Thinking Beyond Wet Age-Related Macular Degeneration

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Wet age-related macular degeneration (AMD), also known as neovascular or exudative AMD is the commonest cause of choroidal neovascularization at the macula. However, several entities mimic wet AMD, which can be distinguished on careful clinical examination and relevant imaging modalities. A high index of suspicion is required to identify these mimickers early in the course of the disease, which can otherwise be missed. Their recognition is of importance owing to varying management strategies and prognosis vis-à-vis wet AMD.

Neha Goel - Q. What are the mimickers / variants of wet AMD encountered in your practice, and how frequently (in percentage)?

Atul Kumar: We prefer using the term Neovascular AMD instead of wet AMD, as the latest internationally accepted nomenclature. Differentials of neovascular AMD (nAMD) include conditions which have features similar to choroidal neovascularization (CNV) at post pole.

Conditions with CNV which mimic nAMD that we see commonly include: Polypoidal Choroidal Vasculopathy (PCV), Retinal Angiomatous Proliferation (RAP), and Macular Telangiectasia (Mac Tel). PCV is seen about 8-15% cases of nAMD, and RAP in approximately 5% cases at our centre. Besides these, Multifocal choroiditis typically presents as a chronic relapsing panuveitis with multiple chorioretinal lesions – and is the most common entity presenting with Idiopathic CNV (1-5% at our centre), pseudoxanthoma elasticum also has CNV as its major complication (seen between 1-2% at RP Centre). Pathologic myopia, or high myopia, is an important cause of secondary CNV in young people. The progressive elongation of the eye is associated with variable morphologic alterations within a posterior staphyloma. Macular CNV is the most common vision-threatening complication of high myopia seen by us, affecting nearly 8-10 percent of patients here.

Mahesh P Shanmugam: Polypoidal choroidal vasculopathy – 70%
CNVM of other etiology – myopic, idiopathic, associated with parafoveal telangiectasia – 20%
Retinal angiomatous proliferation – 5%
Adult Onset Foveomacular Vitelliform Dystrophy (AOFVD), otherpattern dystrophies, subfoveal lymphoma or early choroidal metastasis – 5%

Muna Bhende: PCV, Chronic Central Serous Chorioretinopathy (CSR), vitelliform lesions, other CNV etiologies. I would consider RAP as a subset of AMD.

Raja Narayanan: The common variants of wet AMD are PCV, RAP and AOFVD. PCV comprises 40-50% of cases, stage 1 and 2 RAP constitutes approximately 10% cases, and AOFVD represents less than 5% cases. The remaining 35-
40% cases are typical wet AMD cases of occult or minimally classic CNVM. Predominantly classic CNVM in wet AMD is not common. Rarely, parfoveal telangiectasia with subretinal neovascularization may mimic wet AMD.

Hidetaka Matsumoto: PCV and RAP, AMD: 50%, PCV: 35%, and RAP: 15%. Other variants are myopic CNV, angiod streaks with CNV, CSC, etc.

Summary (Neha Goel): The commonest mimicker of wet (neovascular, exudative) AMD is PCV. RAP (maybe considered a variant of wet AMD) and AOFVD are less common. Other causes of CNV such as myopia, multifocal choroiditis, macular telangiectasia, angioid streaks, CSC need to be kept in mind as well.

Neha Goel - Q. What are the clinical signs which raise suspicion of:

- Polypoidal choroidal vasculopathy (PCV)
- Retinal angiomatous proliferation (RAP)
- Adult-onset foveomacular vitelliform dystrophy (AOFVD)

Atul Kumar: PCV is commonly seen in women above the age of 50 years, especially of oriental origin. The presentation is variable. It may be relatively stable or there may be repeated bleeding and leakage with vision loss and chorioretinal atrophy. Clinically, PCV is characterized by protruding orange-red elevated PED’s or serous detachment often with submacular bleed and surrounding exudates.

RAP is included as initial type 3 neovascular AMD. In this retinal vessels are responsible to form the CNV. Presentation is similar to that of other types of neovascular AMD. Haemorrhages are more common and tend to be superficial and multiple. OCT is very helpful in differentiating it from other types of neovascular AMD.

AOFVD presents asymptomatically or with mild blurring, after the age of 40 years unlike Best’s which is seen earlier. Biomicroscopically, it is characterized by a subretinal deposit of yellowish material that is oval or round, elevated, localized in the macular area, and often centered by a pigmented spot.

