiro, Wildervank syndrome, etc.117 Some of these investiga-
tors also noted the presence of vascular anomalies but
scribed these to be the cause of the noted defects, rather
than the physiologic effects of adaptive collateral vessel
enlargement upstream in response to embolic vascular
occlusive phenomena downstream.113 Hunter114 pro-
vided evidence that inherited thrombophilies were pres-
ent in a large number of those with limb reduction mal-
formations, whereas others115 have felt that vascular
occurrences of uncertain or various etiologies could be
responsible for a wide variety of congenital anomalies.

Thalidomide Embryopathy

Among various congenital defects, including skeletal and
limb malformations, Möbius syndrome, and Duane syn-
drome, aberrant tearing and other substitutive misinnerv-
ations syndromes have frequently been associated with
thalidomide use, specifically during the third to sixth week
postfertilization.117,118 Despite numerous studies, the long-
sought-after teratogenic mechanism and highly erratic
effect of this medication remained elusive.123 Suspect-
ing a vascular origin, Petter124 believed that altered eryth-
roblasts could accumulate in small limb arteries and trig-

Vascular occlusions may also affect other end-
organs, such as the extraocular muscles, to produce hy-
poplasia. Via intrauterine transsaccadic degeneration, this
would lead to a secondary loss of motor neurons to un-
derlie muscle hypoplasia (without fibrosis) with corre-
sponding cranial nerve hypoplasia, as documented in cases
of congenital superior oblique palsy.108 Vascular occlu-
sions affecting bony and cartilaginous mesenchyme may
give rise to bony defects and encephalocoeles. Wherever
tissue scaffold has already been established, but hypoper-
fusion and relative ischemia occurs later during tissue
differentiation, rather than apoptosis, amphiopotentia-
tial cells and tissues may undergo diverted differentiation
because of insufficient metabolic nutrients to form choris-
fects. But just as embolic phenomena are erratic, so are the teratogenic effects of thalidomide.79 The specific timing of thalidomide embryopathy79 may be largely linked to embryonic scaffold development: Duane syndrome may occur with thalidomide use in the third and fourth weeks postfertilization, when blood vessels have formed, but nerves and sheaths have not established contact with target orbital tissues and substitutive innervation is still possible. Similarly for other organs, once the tissue scaffolding (which follows vascular development) is in place to serve as a guide for growth, induction of cellular proliferation and tissue regeneration can proceed without clinical sequelae noted. Hence, when hypoperfusion affects organ development prior to the completion of its scaffolding.

The nature of the malformations depends on the timing of the drug ingestion. The so-called critical period occurs during organ development prior to the completion of its scaffolding. Misspecification of the cranial nerves and sheaths have not established contact with the underlying mesenchyme, giving rise to Möbius syndrome. The derived mechanism, however, is applicable to the entire body without the left-sided asymmetry. The common occurrence of sporadic unilateral ocular malformations has always defied explanation. We conclude that the disparate group of sporadic congenital malformations can be explained by occlusive effects of fibrin emboli within the carotid territory occurring in utero. Their previously unexplained laterality can be accounted for by the particular asymmetry of the thoracic vascular anatomy, while increased susceptibility to fibrin clot formation explains the female predominance. The transparency of ocular tissues and the exquisite demands of binocular vision allow for a more detailed observation of the phenotypic expression of these cephalic malformations. The derived mechanism, however, is applicable to the entire body without the left-sided asymmetry in other vascular territories.

Practical consequences follow. Screening and identification of thrombogenic risk factors may assist in the prevention of such malformations throughout the body.

Submitted for Publication: May 28, 2012; final revision received September 26, 2012; accepted September 27, 2012.

Published Online: December 10, 2012. doi:10.1001/jamaophthalmol.2013.1111

Correspondence: Cameron F. Parsa, MD, Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health—Madison, 2870 University Ave, Ste 206, Madison, WI 53705 (parsa@wisc.edu).

Conflict of Interest Disclosures: None reported.

Previous Presentation: Presented in part as a William F. Hoyt, MD Festschrift at the 19th International Neuro-Ophthalmology Society Meeting; June 17, 2012; Singapore.

REFERENCES


125. Shanske AL, Gurland JE, Mbekeani JN, Bello JA, Campbell D, Kleinhaus S. Possible new syndrome of microcephaly with cortical migration defects, Pe-