Pediatric retinal vascular disorders: From translational sciences to clinical practice

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Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/sjopt.sjopt_63_23

Abstract:

Pediatric retinal vascular diseases are a spectrum with overlapping phenotypes and related genes. Retinal vascular development is biphasic. Vasculogenesis is responsible for the formation of primordial vessels leading to the four major arcades in the posterior retina. Angiogenesis, which is vascular endothelial growth factor dependent, is responsible for the formation of new vessels through budding from existing vessels, forming the peripheral vessels, increasing the capillary density of the central retina, and forming the superficial and deep capillary plexus. This process is controlled by *WNT* signaling, which is important for cell proliferation, division, and migration. Disorders of *WNT* signaling, such as familial exudative vitreoretinopathy (FEVR), have overlapping clinical findings. Conversely, pathogenic variants in some of the FEVR-related genes are reported in conditions such as retinopathy of prematurity (ROP), persistent fetal vasculature, and Coats disease. The various overlapping features and underlying genetic basis in the pathogenesis of pediatric retinal vascular developmental diseases suggest that genetic variants may provide a framework or a background for these conditions, upon which further insults can affect the development at any phase (such as prematurity and oxygenation in ROP), influencing and determining the final phenotype.

Keywords:

Coats disease, familial exudative vitreoretinopathy, *NDP*, peripheral avascular retina, persistent fetal vasculature, *WNT*

Introduction

Pediatric retinal vascular diseases represent a spectrum, rather than being distinct disease entities, with overlapping and sometimes atypical features. Translational research can provide a plausible explanation for the phenotypic behavior of disease processes encountered in clinical practice. Identifying the underlying genetic etiology and exploring the various aspects in its pathophysiology can lead to the understanding of the disease spectrum.

Embryology and Development

Triggers in ocular development

Appreciating the process of development of the eye provides a basis for understanding pediatric retinal vascular diseases. The retina develops from the optic cup, which differentiates first into two layers, the outer layer becoming the retinal pigment epithelium (RPE) and the inner layer, nearest to the lens vesicle, becoming the neural retina.[1] The transcription factor *PAX6* is well-known to play a crucial role in these events and is implicated in cases of microphthalmos and coloboma.[2] There is a differential function of *PAX6* in the retina and RPE and it acts by regulating two other transcription factors, microphthalmia-associated transcription factor (*MITF*) and visual system homeobox 2 (*VSX2*), functioning in a regulatory loop.[3] A reduction in *PAX6* exacerbates RPE to retina transdifferentiation and retina formation by expression of *VSX2*, which antagonizes the expression of *WNT* pathway genes and *MITF*, resulting in the promotion of neural retinal development. In the absence of functional *VSX2*, expression of *WNT* pathway genes and *MITF* is unchecked, leading to RPE overproduction.[4] *MITF* is initially expressed uniformly throughout the early mammalian optic vesicle, while at later stages, its expression is restricted to the

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Submitted: 20-Mar-2023
Revised: 11-Jul-2023
Accepted: 15-Jul-2023
Published: 12-Oct-2023

How to cite this article: Maitra P. Pediatric retinal vascular disorders: From translational sciences to clinical practice. Saudi J Ophthalmol 2023;37:269-75.

RPE, where it is involved in differentiation, proliferation, and pigmentation.[4]

Gene expression analyses show that increase in *PAX6*, together with *MITF,* suppresses the RPE-to-retina transdifferentiation by suppresses the expression of factors such as *Fgf15* and *Dkk3* (which are members of the fibroblast growth factor and Dickkopf families, respectively) that promote retina formation by inhibiting canonical *WNT* signaling (explained further below) and stimulating the expression of genes like *VSX2* (mentioned earlier) responsible for the development and differentiation of the retina.[3]

