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Accounting for disagreements on average cone loss rates in retinitis pigmentosa with a new kinetic model: Its relevance for clinical trials

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ABSTRACT

Since 1985, at least nine studies of the average rate of cone loss in retinitis pigmentosa (RP) populations have yielded conflicting average rate constant values ($-k$), differing by 90–160%. This is surprising, since, except for the first two investigations, the Harvard or Johns Hopkins' protocols used in these studies were identical with respect to: use of the same exponential decline model, calculation of average $-k$ from individual patient k values, monitoring patients over similarly large time frames, and excluding data exhibiting floor and ceiling effects.

A detailed analysis of Harvard's and Hopkins' protocols and data revealed two subtle differences: (i) Hopkins' use of half-life $t_{0.5}$ (or $t_{1/e}$) for expressing patient cone-loss rates rather than k as used by Harvard; (ii) Harvard obtaining substantially more $+k$ from improving fields due to dormant-cone recovery effects and "small $-k$" values than Hopkins' ("small $-k$" is defined as less than -0.040 year^{-1}), e.g., 16% $+k$, 31% small $-k$, vs. Hopkins' 3% and 6% respectively. Since $t_{0.5} = 0.693/k$, it follows that when $k = 0$, or is very small, $t_{0.5}$ (or $t_{1/e}$) is respectively infinity or a very large number. This unfortunate mathematical property (which also prevents $t_{0.5}$ ($t_{1/e}$) histogram construction corresponding to $-k$ to $+k$) caused Hopkins' to delete all "small $-k$" and all $+k$ due to "strong leverage". Naturally this contributed to Hopkins' larger average $-k$. Difference (ii) led us to re-evaluate the Harvard/Hopkins' exponential unchanging $-k$ model. In its place we propose a model of increasing biochemical stresses from dying rods on cones during RP progression: increasing oxidative stresses and trophic factor deficiencies (e.g., RdCVF), and RPE malfunction. Our kinetic analysis showed rod loss to follow exponential kinetics with unchanging $-k$ due to constant genetic stresses, thereby providing a theoretical basis for Clarke et al.'s empirical observation of such kinetics with eleven animal models of RP. In contrast to this, we show that cone loss occurs in patients with increasing $-k$ values during RP progression. And as the Hopkins' protocol selects more advanced RP cases than Harvard's to assure avoidance of ceiling effects (Harvard does this by kinetic monitoring), we show increasing $-k$ kinetics to be the reason Harvard obtains more $+k$ and small $-k$ values. Thus the combined effects of (i) and (ii) produce Harvard's smaller average $-k$ value. The relevance of the increasing biochemical stress model for optimizing clinical trials is discussed.

Introduction

Retinitis pigmentosa (RP) is a heterogeneous group of inherited blinding diseases caused by numerous mutations in over 100 genes, the expression of which is enriched or restricted to rod photo receptors, i.e., the cells responsible for night vision [1]. Thus the earliest manifestation of RP is generally progressive loss of night vision as a result of mutation-induced degradation of rods, which die by highly regulated biochemical processes referred to as programmed cell death or apoptosis. Loss of rods is followed by apoptotic death of cones. Since cones are not directly affected by lethal mutations in RP, the cause of day vision loss and its prevention represent the main challenges of RP research.

Progression of RP may be measured by the rate of cone field decline. It is generally agreed that this follows approximately exponential decay kinetics. The first of such studies with a typical RP population, performed by Berson et al. at Harvard over a 3-year period [2], yielded an average exponential rate constant k of -4.6% year^{-1}. Surprisingly a second study with typical RP patients, performed by Massof et al. at Johns Hopkins' University over a 2.5–10-year period with slightly different measurement techniques [3,4] yielded an average k value of -11.9% year^{-1}. Even more puzzling is the fact that similar large differences in average $-k$ were obtained in Harvard's subsequent studies [5,6], and those by other investigators using the Hopkins' protocol [7–10], even though all

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studies were now performed with identical measurement techniques and similar timeframes. For example, for a typical Usher 2a population, Harvard [5] obtained an average k of -7.0% year^{-1}, while those using the Hopkins' protocol [8,9] obtained values of -12.6% and -13.8% year^{-1}. To date only one, albeit unsuccessful, attempt has been made to resolve these differences [4] (see below). As this unfortunate situation may adversely affect the design of clinical trials, as well as cause confusion and concern to patients and their physicians, it is the purpose of the present report to propose means for resolving these discrepancies in the average k values for cone field loss. Initially this requires a detailed analysis of the Harvard/Hopkins' exponential decline model, their patient selection protocols, measurement procedures, and results. Subtle differences revealed by this analysis are then interpreted in terms of our new kinetic model for cone field loss, which is based on recent insights into the biochemical processes involved in damage, repair, and ultimate apoptosis of cones. The relevance of the new kinetic model for optimizing the design of clinical trials is discussed.

The problem situation

Decline of small central cone fields: floor effects and common measurement problems

In research settings, loss of cone fields in RP is generally measured by Goldmann Perimetry. Bittner et al. [11] have shown that these measurements can be made with a coefficient of reproducibility at the 95% confidence level ($CR_{0.95}$) of ±20% for fields ranging from 740 mm^2 (average normal) to 10 mm^2 (14° diameter). Fields below 10 mm^2 were found to be prone to $CR_{0.95}$ values as high as ±50–100%. Field changes in the 10 mm^2 area, however, maybe more accurately measured by Humphrey Perimetry. This provides two measures of cone function: **(i)** The number of detected light sources out of a presented total of 68, thereby making it analogous to Goldmann visual field measurements allowing determination of patient k values [12]. **(ii)** These light sources are presented to patients at different intensities (dB levels), thereby providing another sensitive cone function parameter by summation of dB readings [12,13]. Although changes in the function of foveal cones cannot be measured by Goldmann or Humphrey Perimetry, they can be measured by visual acuity changes.

