Mizuo Phenomenon in X-linked Retinoschisis

Pathogenesis of the Mizuo Phenomenon

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Four unrelated males with X-linked retinoschisis and a golden fundus reflex had Mizuo-Nakamura phenomenon, which, to our knowledge, has been described only in Oguchi’s disease and X-linked cone dystrophy. These findings, together with experimental observations and data from the literature, led us to hypothesize that the Mizuo-Nakamura phenomenon is caused by an excess of extracellular potassium in the retina as a result of a decreased potassium scavenging capacity of retinal Müller cells.

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The Mizuo phenomenon, also called the Mizuo-Nakamura phenomenon, is a change in the color of the fundus from red in the dark-adapted state to golden immediately or shortly after the onset of light. The color of the fundus reflex in the light state has also been described as flaking golden, gold dusted, golden-yellow, gray-white, and yellow-white. This reflex can appear either homogeneous or streaky. To our knowledge, the phenomenon was first described in connection with, and has been considered to be pathognomonic for, Oguchi’s disease, an autosomal-recessive inherited form of nyctalopia occurring mainly in Japan.

The Mizuo phenomenon, however, has also been described in X-linked recessive cone dystrophy. This is the first report, to our knowledge, of the Mizuo phenomenon in unrelated subjects with X-linked juvenile retinoschisis. A new explanation is suggested for the origin of the Mizuo phenomenon, which, as yet, is still unknown.

SUBJECTS AND METHODS

After giving informed consent, the subjects described their medical and family histories and underwent a complete ophthalmological examination that included indirect ophthalmoscopy and biomicroscopy. Only subjects with X-linked retinoschisis who had a marked golden fundus reflex were included in this study. Since 1987, when one of us (P.T.V.M.J.) first saw the Mizuo phenomenon in a patient with X-linked retinoschisis, eight patients with this disorder, four of whom had a golden fundus reflex, have been seen.

We investigated the Mizuo phenomenon by determining the region of the eye and the fundus demonstrating maximum golden reflex on indirect ophthalmoscopy after pupillary dilatation with 0.5% tropicamide and 5% phenylephrine hydrochloride. Subsequently, all subjects were asked to wear a dark patch that completely occluded the eye with the most marked golden reflex from bedtime until they visited the eye clinic the next morning. They were requested to apply the same drops to the occluded eye in the dark before leaving for the clinic. The shield was removed in the hospital while the subject sat in the dark. The previously defined region with maximum golden reflex was examined with an indirect ophthalmoscope with a halogen light source. The same procedure was repeated at another date, but the patch was removed in front of a fundus camera (TRC-WT 46 or TRC-50 VT, Topcon, Tokyo, Japan). A red filter was placed in the path of the focusing beam of the camera and removed just before color transparencies were taken (EPR 5017, Kodak, Rochester, NY) with a normal flash intensity and color temperature of 5500°K. The first 15 photographs were taken at 2-second intervals, and the remaining photographs at 15-second intervals. For each subject, a fresh role of film was put into the camera so that all exposures were on the same film. In case 1, the procedure was repeated with a red-free filter in the light beam.

Rod densitometry and spectral fundus reflectance were measured according to our standardized procedure after 12-hour occlusion of one eye in two patients. For these measurements, the fundus area that on earlier examination had the clearest Mizuo phenomenon was selected.

REPORT OF CASES

CASE 1—In 1966, a 25-year-old man presented with subnormal visual acuity of 20/100 OD with a refraction of 1.0 diopters (D) sph and 20/100 OS with –2.50 D sph = –2.50 D cyl axis 180°. The patient exhibited macular degeneration that was detectable ophthalmoscopically, mild optic atrophy, and some vitreous veins, but no signs of peripheral retinoschisis. After undergoing an extracapsular cataract extraction with posterior chamber lens implantation, the patient, underwent two more operations in his right eye for retinal detachment. In 1986, a marked golden reflex was noted for the first time; it was most pronounced temporally to the macula and in the equatorial region of his unoperated left eye (Fig 1). Since no explanation for this reflex could be found, a genealogical investigation was begun in 1988. The patient belonged to a family in which the Mizuo juvenile retinoschisis was known; on inquiry, he remembered that his maternal grandfather had always had poor visual acuity and had used a magnifying glass to read, even when young.

