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Presentation of *TRPM1*-Associated Congenital Stationary Night Blindness in Children

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IMPORTANCE Congenital stationary night blindness (CSNB) implies a stable condition, with the major symptom being nyctalopia present at birth. Pediatric clinical presentation and the course of different genetic subtypes of CSNB have not, to our knowledge, been well described in the era of molecular genetic diagnosis.

OBJECTIVE To describe the presentation and longitudinal clinical characteristics of pediatric patients with molecularly confirmed *TRPM1*-associated complete CSNB (cCSNB).

DESIGN, SETTING, PARTICIPANTS This study was conducted at the University of Iowa from January 1, 1990, to July 1, 2015, and was a retrospective, longitudinal case series of 7 children (5 [71.4%] female) with *TRPM1*-associated cCSNB followed up for a mean (SD) of 11.1 (2.8) years.

MAIN OUTCOMES AND MEASURES History, ophthalmologic examination findings, full-field electroretinogram (ffERG) results, full-field stimulus threshold testing results, Goldmann visual field results, optical coherence tomography results, and molecular genetic results were evaluated. Presenting symptoms and signs, the correlation of refractive error with electroretinography, and clinical evolution were analyzed.

RESULTS Seven patients (5 [71.4%] female) presented early in childhood with strabismus (n = 6 [86%]), myopia (n = 5 [71%]), and/or nystagmus (n = 3 [43%]). The mean (SD) age at presentation was 8 (4) months and for receiving a diagnosis by ffERG was 7.3 years, with molecular diagnosis at 9.7 years. The mean (SD) length of follow-up was 11 (2.8) years. The best-corrected visual acuity at the most recent visit averaged 20/30 in the better-seeing eye (range, 20/20-20/60). The mean (SD) initial refraction was −2.80 (4.42) diopters (D) and the mean refraction at the most recent visit was −8.75 (3.53) D (range, −4.00 to −13.75 D), with the greatest rate of myopic shift before age 5 years. Full-field electroretinogram results were electronegative, consistent with cCSNB, without a significant change in amplitude over time. No patient or parent noted night blindness at presentation; however, subjective nyctalopia was eventually reported in 5 of 7 patients (71%). The full-field stimulus threshold testing results were moderately subnormal (−29.7 [3.8] dB; normal −59.8 [4.0] dB). Goldmann visual field results were significant for full I-4e, but constricted I-2e isopter. Eight different mutations or rare variants in *TRPM1* predicted to be pathogenic were detected, with 3 novel variants.

CONCLUSIONS AND RELEVANCE Children with *TRPM1*-associated cCSNB presented before school age with progressive myopia as well as strabismus and nystagmus (but not nyctalopia), with stable, electronegative ffERG results, mildly subnormal full-field stimulus threshold testing results, and a constricted I2e isopter on perimetry. These findings suggest that ffERG and cCSNB genetic testing should be considered for children who present with early-onset myopia, especially in the presence of strabismus and/or nystagmus, and that *TRPM1*-associated cCSNB is a channelopathy that may present without complaints of night blindness in childhood.

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Congenital stationary night blindness (CSNB) is a group of genetically and clinically heterogeneous retinal disorders described as manifesting nonprogressive nyctalopia and an electronegative full-field electroretinogram [ffERG] result.[1] Recently, genetic testing has been added to the diagnostic armamentarium, with at least 17 genes found to be associated with CSNB.[1] This list includes genes encoding proteins involved in phototransduction, photoreceptor to bipolar cell signaling cascades, and retinoid recycling (https://www.omim.org/phenotypicSeries/PS310500).

Complete CSNB (cCSNB) can be X-linked or autosomal recessive and is caused by mutations in genes encoding proteins involved in the ON-bipolar signaling cascade, including *NYX* (Xp11.4; OMIM 300278),[2,3] *GRM6* (5q35.3; OMIM 257270),[4] *GPR179* (17q12; OMIM 614515),[5,6] *LRIT3* (4q25; OMIM 615058),[7] and *TRPM1* (15q13.3; OMIM 603576).[8-10] Patients with cCSNB present with early high myopia, nystagmus, and strabismus.[1,11] Visual acuity ranges from 20/20 to 20/125,[10,12,13] with most patients requiring no academic accommodations due to vision. Not all patients report nyctalopia initially, especially when living in environments with artificial illumination; however, some patients report difficulty navigating in dim light.[11,12] To our knowledge, accounts of subjective nyctalopia have rarely been stratified based on molecular genetic subtype. In patients who present with moderate to high myopia in early childhood, both primary ocular disorders and systemic disorders associated with myopia are considered. Ocular causes include keratoconus, infantile glaucoma, retinopathy of prematurity, or history of persistent macular hemorrhage. Systemic diagnoses, such as Stickler syndrome, Knobloch syndrome, Cohen syndrome, Ehlers Danlos syndrome type 6, and other connective tissue disorders, including those associated with ectopia lentis, may be investigated.[14,15] For early-onset nystagmus without apparent ocular cause, neuroimaging is often completed.[16-19] Unnecessary testing can be avoided by a careful history combined with salient clinical features, ffERG, and molecular confirmation.

We present a series of pediatric patients with *TRPM1*-associated cCSNB who had long-term clinical follow-up starting in infancy or early childhood. To our knowledge, this is one of the first studies to document longitudinal visual function and serial electroretinography and to assess dark-adapted (DA) retinal light sensitivity using full-field stimulus threshold testing (FST) in children who have received a molecular diagnosis.

Key Points

Question What is the childhood presentation and course of transient receptor potential cation channel subfamily M member 1 (*TRPM1*)–associated complete congenital stationary night blindness (cCSNB)?

Findings In this longitudinal study, preschool-aged patients with *TRPM1*-associated cCSNB presented with myopia with strabismus, nystagmus, or both, initially without nyctalopia. Goldmann visual field results demonstrated constriction of finer stimuli (I2e), dark-adapted bright-flash full-field electroretinogram results were electronegative, and the full-field stimulus threshold was moderately elevated.

