Clinical Phenotype Associated With the Arg141His Mutation in the X-linked Retinoschisis Gene

X-linked retinoschisis (XLRS) is a rare hereditary disorder characterized by bilateral stellate maculopathy and peripheral retinoschisis. The schisis cavities are usually first noted in the inferotemporal quadrant and often progress to involve the entire peripheral retina. This process often commences within the first year of life and is associated with a wide range of phenotypic expression.1 Histopathologic studies have demonstrated a splitting of the retina at the nerve fiber layer.2 A gene responsible for XLRS, XLRS-1, which maps to Xp22.2, has been cloned and sequenced. The predicted protein sequence contains a highly conserved motif implicated in cell-cell interaction and, thus, may be active in cell adhesion processes.3 We report the clinical and electrodagnostic phenotype associated with a missense point mutation within the fifth exon of this gene that replaces the normal arginine residue with a histidine residue at codon 141 in a family of Hispanic origin.

Report of Cases. The proband was initially seen at age 1 year 5 months, after his parents noted the evolution of an alternating esotropia. Familial review disclosed 2 brothers who had decreased central visual acuity, in one of whom it was associated with esotropia (Table). Examination of the proband and his siblings revealed bilateral, bullous schisis cavities, more prominent in the inferior quadrants, and foveal changes consistent with a diagnosis of XLRS (Figure 1). No retinal breaks or dialyses were noted. Funduscopic examination results of the proband’s mother and sister were normal.

Abbreviated standardized electroretinograms were recorded from each participant in accordance with international standards for pediatric patients (Figure 2). The full-field mesoscopic electroretinograms described here were elicited after 20 minutes of dark adaptation using a 10-microsecond xenon strobe (model PS-22; Grass Instruments, Quincy, Mass) at an intensity of 2.4 candelas/m² and a rate of 0.3 Hz (4 responses averaged). All electroretinograms were recorded with Burian-Allen contact lens electrodes (Hansen Ophthalmic Development Laboratories, Iowa City, Iowa) using the Neuroscan electrodiagnostic system v3.0 (Neurosoft Inc, Herndon, Va). The A wave was of normal amplitude for all participants; however, the B waves were reduced in each of the 3 male siblings under mesoscopic conditions. Electrodiagnostic testing of the proband’s mother revealed a B wave of reduced amplitude but within normal limits. Similar testing of the proband’s sister was normal. The B/A ratio, which shows the relative relationship of B-wave to A-wave amplitude and should be between 1.5 and 1.7 for most normal individuals,3 was severely abnormal in the 3 male siblings (0.77, 0.58, and 0.66), borderline normal in the mother (1.4), and clearly normal in the sister (2.1).

A peripheral blood sample was obtained from each family member and genomic DNA was isolated by proteinase-K incubation followed by phenol/chloroform extraction. Oligonucleotide polymerase chain reaction primers, able to amplify each exon of the XLRS-1 gene, were synthesized (sequences available on request). Fluorescent-labeled dideoxynucleotides were used in direct sequencing of polymerase chain reaction products to study the XLRS-1 gene for each family member. Each exon was aligned to wildtype sequence available on the National Center for Biotechnology Information database (Accession No. AF018958). A G to A transition resulted in the substitution of a histidine residue for an arginine residue at codon 141 of exon 5 for each affected male sibling (Figure 2). The proband’s mother and sister were noted to be heterozygous for this mutation. No other mutation or polymorphism was identified in any

**Clinical, Electroretinographic (ERG), and DNA Analysis Findings**

<table>
<thead>
<tr>
<th>Patient Pedigree No.</th>
<th>Age, y</th>
<th>OD Acuity</th>
<th>OS Acuity</th>
<th>Fundus Status</th>
<th>ERG</th>
<th>DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-2</td>
<td>29</td>
<td>20/25</td>
<td>20/20</td>
<td>Normal OU</td>
<td>Reduced B wave</td>
<td>Heterozygote</td>
</tr>
<tr>
<td>II-1</td>
<td>9</td>
<td>20/80</td>
<td>20/200</td>
<td>Mild RS OU</td>
<td>Absent B wave</td>
<td>Arg141His</td>
</tr>
<tr>
<td>II-2</td>
<td>5</td>
<td>20/100</td>
<td>20/70</td>
<td>Mild RS OD; severe RS OS</td>
<td>Absent B wave</td>
<td>Arg141His</td>
</tr>
<tr>
<td>II-3</td>
<td>2</td>
<td>1/30‡</td>
<td>3/30‡</td>
<td>Severe RS OU</td>
<td>Normal OU</td>
<td>Arg141His</td>
</tr>
<tr>
<td>II-4</td>
<td>10</td>
<td>20/20</td>
<td>20/20</td>
<td>Normal OU</td>
<td>Normal</td>
<td>Heterozygote</td>
</tr>
</tbody>
</table>

*OD indicates right eye; OS, left eye; OU, both eyes; and RS, retinoschisis.