WNT signaling

WNT signaling is an evolutionary cell-to-cell coordination mechanism that is critical for a variety of physiological processes, including cell proliferation, division, and migration.[5] The canonical pathway refers to the standard or established pathway, which in this case refers to the *WNT* signaling mediated by the activation of β-catenin and its translocation into the cell nucleus, which promotes the transcription of *WNT*-associated genes. The activation of β-catenin is key in turning on the expression of target genes that include *c-Myc, Cyclin D1*, and vascular endothelial growth factor (VEGF), which enable cell proliferation and differentiation in specific tissues [Figure 1]. The non-canonical pathway refers to alternate mechanisms wherein *WNT* signaling occurs independent of β-catenin. The *WNT* noncanonical pathway mediates cytoskeletal organization and cell migration.[6] Since angiogenesis requires endothelial cell differentiation and migration during vessel expansion, it has been hypothesized that upregulation of endothelial cell growth occurs through the canonical pathway followed by stimulation of cytoskeletal rearrangement and subsequent expansion of cells to form new vessels through the non-canonical pathway.[7]

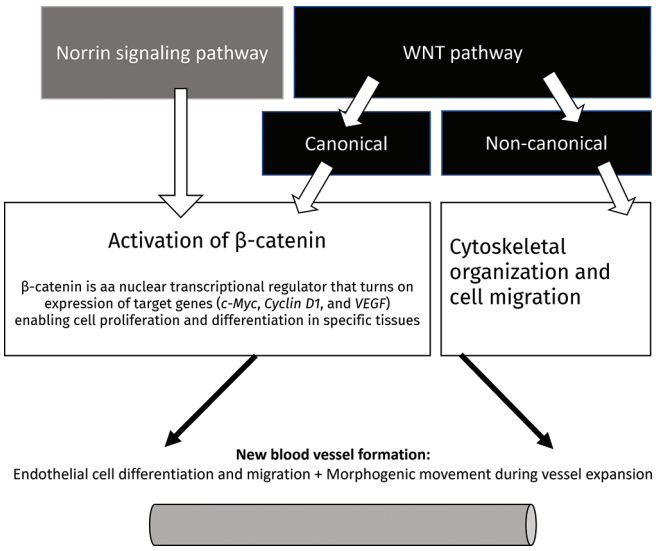

Figure 1: Schematic overview of *WNT*/Norrin signaling pathway. Adapted from: Tauqeer Z, Yonekawa.[6] VEGF: Vascular endothelial growth factor

The genes that participate in the *WNT* canonical pathway also participate in the Norrin signaling pathway, the implications of which will be discussed below.

Vasculogenesis and angiogenesis

The complex process of retinal development can be simplified into two components to aid in understanding: vascular and neuronal development. The two mechanisms work in great synchrony or, rather precisely timed asynchrony.[8] At the time of development of the optic vesicle, *WNT* pathway dormancy supports the retinal progenitor cells to develop into the neurosensory retina rather than the RPE, a process known as retinal differentiation.[3,4] Later on, *WNT* pathway stimulation is required for retinal vascular development and stabilization.[4,9,10] The vascular development is biphasic.[8,11,12] Precursor cells of mesenchymal origin exit from the optic nerve, initially forming cords and later developing lumens capable of carrying blood.[11,12] This phase, known as vasculogenesis, is responsible for the formation of the four major arcades in the posterior retina from primordial vessels. This begins before 14 weeks of gestation (WG) and is complete by 21 WG before the differentiation of retinal neurons.[11,13] This phase is now believed to be independent of VEGF.[8,12] The subsequent phase, known as angiogenesis, is VEGF-dependent and is responsible for the formation of new vessels through budding from existing vessels, forming the peripheral vessels, and increasing the capillary density of the central retina in the form of superficial and deep capillary plexus and the peripapillary radial capillaries[8,11,12] A key event appears to give a drive to this process at this time. Angiogenesis is induced by a transient but physiologic level of hypoxia which occurs as a result of increased metabolic activity of retinal neurons as they differentiate.[14] This results in the upregulation of hypoxia-induced factor (HIF), which, in turn, induces an upregulation of VEGF expression. Astrocytes, which are specialized glial cells and hypoxia sensors, serve as a template to dictate the pattern of the developing retinal vascularization under the control of the HIF pathway. Astrocytes are generated by the optic disc progenitor zone, and a small specialized ring of neuroepithelial cells located at the boundary between the optic cup and stalk, which has its own gene expression profile.[15] In order to arrange themselves as a template for vasculature, astrocytes migrate radially outward and subsequently undergo reorganization/ patterning.[15] Although initially it was believed that astrocytes and vascularization advance together, now it has been recognized that astrocyte migration is independent of vasculature.[15] Astrocyte patterning/maturation occurs later, together with retinal vascularization.[15] Under the effect of increased delivery of oxygen from the arriving vascular front, both these together spread across the retina like a wave.[15] In the developing retina, the tissue ahead of the angiogenic wavefront is hypoxic due to the lack of an intrinsic blood supply. Astrocytes are the only cells in the avascular hypoxic zone that express high levels of VEGF.[15] The positioning of the mature astrocytes just ahead of the leading edge of vessel formation places them in an ideal position to mediate