Conclusion These findings suggest that attention to specific phenotypic features may lead to a prompt diagnosis and avoid unnecessary neurosystemic evaluation; *TRPM1*-associated cCSNB is a channelopathy that should be suspected in preschool-aged children with high levels of myopia even in the absence of night blindness.

Methods

We obtained approval for a retrospective medical record review from the University of Iowa institutional review board. Written consent for research genetic testing and possible publication had also been obtained on a previous University of Iowa institutional review board approval. Ophthalmologic records of children who presented to the pediatric genetic eye disease service from January 1, 2008, to July 1, 2015, were reviewed. Inclusion criteria were a clinical diagnosis of cCSNB, 2 or more complete eye examinations at least 1 year apart with electroretinography, and *TRPM1* variants predicted to be pathologic on genetic testing results.

Clinical information extracted included age at presentation, sex, race/ethnicity, initial diagnosis at presentation, best-corrected visual acuity (BCVA) at age of first optotype acuity and at most recent visit (MRV), initial and final cycloplegic refraction (cyclopentolate, 1%, with retinoscopy at ≥30 minutes postinstallation with manifest in older children), fundoscopic appearance, color vision (Ishihara Color Plates; Kanehara & Co), age at receiving a diagnosis of CSNB, electroretinography (ERG) (Espion E2 V5; Diagnosys), spectral-domain optical coherence tomography of the macula (Spectralis; Heidelberg Engineering), Goldmann visual field results (Haag Streit), and full-field stimulus threshold testing (FST) results (Epsion E; Diagnosys LLC). Parents of preverbal children were routinely asked if their children had difficulty visually locating them in a dark room or tended to cling to parents when walking at night. Older children were asked if they could see the stars at night and whether their eyes took longer to adjust in a dark movie theater or street than their friends'. Full-field ERG testing was conducted in a manner consistent with the International Society for Clinical Electrophysiology of Vision guidelines.[20]

Longitudinal changes in amplitudes for DA combined response 3.0 ERG (3.0), light-adapted 3.0 ERG (light-adapted 3.0) and 30 Hz flicker response were analyzed. A linear mixed-effects model was used to compare initial and final amplitudes of the DA 3.0 b wave, light-adapted 3.0 b wave, and 30-Hz flicker amplitudes. Longitudinal changes in myopic refractive error were compared with ERG b-wave amplitude for DA 3.0- and 30-Hz flicker amplitudes for each patient, also using a linear mixed-effects model. Statistical significance was set at $P \leq .05$.

Full-field stimulus threshold testing was performed as previously described.[21,22] Full-field stimulus threshold testing measures the sensitivity of the entire retina by estimating the lowest luminance (duration, 200 milliseconds) flash that elicits a visual response after dark adaptation. The mean (SD)

Table 1. Clinical Characteristics in Pediatric Patients With Complete CSNB With *TRPM1* Mutations

Clinical Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Presenting age	8 mo ± 4 mo	8 mo ± 4 mo	8 mo ± 4 mo	8 mo ± 4 mo	8 mo ± 4 mo	8 mo ± 4 mo	8 mo ± 4 mo
Strabismus	Yes; X(T)[a] (stereo 6/9)	Yes; E(T) and CN 4 palsy (stereo 0/9)	Yes; X(T) (stereo 5/9)	X (stereo 8/9)[b]	Yes; X(T)[a]	Yes; E(T) (stereo 3/9)	Yes; X(T) (stereo 0/9)
Nystagmus	Yes[c]	No	No	No	Yes[c]	No	Yes
Initial refractive error (SE)	OD: −2.00; OS: −3.50	OD: +1.00; OS: 0.25	OD: −8.50; OS: −8.50	OD: −8.25; OS: −7.75	OD: −1.00; OS: −1.50	OD: −3.50; OS: −3.50	OD: +3.75; OS: +3.75
Systemic studies	Yes (MRI normal)	No	Yes (Stickler syndrome evaluation)	Yes (Stickler syndrome evaluation)	No	Yes (MRI normal)	Yes (MRI normal)
Initial clinical diagnosis	Spasmus mutans	CN 4 palsy	Pathologic myopia	Pathologic myopia	Myopia	Infantile nystagmus	Opsoclonus
Age nyctalopia reported	Progressive, preteen	Progressive, child	Progressive, child	None reported	None reported	Toddler	Child
First BCVA, y	5	5	5	5	6	4	4
First BCVA (Snellen/logMAR)	OD:20/50 (0.400); OS:20/30 (0.176)	OD: 20/50 (0.400); OS:20/70 (0.544)	OD:20/40 (0.301); OS:20/40 (0.301)	OD:20/20 (0.000); OS:20/25 (0.097)	OD: 20/70 (0.544); OS: 20/70 (0.544)	OD: 20/40 (0.301); OS: 20/30 (0.176)	OD: 20/100 (0.699); OS: 20/200 (1.00)
Age final, y	15	14	11	9	9	15	10
BCVA final, Snellen (logMAR)	OD: 20/20 (0.000); OS: 20/20 (0.000)	OD: 20/40 (0.301); OS: 20/70[d] (0.544)	OD: 20/25 (0.097); OS: 20/20 (0.000)	OD: 20/20 (0.000); OS: 20/20 (0.097)	OD: 20/80[d] (0.602); OS: 20/60 (0.477)	OD: 20/20 (0.000); OS: 20/20 (0.000)	OD: 20/40 (0.301); OS: 20/50 (0.398)
Final refractive error (SE)	OD: −4.00; OS: −4.25	OD: −5.50; OS: −6.50	OD: −13.75; OS: −14.00	OD: −9.00; OS: −8.00	OD: −6.50; OS: −6.00	OD: −13.50; OS: −14.00	OD: −9.00; OS: −10.25
Color discrimination	Full	Full	Full	Full	Full	Full	Full
Fundus	ON: tilted; myopic; few hypo-pigmented areas	ON: tilted, temporal pallor; myopic fundus	ON: tilted; myopic, lattice	ON: tilted; myopic, cystic retinal tuft OD	ON: tilted; tessellated, myopic fundus	ON: tilted; myopic	ON: tilted; tessellated, myopic fundus
GVF	NML OU	Mild I-2e depression (full to I-4e) OU; small central scotoma OU	Mild I-2e depression (full to I-4e) OU	Mild I-2e depression (full to I-4e) OU	Mild I-2e depression (full to I-4e) OU	Mild I-2e depression (full to I-4e) OU; small central scotoma OU	Mild I-2e depression (full to I-4e) OU
FST, dB[e]	OD: −34.5; OS: −31.5	OD: −28.2; OS: −26.6	OD: −31.4; OS: −29.6	OD: −26.6; OS: −28.9	OD: −22.5; OS: −27.8	OD: −29.2; OS: −27.4	OD: −36.0; OS: −35.5
ffERG final	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG	Electronegative DA 3.0 ERG
SD-OCT macula, CST, um; CV, mm^2	OD: 226 µm, 8.4 mm^2; OS: 250 µm, 8.5 mm^2	OD: 246 µm, 6.01 mm^2; OS: 234 µm, ND	OD: ND; OS: 387 µm, 11.68 mm^2	OD: 237 µm, 7.85 mm^2; OS: 236 µm, 7.82 mm^2	OD: 259 µm, 8.29 mm^2; OS: 275 µm, 8.01 mm^2	ND	OD: 233 µm, 8.56 mm^2; OS: 235 µm, 7.91 mm^2

