Thromboembolism and Congenital Malformations

From Duane Syndrome to Thalidomide Embryopathy

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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.


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.

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Duane retraction syndrome has spurred much study and interest since its detailed clinical description in 1905. Brainstem autopsy reports and electromyographic studies of the extraocular muscles led to the deduction of a misinnervation mechanism in 1965. 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 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

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found to be applicable to a myriad of other congenital malformations.

NEUROANATOMY OF DUANE SYNDROME

Duane syndrome\(^1\) 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 Nachtigal\(^2\) 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, 15 years later\(^3\) and, more recently, by magnetic resonance imaging studies\(^4\)-\(^6\), repeatedly confirmed and fully established. A century after its initial description, the understanding of underlying causes 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 oculo signs consistent with Duane syndrome.\(^4\) 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 gapevoked nystagmus (as seen in a sixth nucleus syndrome), together with the histological evidence\(^8\),\(^9\) 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 (\textbf{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.\(^10\)-\(^14\) Although considered benign, many cases nonetheless leave a residual sixth nerve paresis, indicating a degree of permanent axonal and substrate damage.\(^15\)

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

We propose that an intruterine 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

\[\text{Figure 1. A. Effects of damage to the sixth nerve trunk occurring in utero, which produces Duane syndrome with its attendant consequences to nuclear anatomy.}\
\[\text{B. The consequences within the orbit of in utero damage to the sixth nerve trunk are}\
\]
cells, which are involved in gaze stabilization. Prior to the complete connective tissue ensheathment 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 versionsal 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 propensity 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 scaffold 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 nonisolated 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 gaze 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 cerebral symptoms (eg, 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 basal 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 regrowth may not always be possible. Usually developing later than Duane syndrome, when nerve sheaths to tar-
get organs may have already been established, substitutive misinnervation less commonly occurs.

The apparent paradox of a vascular disruption causing 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 brainstem directly.

Prenatal Thromboembolism: A Unifying Hypothesis for Craniofacial Malformations

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

A nonneuronal cerebral vascular anatomical variation, persistent primitive trigeminal artery, heretofore inexplicably found more frequently on the left side and in females, can now be understood. It is known that vascular occlusions may cause the persistence of fetal vessels. The occasional postnatal persistence of this artery, which normally joins the carotid and vertebrobasilar 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 carotid circulation distally. Described as one of the most frequent carotid-to-vertebrobasilar fetal arteries to persist, its off-midline position makes it more easily recognizable on imaging.

Persistent embryonic or fetal vasculature (such as the trigeminal artery) may occur frequently and serves to prevent ischemia in the face of upstream vascular occlusion. Within the eye, however, which must become translucent for its unique purposes, the persistence of such blood vessels with subsequent fibrous proliferation postnatally also has negative consequences. The major cause of unilateral congenital cataracts, what was formerly referred to as persistent hyperplastic posterior vitreous, results from persistent fetal vasculature (PFV) as emphasized by Goldberg.

In one bilateral case, such vascular persistence was presumed secondary to thrombi generated intraocularly in the setting of protein S deficiency and, later, in another bilateral case with severe protein C deficiency, such thrombi were confirmed. Nonetheless, although it is known to generally be unilateral, a review of published series of PFV cataracts also reveals a heretofore unappreciated 2:1 left-sided and female predominance, again in similar ratios to Duane syndrome, consistent with emboli of venous and cardiac origin rather than local arterial thrombus formation. Persistent fetal vasculature within the eye is thus also always associated with microphthalmia. The wide range of manifestations of ocular PFV, as listed by Goldberg 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 hyaloid vascular system, diminishing blood flow downstream. 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 pathophysiologically mechanism in some cases of Peters anomaly, another 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 posteriorly in the hyaloid artery, emboli would cause PFV within the lens and congenital cataracts; further posterior, near the level of the retina, this vasoocclusion 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 intermediary tissue can lead to retinal detachments, whereas persistence of the glial tuft (remnants of the hyaloid vessels/Bergmeister papilla) and cilioretinal vessels, 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 thrombothrombotic tendencies, anatomical differences in the optic disc among ethnic groups (including differences in the diameter of the optic disc) may account for the differing prevalences of such prelaminar embolic capture. It is not surprising that the morning glory disk anomaly can be associated with recognized features of PFV. Emboli in the short posterior ciliary arteries can conceivably also produce posterior staphylomatous thinning of the sclera and occasionally anomalies 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</th>
<th>Female Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duane syndrome</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Congenital ptosis</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>Jaw-winking phenomenon</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Congenital facial palsy</td>
<td>77</td>
<td>54</td>
</tr>
<tr>
<td>Ocular and cerebral malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral congenital cataracts</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Morning glory anomaly</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td>Unknown</td>
<td>54</td>
</tr>
<tr>
<td>Persistent trigeminal artery</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Porencephalic cavities</td>
<td>75</td>
<td>58</td>
</tr>
</tbody>
</table>

*With series references indicating their left-sided and female predominance.*

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pose tissue formation, just as is noted with PFV-associated cataracts.\textsuperscript{95} Persistence of proximal hyaloid remnants known as Bergmeister papilla, as well as pre-papillary arterial loops,\textsuperscript{103,104} may develop with vascular occlusions anterior to the disc surface when few compensatory channels are present to drain them.