the angiogenic response to physiologic hypoxia through the upregulation of VEGF165 (an isoform of VEGF-A) expression.[8] The central astrocyte-free zone (with elongated cones and Müller cell processes) limits the development of the vasculature and gives rise to the foveal avascular zone (FAZ). The absence of blood vessels and inner retinal tissue at the fovea is thought to maximize the optical quality of the fovea pit by reducing light scattering. It has been seen that the presence of FAZ precedes the formation of the foveal pit.[16]

Clinicopathophysiology of Pediatric Vascular Developmental Disorders

Familial exudative vitreoretinopathy

Familial exudative vitreoretinopathy (FEVR) is considered a *WNT* signaling disorder as four out of five of the most commonly implicated genes (*NDP, FZD4, LRP5,* and *TSPAN12)* act on the canonical or Norrin signaling pathway. *FZD4* and *LRP5* encode the proteins that act as coreceptors for *WNT* proteins and Norrin. *TSPAN12* plays a role in Norrin signaling only. When *FZD4*, *LRP5*, and *TSPAN12* bind to *WNT* or Norrin, they transduce a signal that inhibits the destruction of β-catenin, allowing it to accumulate within the cytoplasm and subsequently translocate to the nucleus to enhance expression of target genes (*c-Myc, Cyclin D1*, and *VEGF*). In the absence or dysfunction of the receptors and proteins encoded by these FEVR-related genes, cytoplasmic β-catenin gets phosphorylated and undergoes degradation, and this results in its target genes (*c-Myc, Cyclin D1*, and *VEGF*) remaining repressed.[7]

Interestingly, only 50% of genetically confirmed FEVR are caused by pathogenic variants in *NDP, FZD4, LRP5, or TSPAN12*.[17] Other genes implicated in FEVR include *ZNF408*[18] and *KIF11*,[19] and the latter being associated with more severe disease (stage 4 or above).[20]

FEVR has a wide range of phenotypic spectrum ranging from quiescent peripheral avascularity to abnormal vasculature, peripheral neovascularization, exudation, straightening of arcade vessels, retinal folds (extending temporally or in the inferotemporal quadrant), and detachment of varying etiology and severity. The disease often has a progressive course during childhood and becomes latent during adolescence, although exceptions have been reported with complications such as neovascularization, vitreous hemorrhage, and retinal detachments (RDs) that can occur at any age after varying periods of apparent quiescence.[21] Although FEVR can present anytime in early childhood, patients presenting at birth can pose a diagnostic dilemma, especially when there is an advanced phenotype. Differential diagnosis includes Norrie disease in bilateral cases and persistent fetal vasculature (PFV) in unilateral cases. Pedigree analysis can be helpful. Interestingly, some of these advanced phenotypes have been noted in borderline preterm babies, leading to recognition of the entity known as ROPER – a term proposed to describe features of FEVR in the presence of prematurity.[22]

