West African Crystalline Maculopathy

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Objective: To describe the findings of a new crystalline maculopathy exclusively affecting elderly members of the Igbo tribe of southeast Nigeria.

Design: Retrospective, observational noncomparative case series.

Methods: Six patients referred over a 2-year period to the medical retina consultation service of the King/Drew Medical Center (Los Angeles, Calif) were identified as having a characteristic crystalline maculopathy. Each underwent detailed historical questioning and comprehensive ocular evaluation, including formal retinal examination. Color vision testing, fluorescein angiography, Humphrey visual field analysis, and electrophysiologic assessment were also performed.

Results: Each of the 6 patients was an elderly member of the Igbo tribe of southeast Nigeria and demonstrated a unique crystalline maculopathy. A central, superficial cluster of green or yellow, refractile, foveal crystals that were bilateral and asymmetric in distribution was noted in each case. The crystals were benign and unassociated with visual deficit. Retinal sequelae were notably absent and fluorescein angiography results were unremarkable. Additional ancillary testing was generally normal, although 1 patient demonstrated unexplained mild to moderate depression of the scotopic and photopic responses on electrophysiologic analysis.

Conclusions: Elderly members of the Igbo tribe of southeast Nigeria may harbor characteristic bilateral but asymmetric foveal crystals, comprising a novel syndrome of crystalline maculopathy unassociated with obvious visual deficits or retinal sequelae. The etiology of this crystalline maculopathy remains unclear, although genetic, degenerative, and toxic causes are postulated.

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The causes of crystalline maculopathy are many and include toxic, genetic, and degenerative mechanisms. Various drug exposures have been associated with crystalline deposition, including methoxylfluorane, tamoxifen, canthaxanthine, nitrofurantoin, and talc. Primary hyperoxaluria, Bietti crystalline dystrophy, cystinosis, and Sjögren-Larsson syndrome are genetically determined diseases caused by putative molecular events that result in crystalline maculopathy. Local, degenerative causes of crystalline maculopathy include calcific drusen and chronic retinal detachment, while type 2 juxtafoveal telangiectasis represents an acquired vasculopathy associated with macular crystals.

This article describes the findings of a new type of crystalline maculopathy in 6 unrelated West African patients belonging to the Igbo tribe of southeast Nigeria. These patients receive their medical care at the King/Drew Medical Center in Los Angeles (Calif) and appear to represent a clustering of immigrants within the Los Angeles basin. Each patient was found to harbor a bilateral but asymmetric cluster of foveal refractile crystals, the investigation of which failed to conform to any of the aforementioned causes.

METHODS

This retrospective study was approved by the institutional review board of the Charles R. Drew School of Medicine and Science (Los Angeles, Calif). Six patients referred over a 2-year period to the medical retina consultation service of the King/Drew Medical Center were identified as having a unique crystalline maculopathy. Each patient underwent rigorous historical questioning to rule out known causes of crystalline maculopathy and to isolate any demographic or cultural clues related to the deposition of the crystals. A comprehensive ocular examination, including dilated biomicroscopic examination of the macula and indirect ophthalmoscopic evaluation of the retinal periphery, was performed on all patients. Color fundus photography with high-magnification images allowed quantification of the crystals using the following guidelines: mild, less than 5 crystals; moderate, 5 to 10 crystals; and severe, more than 10 crystals. Fluorescein angiography, color vision testing with Ishihara plates, and full-threshold Humphrey visual field analysis (10-2 or 30-2) were also performed in selected cases. Electoretinography and electro-oculography were conducted using standard techniques.
Six unrelated patients (2 men, 4 women) with a characteristic crystalline maculopathy were identified. The demographic and historical data and the results of their oculographic and historical data and the results of their ocular examinations are presented in the Table. The patients ranged in age from 54 to 69 years (median, 63.5 years). All patients were members of the Igbo tribe and had lived for the greater part of their lives in eastern Nigeria (at least 50 years). They had spent less than 5 years in the United States.