Abbreviations: BCVA, best-corrected visual acuity; CN 4, congenital fourth nerve palsy; CSNB, congenital stationary night blindness; CST, central subfield thickness; CV, central volume; DA, dark-adapted; ERG, electroretinogram; ffERG, full field electroretinogram; ffFST, full-field sensitivity threshold test; FST, sensitivity threshold test; GVF, Goldmann visual field; E(T), intermittent esotropia; MRI, magnetic resonance imaging; ND, not done; NML, normal; SD-OCT, spectral-domain optical coherence tomography; SE, spherical equivalent; Stereo, stereopsis by Titmus testing given as number correct; Strab, strabismus; X(T), intermittent exotropia.

[a] Had strabismus surgery.

[b] Initially had orthophoria and then developed exophoria.

[c] Nystagmus resolved by age 2 years in patients 1 and 5.

[d] Amblyopia.

[e] Normal FST is less than or equal to −55.00 dB.

threshold in unaffected participants in our laboratory is −59.8 (4.0) dB, which is similar to published normative data,[21,58] with intertest variability of ±3.1 dB.[22]

Molecular Studies

Blood samples had been sent for commercial testing to the Carver Laboratory at the University of Iowa, GeneDx (Gaithersburg, Maryland), or the Casey Eye Institute at the Molecular Diagnostic Laboratory, and all were confirmed by the Carver Non-profit Genetic Testing Laboratory at the University of Iowa.

Results

Seven patients (5 [71.4%] female) from 5 families were included. Self-reported races/ethnicities included white/Northern European, Hispanic, and Middle Eastern/Ashkenazi Jewish. Patients presented for initial ophthalmologic examination at a mean (SD) age of 8 (4) months (range, 2-15 months) with a mean (SD) follow-up of 11 (2.8) years (range, 7.5-14 years) (**Table 1**). Presenting signs included strabismus (6 of 7 [85.7%]), myopia (5 of 7 [71.4%]), and/or nystagmus (3 of 7 [42.9%], with

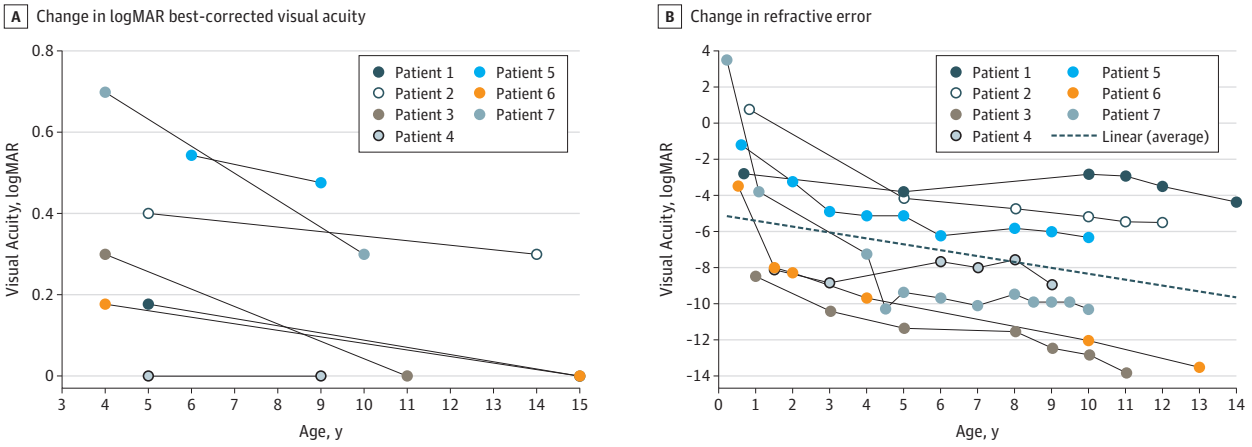
Table 2. Longitudinal Clinical Diagnoses and Molecular Characteristics[a]