†See Figure 2.

‡Indicates Allen Card visual acuity.
other exon. This mutation was not seen in 32 control chromosomes.

Comment. The Retinoschisis Consortium has described a wide spectrum of mutations in the XLRS-1 gene in patients from a variety of ethnic backgrounds.\(^6\) The mutation we report has been previously identified by the Retinoschisis Consortium\(^6\) and is clearly associated with early clinical, visual, and electrophysiologic changes, as the affected proband had central and peripheral retinal changes, as well as strabismus and electroretinographic changes, by the age of 17 months. In addition, DNA sequence analysis permitted the identification of the proband’s sister as a carrier prior to the development of electroretinographic changes. The ability to determine carrier status by molecular techniques is important as many female carriers of XLRS achieve childbearing age prior to the detection of electroretinographic changes. Useful family counseling is enhanced by the development of rapid, reliable genotype assays.

Jeong-Hee C. Park, MD
Sandra H. Ott, BA
Xiaoguang Wang, MD, PhD
Binoy Appukuttan, PhD
Reshma J. Patel, PhD
Gretchen B. Van Boemel, PhD
J. Timothy Stout, MD, PhD
Los Angeles, Calif

We have no proprietary interest in any material relating to this research project.

Figure 1. Fundus photograph of a 5-year-old patient with X-linked retinoschisis—characteristic stellate maculopathy and bullous peripheral retinoschisis in the inferior quadrants with vitreous veils.

Figure 2. Family pedigree. Corresponding DNA sequence for exon 5 and electroretinographic data are aligned beneath each individual. Arrows point to the nucleotide of interest. ERG indicates electroretinogram; B/A ratio, the relationship of B-wave to A-wave amplitude (reference range, 1.5-1.7).
Crystalline Retinopathy


Bietti Crystalline Retinopathy Affecting All 3 Male Siblings in a Family

Three male siblings of a nonconsanguineous Chinese family exhibited characteristic retinal crystalline flecks of Bietti crystalline retinopathy (BCR). The main proband suffered from blurred and distorted vision and also had bilateral submacular scars. To our knowledge, the presence of BCR in this family demonstrated the strongest male preponderance among the reported cases in the English literature. The mode of inheritance could be X-linked recessive, but no conclusion could be made because the pedigree studied was too small.

Report of Cases. Case 1. A 38-year-old Chinese man (the main proband) was referred to our hospital in 1991 for a 1-year history of night blindness, metamorphopsia, and slowly progressive visual loss. The left eye was more severely affected. He was the second child in his family and his parents were not related (Figure 1). He was not obese and findings from the medical and drug history were normal. On examination, visual acuity was 20/70 OD and 20/100 OS. The cornea was clear with no crystals. Findings from full-field electroretinography recorded diminishment in amplitude of all waveforms, especially the cone response. Findings from electro-oculographic examination showed subnormalities with decreased dark to light ratio.

Values from routine blood biochemistry tests, including fasting triglycerides, total cholesterol, low- and high-density lipoprotein cholesterol, and apolipoprotein B were normal. Oxalic acid and amino acid analysis in 24-hour urine samples also gave normal results. Leukocyte cystine level and α-galactosidase A activity were within reference intervals. The expression of the ornithine aminotransferase gene was also normal. The patient had been followed up in our hospital for 7 years. His vision remained stable, but the retinopathy showed advancement in atrophic changes over the retinal pigment epithelial layer, and

Visual field testing using the Humphrey Field Analyzer showed bilateral paracentral scotomas. Color vision tested with the Ishihara color chart was normal. Findings from fluorescein angiography of the late venous phase showed areas of hyperfluorescence interspersed with hypofluorescent regions and the associated prominent choroidal vessels. These features suggested atrophic changes of both the retinal pigment epithelium and the chorionicapillaries. The crystals did not show up on the angiogram. No neovascular membrane, gross leakage and pooling of fluorescein dye from vessels, or gross macular edema was seen. Full-field electroretinography recorded diminishment in amplitude of all waveforms, especially the cone response. Findings from full-field electroretinography showed subnormalities with decreased dark to light ratio.

