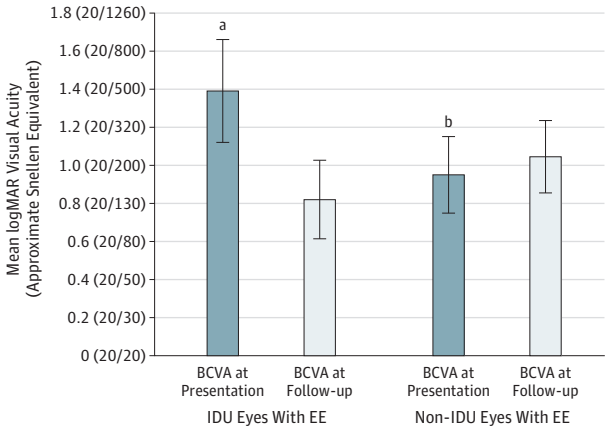
Figure. Mean Visual Acuity Before and After Treatment in Patients With and Without Injection Drug Use (IDU)



Includes 18 eyes, 11 of patients with IDU (61%) and 7 of patients without IDU (39%). Error bars represent SE. BCVA indicates best-corrected visual acuity.

[a] $P = .02$, paired t test, compared with after follow-up.

[b] $P = .59$, paired t test, compared with after follow-up.

Discussion | The peak in IDU EE cases observed in 2016 mirrors the increased in IDU-related deaths in New Hampshire. Patients with IDU EE were young and ambulatory and presented later but were more likely to experience improved vision with treatment compared with patients with non-IDU EE, who fared worse likely because of more chronic comorbidities and advanced age. In addition, microbes were less likely to be recovered in patients with IDU. These observations support the notion that patients with IDU subvert typical patterns of self-care by normalizing injection-related harms and delaying medical treatment until emergencies occur.[6] This delay also makes microbial diagnosis challenging, because the injection-induced transient bacteremia may have resolved by the time of presentation. Furthermore, organisms may be sequestered in tissues difficult to access even with repeated sampling, which may contribute to the frequent nonclearing vitritis seen in patients with IDU and account for the observed higher need for surgical intervention.[7] Although further interpretation is limited by the small sample size at a single hospital, the contrast in initial clinical impression between patients with and without IDU was substantial. The patients with IDU represent a younger and healthier subset of the population with EE and may regain vision with prompt recognition and treatment.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths: United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016;64(50-51):1378-1382.

2. Wu ZH, Chan RP, Luk FO, et al. Review of clinical features, microbiological spectrum, and treatment outcomes of endogenous endophthalmitis over an 8-year period. *J Ophthalmol*. 2012;2012:265078.

3. Shamsuddin D, Tuazon CU, Levy C, Curtin J. *Bacillus cereus* panophthalmitis: source of the organism. *Rev Infect Dis*. 1982;4(1):97-103.

4. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

5. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing Snellen visual acuity measurements. *Retina*. 2010;30(7):1046-1050.

6. Morrison A, Elliott L, Gruer L. Injecting-related harm and treatment-seeking behaviour among injecting drug users. *Addiction*. 1997;92(10):1349-1352.

7. Tirpack AR, Duker JS, Baumal CR. An outbreak of endogenous fungal endophthalmitis among intravenous drug abusers in New England. *JAMA Ophthalmol*. 2017;135(6):534-540.

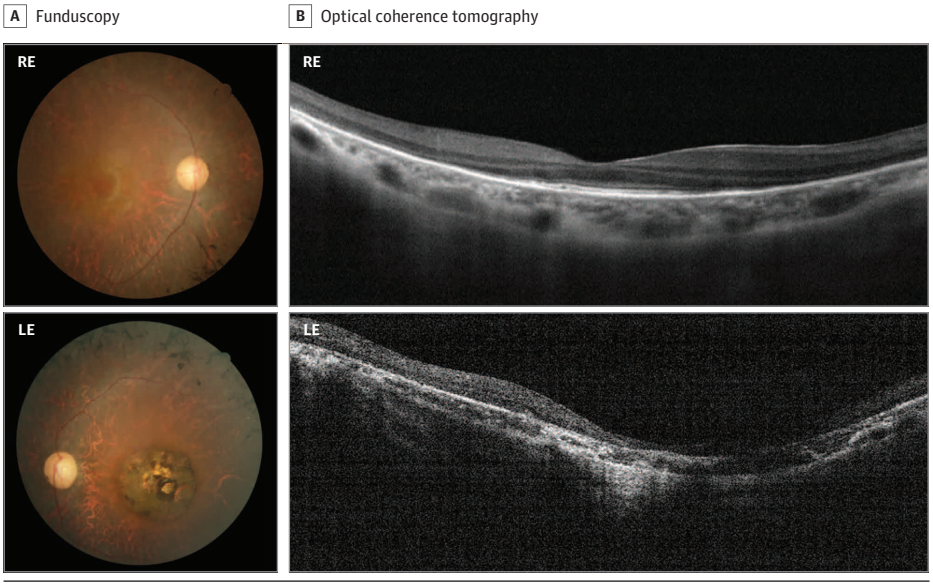
OBSERVATION

A Case of Unexpected Adult-Onset Neurologic Decline in *CLN3*-Associated Retinal Degeneration

