

Need for Refinement of International Retinopathy of Prematurity Guidelines and Classifications

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J Ophthalmic Vis Res 2015; 10 (4): 355-357.

We recently developed a prototype online program for training residents and fellows about retinopathy of prematurity (ROP). We were motivated by the lack of adequate training in this important area.^[1-5] Since ROP is a rapidly progressive disease that can result in blindness, adequate and efficient knowledge regarding ROP should be expected of retina and pediatric ophthalmology fellows and at least available to all ophthalmology residents.^[1-5] Although for teaching purposes it might be best for all training in ROP to take place in the NICU, this is not practical because of constraints in time and resources as well as the safety of affected infants. Fortunately, high quality wide-angle images of the fundus can now be readily obtained for teaching and telemedicine.

In the course of development of our program, it became clear that significant variability still exists among ROP practitioners in grading fundus photographs of infants with ROP. This has been previously discussed among experts.^[6-9] In addition, we realized that the most recent International Classification of ROP^[10] does not fully reflect current thought, and that follow-up schedules recommended in the latest consensus paper^[11] do not fully take newly described features of the disease into account.

Plus disease is defined as retinal vascular dilation and tortuosity. A standard photograph illustrating plus disease has been used for diagnosis since a consensus agreement for the CRYO-ROP study in 1988.^[12] Recognition of plus disease is critical because ROP diagnosis and treatment guidelines are now dependent on the presence or absence of this finding.^[13] Thus, it has important implications for clinical care, development of computer-based image analysis methods, and also telemedicine systems. Unfortunately, significant subjectivity in determination of plus disease remains a problem.^[6,7,9,14,15] Using standard dilated ophthalmoscopy, disagreement was found in 12% of cases regarding a diagnosis of threshold disease in a report based on the CRYO-ROP and LIGHT-ROP studies.^[14] Using image-based diagnosis for identification

of plus disease, one study in 2007 found that 22 experts agreed on the diagnosis of plus disease in only 21% (7/34) of images, with a mean kappa of 0.19-0.66 for each expert compared to all others.^[15]

Although the standard photograph has been used for diagnosis of plus disease, more recently an international committee for classification of ROP has stated that 2 quadrants of vessel dilation and tortuosity are sufficient for a diagnosis of the condition.^[10,16]

Images used for diagnosis of ROP are frequently captured with a contact camera with a 130° field of view, in contrast with standard binocular indirect ophthalmoscopy with a 40° to 50° field of view. Both are in contrast to the aforementioned standard photograph, which is a higher magnification image of the posterior pole. This difference in perspective may cause confusion in the diagnosis of plus disease.^[6] The standard photograph gives the impression of intense four quadrant vein dilation and arterial tortuosity, while the indirect ophthalmoscopic view and 130 images for ROP assessment seem to show relatively less dilation. It is difficult to compare the magnitude of vein dilation at different levels of magnification or using indirect ophthalmoscopy.^[17] It is also confusing as to whether the ophthalmologist should rely on the standard photograph or on the description of two quadrants of venous dilation and arterial tortuosity which may be different from the standard photograph with 4 quadrant vessel dilation.

The latest international classification of ROP in 2005 addressed an intermediate stage, called pre-plus as a new entity. It is described as "abnormalities of the vessels that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilation than normal."^[18]

Disagreement in the diagnosis of plus versus non-plus versus pre-plus has also been addressed.^[9,15] Inter-expert agreement has been reported as fair for diagnosis of plus disease ($\kappa=0.32$).^[9] In a study by Chiang et al, categorization of plus versus non-plus versus pre-plus was similar in only 4 out of 34 images among 22

experts.^[15] Pre-plus has been defined as vessel dilation less than plus,^[9] but it is not clear whether the findings have to be assessed in the posterior pole alone. Peripheral dilation and tortuosity are not normal but it is not clear how these findings should influence staging and treatment. The clinical significance of pre-plus disease is not completely clear, given that it was not considered in clinical trials such as CRYO-ROP or ETROP which we apply for management of ROP patients. Another issue to address is follow-up schedules for infants with pre-plus disease. As pre-plus is not considered in follow-up recommendations by the most recent consensus document,^[11] follow-up recommendations for patients with this finding are not clear. It has been demonstrated, for example, that patients with pre-plus have a higher risk of progression.^[17]

