Commentary: Understanding angiogenic factors in pathogenesis of persistent fetal vasculature

Persistent fetal vasculature (PFV) is a congenital pathology where remnants of the hyaloid artery system fail to regress.[1] Presentation varies from anterior, posterior, or mixed variety based on structures involved from pupil and lens to optic disc. Anterior presentation includes persistent pupillary membrane, enlarged ciliary processes, cataract, capsular plaque with vessels, retrolental membrane, glaucoma, and/or Mittendorf dot.[2] Posterior presentation includes Bergmeister's papilla, PFV stalk, falciform fold, and/or retinal detachment. The most common is the mixed variety where there is overlap of anterior and posterior presentation.

During fetal development, hyaloid artery system provides circulation of oxygen and nutrients throughout the eye (both anterior and posterior segments). It starts developing in the first month, and by third month, there are extensive vascular anastomosis present.[1,2] The regression of vessels by apoptosis starts by the fifth month of gestation and normally completes by birth.[3] If it fails to regress by birth, it leads to PFV and associated abnormalities. The reasons for failure of regression are incompletely understood.[4] These vessels which persists after birth ooze at the time of surgery and result in complications. Presence of pink hue from capsular plaque known as "salmon patch sign", is suggestive of PFV.[5]

This study introduces an interesting hypothesis.[6] Antiangiogenic factors (arresten, canstatin, tumstatin, and endostatin) and regulatory molecules such as matrix metalloproteinase (MMP) 2 and 9 which are evaluated in the study are hypothesized to have a role in PFV. These are collagen-derived antiangiogenic factors present in lens epithelial cells and hence can be studied in capsulorhexis sample.

Various studies have been conducted in the past to understand pathogenesis and the role of various factors in animal models. In these studies, angiogenic factors including *vascular endothelial growth factor* and *placental growth factor* have been noted to have a modulatory role in hyaloid regression.[7] In addition, in macrophage-ablated mouse, persistence of the hyaloid vessels and the pupillary membrane has been noted, which is a direct evidence that the *macrophage* plays a role in the regression of these vessels.[8] Persistent hyaloid artery also occurs in *p53-deficient* and *Bax/Bak proapoptotic Bcl-2-deficient* mice, hence implicating them in pathogenesis.[9] The existing literature provides evidence that angiogenic and apoptotic factors have a role in regression of hyaloid artery system.

Antiangiogenic factors such as arresten and regulatory molecules (MMP-2 and MMP-9) have not been studied previously. The current study has found significantly lower

level of arrestin mRNA and higher level of MMP-2, tumstatin, and canstatin. Since arresten, a known antiangiogenic factor, is found significantly low in the study, it is speculated to have a more important role than other factors. The reason for this is not fully understood. The major shortcoming of this study is a small sample size (13 eyes) and wide age of presentation chosen (1–108 months); which may affect the results. To validate the results and draw a satisfactory conclusion, a study should be designed to include more eyes with narrow age group (preferably in the first 3 months) for both cases and controls. Since capsulorhexis samples cannot be derived from clear lens, cadaveric eyes with clear lens may be alternate for control.

There is limited literature on use of capsulorhexis tissue for molecular studies. Hence, this study provides a human model where capsulorhexis tissue can be used in better understanding of lenticular abnormalities associated with a preexisting pathology including PFV, capsular plaques, toxoplasma, rubella, cytomegalovirus and herpes (TORCH) infections, and so on. It would be interesting to use such models in various ocular abnormalities in future research.

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