	Initial Clinical Diagnosis	Age of cCSNB Diagnosis	Intron/Exon	Nucleotide	Protein Effect	Reported Mutation
Patient 1	Spasmus mutans	Preteen	IVS8, exon 5	c.1023 + 1 G>A, c.1406 *t* > C	Splice site, p.L469S	Yes, EPP3
Patient 2	4th Nerve palsy	Child	IVS8, exon 5	c.1023 + 1 G>A, c.1406 *t* > C	Splice site, p.L469S	Yes, EPP3
Patient 3	Pathologic myopia	Child	Exon 4, exon 4	c.215A>G, c.215A>G	p.Y72C, p.Y72C	Yes, yes
Patient 4	Pathologic myopia	Toddler	Exon 4; exon 4	c.215A>G, c.215A>G	p.Y72C, p.Y72C	Yes, yes
Patient 5	Nystagmus	Child	Exon 4; exon 20	c.296T>C, c.2597-2599del	p.L99P, p.Ser866del	Yes, EPP3
Patient 6	High myopia	Child	Exon 20	c.2894A>C, deletion of exon 2-7	p.D965A, no functional protein	No-novel VUS, Yes
Patient 7	Opsoclonus	Child	Exon 16, deletion of *TRPM1*	c.1871G>A, undefined large deletion encompassing *TRPM1*	p.R624H, lack of protein	Yes, no

Abbreviations: CSNB, congenital stationary night blindness; EPP, estimate of pathologic probability; NA, not applicable; VUS, variation of unknown significance; XL, x-linked.

[a] EPP of 3 and 2 mean chance probability of mutation causing disease is highly likely and possibly likely, respectively. EPP of 0 being a known benign polymorphism, and EPP 1 being a potentially low penetrance or modifying allele. Nucleotide numbering is based on reference sequence of *TRPM1* (NM_002420.5), where A of the ATG initiation codon is 1.

Figure 1. Visual Acuity and Refractive Error



A, Change in logMAR best-corrected visual acuity in the better-seeing eye of patients from time of initial recognition acuity to most recent visit. B, Change in refractive error from initial examination to most recent visit. The dotted line represents the average myopic change of the entire cohort.

two-thirds resolving by age 2 years. Systemic evaluation was completed in 5 of 7 patients (71.4%) and included magnetic resonance imaging (3 of 7 [42.9%]; all normal results), and clinical and molecular evaluations for connective tissue disorders associated with high myopia (3 of 7 [42.9%]; all negative results). Initial diagnoses included pathologic myopia, congenital motor nystagmus, spasmus nutans, strabismus, retinitis pigmentosa, Stickler syndrome, Ehlers Danlos syndrome type 6, opsoclonus, and ametropic amblyopia (**Table 2**).[1,8,10,23-25] At the MRV, all patients had strabismus and decreased stereopsis (Table 1). Congenital stationary night blindness was not initially suspected, and a clinical diagnosis was made at the mean (SD) age of 7.4 (2.4) years (Table 2) following a diagnostic ERG. Five previously reported mutations[1,8,10,23] and 3 rare sequence variations, including 2 deletions predicted to be pathogenic, were identified (Table 2).

Sibling patients 1 and 2 shared 2 mutations, one known to be pathologic and the other novel and predicted to be pathologic. Sibling patients 3 and 4 were homozygous for mutation c.215A>G (p.Y72C); each parent was heterozygous. Patient 5 had 1 known pathologic mutation and a novel inframe deletion predicted to be pathologic on separate alleles based on parental testing results. Patient 6 had 1 known mutation and 1 variant of uncertain significance. Patient 7 was heterozygous for a reported[1] rare variation predicted by PolyPhen-2 to be deleterious and a large deletion predicted to be deleterious, which are on separate alleles based on parental testing results.

Best-corrected visual acuity improved with age (**Figure 1**A). At MRV, the average visual acuity of the better-seeing eye for all patients was 20/30 (range, 20/20-20/60; logMAR, 0.19 ± 0.25). The average initial spherical equivalent was −2.75 diopters (D) (range, +3.75 to −8.50) and the final spherical equivalent at MRV was −8.75 D (range, −4.00 to −14.00) at the mean age of 12 years (Figure 1B). Average change in myopic refractive error from the initial visit to 5 years of age was −1.07 D/y and between age 5 years and MRV age was −0.25 D/y.

Fundus examination results were similar in all patients, with myopic tilting of the optic nerves, tessellation of the

posterior pole, and absence of peripheral pigmentary changes (**Figure 2**A). The spectral-domain optical coherence tomography of the macula demonstrated a normal lamination pattern with an intact ellipsoid zone, with staphylomatous excavation in several of the patients (Figure 2B). In all patients, Goldmann visual field results were full to Stimulus I4e, with constriction of the I2e isopter in 6 of 7 patients (85.7%). One patient had small central scotomas. Mild constriction of the I2e isopter was found whether patients were tested with glasses or contact lenses (Figure 2C; eFigure 1 in the Supplement).

All patients had more than 1 ffERG performed over an average of 44 months (range, 12-60 months). The ERG results were consistent with cCSNB, and ffERGs were almost superimposable among patients (Figure 2D; eFigure 2 in the Supplement). All patients demonstrated very low-amplitude DA dim flash (DA 0.01) responses, and electronegative DA bright flash response (DA 3.0) as well as biphasic oscillatory potentials and flattened photopic a-waves (eFigure 2 in the Supplement). When viewed individually, patients 1, 2, and 6 appear to have clinically meaningful decline (≥20%-25% change in amplitudes) in DA 3.0 b wave amplitudes (**Figure 3**). However, when analyzed collectively, there was no statistically significant decline in the DA 3.0 b-wave amplitude (95% CI, −20.136 to 23.050; $P = .90$) or b/a ratio (95% CI, −0.078 to 0.056; $P = .76$) (Figure 3). The photopic light-adapted 3.0 b wave amplitude (light-adapted 3.0) and 30-Hz flicker response declined more than the DA amplitudes; however, they were not statistically significant (95% CI, −28.183 to −0.817; $P = .06$; and 95% CI, −24.552 to −0.264; $P = .07$, respectively) (Figure 3). The decline in DA 3.0 b-wave and 30-Hz flicker amplitudes did not correlate with increase in myopic refraction (95% CI, −0.030 to 0.027; $P = .92$; and 95% CI, −0.039 to 0.004; $P = .16$, respectively) after controlling for the association of age. There is a significant association of age with the change in myopic refraction (95% CI, −1.17 to −0.30; $P = .01$) after controlling for b wave difference (95% CI, −1.02 to −0.14; $P = .03$ after controlling for 30-Hz difference).