![Figure 1. Pedigree chart of the family. Numbers 1, 2, and 3 indicate patients 1, 2, and 3.](image1.png)

![Figure 2. Patient 1 (the main proband). Color fundus photographs of the right (left) and left (right) eyes showing glistening crystals scattered throughout the posterior fundus and extended into the periphery, patches of pigment clumping, and retinal pigment epithelial hypopigmentation and atrophy. Subretinal scars (arrows) were found in the macular area of both eyes.](image2.png)
the crystals became less prominent.

Case 2 and Case 3. Cases 2 and 3, aged 34 and 36 years, respectively, were the younger brothers of the main proband. Both of them were asymptomatic, had an unremarkable medical or drug history, and their visual acuity was 20/20 OU. Findings from ocular examination were normal except for the presence of bilateral multiple crystalline flecks in the retinas. These retinal flecks were confined to the posterior pole. There were fewer deposits when compared with that of the proband (Figure 3), and the youngest brother had the fewest deposits (Figure 4). Both corneas were clear with no deposits. Findings from systemic and ocular testing, including blood biochemistries, molecular analyses, visual field, electroretinogram, and electrooculogram, were all normal.

Comment. The normal drug and medical history, results of ophthalmologic examination, biochemistry tests, and molecular analysis support the diagnosis of BCR without corneal involvement. We have conducted comprehensive ocular examinations for all other family members as shown in the pedigree tree (Figure 1). Findings from these examinations were normal.

The presence of refractile bodies and crystalline deposits over both retinas may be owing to primary eye diseases or secondary effects of inherited or acquired metabolic diseases. Differential diagnosis is important for appropriate treatment. Diffuse crystalline retinal deposits may occur in systemic oxalosis, cystinosis, hyperornithinemia, talc retinopathy, Sjögren-Larsson syndrome, and excessive intake of tamoxifen or canthaxantine. Clinical and biochemical features of our cases are not consistent with any of these disorders.

There are about 90 reported cases of BCR with considerable variation in symptoms and retinopathy. Some have characteristic fundal pictures as originally described by Bietti. Some have simultaneous corneal and retinal involvement. Pure retinal involvement appears to be more common in Asian than white people. This intrafamilial phenotypic variability typifies the heterogeneity of BCR and has been well shown in our cases.

Our main proband had neither high myopia nor a history of choroiditis. He had bilateral crystalline retinopathy with subretinal fibrosis in the posterior poles. Maculopathy in Bietti dystrophy is uncommon. Macular holes have been reported in 2 cases in which 1 was highly myopic. The submacular scar in the first patient could be...
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Corresponding author: Dennis S. C. Lam, FRCS, FRCoPhth, Chairman, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong (e-mail: dennislam@cuhk.edu.hk).


Macular Hole Surgery in the Presence of Prominent Macular Drusen

Current vitrectinal surgical techniques often achieve good visual acuity outcomes in eyes with idiopathic macular holes. However, the effect of concurrent prominent macular drusen on the outcome of macular hole surgery has not been reported. We describe 3 patients with prominent macular drusen and idiopathic macular holes. Macular hole surgery was performed and a follow-up of at least 3 months was obtained.

Report of Cases. Case 1. An 83-year-old white woman was seen with a 2-month history of decreased vision in her left eye. Best-corrected visual acuity was 20/50 OD and 20/400 OS. The anterior segment examination showed 1+ nuclear sclerosis in both eyes. The posterior segment examination of the right eye showed multiple drusen in the macula. Examination of the left eye revealed multiple drusen with a 200-µm stage 4 macular hole and surrounding cuff of sub-retinal fluid (Figure 1, A). The Watzke sign was positive. Fluorescein angiogram showed hyperfluorescence corresponding with the hole. The patient underwent pars plana vitrectomy, membrane peeling, fluid-air exchange, and injection of 16% perfluoropropane (C2F6). Two weeks of prone positioning was accomplished and the hole was closed. One year later, her best-corrected visual acuity was 20/30 OS (Figure 1, B).