Optic pits, considered by some to arise from the tissue surrounding the hyaloid artery and from aberrations of Bergmeister papilla,\textsuperscript{105,106} may arise subsequent to a delayed regression of cilio-hyaloid artery anastomoses,\textsuperscript{103} themselves produced by vascular occlusions near the lamina scleræs. As other collateral channels develop and decrease flow to cause their eventual regression, remodeled tissue “conduits” may be left in their wake. A small cilioretinal vessel may remain as evidence of a previously larger hyaloid vessel. It follows that various areas of ocular hypoplasia or remodeling, generalized or segmental, may persist as “footprints in the snow” of this local vasoocclusion. For example, focal retinochoroidal defects, sometimes called “atypical” colobomas when the defect lies outside the inferonasal meridian\textsuperscript{107} where failure of closure of the optic vesicle could be causal, could also be related to an intrauterine thromboembolic vascular occlusive mechanism.

For patients with morning glory anomaly, ipsilateral anomalies of the carotid and other cerebral arteries may be primary in nature, with peripheral arterial vascular anomalies causing local thrombo-occlusive phenomenon or sending emboli downstream. However, the 2:1 left to right prevalence ratio of carotid vessel anomalies indicates that these anomalies are also secondary to emboli emerging upstream from the branching of the carotid arteries from the brachiocephalic artery and aortic arch (ie, from the heart) and having initially formed in the slower-flow venous circulation. Correspondingly, left-sided carotid agenesis is more frequent than right-sided agenesis.\textsuperscript{73} Little evidence exists, moreover, to implicate embolic phenomena upstream to the disc surface when few compensatory channels are present to drain them.

Vascular occlusions may also affect other organs, such as the extraocular muscles, to produce hypoplasia. Via intrauterine transsynaptic degeneration, this would lead to a secondary loss of motor neurons to underlie muscle hypoplasia (without fibrosis) with corresponding cranial nerve hypoplasia, as documented in cases of congenital superior oblique palsy.\textsuperscript{108} Vascular occlusions affecting bony and cartilaginous mesenchyme may give rise to bony defects and encephalocyes. Wherever tissue scaffold has already been established, but hypoperfusion and relative ischemia occurs later during tissue differentiation, rather than apoptosis, amphipotential cells and tissues may undergo diverted differentiation because of insufficient metabolic nutrients to form choriosomes. Readily visible within PFV cataracts,\textsuperscript{86} they are also present in some instances of morning glory anomaly and posterior staphylomas, including hemifacial microsomia\textsuperscript{109} in the region of the external carotid artery, and can be noted elsewhere in the body.

Noncephalic 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,\textsuperscript{110} lung aplasia, fistulas, hernias, and forms of arthrogyrosis 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 pathophysiology of some congenital limb defects by Hoyme, Van Allen, and colleagues.\textsuperscript{111,112} Some of these investigators also noted the presence of vascular anomalies but ascribed 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.\textsuperscript{113} Hunter\textsuperscript{114} provided evidence that inherited thrombophilias were present in a large number of those with limb reduction malformations, whereas others\textsuperscript{115} have felt that vascular occlusions of uncertain or various etiologies could be responsible for a wide variety of congenital anomalies.

Unsurprisingly, limb defects are often seen in association with misinnervation syndromes or with persistence of fetal vasculature.\textsuperscript{116} When they occur with Duane syndrome, they may sometimes be given eponyms such as Okihiro, Wildervanck syndrome, etc.\textsuperscript{117,118} They may also be part of Poland-Möbius, Möbius-plus, VATER/VACTERL, Hanhart syndrome, etc.\textsuperscript{70,119,120} and are also prominent in thalidomide embryopathy. The association of such syndromes with cardiac malformations has been noted,\textsuperscript{121} but without any causal link heretofore recognized.

Thalidomide Embryopathy

Among various congenital defects, including skeletal and limb malformations, Möbius syndrome, and Duane syndrome, aberrant tearing and other substitutive misinnervation syndromes have frequently been associated with thalidomide use, specifically during the third to sixth week postfertilization.\textsuperscript{92,70,122} Despite numerous studies, the long-sought-after teratogenic mechanism and highly erratic effect of this medication remained elusive.\textsuperscript{123} Suspecting a vascular origin, Petter\textsuperscript{124} believed that altered erythroblasts could accumulate in small limb arteries and trigger local thrombosis and necrosis.

If one now considers the recognized prothrombotic properties of thalidomide\textsuperscript{125,126} in the context of embolic mechanisms for congenital malformations currently being proposed, a mechanistic picture comes into sharper focus. Synergistic effects take place when thalidomide is used in the presence of other thrombogenic influences,\textsuperscript{125,126} and variability in dose dependence across species can be related to differences in thrombogenic ef-
fects. But just as embolic phenomena are erratic, so are the teratogenic effects of thalidomide. The specific timing of thalidomide embryopathy 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 support orbital tissues and substitutive innervation is still possible. Hence, when hypoperfusion affects the brainstem substrate and cranial nerve nuclei, axonal regrowth is impaired, giving rise to Möbius syndrome. 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.

Misoprostol, a prototype teratogen acting on vascular pathways during the critical period of embryonic development, may provoke similar clotting. Other thrombogenic influences such as malnutrition, dehydration, alcohol, infections, trauma, ionizing radiation, antiphospholipid syndrome, and other autoimmune disorders may act synergistically with inborn predispositions to produce focal vasoocclusion. Since the opportunity for venous emboli to migrate arterially diminishes dramatically around birth when right-to-left shunts disappear, few vasculopathic tendencies are noted thereafter.

CONCLUSIONS

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 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.

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