Computer-based image analysis programs such as ROP tool,^[19-21] RISA,^[22] Vessel Map,^[23] and CAIAR^[24] have been developed for diagnosis of plus disease. These programs show promise for identification of plus disease using quantitative methods, but their exact role in the diagnosis of ROP requiring treatment in routine practice has not been determined yet.^[25] Studies comparing computer-based (Retinal Image multiScale Analysis [RISA]) and individual expert diagnosis in relation to a reference standard diagnosis based on expert consensus found that the accuracy of ROP experts for diagnosis of plus disease is much lower than computer-based diagnosis.^[26,27]

Another prominent area of disagreement is in determining whether findings are in zone I or posterior zone II. This is a critical determination for management because any stage in zone I with plus, and stage 3 in zone I without plus have a poor prognosis and should be treated.^[12] Locating the fovea is difficult in fundi of premature infants, and this is the major problem in defining zone I in our experience and in a study by experts.^[8,28] A practical way to locate the fovea in fundus photographs would lead to less disagreement. Patel et al addressed this by using fluorescein angiography (FA) for locating the fovea; however, they showed that adding angiography does not increase the sensitivity of zone diagnosis. Mean sensitivity for detection of zone I by experts in comparison to a consensus reference standard diagnosis when interpreting color images alone versus interpreting the color fundus image and FA images was 47% vs. 61.1%, respectively, which was not statistically significant ($P=0.073$).^[28] Performing FA in premature infants is not easy, and it is not clear that this should be considered as standard care. It is also impractical for telemedicine. The 2005 classification describes a practical way to determine the extent of zone I by using a 28 or 30 diopter lens with indirect ophthalmoscopy,^[10] but no simple method exists for photographs. Another issue in using photographs for ROP diagnosis is the lack of stereopsis. This can cause difficulty distinguishing stage

1 from stage 2^[9] and is an issue in telemedicine as well as in teaching.

AP-ROP was described in 2005^[10] and defined as flat neovascularization and plus in zone I or posterior zone II. Its diagnosis and prompt treatment is very important as it carries a poor prognosis.^[29-32]

Inter-expert diagnostic agreement regarding AP-ROP has been reported to be imperfect. Eight ROP experts interpreted 15 retinal images for AP-ROP and plus disease and mean kappa for each expert for AP-ROP diagnosis ranged from -0.15 (no agreement) to 0.42 (moderate agreement).^[33] The lack of a "gold standard" for AP-ROP diagnosis hinders work in this area. When there is substantial disagreement among experts it is difficult to use expert consensus in developing standards.

Flat neovascularization is different from classic stage 3 which is defined as extraretinal fibrovascular proliferation (occurring on a peripheral ridge). Though it seems that flat neovascularization is a type of stage 3 disease (since neovascularization is the key feature of both), this has not been addressed in formal classifications.

This is an area of confusion in teaching ROP staging. Flat neovascularization is difficult to diagnose, particularly for the novice, and it may easily be overlooked. There are, however, usually retinal arteriovenous anastomoses^[10,34] at the anterior extent of vascularization or more posteriorly in the retina in cases of AP-ROP. Newer classifications might consider this as one of the features of AP-ROP.

Addressing these issues is clearly important for diagnosis and treatment of ROP. These issues also compound the difficulty of training residents and fellows about ROP.

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Access this article online	
Quick Response Code: 	Website: www.jovr.org
	DOI: 10.4103/2008-322X.176902

How to cite this article: Roohipoor R, Loewenstein JI. Need for refinement of international retinopathy of prematurity guidelines and classifications. *J Ophthalmic Vis Res* 2015;10:355-7.