CASE 2.—In 1961, a 13-year-old boy presented with visual acuity of 0.3 OD and finger counting at 4 m OS. The lack of a macular reflex was noted, as was a cystoid foveal structure. Retinoschisis that extended to the optic disc was found in both lower fundi. The patient’s brother and maternal uncle also had X-linked retinoschisis; the pedigree has been described elsewhere. In 1988, we were struck by the golden reflex of the left retina. This reflex extended from an area with retinoschisis to an area without it (Fig 2).

CASE 3.—This patient has been described elsewhere. In 1969 a 7-year-old boy presented with a visual acuity of 0.8 OD and 0.4 OS. One year later, his visual acuity was 0.30. His fundus was described as having foveal retinoschisis and silver-grayish glinting reflexes in some parts of the retinal periphery. In 1988, the patient’s visual acuity was 0.15 OS; both eyes exhibited a slight macular degeneration with some foveal schisis still visible in the left eye. No peripheral schisis could be found. There was a striking golden reflex that was maximal about 15° temporally to the fovea as well as outside the temporal vascular arcade in both eyes; it was much less pronounced in the dark (Fig 3).

CASE 4.—A 7-year-old boy presented because of visual problems he had in school. His best corrected visual acuity was 0.30 due to foveal schisis. In the lower quadrants of the right eye, a peripheral schisis was found along with a sharply demarcated golden reflex (Fig 4). No retinoschisis was found in the left eye. A golden reflex was visible temporally to the macula. The patient’s mother had a healthy son from a first marriage; she was Eurasian and knew nothing about a family history of poor visual acuity.
Fig 1.—Case 1. Top, Golden fundus reflex temporally to the left macula. Note the red reflex along the inferior vessels (arrows). Bottom, Contact lens view of equatorial region of the same eye. Sharply demarcated areas with normal color were scattered over regions with golden reflexes.

Fig 2.—Case 2. Golden reflex in the left inferior retina. The reflex did not change between areas with retinoschisis (below arrows) and without retinoschisis.

Fig 3.—Case 3. Top, Third photograph of the left eye taken after two flashes. Bottom, Same area after full light adaptation. Note the change in color.

Fig 4.—Case 4. Right inferior fundus exhibits sharply demarcated golden reflex with darker red speckles in the retinoschisis area (arrow).
RESULTS

In all of these cases the golden fundus reflex and Mizuo-Nakamura phenomenon were most marked temporal to the fovea. It was, however, difficult to capture the Mizuo phenomenon on film; the best example is shown in Fig 3. In case 1, the first change became visible within 10 seconds of ophthalmoscopy and after five flashes, with a maximum change in color after 16 flashes within about 30 seconds. On the red-free photographs a change in color could also be seen. In case 2, no change could be recorded on film, but during ophthalmoscopy changes became visible after 15 seconds. In case 3, it took six flashes and about 10 seconds to see the first color changes; the maximum effect was already visible on the 10th photograph within about 26 seconds. No photographs of patient 4 were taken after patching, but the golden reflex was visible after 30 seconds of ophthalmoscopy. Patients 1 and 3 exhibited a normal red reflex along some vessels in areas with the golden fundus reflex (Fig 1).

Biomicroscopy with a +60 D fundus lens showed that in patients 2 and 3 the golden reflex was located deep in the neuroretina and was continuous across areas with and without retinoschisis (Fig 2).

Rod densitometry showed normal results. The results of spectral fundus reflectance are shown in Fig 5 for patients 1 and 3. In both cases, no significant changes occurred during light adaptation.

Results of all recent psychophysical and electrophysiological tests are provided in the Table.

COMMENT

This is the first report, to our knowledge, describing the Mizuo phenomenon in males with X-linked juvenile retinoschisis. In all four subjects little or no golden reflex was observed directly after removal of the eye patch, but within 10 to 20 seconds it became visible on indirect ophthalmoscopy. Thus, this is the third disorder, in addition to Oguchi's disease and cone dystrophy, that is accompanied by this phenomenon.

As far as we know, the origin of the Mizuo phenomenon in Oguchi's disease has not yet been determined. There have been contradictory autopsy reports of an abnormal pigmented layer next to the photoreceptors and fuscin bodies in the pigment epithelium as well as pigment granules in the nerve fiber layer. Electrophysiologic methods have also not solved the question of the pathogenesis of Mizuo's phenomenon. Electrophysiologic recordings of photoreceptor function and rod densitometry have shown that the concentration and regeneration as well as the photosensitivity of rhodopsin in Oguchi's disease might be normal. The scotopic b-wave of the electretoretinogram was found to be absent even when the normal scotopic threshold was reached after 4 hours of dark adaptation. Carr and Rips concluded that the visual problems were due to defective neural processes within the retina.