Retinopathy of prematurity

Retinopathy of prematurity (ROP) has been of increasing incidence as improved neonatal care allows extreme preterm babies to survive. The first case reports of ROP were described by Terry in 1942, and he suspected that the formation of grayish retrolental fibroblastic overgrowth was predisposed by prematurity.[23] Today, we are aware of a number of external factors predisposing to or contributing to the severity of ROP, and therefore, ROP is largely believed to be an acquired condition.[24]

The physiological pattern of retinal vascularization starting at the optic nerve head is typically "butterfly"/lobular in shape.[8] It shows a four-lobed topography. The temporal wedge of a vascularity thus formed naturally and sometimes in association with stages of ROP can encroach into zone 1 in posterior ROP. This temporal wedge of the avascular retina in the setting of ROP has been recently recognized separately as a "notch" in ICROP third edition.[25]

Much of what we understand about the pathophysiology of ROP was established from observations in experimental models.[26] Two such important models include the oxygen-induced retinopathy (OIR) model and hyperoxia-induced proliferative retinopathy (HIPR) model.[27,28] In the OIR model, oxygen exposure to rodents is limited to 5 days starting at day 7 postnatal and results in the typical stage 1 of vaso-obliteration and stage 2 of preretinal neovascularization of ROP. The role of astrocytes in ROP was not clear based on the findings of the OIR model. However, in experimental models where high oxygen is given from the day of birth, astrocyte proliferation leading to massive overproduction and disruption in astrocyte patterning has been noted. The severity of the vascular phenotypes in animal models has been found to be proportional to the amount of excess astrocytes.[15] In the HIPR model, 75% oxygen exposure was maintained continuously for 2 weeks with no exact hypoxic phase, and this resulted in the presence of neovascularization within the central retina, severely disorganized vasculature, persistence of hyaloid vasculature, and fibrinogen within the retina indicating the presence of vascular leakage and exudative RD.[28] This is compatible with many varieties of atypical ROP such as volcano tractional RD (TRD) (described in ICROP Third edition) and exudative/blister ROP.[25]

The key similarity between the pathogenesis of ROP and FEVR is delayed physiologic retinal vascular development.[29] This was earlier described as phase 1 of ROP. Fundus fluorescein angiography (FFA) findings such as peripheral avascularity with arteriovenous loops and circumferential vessels are common features in ROP and FEVR, making ROP and ROPER extremely challenging to distinguish clinically and on angiogram.[22]

In ROP, the avascular retina becomes hypoxic and stimulates the expression of angiogenic growth factors. However, instead of causing angiogenesis to grow into the retina, it grows into the vitreous (phase II).[30] In humans, a late component of phase 2

can be described as phase 3, where increase in VEGF activates plasminogen activators that convert plasminogen to plasmin, which in turn activates transforming growth factor beta 1, the master regulator of fibrosis contributing to the evolution of detachment (stage 4 and 5 ROP).[31] A similar pathophysiology can be assumed to cause detachment in FEVR as well. However, unlike ROP, for which these processes occur soon after birth, for FEVR, it can occur unpredictably at any time, usually in childhood, the trigger for which remains unknown.

In ROP, the astrocyte layer becomes thicker and clumped ahead of the angiogenic wavefronts, possibly due to excess astrocytes or alterations in astrocyte patterning.[15] This could cause vascular anomalies or incomplete vascularization of the periphery/persisting avascular retina (PAR) even after an anti-VEGF injection, as noted often in our clinical practice. Whether a similar occurrence contributes to vascular anomalies or incomplete vascularization of the periphery seen in FEVR is not established. The PAR in ROP behaves differently. A high risk of development of peripheral retinal lesions (>50%) and rhegmatogenous RD (RRD) (39%) has been reported in untreated ROP eyes.[32] This is higher than the risk of similar findings in FEVR, where the development of retinal breaks and RRD was 17% for each.[21] Experts believe PAR after anti-VEGF monotherapy is akin to iatrogenic FEVR, and many practitioners suggest performing laser photocoagulation of PAR in early life to prevent late reactivations and RRD.[33]