Five of the 6 patients had a history of malaria but all were treated with low cumulative and nontoxic dosages of chloroquine; patient 1 was additionally treated with quinine. The typical daily dose of chloroquine was 1 to 2 g/d. None of the patients had a history of tamoxifen, canthaxanthine, or nitrofurantoin use or intravenous drug abuse. Patient 5 had undergone general anesthesia for uncomplicated surgery many years ago but the anesthetic used was not known. None of the patients had a history of kidney disease except for patient 5, who also had diabetes (patients 1 and 3 had diabetes but without nephropathy). All patients had a history of chewing kola nuts for most of their adult lives, although the amount ingested varied from patient to patient. The number of crystals found on examination did not appear to correlate with the amount of kola nuts ingested by each patient.

The visual acuities varied from 20/20 to 20/200. In all patients, the degree of visual impairment could be accounted for by irregular corneal astigmatism, cataract, macular hole, or epiretinal membrane. Eyes without any of the aforementioned pathologic conditions had normal visual acuity in association with the crystalline maculopathy. Moreover, the severity of the crystalline maculopathy did not appear to have any correlation to the degree of impairment of visual acuity.

The crystals were superficial, refractile, yellow or green in appearance, bilateral and asymmetric in distribution, and focally deposited within the fovea. Associated retinal vascular and retinal pigment epithelial ab-normalities were notably absent. Peripheral retinal examination results were clear. Fluorescein angiography was selectively performed and revealed normal results (patients 1, 3, 4, 6), although patient 3 demonstrated angiographic correlation of clinically significant macular edema associated with nonproliferative diabetic retinopathy in the right eye, and patient 4 demonstrated a central transmission defect associated with a stage 2 macular hole in the right eye.

Patients 4, 5, and 6 underwent normal color vision testing with Ishihara plates. Patients 1, 3, and 4 had normal central visual fields. Patient 6 had generalized depression of the central visual field. This same patient was noted to have a borderline depression of the photopic electroretinogram (ERG), with mild to moderate depression of the scotopic ERG and a decreased b/a wave ratio, raising the possibility of crystalline toxicity of the inner retina. The electro-oculogram (EOG) result was normal in the right eye (Arden ratio of 2.1) and borderline low in the left eye (Arden ratio of 1.7). Patient 5 had mild depression of the photopic and scotopic ERG responses that could be explained by ischemic diabetic retinopathy in both eyes and panretinal photocoagulation scars in the right eye. Electro-oculogram responses were normal, with Arden ratios of 1.9 OD and 2.0 OS. Patient 4 had normal results on ERG and EOG (Arden ratios of 2.7 OD, 2.8 OS).

Comprehensive pedigree analysis was not performed but selected family members (daughter of patient 4 and son of patient 6) were examined and failed to harbor evidence of a crystalline maculopathy. Each patient denied a family history of eye disease or consanguinity.

### Summary of Clinical Findings

<table>
<thead>
<tr>
<th>Patient/ Age, y/Sex</th>
<th>BCVA</th>
<th>Crystals</th>
<th>Fundus</th>
<th>PMH</th>
<th>Color Vision</th>
<th>HVF</th>
<th>ERG*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/66/M 20/30 OU</td>
<td>Moderate</td>
<td>Severe</td>
<td>ERM OD FA WNL</td>
<td>Malaria, diabetes, prostate cancer</td>
<td>...</td>
<td>Normal</td>
<td>...</td>
</tr>
<tr>
<td>2/64/F 20/40 OD</td>
<td>Severe</td>
<td>Severe</td>
<td>...</td>
<td>Malaria</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3/54/M 20/20 OU</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild NPDR, FA WNL OU, CSME OD</td>
<td>Diabetes</td>
<td>...</td>
<td>Normal</td>
<td>...</td>
</tr>
<tr>
<td>4/63/F 20/200 OD</td>
<td>Mild</td>
<td>Severe</td>
<td>MH OD, FA WNL</td>
<td>Malaria</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5/60/F 20/70 OD</td>
<td>Severe</td>
<td>Severe</td>
<td>PDR OD, PPDR OS, PRP OD</td>
<td>Malaria, diabetes, HTN</td>
<td>Normal</td>
<td>...</td>
<td>↓ a and b waves of photopic, scotopic responses</td>
</tr>
<tr>
<td>6/69/F 20/20 OU</td>
<td>Severe</td>
<td>Moderate</td>
<td>FA WNL</td>
<td>Malaria, HTN, Bell palsy</td>
<td>Normal</td>
<td>Generalized depression</td>
<td>↓ amplitudes in rod-cone pattern with decreased b/a ratio</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; CSME, clinically significant macular edema; FA, fluorescein angiography; ERG, electroretinogram; ERM, epiretinal membrane; HTN, hypertension; MH, macular hole; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, pan retinal photocoagulation; WNL, within normal limits; ↓, decrease.
REPORT OF CASES