In view of the histologic findings and normal visual pigment kinetics of Oguchi's disease and X-linked retinoschisis demonstrated in this study, it is unlikely that abnormal rhodopsin kinetics plays a role in the Mizuo phenomenon. We could not find a distinct change in fundus reflectance with fundus reflectometry for the area with the golden sheen; this could imply that the change in fundus color is too subtle to be detected by this technique.

Photographs of the Mizuo phenomenon can be quite difficult to obtain with fundus photography. The angle between incident and emerging rays is greater in a fundus camera than an ophthalmoscope, which is why it is more easily seen than photographed. If this angle exceeds 15°, the Mizuo phenomenon cannot be photographed. According to Sato and Baba, the Mizuo phenomenon could not be elicited in patients with a retinal sheen, eg, in cases of retinitis pigmentosa or retinitis punctata albescens or in dogs with a prominent tapetal light reflex. In addition, the possibility that the Mizuo phenomenon is due to polarization of the light was excluded by means of experiments with polarizing filters. The paravascular red fundus in areas with golden reflex, as seen in our patients 1 and 2, was also observed in a patient with cone dystrophy and Mizuo phenomenon.

In our patients with X-linked retinoschisis, the reappearance of the golden reflex occurred within 15 to 30 seconds. This is much faster than that described in the literature for Oguchi's disease, where it took from 10 minutes to 10 to 15 minutes to 30 minutes to 45 minutes.

EXPLANATION FOR THE MIZUO PHENOMENON

One of us (E.Z.) repeatedly observed that small amounts of 3-mol/L potassium chloride leaking from a defective microelectrode into the inner retina of a cat and monkey produced a yellow-golden sheen very similar to that observed in subjects with Mizuo phenomenon. This golden reflex disappeared a short time after the electrode was retracted. When non-potassium-containing solutions were used, the reflex was much less pronounced.
Interestingly, a similar whitish-yellow sheen travels across the retina in the event of spreading depression of electrical activity. Spreading depression releases a wave of high ionized potassium (K⁺) concentration that travels at a low speed across the retina. From these observations, it seems reasonable to assume that increased concentrations of K⁺ or potassium chloride can produce a yellowish fundus reflex similar to that seen in the Mizuo phenomenon.

If we assume that the ophthalmoscopic findings of the Mizuo phenomenon are based on exceedingly high K⁺ levels, we must ask what mechanisms of K⁺ release and uptake exist in the retina, and to what extent such mechanisms are affected by retinoschisis. Light falling on the retina results in hyperpolarization of the photoreceptors and in increased extracellular K⁺; in the dark-adapted state, the extracellular K⁺ concentration is much lower again. The Müller cell transports K⁺ away from the retina; 94% of the supernumerous K⁺ passes from the Müller cell through the endfoot process into the vitreous cavity. The Müller cell is a passive K⁺ exchanger whereby the exchange rate depends on the concentration gradient between source and sink sides, the vitreous being the sink. On the basis of histologic findings we can assume that Müller cells in the posterior retina become longer in the course of the development of retinoschisis. This elongation will have a pronounced effect on the K⁺ turnover since the optimum length of the Müller cell for K⁺ uptake is in the range of 115 μm. Longer Müller cells exhibit a greatly reduced K⁺ uptake and clearance that lead to an excess of K⁺ in the extracellular space.

In X-linked retinoschisis, the nerve fiber and ganglion cell layers undergo retinal splitting. Normally, Müller cells cross this interface, but intraretinal filaments thought to be derived from defective Müller cells have been described in X-linked retinoschisis. In advanced stages of this schisis, the endfoot part of the elongated Müller cell ruptures so that there is no longer direct communication with the vitreous body. Consequently, all of the K⁺ at the proximal end of the Müller cell will leak into the schisis cyst, which then becomes the K⁺ sink instead of the vitreous cavity. Another explanation for an excess of extracellular K⁺ might be found in the nature and distribution of K⁺ channels within Müller cells. Potassium is taken up via inwardly directed K⁺ channels in the Müller cell membrane in the region of the inner plexiform layer. Inadequate functioning of these channels would thus lead to higher extracellular K⁺ concentrations in the inner plexiform layer.