In India, where heavier babies develop aggressive/atypical ROP, other pathways and underlying abnormalities are suspected. There is a hypothesis that genetic influences may play a role in the development of severe ROP and contribute to the unpredictability of ROP in some premature infants.[34] *WN*T pathway variants in genes such as *FZD4*, *LRP5*, and *TSPAN12* have been found in patients with advanced ROP.[35,36] Whether these could be polymorphisms making an individual more susceptible to oxygen and for ROP to develop remain to be established. From a genetic point of view, it appears that some specific nonconventional variants of ROP could be FEVR/ROPER, harboring underlying pathogenic variants with superimposed varying postnatal insults like oxygenation. Even diseases beyond those in the discussion here, like cerebral palsy, are also now known to be caused by more than just birth trauma. It is believed that developmental injury starts *in utero*.[37]

Despite there being some reports of pathogenic variants in ROP babies, ROP is not believed to be a genetic disease. As mentioned above, as many as 50% of FEVR patients are associated with known genetic pathogenic variants of the *WNT* pathway.[17]

Persistent fetal vasculature

The hyaloid vasculature is a temporary circulatory system that is supposed to regress. Persistence of this hyaloid system and resultant associated problems are termed as PFV, sometimes clinically indistinguishable from FEVR and a close differential diagnosis to ROP. In mouse models, VEGF is shown to maintain hyaloid vessels through endothelial VEGF receptor 2 (VEGFR2).[38] In addition, neonatal neurons in mouse models sequester protein in the vitreous cavity through binding to VEGFR2, causing endothelial apoptosis, and switching the eyes from a fetal to a postnatal circulatory system by programmed regression of hyaloid vessels.[38] In contrast to intraretinal vessels, *WNT* signaling promotes regression of the hyaloid vasculature.[10] Multiple signaling pathways, such as VEGF/VEGFR2 signaling, noncanonical WNT signaling, and blood flow-induced signaling, have been identified to regulate and control vessel regression.[10] It has been established that the *NDP* gene product, implicated in Norrie disease (X-linked severe retinal dysplasia), is necessary for the regression of hyaloid vessels in mouse models.[39] In one case report, an *NDP* pathogenic variant was suggested to be associated with a case of PFV.[40] PFV is known to be primarily a unilateral condition. However, recently widefield FFA has added novel insights with fellow eye findings such as peripheral avascularity and leakage, abnormal circumferential vessels, supernumerary branching in the periphery, and abnormal vessel straightening. These features are otherwise typical of FEVR.[41-43] Although most cases of PFV are sporadic, it is possible that there is a genetic basis for bilateral PFV, which can be inherited in autosomal dominant or recessive inheritance patterns. In experimental animal models, abnormalities in normal apoptosis and defects in the *WNT* signaling pathway (*NDP* and *LRP5* pathogenic variants) have been implicated in the pathogenesis of PFV.[44] With the unraveling of a pathogenic variant in the *COX15* gene in one case of PFV, there is a hypothesis that the pathology could be due to the proximity of *COX15* to the *WNT 8B* gene on chromosome 10, additionally affecting the *WNT* signaling related to *COX15* pathogenic variants.[45] The *ATOH7* gene is a transcription factor gene, which has also been identified in association with the PFV phenotype in both humans and mice.[46] Multiple recent animal studies reported the involvement of various signaling pathways in the pathogenesis of PFV, including proto-oncogene *ski, p53*, tumor suppressor gene *Arf, ephrin-B2, LRP5, ang-2 Bax* and *Bak, FZD4*, and *ephrin-A5*. Neogenin is a multifunctional transmembrane receptor belonging to the immunoglobulin superfamily, implicated in tissue morphogenesis, angiogenesis, and myoblast differentiation. Another suggestion is that neogenin loss in neural crest cells results in persistent hyperplastic primary vitreous formation.[47]