Mahesh P Shanmugam: PCV lack / relatively less drusen in either eye, subretinal orange red polyps and / or branching vascular network visible with green illumination, larger quantum of subretinal / sub RPE hemorrhage, exudative changes in relatively younger patient, peripapillary location, central serous retinopathy like presentation, serous and notched PED’S.

RAP predominantly intraretinal hard exudates, and intra /pre retinal hemorrhages along with intraretinal edema, associated pigment epithelial detachment beneath it, at times retinochoroidal, retino-retinal anastomosis.

AOFVD subfoveal dull yellow deposit, bilaterality, absence of exudates and hemorrhages.

Muna Bhende: PCV Dilated choroidal vascular channels with terminal orange, bulging polypoid dilatations, serosanguinous PEDs, recurrent hemorrhagic and/or serous detachments of the RPE

RAP When an AMD neovascular lesion is associated with intraretinal hemorrhages and edema in conjunction with retinal telangiectatic vessels diving into it on a serous PED with a notch

AOFVD Yellowish mildly elevated lesions in the foveal/perifoveal region 1/3rd to 1/2 DD in size. Central hyperpigmentation may be seen. Later stage lesions may be atrophic.

Raja Narayanan: PCV A large subretinal hemorrhage of more than 2 disc diameter, large pigment epithelial detachment, orangish subretinal lesions, intraretinal and subretinal exudates which cannot be explained in the absence of branch vein occlusion or diabetic retinopathy. The index of suspicion should be high in any case of wet AMD in the Indian population, because it is very common.

RAP Stage 1 and 2 RAPs typically have small intraretinal hemorrhage (blot hemorrhage such as seen in diabetic retinopathy), rather than the streaks or large subretinal hemorrhage seen in PCV or CNVM. Intraretinal exudates, cystoid macular edema and PED are common in RAP. However, stage 3 RAP may be difficult to differentiate clinically from wet AMD CNVM, and only an ICG angiography can give a definitive diagnosis.

AOFVD A Large dull brown subretinal lesions without any visible membrane or subretinal hemorrhage, no significant macular edema, relatively good vision, and no leak on FA are suggestive of AOFVD. There is no thickening of the RPE-CC complex on OCT. They generally do not respond well to anti-VEGF agents.

Hidetaka Matsumoto: PCV Orange lesion (polypoidal lesion), network vessel, hemorrhagic retinal pigment epithelium detachment (PED), and subretinal hematoma.

RAP Intraretinal hemorrhage, intraretinal edema, multiple soft drusen in the macula, reticular pseudodrusen, and serous PED.

AOFVD Bilateral, symmetrical, grayish-yellow, and round or oval-shaped lesions in the macula

Summary (Neha Goel):

- The presence of subretinal orange-red lesions, sub-RPE or / and subretinal hemorrhage and exudation should alert one to look for PCV (Figure 1 a).
- The presence of intraretinal hemorrhages, exudates and edema and associated serous PED could point towards a RAP lesion (Figure 2 a).
- AOFVD is clinically characterized by bilateral subfoveal yellowish elevated lesions in the absence of hemorrhages.

Neha Goel - Q. On OCT, what features suggest the presence of:

- Polypoidal choroidal vasculopathy (PCV)
- Retinal angiomatous proliferation (RAP)
• **Adult-onset foveomacular vitelliform dystrophy (AOFVD)**

   **Atul Kumar:** PCV In most PCV cases, optical coherence tomography (OCT) revealed a sharply elevated PED with/without connecting lower PEDs. OCT also reveals, hyper-reflective projections which are actually polyps adherent to the posterior surface of the elevated RPE line and anterior to Bruch membrane.

   **RAP** On OCT we typically see intra-retinal cysts with neurosensory and pigment epithelial detachment, with advanced stage III RAP revealing retinal vessels dipping into the sub-RPE space, to form Retinochoroidal anastomosis (RCA).

   **AOFVD** Seen as a dome shaped hyper-reflective material in the subretinal-space.

   **Mahesh P Shanmugam:** PCV sharply elevated PED with polyp attached to the inner surface of it, double layer sign and absence of subretinal CNV.