No patient or parent noted nyctalopia at presentation; however, 5 of 7 patients (71%) eventually endorsed some nyctalopia with a mean (SD) age at onset of 6 (3.1) years (range, 2-10 years). Two patients identified it as disrupting their activities, and 3 noted progressive nyctalopia. Dark-adapted FST results were subnormal in all patients who were tested. The mean (SD) FST scores were −29.7 (3.6) dB OU, −29.8 (4.1) dB OD (range, −36 to −22.5), and −28.6 dB OS (range, −35.5 to −26.6) compared with the normal mean (SD) of −59.8 (3.6) dB OD and −59.9 (4.5) dB OS for our laboratory (eFigure 3 in the Supplement). Patients without complaints of nyctalopia did not have different FST results from those who did.

Discussion

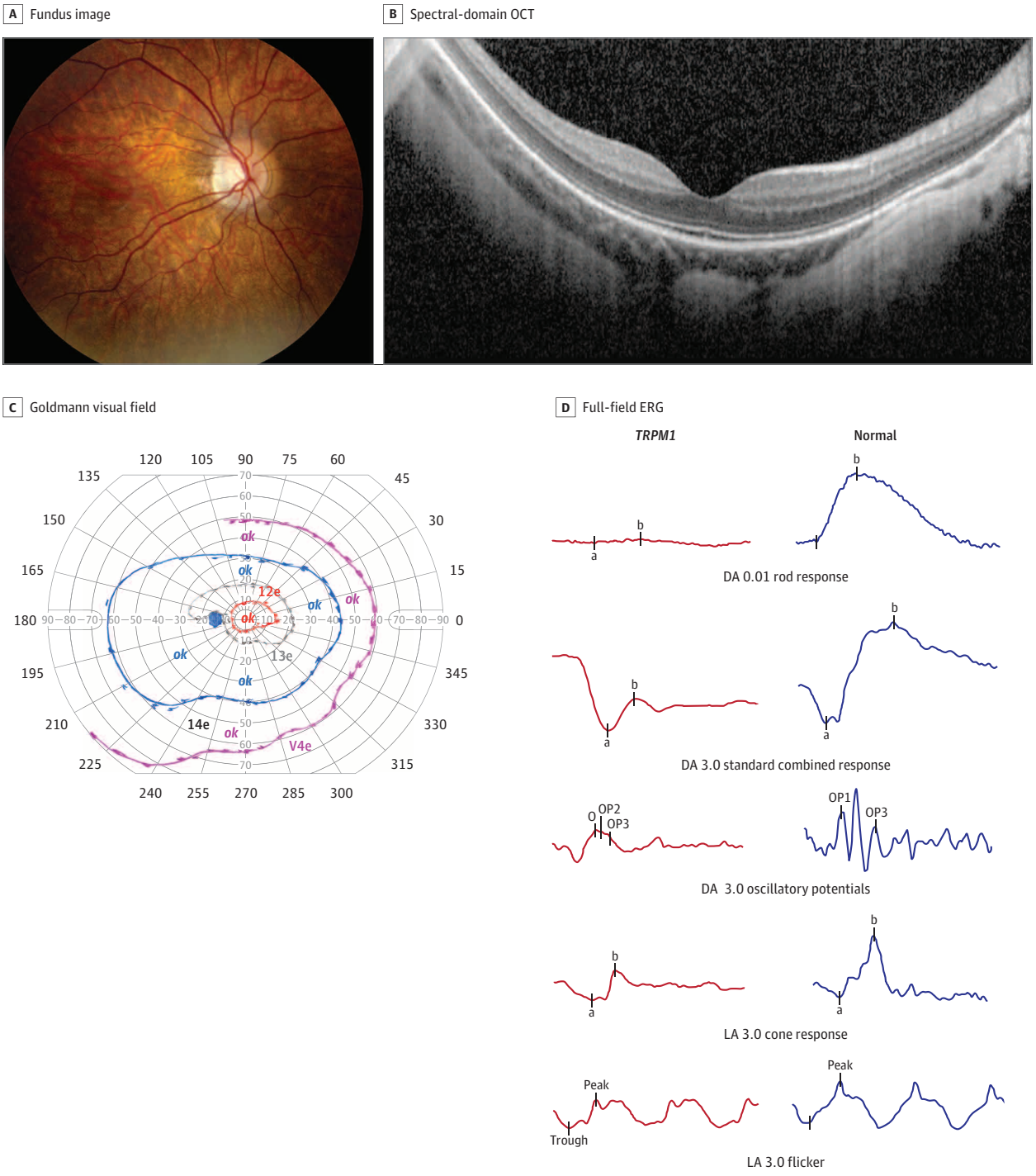
Our study describes the pediatric presentation and childhood course of *TRPM1*-associated cCSNB. This is one of the first reports, to our knowledge, of serial ffERGs and FST testing in children with this disorder. Our data suggest that young children presenting with high myopia, strabismus, and nystagmus should be offered ERG evaluation even in the absence of complaints of night blindness. It is possible that the night vision deficit is only noticed at older ages when more activities are done independently vs a true worsening of night vision. In other disorders with congenital or early-onset night blindness, such as rhodopsin-associated retinitis pigmentosa or *RPE65*-associated Leber congenital amaurosis (LCA), parents notice from the earliest months of life that the child cannot see them in a dark room; that was not the case for these infants with *TRPM1* mutations, although most parents and children noted decreased vision in the dark.