While ROP follows a symmetrical presentation in both eyes, in FEVR, variable degrees of asymmetry are typical. The unilateral presentation, along with associated features such as nasal dragging/TRD, microphthalmos, and cataract is in favor of PFV.[44]

Coats disease

Coats disease is characterized by abnormal development of the blood vessels in the retina, specifically telangiectatic vessels, with variable amounts of exudation, with or without RD. Coats disease has been so synonymous with exudation that the term "Coats-like response" is often used as a blanket term to denote

exudation in other pathologies such as retinitis pigmentosa, ROP, and morning glory disc anomaly.[48-50] Angiographic studies have revealed telangiectatic and aneurysmal changes along with areas of peripheral avascular retina.[51] In addition, bilateral vascular abnormalities are found in about two-thirds of presumed unilateral disease, with peripheral nonperfusion of more than two disc diameters in contralateral eyes.[52] With the evidence for approximately 9% presumed unilateral Coats disease cases having peripheral retinal nonperfusion in the contralateral eye, and few patients even requiring laser photocoagulation due to peripheral leakage with telangiectatic vessels, it appears that Coats disease may more often have subtle bilateral disease with asymmetry than previously thought.[53] There have been case reports of somatic pathogenic variants in the *NDP* gene encoding for Norrin in a few cases of Coats disease.[54,55] The *CTC1* gene provides instructions for making a protein that plays an important role in the maintenance of chromosomal structures known as telomeres, which normally prevents chromosomal degradation during cell divisions. A variant of Coats disease, known as Coats-plus syndrome (a rare recessive disorder characterized by intracranial calcifications, osteopenia, hematological abnormalities, and retinal vascular defects), is associated with *CTC1* pathogenic variants.[56] There is also a report in the literature of coexistent pathogenic variants in *CTC1* and *NDP* in a patient with Norrie disease.[57]

The Spectrum

Smoldering phenotypes of the above-described pathologies can be incidentally discovered in the pediatric age group. Retcam (Clarity Medical Systems, Pleasanton, CA) and widefield fundus imaging are indispensable in pediatric retinal vascular diseases. In many instances, widefield FFA has added to our understanding of the disease process. Peripheral avascularity, neovascularization, telangiectasia, and exudation are common overlapping features [Figure 2] and severe phenotypes usually have RD associated with traction or exudation, with or without a rhegmatogenous component. The advanced phenotypes of these diseases, which require surgery, are often clinically indistinguishable from each other, making the diagnosis uncertain. Moreover, overlapping genes cause further dilemma [Figure 2]. The greatest dilemma, however, is the sequelae of these diseases characterized by atrophic retina with pigmentation and falciform folds with variable degrees of peripheral fibrosis, which can also be associated with infectious retinal diseases like toxocariasis.

Relationship with other developmental anomalies

In cavitary disc disorders which are of mesenchymal origin, *PAX6* is sometimes implicated.[58] In clinical practice, we do also rarely come across hyaloid remnants in association with these developmental disorders of the disc. It appears that morning glory disc anomaly can be associated with the process of hyaloid regression/PFV[59] and may also occur in association with peripheral capillary nonperfusion areas in 85% of cases on fluorescein angiography, with some cases showing leakage, fibrous proliferation, and tractional detachment as well.[60] Moreover, *ZNF408* pathogenic variants, which have been earlier implicated as one of the only non-*WNT* signaling mutations in FEVR, have recently been reported in a patient with morning glory disc anomaly with PFV.[61]

Anatomical Considerations

The well-defined phenomenon of worsening of preexisting fibrosis and accelerated TRD in response to anti-VEGF