   **RAP** Intraretinal neovascularization, predominant intraretinal edema with underlying fibrovascular PED (in stage II and III of RAP) and SRF. Protrusion of tissue from the retina into the PED may at times be seen.

   **AOFVD** Dome shaped hyper-reflective material between RPE and photoreceptor layer if unassociated with CNVM. Stages such as vitelliform, pseudohypopyon, vitelliruptive and atrophic stages have been described with the dome-shaped OCT appearance in vitelliform, an optically empty space with hyper-reflective material inferiorly in pseudohypopyon, collapse of the dome with hyper-reflective clumps within inner retina in vitelliruptive stages.

   **Muna Bhende:** PCV Double layer sign, pigment epithelial detachment with either clear and/ or hemorrhagic component, and the “peaked” PED or thumb-like elevation...
suggestive of polyps

**RAP** Intraretinal cysts, serous subretinal fluid, serous or fibrovascular PED, tubular structure that represents the retinochoroidal anastomosis. The pre RPE and sub RPE components are better defined in the advanced stages and are not seen in stage 1.

**AOFVD** Vitelliform material is seen as a highly reflective dome-shaped lesion located between the photoreceptor layer and the RPE. The RPE itself may appear normal.

**Raja Narayanan: PCV** While ICG is the confirmatory test to document polyps, OCT clues to PCV. The double layer sign, which represents split between RPE and Bruch’s membrane without a significant elevation of the RPE (as seen in PED) is an important clue for PCV. The split between RPE and Bruch’s membrane most probably represents the fine vascular network seen on ICG, and represents activity in PCV. A peaked PED with shallow ascending and descending limbs is also a feature of PCV. Notching of PED and high reflectivity under the peak of PED may also suggest PCV. Traditionally, in PCV, sub-retinal fluid is more than the intra-retinal fluid compared to AMD CNVM.

**RAP** Stage 1 and 2 RAP are easier to pick up on OCT. Small intra-retinal hyper-reflective lesion, CME and PED without subretinal components are highly suggestive of RAP.

**AOFVD** Lack of intra-retinal fluid, presence of sub-retinal fluid without thickening of the RPE-CC complex are important features in AOFVD. Autofluorescence is a useful diagnostic modality in AOFVD.

**Hidetaka Matsumoto: PCV** Dome-shaped anterior protrusion of retinal pigment epithelium (RPE) (polypoidal lesion)\(^2\) double layer sign\(^3\), and PED with tomographic notch sign.\(^4\)

**RAP** Intraretinal edema, serous PED with a disruption of RPE line beneath the intraretinal neovascularization\(^3\), and intact line of Bruch membrane.

**AOFVD** Moderate reflective mass (vitelliform lesion) located between the RPE and photoreceptor layer, which is sometimes accompanied with serous retinal detachment and/or damage of photoreceptor outer segments.
Summary (Neha Goel):

- In PCV, OCT demonstrates a sharply elevated PED with moderate reflectivity within the peak, tomographic notch in the PED and “double layer sign”, consisting of two hyperreflective lines one at the level of the RPE and another beneath the RPE (Figure 1B, 3).
- OCT features of RAP include a serous (or fibrovascular) PED with intraretinal cysts and/or subretinal fluid. An intraretinal hyperreflective lesion or protrusion of tissue from the retina extending into the PED may sometimes be visible (Figure 2B, 4, 5).
- AoFVD is characterized by presence of dome-shaped hyperreflective material between the photoreceptor layer and the RPE.

Neha Goel - Q. Should ICG angiography (ICGA) be performed routinely, at the time of first diagnosis, in all cases of wet AMD? How often do you perform ICGA in your practice?

Atul Kumar: Routinely I do not recommend ICGA at first diagnosis of suspected wet AMD. However when we suspect the following, it is recommended: (1) identification of polypoidal choroidal vasculopathy, (2) recurrent or resistant (hard to treat) to treat choroidal neovascular membranes, (3) submacular hemorrhage, (4) large PEDs, (5) peripapillary location of CNV. These are all conditions in which ICG contributes to the identification of lesions that may be treatable.

Mahesh P Shanmugam: In all patients with occult and mixed CNVM.