Mutations in *CLN3* (OMIM #204200) lead to retinal degeneration in childhood, with additional development of cerebral neurodegeneration around the same age (classic CLN3) or up to adulthood (protracted CLN3).[1] However, recent research claims that a subset of mutations in *CLN3*, notably the R405W missense mutation, give rise to isolated retinal degeneration.[2,3]

We describe a man in his early 30s homozygous for the R045W mutation initially diagnosed with isolated retinitis pigmentosa. In the past few years he started exhibiting neurologic decline.

Figure. Funduscopy and Optical Coherence Tomography (OCT) of Patient With *CLN3*-Associated Retinal Degeneration



Patient's funduscopy and OCT at recent examination. A, Funduscopy shows narrow vessels, pale optic discs, and peripheral pigmentations in both eyes, a relatively intact macula in the right eye (RE), and macular pigment alterations and atrophy in the left eye (LE). B, Optical coherence tomography shows macular atrophy in the LE vs foveal sparing in the RE.

Report of a Case | Retinitis pigmentosa was diagnosed in a man in his early 30s of Iraqi descent born to consanguineous parents after onset of slowly progressive vision loss, in particular night blindness and peripheral vision loss, from approximately age 12 years. The patient received mainstream education and subsequently worked as a factory worker and gardener. Genetic analysis performed during his mid-20s yielded a homozygous c.1213C>T (R405W) missense mutation in *CLN3*. This finding fit the isolated retinitis pigmentosa observed at that time. Light microscopy analysis revealed the presence of vacuolated lymphocytes, although less pronounced than usually seen in (classic) CLN3 disease.[4]

Over time, his best-corrected visual acuity deteriorated to 2.00 logMAR (approximate Snellen equivalent, 3/300) in his left eye, but, on recent examination, his best-corrected visual acuity was 0.4 logMAR (approximate Snellen equivalent, 20/50) in his right eye. Optical coherence tomography showed foveal sparing with photoreceptor loss from the perimacular area outward in his right eye and generalized photoreceptor loss, including macular atrophy, in his left eye (**Figure**). Despite the relatively intact central vision in his right eye, full-field electroretinography demonstrated undetectable rod and cone responses in both eyes.

Until his late 20s, the patient exhibited no extraocular symptoms, in particular, no neurologic problems. However, in the past 5 years, he gradually developed motor problems most prominent in his legs that were not explained by extensive analyses (magnetic resonance imaging of his lumbar spine, electromyogram, and muscle echography). On recent neurologic examination, he displayed a bipyramidal spastic paraparesis gait pattern, including lively reflexes in his legs, and low to normal reflexes and a cog-wheel rigidity in his arms. In addition, the patient increasingly experiences forgetfulness and word-finding difficulties. Of note, the patient has a brother reportedly showing a similar combination of retinal and neurologic deterioration who has the same homozygous R405W missense *CLN3* genotype.

Discussion | We describe a patient who initially presented with *CLN3*-associated isolated retinal degeneration but developed adult-onset neurologic decline, contrasting with the previous exclusive association of the R405W mutation with isolated vision loss.[2,3] This observation indicates that some patients sharing this mutation—and perhaps other *CLN3* mutations presently considered to be associated with isolated retinal degeneration—may be at an unknown risk for subsequent development of neurodegeneration.

The marked phenotypic heterogeneity in patients sharing the same "mild" genotype suggests differences in the amount of residual protein activity between patients and implies a significant role for genetic and nongenetic modifying factors.[5] It is known that the propensity of proteins to fold properly despite subtle errors is influenced by the availability of chaperones that aid the folding process.[6]

Future studies will have to delineate whether the onset of the ocular symptoms, which developed significantly earlier in our patient compared with other patients homozygous for the *CLN3* R405W missense mutation,[3] may serve as a predictor of the disease course. Until then, prudence may be warranted when counseling young patients with *CLN3* variants and apparently isolated retinal degeneration.

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1. Kousi M, Lehesjoki AE, Mole SE. Update of the mutation spectrum and clinical correlations of over 360 mutations in eight genes that underlie the neuronal ceroid lipofuscinoses. *Hum Mutat*. 2012;33(1):42-63.

2. Wang F, Wang H, Tuan HF, et al. Next generation sequencing-based molecular diagnosis of retinitis pigmentosa: identification of a novel genotype-phenotype correlation and clinical refinements. *Hum Genet*. 2014;133(3):331-345.