Case 2. An 82-year-old woman was referred for possible choroidal neovascularization from age-related macular degeneration in her left eye. She had noticed decreased visual acuity in the affected eye for a few weeks and had previous cataract extraction in both eyes 2 years earlier. The best-corrected visual acuity was 20/30–2 OD and 20/200 OS. There were macular drusen in both eyes. Contact lens biomicroscopy of the left eye showed a small macular...
hole, surrounded by a cuff of subretinal fluid (Figure 2, A). The Watzke sign was positive. There was also evidence of a superonasal branch vein occlusion, which was distant from the macula. Fluorescein angiography revealed a discrete area of hyperfluorescence corresponding with the macular hole (Figure 2, B). Pars plana vitrectomy, membrane peeling, and fluid-air exchange with 16% C3F8 gas was performed, followed by 2 weeks of prone positioning. The macular hole was closed and the visual acuity improved to 20/60 at the 3-month follow-up examination (Figure 2, C).

Case 3. A 74-year-old white woman was seen for a 1-month history of decreased vision in her right eye. Six months earlier, she was diagnosed as having prominent macular drusen in both eyes by another retina specialist and had received grid laser treatment in both eyes with partial resolution of the drusen. She also had cataract extraction in both eyes 1 year earlier. Best-corrected visual acuity was 20/200 OU and 20/30 OS. Dilated fundus examination of the right eye showed prominent drusen with a stage 4 macular hole. Examination of the left eye revealed prominent macular soft drusen. Pars plana vitrectomy, membrane peeling, fluid-air exchange, and injection of 16% C3F8 gas was performed on the right eye. The macular hole was closed after 2 weeks of prone positioning. At 18-month follow-up, best-corrected visual acuity was 20/25 OD.

Comment. With current vitrectomy techniques, anatomic closure rate in macular hole surgery has been reported in up to 91% of cases and the majority of anatomically successful cases achieve 2 or more lines of visual acuity improvement.1,2 After successful surgery, macular hole closure is believed to result from glial proliferation and contraction,3 and the visual acuity may return to near-normal function.

Prominent macular drusen may sometimes mask the presence of a full-thickness macular hole (Figure 2, A). Case 2 was referred with the diagnosis of exudative macular degeneration. The correct diagnosis of macular hole and prominent macular drusen was made with the aid of contact lens biomicroscopy.

The effect of prominent macular drusen on the anatomic and functional success of macular hole surgery has not been previously reported. Banker and associates4 correlated macular retinal pigment epithelium changes with poorer visual outcomes. The described retinal pigment epithelium alterations presumably result from light toxicity or anatomic debridement during macular hole repair.5,5

In the present report, all 3 patients had prominent preoperative macular drusen, which remained essentially unchanged following macular hole surgery. Although these 3 patients represent a limited experience, patients with prominent macular drusen and a macular hole can achieve similar anatomic and visual success compared with patients without drusen. Therefore, the presence of prominent drusen in the macula does not constitute a contraindication to macular hole surgery.

Corresponding author: Harry W. Flynn, Jr, MD, Bascom Palmer Eye Institute, 900 NW 17th St, University of Miami School of Medicine, Miami, FL 33136.


Synkinesis Following Diabetic Third Nerve Palsy

A 59-year-old man developed a left pupil-sparing third nerve palsy related to diabetes that recovered gradually over 5 months; the only deficit remaining at 8 months was a trace underaction of adduction. Oculomotor synkinesis was evident at this time, manifest as left upper lid retraction on adduction and on downgaze. There were no signs of oculomotor or pupillary synkinesis. High-resolution magnetic resonance imaging of the third nerve pathway revealed no abnormality. Oculomotor synkinesis following diabetic third nerve palsy is extremely rare, with only one report in the literature to date.

Synkinesis may occur during the recovery phase of a traumatic third nerve palsy or after long-standing compression. The abnormal movements that constitute synkinesis may involve the upper lid, oculomotor...
system, and the pupil. Synkinesis is rare when the cause is ischemia and we have found only one previous report of synkinesis following diabetic third nerve palsy. Our report adds a second to the literature.

**Report of a Case.** A 59-year-old man with type 2 diabetes mellitus was seen with a 2-week history of left ocular and retro-orbital pain, progressive left upper lid ptosis, and diplopia in all directions of gaze. Diabetes was well controlled and there was no history of hypertension or previous neurologic disturbance. Medication consisted of oral hypoglycemic agents only.