Muna Bhende: ICG is preferable in eyes where an occult CNV is diagnosed, mainly to rule out PCV or RAP, based on the clinical findings as mentioned above.
Raja Narayanan: Ordering for investigations is always a challenge in the field of medicine. While we have enumerated the clinical features and OCT findings of the various wet AMD lesions, it is important to understand the pre-test probability (prevalence of the variants) in your patient population. In a clinical setting, we should go with our clinical judgment of PCV/RAP and advise ICGA whenever we suspect these lesions. In my practice, almost 60% of cases fall into these 2 categories. Considering the high percentage, it may be easily justified to routinely order in all cases in wet AMD, but I would caution against such a practice. Initial treatment with anti-VEGF may cause regression of polyps in many cases, although complete regression occurs in less than 30%. Since incomplete or complete regression of polyps on ICG occurs in majority of cases treated with anti-VEGF, performing ICGA after initiating treatment may miss detecting the polyps. One should have a low threshold to advice ICG in our population, but clinical findings should guide any investigation.

Hidetaka Matsumoto: We perform ICGA routinely because ICGA is useful for detecting intraretinal neovascularization in RAP and sub-RPE lesions in all AMD subtypes. We choose a treatment according to the diagnosis.

Summary (Neha Goel): While some clinicians routinely perform ICG angiography in all patients with wet AMD / occult or mixed CNVM, others reserve it for cases with high suspicion of PCV, RAP or resistant CNV. Performing ICG angiography after initiating treatment in PCV may miss picking up polyps due to their regression.

Neha Goel - Q. What are the diagnostic features of PCV and RAP on ICGA?

Atul Kumar: PCV A Branching Vascular Network (BVN), with polyp-like terminal bulbs, are highly suggestive of PCV on ICG.

RAP is seen as a hyperfluorescent area, hot spot on ICG.

Mahesh P Shanmugam: PCV Single and multiple nodular hyperfluorescent areas with or without branching vascular network filling within 6 minutes.

RAP Intraretinal neovascular complex appearing that may washout in late phase. Retino-retinal / retina-choroidal anastomosis appearing as sudden cessation and angulation of retinal vessels may be seen in the early phases of the ICG and hyperfluorescent hot spots corresponding to areas of neovascularization. Area of choroidal neovascularization within the PED that is larger than the intraretinal component can at times be seen in stage III RAP lesions.

Muna Bhende: PCV Polyps typically appear within first five minutes of ICGA but may appear at a later phase. In mid phase they are seen to appear usually in clusters at the termination of choroidal network of vessels. Occasionally polyps may be solitary or large. Late phase of the angiogram shows either washout of the dye from the polyps with staining of its wall or retention of the dye within the polyp and leakage into the surrounding tissue. Other features include the presence of hypofluorescent halo around the lesion, presence of pulsation on ICG videoangiography, and association with a branching vascular network.

RAP Hot spots corresponding to the neovascular lesion that become increasingly hyperfluorescent during the mid and late phases of the ICG angiography, a defined anastomosis connecting the retinal circulation to the neovascular complex, or on dynamic ICGA- blood flowing from the retinal artery to the intraretinal complex, and then to the retinal venule.

Raja Narayanan: PCV has varied features on ICG, but most notable presence of a hyperfluorescent polyp with or without a large network of vessels is seen in all cases. However, once a polyp has regressed, it becomes difficult to label a case as PCV. BVN tends to persist, but fine vascular network (FVN) can regress with treatment. Early recurrence is detected by recurrence of FVN, even though there may not be recurrence of polyps. Choroidal vascular permeability away from the BVN and polyps may be present in some cases. Hemorrhagic PCVs with polyps in the extramacular regions usually have polyps but do not have associated BVN.

RAP commonly has a retina-retinal anastomosis, and in stage 2 and 3, a retinochoroidal anastomosis is typically seen. A small hyperfluorescent spot correlating with the intra-retinal origin of RAP is seen in all cases.

Hidetaka Matsumoto: PCV Network vessels with polypoidal lesion(s)

RAP Intraretinal neovascularization (hot spot) with retinal-retinal anastomosis.

Summary (Neha Goel)
- ICG angiography in PCV demonstrates single or multiple hyperfluorescent polyps filling within the first 5 minutes that maybe associated with a branching vascular network (BVN) (Figure 1D, 3A).
- Intraretinal neovascularization in RAP appears as a small hyperfluorescent “hot spot” on ICG angiography (Figure 2D, 4A). Retino-retinal or retina-choroidal anastomoses maybe visible.