3. Ku CA, Hull S, Arno G, et al. Detailed clinical phenotype and molecular genetic findings in *CLN3*-associated isolated retinal degeneration. *JAMA Ophthalmol*. 2017;135(7):749-760.

4. Anderson G, Smith VV, Malone M, Sebire NJ. Blood film examination for vacuolated lymphocytes in the diagnosis of metabolic disorders; retrospective experience of more than 2,500 cases from a single centre. *J Clin Pathol*. 2005;58(12):1305-1310.

5. Lebrun AH, Moll-Khosrawi P, Pohl S, et al. Analysis of potential biomarkers and modifier genes affecting the clinical course of CLN3 disease. *Mol Med*. 2011;17(11-12):1253-1261.

6. McCabe ERB. Modifier genes: moving from pathogenesis to therapy [published online May 30, 2017]. *Mol Genet Metab*. doi:10.1016/j.ymgme.2017.05.018

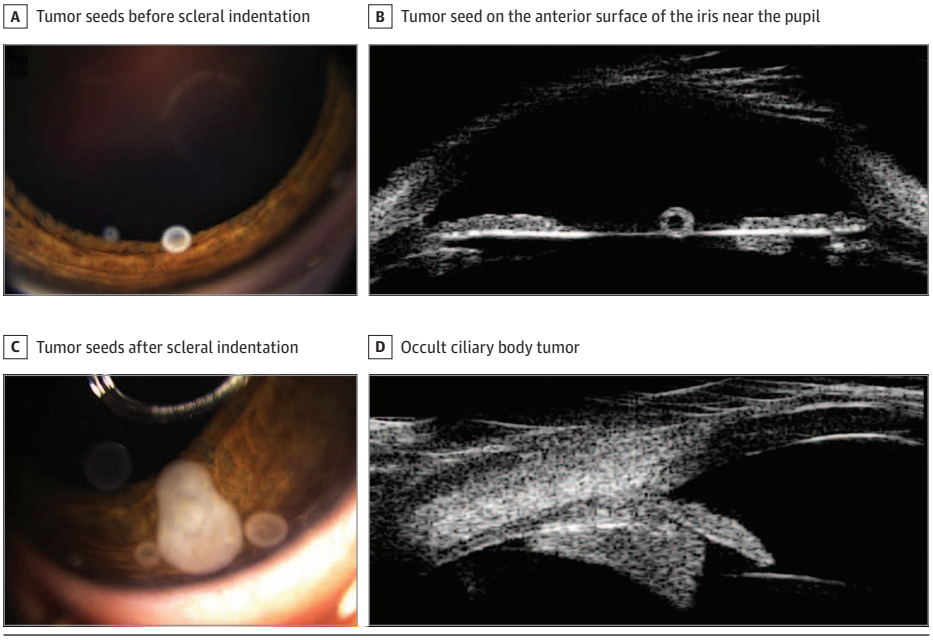
Intracameral Topotecan Hydrochloride for Anterior Chamber Seeding of Retinoblastoma

Anterior chamber seeding is a high-risk characteristic of retinoblastoma that often results in enucleation. We describe the complete and sustained regression of anterior chamber tumor seeding using an intracameral injection of topotecan hydrochloride in the better-seeing eye of a child with bilateral retinoblastoma.

Report of a Case | A 9-month-old girl presented with International Classification of Retinoblastoma[1] group A retinoblastoma in the right eye and group C retinoblastoma in the left eye. The left eye was treated with 3 sessions of intra-arterial chemotherapy using melphalan hydrochloride, 4 mg, carboplatin, 30 mg, and topotecan hydrochloride, 0.3 mg, followed by diode laser therapy, which resulted in stable tumor regression but limited visual potential due to a calcified tumor remnant in the macula.

In the right eye, 2 small retinal tumors were noted in the inferonasal periphery, each measuring 2 × 2 × 1 mm. These tumors were treated with diode laser therapy, resulting in tumor regression and residual chorioretinal scars. After 18 weeks of stable tumor regression, 6 new spherical tumor seeds were identified in the anterior chamber angle between the 4-o'clock and 9-o'clock positions (**Figure 1**A-C). Scleral depression and results of high-resolution anterior segment

Figure 1. Right Eye Prior to Intracameral Topotecan



A, Anterior segment photograph prior to scleral indentation, showing several small spherical tumor seeds. B, High-frequency anterior segment ultrasound demonstrating a tumor seed on the anterior surface of the iris near the pupil. C, Anterior segment photograph after scleral indentation inferonasally, which revealed multiple tumor seeds of varying sizes. D, High-frequency anterior segment ultrasound demonstrating an occult ciliary body tumor at the 4:30 clock position measuring 3.5 × 3.2 × 1.4 mm.