The 10 mm^2 field (14° diameter, 1.3% of normal field) falls with respect to its size between the perifovea (also referred to as the anatomical macula), which has an area of 24 mm^2 (18°20′ diameter, 3.2% of normal field) and the parafovea with an area of 4.9 mm^2 (8°20′ diameter, 0.66% of normal field). The fovea (also referred to as the clinical macula) consists at its center exclusively of cones at an approximately 20-fold higher concentration than cones in the peripheral retina; it has an area of 1.76 mm^2 (5° diameter, 0.23% of normal field).

In RP it is generally recognized that cones in the anatomical macula, especially in the parafovea and fovea, are more resilient than cones in the peripheral retina and are thus lost at a much slower rate than peripheral cones. This is illustrated in Fig. 1 by the tail section JKL of exponential kinetic graph IJ, where JK represents approximately the cone field area below 10 mm^2, and KL the foveal region, which cannot be measured by Goldmann or Humphrey Perimetry. In our discussion of the biochemical processes leading to cone damage and cone death, we will, on the basis of the distinctly different biochemical and structural milieu of cones in the 10 mm^2 region, present possible biochemical mechanisms for their slower rate of decline. Because of these differences and decreased measurement accuracies, we consider it inappropriate to combine rate constants from peripheral cone fields (IJ region,

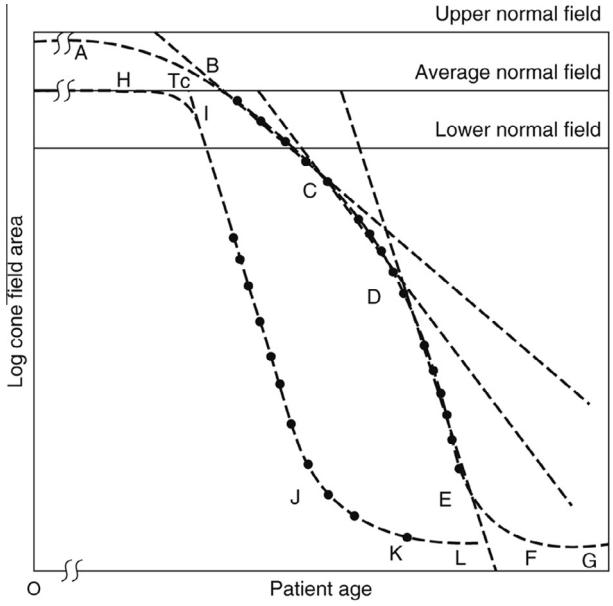

Fig. 1. (HIJ) Standard kinetic model of cone field loss; (ABCDE) increasing biochemical-stress kinetic model of cone field loss. (JKL) and (EFG) Identical cone field loss kinetics from 10 mm^2 retinal fields (approximately 1.3% of normal field). T_c, Critical Age of patient. (The different starting points for cone loss, A and H, were chosen for illustrative convenience.)

Fig. 1) with those derived from measurements when fields were in the 10 mm^2 range (JK region). This situation is generally referred to as the floor effect problem. Hopkins' had 0% of their cohort below 10 mm^2 (Fig. 5, Ref. [4]), whereas Harvard had 3% with fields in the 20–9° diameter range at commencement of their study.

The Harvard kinetic model and procedures for measuring average rate of cone field loss

In 1985 Harvard published a 3-year study of changes in the following ocular functions in a typical RP population: cone field, full-field ERG (with 0.5-Hz, 30-Hz, 37 or 42-Hz stimuli), foveal ERG, dark-adaptation threshold, and visual acuity. For each outcome measure they computed the mean change over the entire group, which was expressed either in their original or natural logarithmic (ln) units. In the present communication, we will deal only with changes in cone field area. Although conversion to ln units may initially have been adopted to change skewed to more normal data distributions, it was in much later studies [5] that Harvard justified their conversion to ln units on the basis that "an exponential model has been shown to be optimal for evaluating cell loss over time in animal models of retinitis pigmentosa". The work referred to is that of Clarke et al. [14], regarding the cell-death kinetics of different cell types as a result of their unique genetic mutations, e.g., Huntington's and Parkinson's diseases, RP, etc. In the case of RP, mutation-induced cell death obviously refers only to rod death. The data from eleven animal models of RP were found to follow exponential decline kinetics from birth. The possibility that cone loss may have influenced these kinetics is excluded by them on the basis "that 97% of mouse photo receptors are rods and only 3% are cones. This proportion of cones is too small to influence the overall kinetics of photoreceptor death."

The equation used by Harvard in their 1985 study for calculating the average loss of remaining cone field per year (k) is:

$$\ln [C]_{t1} - \ln [C]_{t_2} / t_1 - t_2 = k \quad (1)$$

where $[C]_{t1}$ and $[C]_{t2}$ is the average size of their cohort's cone field at time t_1 and t_2, cone field area being expressed in degrees^2. This