PATIENT 1

Patient 1 was a 66-year-old black man from East Nigeria belonging to the Igbo tribe. He had a history of non–insulin-dependent diabetes and malaria treated with limited doses of quinine and chloroquine. He denied any history of general anesthesia or intravenous drug abuse. He has used the kola nut for most of his adult life.

His best-corrected visual acuity was 20/30 OU. Refraction showed marked astigmatism and anisometropia in the left eye. Anterior segment examination results were normal, with pseudophakia in both eyes. The results of dilated ophthalmoscopic examination were remarkable for an enlarged cup-disc ratio in both eyes (0.6 OD and 0.5 OS). Macular examination revealed inner retinal refractile, greenish crystals focally clustered in the foveal region of the left eye (Figure 1). Subtle crystals at the fovea were noted in the right eye, with an associated epiretinal membrane. Signs of chloroquine maculopathy were notably absent,41-47 and the results of macular and peripheral retinal examinations were otherwise unremarkable in both eyes. Fluorescein angiography results were also unremarkable. A visual field examination revealed nonspecific generalized depression in both eyes. The central 20° of the visual field demonstrated normal sensitivities. Glaucoma therapy was initiated because of the suspicious disc appearance.

PATIENT 2

Patient 2 was a 64-year-old black woman from the Igbo tribe in East Nigeria. She had a history of malaria treated with low cumulative doses of chloroquine but denied any history of tamoxifen use, general anesthesia, or intravenous drug abuse. She has used the kola nut for most of her adult life.

Her best-corrected visual acuity was 20/40 OD and 20/25 OS. Anterior segment examination revealed a moderate cataract in the right eye and a mild cataract in the left eye. Fundus examination results were notable for inner retinal refractile, yellow-green crystals locally deposited in the fovea in both eyes (Figure 2 and Figure 3). There was no evidence of chloroquine toxicity,41-47 and results of a retinal examination were otherwise within normal limits in both eyes.

PATIENT 5

Patient 5 was a 61-year-old black woman from the Igbo tribe in East Nigeria. She had a history of type 2 diabetes mellitus and hypertension complicated by retinopathy and nephropathy. Her malaria was treated in the past with low cumulative doses of chloroquine. She had a history of uncomplicated general anesthesia for placement of a ventricular shunt. The patient admitted to kola nut ingestion on a social basis.

Her best-corrected visual acuity was 20/70 OD and 20/40 OS. Anterior segment examination revealed moderate nuclear sclerosis in both eyes. Fundus examination results were significant for low-risk proliferative diabetic retinopathy associated with incomplete panretinal photocoagulation scars in the right eye and preproliferative diabetic retinopathy in the left eye. Clinically significant macular edema was absent in both eyes. Inner retinal refractile, yellow-green crystals were noted in the fovea in both eyes (Figure 4). These crystals were not consistent with methoxyflurane exposure.1-3 Her color

Figure 1. Inner retinal, refractile crystalline deposits in the macula of the left eye of patient 1.

Figure 2. A, Color fundus photographs of the left eye of patient 2. Note the refractile crystals in the macula. B, Magnified view of the superficial crystalline deposits.
vision was intact. Fluorescein angiography was denied. The ERG and EOG results were previously described.

PATIENT 6

Patient 6 was a 69-year-old black woman from the Igbo tribe in East Nigeria. She had a history of malaria treated with low cumulative doses of chloroquine but denied any history of tamoxifen use, general anesthesia, or intravenous drug abuse. She had used the kola nut for most of her adult life.

