Alteration of the blood-retinal barrier and vitreous in sickle cell retinopathy

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Abstract

Nineteen eyes with background sickle cell retinopathy, eleven from patients with SC disease, eight from patients with SS disease, and twelve eyes with proliferative sickle cell retinopathy were examined by direct and indirect ophthalmoscopy, slit-lamp, fluorescein angiography and vitreous fluorophotometry. Calculation of the alteration of the blood-retinal barrier (BRB) and estimation of the diffusion coefficients of fluorescein in the vitreous were performed by fluorophotometry.

In background sickle cell retinopathy, the results show a normally functioning BRB in the posterior pole. Abnormally increased fluorescence values to the mid-vitreous (peripheral leakage) were found only in 3 of these 19 eyes, at the two-hour examination (all SC patients). Similarly, mid-vitreous fluorescence values at the two-hour examination were $4.19 \pm 1.52$ ng/ml in eyes of patients with SC disease, compared with $2.65 \pm 0.56$ ng/ml in eyes of patients with SS disease. All eyes with background sickle cell retinopathy, except one, showed values for the coefficient of diffusion of fluorescein within normal limits, indicating normal vitreous gel structure.

In proliferative retinopathy, the mid-vitreous fluorophotometry readings were abnormally increased, correlating well with the extent of the peripheral angiographic changes (neovascularization). The coefficient of diffusion of fluorescein in the vitreous was generally increased in the eyes with proliferative retinopathy ($15.0 \pm 8.4 \times 10^{-4} \text{cm}^2/\text{min}$) in comparison with a mean value of $5.4 \pm 1.4 \times 10^{-4} \text{cm}^2/\text{min}$ in the eyes with background sickle cell retinopathy, suggesting an alteration of the vitreous structure eyes with proliferative retinopathy.

Fluorophotometry is considered a useful tool to follow patients with sickle cell retinopathy by quantitating peripheral retinal vascular leakage.

Introduction

Sickle cell disease includes several genotypes that have a common pathogenesis considered to be due to the presence of sickle cell hemoglobin (Hb S). All of these genotypes are characterized by intravascular sickling, which results in a tendency to small vessel obstruction. In the eye, involvement of the retina is of major clinical significance because it may cause marked visual dysfunction or blindness.

The natural history of sickle cell retinopathy is relatively well understood. The disease develops...
through a series of stages, starting with peripheral retinal vessel occlusions and ending in vitreous hemorrhages and retinal detachment, generally associated with retinal neovascularization. Its precise pathophysiology is, however, far from clear. For example, the role played by vascular endothelial cells in the early stages of the disease is not known yet. Is the blood-retinal barrier damaged early in the disease process? Do the abnormal red cells initiate the retinopathy by altering the vessel walls (blood-retinal inner barrier), or do they induce vascular occlusions in the presence of a healthy vascular endothelium?

Vitreous fluorophotometry is a new technique that can detect and quantitate early changes in the blood-retinal barrier. We decided, therefore, to examine a series of sickle cell patients showing early stages of retinal pathology using vitreous fluorophotometry.

Other questions that were of major interest to us were: Is vitreous fluorophotometry an appropriate technique to quantitate and follow changes in peripheral neovascularization, and when do vitreous changes occur in sickle cell disease?

**Subjects and methods**

Ten patients with background sickle cell retinopathy (six SC and four SS) and six with proliferative sickle cell retinopathy were included in the study. Each patient underwent hemoglobin electrophoresis for determination of hemoglobin type. A complete eye examination, including direct and indirect ophthalmoscopy, Goldmann three-mirror contact lens examination, retinal drawing, fluorescein angiography, and vitreous fluorophotometry, was performed. Each eye was evaluated according to the sickle cell retinopathy classification proposed by Goldberg (1).

**Vitreous fluorophotometry examination**

Vitreous fluorophotometry measurements were made with a fluorophotometer (Fluorotron Master); this procedure has been described in detail elsewhere (2). Scans were taken before the administration of a 14 mg/kg intravenous injection of fluorescein and at 60 minutes and (when considered necessary) 120 minutes later. Once the fluorophotometric data were saved on magnetic diskettes, they were processed to correct for background fluorescence and to provide numerical values for the amount of fluorescein that penetrated into the vitreous.

**Calculation of the alteration of the blood-retinal barrier**

The measurement scans were first corrected by subtracting the preinjection scan. Calculations were then performed to quantitate the leakage of fluorescein across the blood-retinal barrier and the rate of fluorescein diffusion in the vitreous.

The fluorophotometer scans are performed along the optical axis of the eye. This means that in the normal eye the posterior vitreous fluorescein measurements taken at one hour disclose only fluorescein penetration from the posterior pole. To obtain information regarding fluorescein penetration from the equatorial and peripheral regions of the retina, it is necessary to measure the fluorescence in the middle region of the vitreous (3). In situations in which the blood-retinal barrier is normal or only minimally altered, the fluorescein in the midvitreous remains extremely low one hour after the fluorescein injection and the examination must be repeated at longer time intervals, e.g., two hours.

Fluorescence values for the midvitreous were obtained by averaging the scan measurements obtained between 8 and 10 mm in front of the chorioretinal peak, after correction for preinjection levels. The midvitreous fluorescence values were normalized for a fluorescence plasma integral of $2.5 \times 10^6$ (for the first hour after injection). Plasma fluorescence values were calculated according to methodology previously described (4).

Normal midvitreous (MV) fluorescence ($0.8 \pm 0.5$ ng/ml) values have been reported previously for the one-hour time interval (MV 60). For the two-hour time interval (MV 120) results from a series of 24 normal eyes examined in previous studies were obtained from the stored diskettes ($3.4 \pm 0.9$ ng/