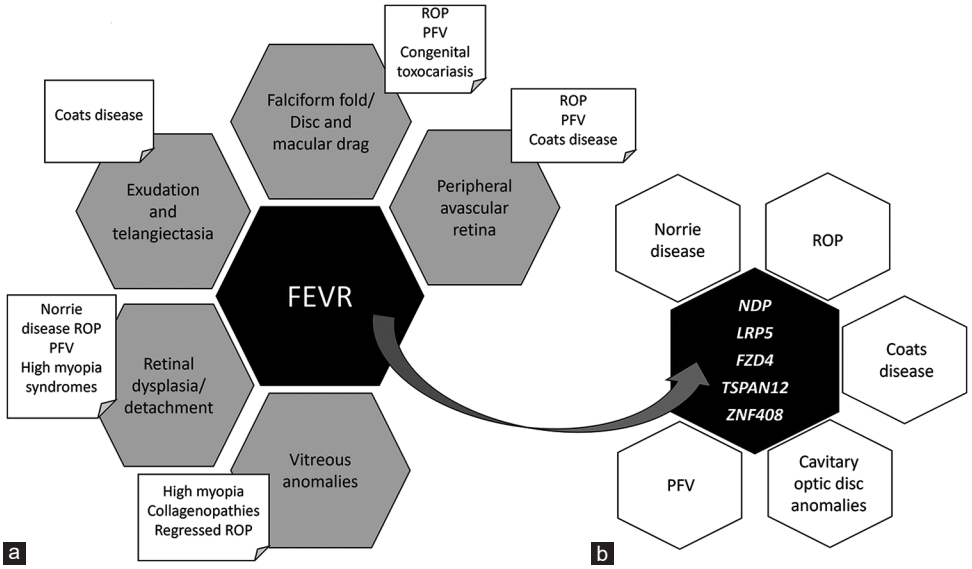

Figure 2: (a) A list of the various common clinical findings in familial exudative vitreoretinopathy (FEVR), along with an adjacent list of conditions that share the same clinical feature and have potential clinical overlap. (b) List of genes that have been associated with FEVR and some of these genes have been identified in other phenotypes as well, as listed here (details in text). FEVR: Familiar exudative vitreoretinopathy, ROP: Retinopathy of prematurity, PFV: Persistent fetal vasculature

treatment in ROP is known as the crunch phenomenon.[62] In pediatric vascular retinal disorders, the prepapillary area is an area of interest and concern due to the presence of the involuting hyaloid system. The remnant cells from the regressed hyaloid system appear to be responsive to VEGF or fibroblastic mediators, a phenomenon seemingly responsible for one of the unique configurations of crunch detachments in ROP – the prepapillary type of crunch detachment, where preexisting fibrosis is not prominent.[62,63] This may even explain the mechanism of closed funnel RD early on in pediatric retinal vascular developmental disorders. The predominantly TRD of ROP is influenced by the involuting hyaloid system and tunica vasculosa lentis, where a central stalk is best appreciated with endoillumination during vitreous surgery.

Conclusion

Analysis of the various overlapping features of pediatric retinal vascular developmental diseases and understanding the underlying genetic basis in their pathogenesis suggest that genetic pathogenic variants can provide a framework or a background for these conditions, upon which further insults can act to affect the developmental system at any of the phases (such as prematurity and oxygenation in ROP) influencing and determining the final phenotype. Advances in genetics, histopathology, immunohistochemistry and cellular biology , and our knowledge of these translational sciences may assist in further unraveling the unique aspects of the pathophysiology of these conditions, which can help in explaining atypical phenotypes and possibly provide some therapeutic targets for effective intervention in the future.

Acknowledgments

The content of this article has been drafted from the insights I developed from discussions with my mentors in the field of inherited pediatric retinal disease – Dr. Parveen Sen, Dr. Parag K Shah, and Dr. Wei Chi Wu, whom I would like to acknowledge here.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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