Strengths and Limitations

The limitations of this study that limit the confidence in the definitiveness of the conclusions include the small number of patients evaluated and the retrospective nature of the data collection. *TRPM1* encodes the transient receptor potential melastatin 1 (TRPM1) cation channel located in the dendritic tips of ON-bipolar cells.[26,27] Failed expression or localization of TRPM1 leads to loss of the ON-bipolar response and cCSNB.[26,27] Transient receptor potential melastatin 1 localization and function depends on its protein-to-protein interactions with a large multiprotein complex,[27] including cCSNB-implicated proteins glutamate receptor metabotropic 6 (GRM6),[4] probable G-protein coupled receptor 179 (GPR179),[5,6] leucine-rich repeat immunoglobin-like and transmembrane domains 3 (LRIT3),[7] and nyctalopin (NYX).[2,3] In the dark, increased calcium influx into the rod axon leads to glutamate release in the synapse and is detected by GRM6, which subsequently binds the heterotrimeric G-protein, leading to the closure of the nonselective TRPM1 channel and hyperpolarization of the ON-bipolar cell.[26,28,29] In response to light, glutamate concentration is decreased in the synapse and leads to TRPM1 channel opening, depolarizing the ON-bipolar cells that contribute to the b wave. The DA 0.01 pathway originates in the rod photoreceptors and is transmitted to rod ON-bipolar cells then to A11 amacrine cells (and cone bipolar cells) and finally to the ganglion cells.[30] The absence or dysfunction of any proteins involved with the expression, localization, or function of TRPM1, or from mutations affecting the TRPM1 channel itself, leads to diminished signal transduction of rod ON-bipolar cells, leading to diminished DA 0.01 dim flash amplitudes and an electronegative DA 3.0 bright flash response.[19,23,31-34] To date, 73 nonsense, missense, frameshift, splice site, and large or microdeletions have been identified in *TRPM1,* with 67 of those causing a CSNB phenotype.[1,8-10,35-47] Some mutations, such as splice site, result in loss of TRPM1 function, while some missense mutations lead to a mislocalization of TRPM1.[23] Genotype-phenotype studies will help delineate the mechanisms for specific mutations in *TRPM1*.

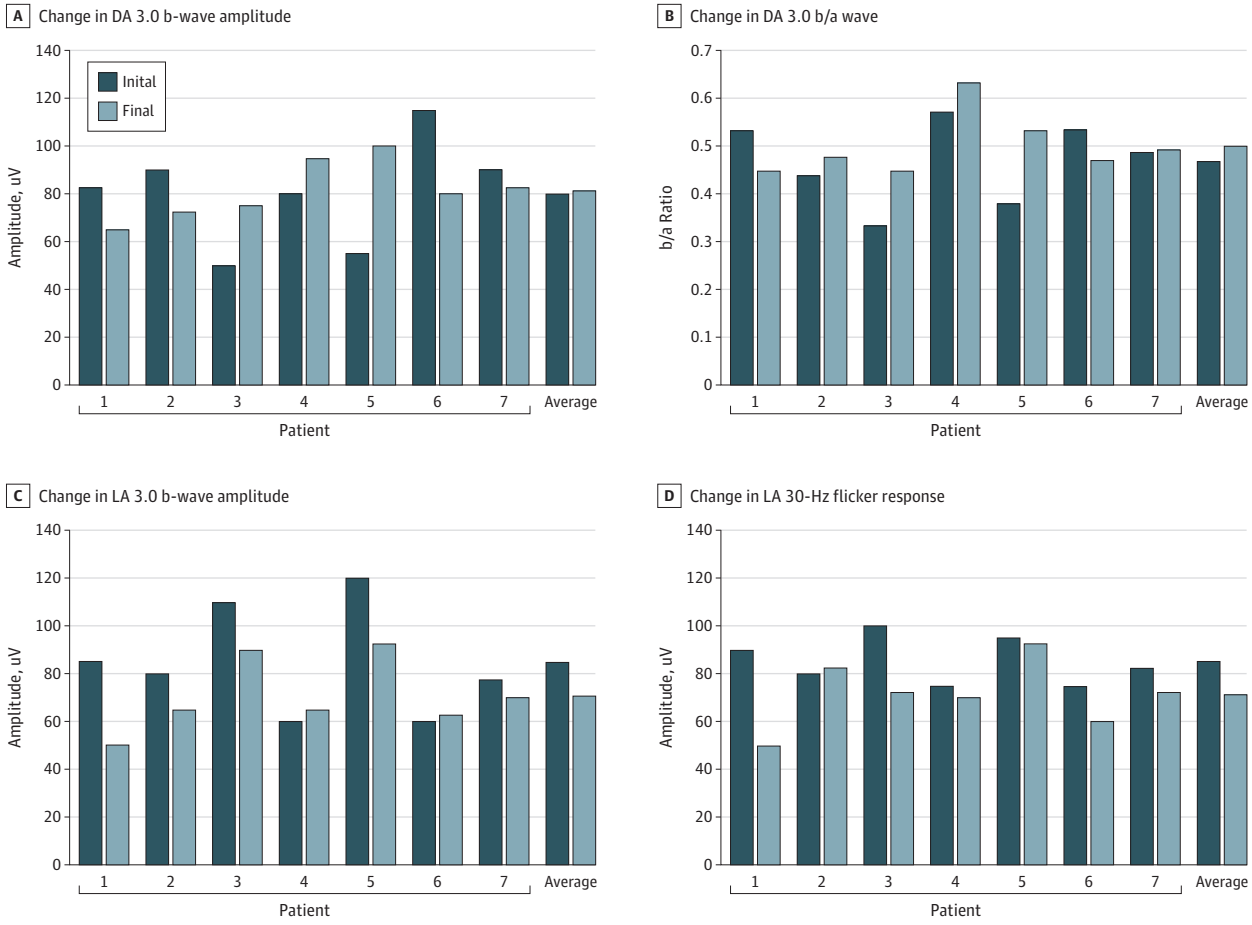
Visual acuity in our cohort at MRV averaged 20/30 in the better-seeing eye (range, 20/20-20/70). Vision improved, likely reflecting improved testing performance with advancing age (Figure 1A). The BCVA in this cohort concurs with other studies of patients with cCSNB;[42] however, a range of BCVA from 20/20 to 20/125 has been reported.[10] Our study also concurs with others that report nystagmus diminishing or resolving over time;[48] however, 1 of the patients had large-amplitude,