The examination revealed corrected visual acuity of 20/30 OU, normal color vision, and full visual fields. The pupils were 4 mm in diameter and reacted briskly to light. There was no proptosis. The upper lid and ductions in the right eye were normal. On the left side, there was complete ptosis with no levator function. The left eye was exotropic, adduction and elevation were absent, and depression was markedly limited. Intorsion on attempted downgaze was present. The remainder of the cranial nerves were normal. A diagnosis of diabetic left pupil-sparing third nerve palsy was made and the patient was observed.

At 2 months, his pain had resolved completely, and left upper lid ptosis was only 3 mm with 5 mm of levator function. The left eye could be adducted just beyond the midline and there was improved but still limited upgaze and inferior rectus function. There was 2 mm of left upper lid retraction on attempted adduction, with the right upper lid remaining stationary on right gaze. There was complete descent of the left upper lid on downgaze at this time. Because of the signs of oculomotor synkinesis, a magnetic resonance scan of the third nerve pathway was obtained, but no intracranial abnormality from the midbrain to the orbit was found.

At 5 months, the patient was asymptomatic and had almost completely recovered. The patient had no ptosis or pupillary abnormality, normal levator function, and full motility except for a trace underaction of adduction on the left. Retraction of the left upper lid on adduction was unchanged and there was a new incomplete descent of the left upper lid by 2 mm on downgaze (Figure).

Although the patient’s third nerve palsy had recovered almost completely, definite signs of oculomotor synkinesis were evident. These synkinetic movements were unchanged at the last examination, 8 months after the onset of symptoms.

**Comment.** Third nerve palsy is the commonest cranial mononeuropathy in patients with diabetes. Although the precise etiological role of diabetes-related third nerve palsy is uncertain, diabetes-related ischemia of the peripheral nerve may be important. And, with the use of magnetic resonance imaging, it is now apparent that isolated third nerve palsy (with or without pain and without pupillary involvement) in a diabetic individual may uncommonly be due to midbrain infarction or hemorrhage. It should be noted that if the third nerve palsy in a diabetic patient fails to recover, it is likely to be due to a coexistent compressive lesion such as a tumor or an aneurysm.

Recovery of third nerve palsy in diabetes usually occurs within 3 months. The mechanism of recovery is not known, but almost certainly involves remyelination, present at 6 months and complete by 3 years. Synkinesis may occur during recovery of any third nerve palsy.

A, Right gaze demonstrates slight underaction of left medial rectus and elevation of left upper lid. B, Left gaze demonstrates the normal lower position of the left upper lid. C, On downgaze, the left upper lid does not descend fully.
particularly following traumatic and compressive lesions, but only rarely when the nerve palsy appears to be due to microvascular disease or ischemia related to giant cell arteritis. Oculomotor synkinesis is manifest as abnormal movements of the upper lid, globe, or pupil, occurring in isolation or in a variety of combinations that may be subtle and easily missed by the examiner.

There are currently 3 contesting theories on the pathogenesis of oculomotor synkinesis (see review by Sibony et al17): (1) Aberrant regeneration of injured nerve fibers in which regenerating axons that grow into the wrong nerve sheaths are directed to incorrect targets. (2) “Release” phenomenon or synaptic reorganization of the third nerve prenuclear or nuclear complex.18,19 (3) Abnormal signal conduction (ephaptic transmission) between peripheral axons where there is a secondary partial or complete loss of myelin.

In our patient, it is assumed that the third nerve palsy was due to a lesion of the peripheral nerve since magnetic resonance imaging revealed no evidence of a brainstem, cavernous sinus, or subarachnoid lesion along the third nerve pathway. Magnetic resonance imaging is unhelpful in confirming the peripheral location of the lesion in diabetic third nerve palsy since, as occurred in our patient and in other studies, the third nerve did not enhance. Histological studies of diabetic third nerve palsies may provide insight about the pathogenesis of synkinesis in our patient. These studies found that the predominant feature was central focal demyelination of the subarachnoid, intracavernous third nerve with relative axonal sparing. The fascicles and nuclei were normal in two of the examinations. These findings mitigate against the misdirection and central theories but favor the ephaptic theory of electrotonic conduction between bare axons in our case.

In conclusion, this case report is the second of synkinesis following diabetic third nerve palsy. It is emphasized that signs of oculomotor synkinesis may be subtle and thus easily missed unless specifically looked for, but the diagnosis of synkinesis following diabetic third nerve palsy remains a diagnosis of exclusion.