Her best-corrected visual acuity was 20/20 OU. Anterior segment evaluation revealed mild cataract in both eyes. Fundus examination results were notable for refractile, yellow-green crystals focally deposited in the superficial fovea in both eyes. There was no evidence of chloroquine toxicity, and retinal examination results were otherwise within normal limits in both eyes. Ishihara plate test results were normal. Formal Humphrey visual field testing demonstrated generalized depression in both eyes. Electoretinogram testing revealed borderline depression of the photopic ERG, with mild to moderate depression of the scotopic ERG and a decreased b/a wave ratio. Retinal diseases associated with inner retinal degeneration, eg, retinitis pigmentosa, melanoma-associated retinopathy, congenital stationary night blindness, quinine toxicity, X-linked schisis, and central retinal artery occlusion, were notably absent. Toxic effects to the retina associated with crystalline deposition could not be definitively ruled out. Her 45-year-old son was present, and his ophthalmoscopic examination results were normal.

COMMENT

West African crystalline maculopathy represents a novel syndrome of iridescent foveal crystals present in elderly Nigerian Igbo tribe members. The syndrome is bilateral and asymmetric and is characterized by a focal cluster of inner retinal, green or yellow, refractile deposits that do not affect vision. Although the crystals appear benign and unassociated with obvious retinal or angiographic complication, toxic effects to the retina cannot be definitively ruled out due to the unexplained abnormal ERG results in patient 6.

Extensive inquiry of each patient failed to reveal any history to suggest a toxic mechanism. All patients denied ingestion of tamoxifen, canthaxanthine, or nitrofurantoin. Intravenous drug abuse suggestive of talc retinopathy was also denied. With the exception of 1 patient with nephropathy, a history of renal disease was absent, eliminating hyperoxaluria, methoxyfluorane, cystinosis, and Sjogren-Larsson syndrome as possible causes.

The intraretinal crystals found in this study were focally deposited within the fovea. There was neither evidence of the “doughnut” configuration of canthaxanthine retinopathy, nor was there evidence of intravascular localization typical of talc and oxalate crystals. Moreover, the deposits demonstrated a green or yellow hue, a unique feature of this maculopathy. Retinal detachment and telangiectasis were absent on ophthalmoscopic and angiographic examination.

Retinal pigment epithelial abnormalities are characteristic of tamoxifen retinopathy, Bietti dystrophy, and cystinosis, but were notably absent among the patients in this series. Age-related macular degeneration has been well documented in Nigeria despite the relative low prevalence of this disease among Africans in general. The patients in this study failed to demonstrate signs of age-related macular degeneration, such as drusen, retinal pigment epithelial atrophy, or choroidal neovascularization.

The cause of this peculiar maculopathy remains unclear. A genetic basis is possible given the presence of these crystals only in Igbo tribe members, to our knowledge. However, the 6 patients in this study were unrelated, and selected examination of close blood relatives failed to reveal the presence of the crystals. An extensive pedigree analysis would better address this possibility. A degenerative association is plausible given the presence of these crystals exclusively in the elderly Igbo population.

An unidentified toxic mechanism may have been the cause of the crystalline deposits. Several patients within this case series reported a history of limited chloroquine ingestion. The use of chloroquine is widespread in Nigeria, an endemic region of malaria. However, treatment requires only a 2-day regimen of approximately 1 to 2 g of chloroquine, well below the threshold cumulative toxic dose of 100 g. Moreover, none of our patients demonstrated any of the classic signs of chloroquine toxicity,
and formal central visual field testing and color testing failed to reveal consistent abnormalities. Crystalline maculopathy has never been reported in the context of chloroquine toxicity or malarial disease to our knowledge.

The ingestion of the kola nut, a raw seed with a stimulatory effect and addictive potential, is a characteristic ritual at social gatherings of Igbo members and was eaten regularly by many of the Igbo patients of this study. The kola nut contains caffeine, and the extract is used in the production of the cola soft drink. Additional constituents include xanthines, various pigments and dyes that may be deposited in certain tissues with chronic ingestion.33-35 However, kola nut consumption is not limited to Igbo tribe members, and use of the nut is widespread throughout Nigeria and other parts of Western Africa.

This report summarizes the findings from 6 elderly Igbo tribe members of southeast Nigeria, each manifesting a brilliant crystalline maculopathy. These crystals were noted to be bilateral but asymmetric, refractile, green or yellow in color, and focally clustered within the superficial fovea. Interventional therapy is not mandated; however, adverse effects on the neurosensory retina may be delayed.26 Further work is needed to reveal consistent abnormalities. Crystalline maculopathy associated with methoxyflurane anaesthesia.27

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REFERENCES