Figure 2. Representative Composite of Imaging and Visual Function Studies for Patients With *TRPM1*-Associated Complete Congenital Stationary Night Blindness



A, Typical fundus appearance of a patient with *TRPM1* mutations. The right eye demonstrates myopic fundus with tilting of the optic disc and a peripapillary crescent. These features were universal, and no patients had bone spicule–like pigmentation or arteriolar narrowing. B, Spectral-domain optical coherence tomography (OCT) of right eye of patient 5. Note the normal lamination pattern with preservation of the outer retinal layers and staphylomatous excavation of the overall contour. All OCTs were similar. C, Goldmann visual field results for patient 5. Patient 5 demonstrates a small central scotoma and constriction of the I2e isopter. The central scotoma was not uniformly present; however, constriction of the I2e isopter was present in 6 of 7 patients (85.7%) (eFigure 1 in the Supplement). Ok indicates that the area was tested and was within normal limits. D, Representative full-field electroretinography (ERG) waveforms of patient 5 at age 13 years compared with a normal ERG waveform. Note the electronegative standard combined response (dark-adapted [DA] 3.0), biphasic oscillatory potentials and flattened, broad a wave on light-adapted (LA) 3.0 bright flash (LA 3.0).

Figure 3. Change in Electroretinogram for Each Individual Patient and Average for Cohort



A, Change in dark-adapted (DA) 3.0 b-wave amplitude (P = .90). B, Change in DA 3.0 b/a wave (P = .78). C, Change in light-adapted (LA) 3.0 b-wave amplitude (P =.07). D, Change in LA 30-Hz flicker response (P = .07). While the average change for the cohort was greatest for LA responses, it was not statistically significant.

persistent nystagmus that was initially suspected of being opsoclonus. This patient had a gross deletion of 1 copy of *TRPM1*, which may have led to a more severe phenotype, or the patient's genetic background may have influenced the severity (Table 2).

No decline between initial and final ERG amplitudes for the group of patients occurred, consistent with a stationary disorder (Figure 3). Some individual patients, such as patient 1, had a decline in amplitudes over time, which might have led the clinician to suspect photoreceptor degeneration. High intertest variability inherent to ERG (up to 20%-25%)[49,50] and our small sample size make interpretation difficult.

Some variability was present between siblings sharing identical mutations. Patient 1 exhibited higher and earlier myopia and nystagmus than his sibling, patient 2, but ended with better BCVA and stereopsis and less myopia (Table 1). Both siblings had strabismus; patient 1 had exotropia and patient 2 had esotropia and fourth nerve palsy. Both complained of progressive nyctalopia. Patient 3 had better retinal sensitivity on FST than sibling patient 4; however, only patient 3 reported nyctalopia.

From the earliest reports of *TRPM1*-associated cCSNB in humans by Audo et al,[8] high myopia has been consistently reported.[9,10,23] Myopia has been reported to occur in all genetic types of cCSNB.[1] Transient receptor potential melastatin 1 may play a role in emmetropization, supported by the finding that the patients did not have the usual course of juvenile myopia. In contrast to "school-age" or juvenile-onset myopia, in which myopic progression is most pronounced from ages 6 to 15 years (0.35-0.60 D per year),[51-53] *TRPM1*-associated myopia progressed most rapidly in the first 5 years of life, with mean (SD) myopic correction at age 5 years of −7.3 (2.9) D and a mean (SD) change from initial visit to 5 years of age of −1.07 (.897) D/year. Refractive error change was minimal during the school-age years (−0.25 D/year). At MRV, average age 12 years, refraction was −8.8 (3.8) D. This suggests a different mechanism from typical juvenile myopia. Hendriks et al[54] reported that disorders disrupting bipolar cells have the highest risk of high myopia and that the involved cell type in retinal dystrophies correlate with different refractive errors.

Full-field stimulus threshold testing is a psychophysical test that measures the DA retinal intensity threshold.[22] Young

children are able to perform FST, which has been used in clinical treatment trials for LCA.[21,55-58] Full-field stimulus threshold testing in patients with *TRPM1* revealed mild to moderate loss of sensitivity of −29.7 (3.8) dB compared with −59.8 (4.0) dB in controls. Other conditions causing nyctalopia, such as *RPE65* LCA (FST, approximately −9 dB),[55] *CEP290* LCA (lack of rod sensitivity, variable cone sensitivity),[59] and *GUCY2D* retinopathy (−19 dB [data not shown]; rod sensitivity reduced by 0.5 to 5 log units in LCA),[60] show greater loss. Van Genderen et al[10] reported that Goldmann Weekers dark adaptometry was abnormal in a patient with *TRPM1*-associated cCSNB. This test measures the length of time to recover function after a bleaching light; the rods were not recovered after 20 minutes. In contradistinction, FST measures retinal sensitivity after 45 minutes of dark adaptation. Dark-adapted retinal sensitivity is more mildly affected in young patients with *TRPM1* than would be predicted based on previously reported dark adaptometry. Thus, while the dark adaptometry curve appears to show little rod response, the sensitivity of the retina after 45 minutes of dark adaptation is only 40% to 50% reduced in the pediatric patients. The variable nyctalopia in our cohort differs from previous studies by Bijveld et al[42] in which 100% of Dutch patients with cCSNB reported nyctalopia. However, in other studies, the authors concluded that symptoms might be subtle and not disabling in modern artificial light conditions.[13] In controlled lighting conditions, patients with cCSNB experienced blindness at low intensities (equal to starlight) and quickly regained function at light intensities equal to moonlight.[13] Interestingly, in our cohort of 5 patients who eventually reported nyctalopia (at a mean [SD] age of 6 [3.1] years), 3 (60%) reported progression. Nyctalopia may not be progressive; older children may recognize night vision deficits with more independent activities at night. It is possible that the older age of participants (median, 18 years) in the Bijveld et al study[42] resulted in their higher number of patients with nyctalopia.