Dai Barr, FRCOphth
Mark Kupersmith, MD
Roger Turbin, MD
Sherry Yang, MD
Raymond Iezzi, MD
New York, NY

Corresponding author: Mark J. Kupersmith, MD, INN at Beth Israel North, 170 East End Ave, New York, NY 10128 (e-mail: mkuper@bethisraelny.org).


Oral Ivermectin Therapy for Phthiriasis Palpebrum

Pediculosis pubis, as well as phthiriasis palpebrum, is caused by the cosmopolitan crab or Pthirus pubis. This wingless, blood-sucking insect not only infests eyelashes and pubic regions, but occasionally inhabits the hair of the face, axillae, chest, and rectal regions. Unlike the head louse, a crab has a serrated surface on its first tarsal claws, allowing this organism traction on flat, hairless surfaces. Thus, this louse species can navigate over the entire skin surface. Although docile when exposed to light, P pubis can be rather mobile in the dark. These characteristics explain the prominent role that fomite transmission plays with crab lice, as well as its occasional migration to the eyelids.

Pubic lice have been challenging to eradicate, as they often inhabit several hairy areas on individual patients. Lice need host hair to cling to when sleeping, and for attachment of their eggs. In children, the tendency to inhabit eyelashes relates to specific temperature and moisture requirements, as well as the lack of terminal hairs on most body regions in children of prepubertal age. Thus, topical therapy may fail if one does not apply insecticide to all hairy areas, including the pre-rectal region.

Numerous insecticide formulations in aqueous vehicles and applied with cotton sticks have been suggested for phthiriasis palpebrum, including lindane, malathion, and pyrethrin. Additionally, various other reported treatments for pediculosis ciliaris include mechanical removal with fine forceps, yellow mercuric oxide eye ointment, cryotherapy, 20% fluorescein solution, physostigmine ointment, petrolatum jelly, and argon laser phototheraphy. Alcoholic formulations...
should be avoided owing to ocular irritation, and allergic reactions can occur in people sensitized to excipient components. Of note, delayed corneal damage has been reported with insecticidal use. Oral ivermectin (Stromectol; Merck and Co Inc, Whitehouse Station, NJ) has been purported to be effective for pubic lice, but to our knowledge no case reports of its use for phthiriasis palpebrum have been reported. For this reason, we report our experience with 4 cases of phthiriasis palpebrum.

Report of Cases. Four patients, ranging in age from 3 to 10 years, had complaints of itching and irritation of the eyes for several weeks. On clinical examination, all revealed reddened, crusty lid margins with grayish discoloration at their bases. On closer examination, numerous nits and mobile parasites were noted on the eyelashes. All 4 patients had bilateral involvement, with 1 additionally having infestation with crab lice in the scalp hair. Three of the 4 patients had been previously unsuccessfully treated with 1% gamma benzene hexachloride shampoo and topical physostigmine. All patients were treated with both 200-µg/kg doses of oral ivermectin (Stromectol) given a week apart. No topical treatments were applied to the eyelids.

All 4 patients were cured with this therapy. All adult lice were eradicated within 2 days, while the nits remained attached to the eyelashes but dissipated during the following month as the eyelid hairs grew out.

Comment. Ivermectin is an anthelminthic agent that has proved to be an excellent antiparasitic drug for veterinary medicine since its introduction in 1981. Approved by the Food and Drug Administration for human use on onchocerciasis and strongyloidiasis in 1996, ivermectin has also been effective for loiasis, bancroftian filariasis, cutaneous larva migrans, scabies, and lice. 10,11 Ivermectin acts by blocking chemical transmission across nerve synapses that use glutamate or γ-aminobutyric acid (GABA). In vertebrates, like lice, are selectively paralyzed by ivermectin, as glutamate and GABA are the neurotransmitters for peripheral motor function. The neuromuscular system in humans does not operate via glutamate or GABA, and thus is not affected by the presence of this drug. As ivermectin has a half-life of 16 hours, a single dose of ivermectin does not allow sufficient drug levels in the bloodstream to kill nymphs as they hatch from their nit capsule 1 week later. 12 Pubic lice feed on human blood several times during each day and young lice require a blood meal soon after hatching from the egg. Ivermectin has no oviducal activity, and requires the louse to obtain the drug via blood meals. Similar to our experience with public lice in the groin, 2 doses of ivermectin, given a week apart, are required to eradicate phthiriasis palpebrum. There are 2 caveats with ivermectin. First, one needs to avoid treating persons weighing less than 15 kg, and to use caution in use in pregnant or breastfeeding women. 16,17 This restriction is based on the drug’s ability to potentially cross poorly developed blood-brain barriers. Second, there has been one report of possibly increased incidence of death in elderly patients. 18 However, there have been more than 10 million people treated worldwide for onchocerciasis and strongyloidiasis without any reported ramifications in older populations. 17