Neha Goel - Q. What treatment protocol do you follow in PCV? (Monotherapy with anti-VEGF / PDT / combination therapy)?

Atul Kumar: Typically we prefer reduced fluence PDT, combined with anti-VEGF.

Mahesh P Shanmugam: If associated with thick subretinal hemorrhage obscuring the lesion or a high PED, anti-VEGF initially and subsequently with PDT. Prefer combination treatment for subfoveal polyps and use only photodynamic therapy for extrafoveal polyps; laser photocoagulation also is an option in extrafoveal polyps.

Muna Bhende: Preferably combination of PDT with anti VEGF depending on the extent of the lesion and location of
the polyps. In case of extrafoveal polyps- focal laser. Polyps very close to disc- anti VEGF to start with. Very extensive area of polyps- only anti VEGF. Hemorrhagic lesions under fovea- pneumatic displacement followed by imaging and then treat as required.

Raja Narayanan: I usually combine treatment. Rarely, I treat extrafoveal polyps with thermal laser. However, FVN is difficult to treat with thermal laser because it is a large lesion. Recurrence of fluid on OCT is treated with anti-VEGF alone, whereas recurrence of polyps is treated with PDT. I repeat ICG in 4 to 6 months to look for recurrence of polyps. Cost of PDT is the most important factor restraining us from following the ideal practice of combined therapy in all cases. When we consider cost, component of patient-perceived value should be taken into account. Patients are ready for LASIK or femto-assisted cataract surgery, however, the value of PDT is not as high as refractive surgeries because the final visual acuity achieved is not 100%, improvement is not certain, and recurrences are almost certain.

Hidetaka Matsumoto: We treat RAP by intravitreal injection of aflibercept (2mg/0.05ml), following a treat-and-extend dosing regimen according to previous reports. The scheduled treatment interval is extended to a maximum of 12 weeks. When the exudation is persistent with the monthly injection of aflibercept, we add a photodynamic therapy.

Summary (Neha Goel): Combination therapy consisting of anti-VEGF and PDT is preferred in PCV. Anti-VEGF are given initially in lesions associated with thick subretinal hemorrhage or lesions close to the disc and maybe used as monotherapy in extensive area of polyps or recurrences of fluid on OCT. Focal laser can be done to extrafoveal polyps.

Neha Goel - Q. What is your treatment plan in a case of RAP?

Atul Kumar: Anti-VEGF form the mainstay of treatment in RAP. We use reduced fluence PDT in non-responsive cases.

Mahesh P Shanmugam: Combination treatment with anti-VEGF, PDT and intravitreal long acting steroid is preferred. Would however start with anti-VEGF monotherapy due to cost constraints and consider combination treatment in partial or non-responders. RAP patients may need anti-VEGF more frequently as well.

Muna Bhende: Anti VEGF in early lesions and those with a large PED. If a focal lesion is noted on ICG may add on focal treatment either laser or PDT. One PED height reduces, may add focal treatment.

Raja Narayanan: I usually initiate and maintain on anti-VEGF. They respond to anti-VEGF, but recurrence is very frequent. In my experience, PDT does not reduce the number of anti-VEGF injections or prevent any recurrence.

Hidetaka Matsumoto: We treat RAP by intravitreal injection of ranibizumab (0.5mg/0.05ml), following a treat-and-extend dosing regimen according to previous reports. The scheduled treatment interval is extended to a maximum of 12 weeks. Anti-VEGF therapy is effective for the treatment of intraretinal neovascularization in RAP. However, the choroidal thickness in RAP is thinner than other AMD subtypes. Also, RAP is highly associated with geographic atrophy. Therefore, we believe that the anti-VEGF agent, which has a minimum effect on the choroid, is better to be used for the treatment of RAP.

Summary (Neha Goel): Treatment with anti-VEGF (monotherapy) is preferred in RAP. Combination with PDT is an option in non-responders.

Neha Goel - Q. How to diagnose and manage AOFVD?

Atul Kumar: Diagnosis is based on clinical presentation described above, and further confirmed on OCT. One of the major differentials for AOFVD is Best's macular dystrophy. But unlike Best's, in AOFVD the EOG is usually normal or only mildly sub-normal. Visual outcome is favourable except when a CNV is suspected and treatment initiated, and should be watched for in follow-ups.