Visual fields are reportedly normal in both incomplete and complete forms of CSNB.[1] Six of the 7 patients (85.7%) had depression of the I2e isopter regardless of BCVA, refractive error, FST, or contact lens vs glasses correction, and 1 patient (14.3%) had small central scotomas (eFigure 1 in the Supplement). This may be related to myopic fundus changes with the stretching of the posterior pole changing the spacing between cone photoreceptors and the decreasing resolution of small targets,[61] or to primary cone dysfunction. In the Appaloosa horse, a naturally occurring animal model of *TRPM1*-associated CSNB, acuity in bright light sometimes decreases over time.[8,62,63]

Most of the patients presented with horizontal strabismus (esotropia or exotropia) and all had diminished stereopsis. The *TRPM1* Appaloosa horse has also been reported to exhibit strabismus.[62,64] To our knowledge, the effect of *TRPM1* mutations on the oculomotor system is unknown. Retinal degenerations that decrease peripheral vision often exacerbate phorias or latent strabismus due to loss of peripheral fusion necessary to stabilize ocular alignment; however, the patients had full peripheral visual fields. The synaptic function of *TRPM1* may contribute to retinogeniculate projections or other neuroretinal functions that play a role in oculomotor alignment.

Conclusions

The prominence of "night blindness" in the term *CSNB* should not lead physicians away from considering this diagnosis for children who present with preschool myopia without complaints of nyctalopia, especially if strabismus and/or nystagmus are also present. Full-field electroretinography should be offered, and if a characteristic electronegative pattern is identified, molecular genetic testing of cCSNB genes should be considered. If *TRPM1* mutations are present, parents can be counseled to make subtle modifications, such as having children carry a flashlight or cellular phone to provide illumination if the conditions require it. Myopia and subjective nyctalopia may progress over time, while nystagmus may decrease.

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Invited Commentary

Revisiting Congenital Stationary Night Blindness in the Molecular Era

Robert K. Koenekoop, MD, PhD

Once in a while an article appears that asks important questions, makes us think, and provokes change. In this issue of *JAMA Ophthalmology*, the article by Miraldi Utz et al[1] does just that.

We are in the midst of an unprecedented and exciting paradigm shift in ophthalmology and the visual sciences. We are deepening our understanding and appreciation of novel therapies for inherited retinal diseases (IRDs), diseases that we thought were untreatable only 20 years ago. However, to develop treatments for IRDs, we must understand the molecules of vision and we need to match the new IRD-associated genes to their phenotypes. Arguably, a second earlier and equally exciting paradigm shift was the elucidation of molecular players of the phototransduction cascade, the retinoid cycle, and intraflagellar transport. George Wald's elucidation of the phototransduction cascade in 1965 led to the discovery of the first molecules of vision, which in turn led to the involvement of these mutant proteins in different IRD diseases, and subsequently the Nobel prize for Wald. The "Wald cycle," or phototransduction cascade, starts the visual process by the biological conversion of photons of light, leading to the excitation of retinal molecules and electrical signaling from photoreceptors to bipolar cells followed by visual perception in the cerebral cortex.

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It was these discoveries and subsequent assignments of molecules to phenotypes (ie, rhodopsin to retinitis pigmentosa [RP], cone cyclic nucleotide-gated channel proteins to achromatopsia, guanylate cyclase to Leber congenital amaurosis, and many others) that prompted this paradigm shift. This revolution started in 1990 by Dryja et al[2] for RP and rhodopsin and Cremers and colleagues[3] for choroideremia and rab escort protein 1, who identified the corresponding *RHO* and *CHM* genes using candidate gene and positional cloning approaches, respectively. Today we know that approximately 250 genes that are associated with IRDs. In addition to gene discoveries and matching retinal genes to specific phenotypes, it is also imperative to study the natural history of each genotype and phenotype, as it is crucial to measure the rates and slopes of visual decline to allow documentation of changes in these declines (slow down, arrest, or improve) due to experimental treatments.

Miraldi Utz et al[1] report the first natural history study of a genetic subtype of complete congenital stationary night blindness (CSNB) caused by biallelic mutations in *TRPM1*. Although small in size, this study is large in its results, its conclusions, and the resulting important questions that emerge.

Congenital stationary night blindness is a common group of IRDs that can be subcategorized in 3 inheritance groups (X-linked, autosomal recessive, and dominant) and 2 functional groups (complete and incomplete). We currently know of 16 genes mutated in CSNB, 11 in autosomal recessive CSNB, 2 in X-linked CSNB, and 3 in dominant CSNB.

In 1952, before the Wald cycle was described, Schubert and Bornschein[4] discovered that some patients with CSNB may have an abnormal, interesting looking electroretinography (ERG) image. Whereas a normal ERG consists of a small a wave generated inside the photoreceptors and the much larger B wave generated in the bipolar cells, and whereas patients with RP often have extinguished a and b waves and ERG results, patients with CSNB may have an ERG in which the a wave is larger than the b wave, therefore called an electronegative ERG, aka the "Schubert-Bornschein ERG."