Craig N. Burkhart
Craig G. Burkhart, MSPH, MD
Sylvania, Ohio

Corresponding author: Craig G. Burkhart, MSPH, MD, Department of Medicine, Medical College of Ohio at Toledo, 5600 Monroe St, Suite 106B, Sylvania, OH 43560.


Full-Thickness Skin Grafting of Eyelids in a Patient With Generalized Morphea Taking Thalidomide

Thalidomide, formerly a medical “outcast,” has enjoyed a resurgence of interest as a drug capable of treating many medical conditions by the same mechanisms that once demonized it. With its anti-inflammatory and antiangiogenic effects, thalidomide is now being effectively applied to a variety of autoimmune and dermatologic disorders such as erythema nodosum leprosum, discoid lupus erythematosus, Behc¸et syndrome, and Langerhans cell histiocytosis. 1 Additionally, more and more research is exploring the effects and applications of thalidomide to angiogenesis-dependent medical conditions such as diabetic retinopathy, certain cancers, and wound healing. This case report is followed by a discussion of the effects of thalidomide on factors involved in wound healing.

Report of a Case. A 50-year-old white woman was referred for evaluation of severe cicatrical eyelid retraction and ectropion (Figure 1)
due to generalized morphea—a scleroderma variant of progressive systemic sclerosis without systemic involvement. The patient had been taking 800 to 1000 mg/d of thalidomide for several months prior to repair, and continued taking the drug for the duration of our involvement in her care. Given her skin condition and the lack of literature describing skin grafting in patients taking thalidomide, we initiated a staged repair. Using the only normal-appearing patch of skin from the left scapula, full-thickness skin grafting to the patient’s right upper eyelid was performed first, because of the presence of an exposure-induced corneal ulcer. The patient’s wounds healed satisfactorily. Eight months later, a 3-mm lateral tarsorrhaphy was added to the right lateral eyelids. Four months later, the patient underwent similar repair of the left upper and lower eyelids. Normal-appearing skin from the left scapula was again used to cover the defects that remained after dissection, undermining, and reapproximation of the eyelid to the globe. Again, the wound healed satisfactorily (Figure 2). One year after the procedure, the patient continues to have good eyelid approximation to the globe (3 mm of lagophthalmos on the right and 2 mm on the left) and no further episodes of corneal exposure despite disease progression.

Comment. This case is an example of successful skin grafting performed on a patient taking thalidomide who has a degenerative, fibrotic dermatologic disorder such as generalized morphea. Other reports of skin grafts on nonhealing peripheral skin ulcers in patients with scleroderma have been published. However, to our knowledge, this is the first case report of a successful skin grafting procedure performed on a patient taking thalidomide.

The precise mechanism(s) of thalidomide’s anti-inflammatory, antiangiogenic, and teratogenic effects are still under investigation. However, thalidomide seems to inhibit the fibrotic effects of tumor necrosis factor α, antagonize the angiogenic effects of beta fibroblast growth factor, and inhibit the expression of certain beta integrin subunits. Integrins are cell surface proteins involved in important cell-cell and cell-matrix interactions. By decreasing the expression of integrins, cell migration-dependent processes such as inflammation, angiogenesis, and embryogenesis would thus be limited. Theoretically, thalidomide’s therapeutic anti-inflammatory, antifibrotic, and antiangiogenic effects could become a liability in successful wound healing. This patient healed well after skin grafting while taking thalidomide, further illustrating the remarkably complex relationship between integrins, cytokines, normal cellular processes, and disease states.

Laura M. Periman, MD
Bryan S. Sires, MD, PhD
Seattle, Wash

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Corresponding author: Bryan S. Sires, MD, PhD, University of Washington, Ophthalmology, Box 356485, Seattle, WA 98195-6485 (e-mail: bsires@uwashington.edu).