Alternatively, a high extracellular K⁺ concentration might also be created by excess K⁺ formation instead of decreased uptake by the Müller cells. This mechanism is unlikely since the photoreceptor layer and phototransduction process can be expected to be normal in X-linked retinoschisis, as inferred from histologic findings, electro-oculography, and fundus reflectometry. In the subretinal space, excess K⁺ might also develop due to loss of the K⁺ buffering capacity of the retinal pigment epithelium. The normal electro-oculographic values in both Oguchi’s disease and X-linked retinoschisis do not support this last possibility as a probable cause of the Mizuo phenomenon.

The hypothesis that defective Müller cells cannot act properly as K⁺ scavengers in Oguchi’s disease as well as in X-linked retinoschisis would also easily explain the electrophysiologic data that characterize these disorders. The b-wave is generated by K⁺ flow through the Müller cells mainly as a result of light-evoked depolarization of “ON” bipolar neurons. “ON” bipolar
neurons depolarize when light falls on their related photoreceptors, while "OFF" bipolar cells hyperpolarize in that situation. If Müller cells are unable to take up extracellular light-released $K^+$ in the normal manner, the electroretinographic b-wave would be absent or reduced in a light-adapted eye, as is the case in Oguchi's disease, in X-linked retinoschisis, and in our patients.

The assumption of a normal situation in the retinal pigment epithelium and photoreceptor layer is supported by a normal electro-oculographic value and the normal rhodopsin density. Questions remain about why the macular region in particular is affected by X-linked retinoschisis and why the Mizuo phenomenon is clearest temporally to the fovea. Cones are most common in the macular region, and light-induced $K^+$ leakage occurs faster in cones than in rods. Illumination of the cones should result in a rapid rise in the extracellular $K^+$ concentration in the fovea that would be prolonged due to defective Müller cells. This might also account for the lower visual acuity in these patients. The maximum visibility of the Mizuo phenomenon temporal to the fovea, despite the slower $K^+$ exchange in rods, could be explained by the fact that rods outnumber cones by a factor of 20 in that region.

The normal red reflex along some vessels in the area with the golden reflex may be explained by the phenomenon seen in miniature pigs; the paravascular $K^+$ concentration is low during light stimulation but rises farther away from the vessels. These results also support our hypothesis.

One could wonder why the b-wave and Mizuo phenomenon do not follow strictly parallel courses. Since we assume, however, that the primary defect that leads to the Mizuo phenomenon is located in Müller cells, it is not surprising that electroretinography is affected permanently, while the Mizuo phenomenon appears and disappears depending on the state of $K^+$ metabolism, which in turn depends on illumination.

The nuclei of Müller cells lie in the inner portion of the inner nuclear layer. Unfortunately, no details have been presented on either Müller cells or the inner nuclear layer in available reports on the histologic characteristics of Oguchi's disease. It would be interesting to focus attention on this layer in the future.

Even though our hypothesis of the origin of the Mizuo phenomenon seems to embrace most known data, there remain differences between X-linked retinoschisis and Oguchi's disease. Our patients had a lower visual acuity than did patients with Oguchi's disease, which might be explained by the foveal abnormalities in X-linked retinoschisis. Moreover, after 35 minutes, the dark adaptation thresholds in our patients were elevated by only 0.5 to 1.5 log units, thus resembling those in X-linked recessive cone dystrophy. In patients with Oguchi's disease these thresholds were elevated 4 log units after 90 minutes, and reached normal values only after 3 hours or more.

This difference could be explained by assuming that the defect in the K+ metabolism affects all Müller cells equally in Oguchi's disease while the defects in X-linked retinoschisis are less evenly distributed. This leaves many relatively intact areas in between that can mediate low psycho-physical thresholds. Thus, the dark adaptation test with total retinal illumination determines the threshold of the best retinal part, while electroretinography with total illumination gives a summation of all elements generating the b-wave, and thus gives the threshold for the worst retinal part.

Future research will need to show whether altered K+ flux may also be responsible for the tapetal reflexes, not only in Oguchi's disease and X-linked retinoschisis, but also in various tapetoretinal disorders.

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References