Mahesh P Shanmugam: Presence of round, yellowish subretinal macular lesion in patients in their 5-6th decade. Shows hyper-autofluorescence, EOG / ERG showing normal or subnormal results. OCT shows a vitelliform lesion located at the RPE or between RPE and photoreceptors.

AOFVD patients can be managed with vision aids if vision is impaired in the vitelliform and atrophic stages. If AOFVD is associated with choroidal neovascularization, it can be treated with anti-VEGF agents.

Muna Bhende: Typically causes mild visual impairment that may be non progressive unless there is development of CNV or rarely subretinal fluid. Clinical features and OCT as described above. FFA demonstrates an early central hypofluorescent spot surrounded by an irregular ring of hyperfluorescence or may only show faint late staining, EOG may be normal or slightly subnormal. Management is conservative unless there is an associated CNV.

Raja Narayanan: I like to keep them under observation and watch out for development of CNVM in such cases, which would require prompt treatment. Some patients have improvement in metamorphopsia with anti-VEGF, but most patients do not perceive any significant change in visual symptoms.

Hidetaka Matsumoto: We routinely perform OCT and fundus autofluorescence (FAF) to diagnose AOFVD. OCT shows a moderate reflective mass between the RPE and photoreceptor layer corresponding to the vitelliform lesion, which reveals hyper autofluorescence in FAF. There are no effective treatments for AOFVD. When the choroidal neovascularization occurs at the site of vitelliform lesion, we treat it by intravitreal injection of anti-VEGF agent.

Summary (Neha Goel): In addition to the clinical features and OCT picture of AOFVD described above, hyper autofluorescence on FAF is diagnostic. EOG is normal or mildly subnormal in AOFVD unlike Best vitelliform macular dystrophy. While a
conservative approach to management is followed in AOFVD, the occurrence of CNV necessitates anti-VEGF therapy.

Neha Goel - Q. How does the prognosis differ in these entities vis-a-vis wet AMD?

Atul Kumar: PCV typically responds well to PDT combined with anti-VEGF injections and prognosis is favourable, however we do have cases which keep recurring despite multiple treatment.

RAP is a variant of nAMD, and response is variable to anti-VEGF treatment, with fibrosis and scarring often occurring in the long run.

AOFVD as mentioned, requires no active intervention and has a slow visual decline often, except of course, if CNV occurs.

Mahesh P Shanmugam: AOFVD patients would maintain vision until a CNVM develops or collapse of the vitelliform with atrophy occurs. PCV, particularly limited disease would have a better prognosis as compared to wet AMD; RAP is typically not as responsive as wet AMD and PCV and is likely to be associated with poorer prognosis.

Muna Bhende: PCV lesions may be asymptomatic to start with and generally have a good prognosis until they bleed in which case the course may be stormy leading to severe visual loss including loss of light perception. AOFVD lesions are either non progressive or very slowly progressive and do not usually cause severe visual loss.

Raja Narayanan: The major concern with PCV is massive subretinal hemorrhage. This event could cause significant permanent loss of vision. Recurrence is common in RAP and PCV.

PDT appears to be an important treatment modality in PCV, whereas in AMD CNVM, PDT does not have a substantial role.

Hidetaka Matsumoto: PDT or/and anti-VEGF therapy is/are effective for the treatment of PCV. However, PCV is sometimes associated with massive subretinal hematoma which damages photoreceptor cells. When subfoveal hematoma develops, the hemorrhage should be removed from subfovea by intravitreal gas injection or vitrectomy. RAP is known to progress faster than other AMD subtypes. Once the RAP lesion progresses, visual acuity is hard to recover even if the lesion resolves after treatment. Hence, RAP should be treated in the early stages to obtain good visual acuity after treatment. RAP is highly associated with geographic atrophy which is a critical predictor of visual prognosis. Therefore, it is ideal to treat RAP lesion without the damage of choroid and RPE.

Summary (Neha Goel)

- PCV has a favorable prognosis except in cases with massive subretinal hemorrhage, involving the fovea. Recurrences are common.
- RAP has a poorer prognosis in terms of progression of the disease and response to therapy. Recurrences are common.
- AOFVD patients have a gradual, slow visual decline unless CNV develops.

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