Ocular phenotype in patients with methylmalonic aciduria and homocystinuria, cobalamin C type

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PURPOSE To assess and compare longitudinal visual function and retinal morphology in patients with methylmalonic aciduria with homocystinuria, cobalamin C type (*cblC*), and identified mutations in the *MMACHC* gene.

METHODS Vision function, anterior segment, and fundi were evaluated in patients with homozygous or compound heterozygous *MMACHC* mutations. Best-corrected visual acuity, full-field electroretinogram (ERG), refractive error, and retinopathy were assessed and compared for different genotypes and ages at onset, defined as early (<1 year of age) or late (>5 years).

RESULTS We identified 7 patients (homozygous mutation: 6 of 7; compound heterozygous mutations: 1 of 7) between the ages of 3 months and 20.6 years. Six patients were reexamined after 3.2 to 11.5 years (mean, 6.5) Ocular phenotype ranged from normal to severely compromised visual function. Visual acuity was reduced from 0.2 logMAR to counting fingers and from 0.0 to 0.3 logMAR in the early- (3 of 7) and in the late-onset group (4 of 7), respectively. No retinopathy was evident in the late-onset group. Only patients with the homozygous c.547_548 delGT mutations (n = 2) demonstrated advanced retinopathy associated with cone-rod or rod-cone dysfunction. Retinopathy occurred despite systemic treatment for *cblC*.

CONCLUSIONS Ocular phenotype in patients with *cblC* is variable. Ocular involvement seems to be correlated with age at onset. Patients with early-onset *cblC* developed generally progressive retinal disease ranging from subtle retinal nerve fiber layer loss to advanced macular and optic atrophy with "bone spicule" pigmentation. Patients with late-onset disease showed no definite evidence of retinal degeneration. (J AAPOS 2008;12:591-596)

Methylmalonic aciduria with homocystinuria, cobalamin C type (*cblC*) is the most common inborn error of vitamin B12 metabolism. *CblC* is an autosomal-recessive disorder caused by mutations in the *MMACHC* gene.[1,2] Early- and late-onset subgroups are distinguished based on the age at onset. Patients with early-onset (>1 year old) disease seem to be affected more severely than those with later onset. Patients within the early-onset subgroup show acute neurological deterioration, multisystem pathology, pancytopenia, megaloblastic anemia, moderate-to-severe cognitive disabilities, and progressive retinopathy. Findings in the late-onset subgroup include gait abnormalities, extrapyramidal symptoms, psychiatric disturbances, dementia, and mild-to-moderate cognitive disability but no retinopathy.[3,4] Lerner-Ellis et al[1] and Morel et al[2] demonstrated a correlation between genotype and age at onset and identified a founder effect of mutations among certain ethnicities. Systemic treatment of *cblC* typically includes hydroxycobalamin, betaine, vitamin supplementation, and carnitine.

Few case reports or longitudinal data about the ocular involvement associated with *cblC* have been published.[5-17] None of these reports provides longitudinal data of patients with genetically identified *cblC*. Here, we present detailed ocular function data over a relatively long follow-up period of patients with *cblC* and identified mutation in the *MMACHC* gene. We found that patients with early-onset disease showed reduced vision function and progressive or stationary retinal dysfunction in contrast to patients with late-onset disease.

Methods

Patients with *cblC* were identified through the database of the Division of Clinical and Metabolic Genetics at The Hospital for Sick Children, Toronto, Canada. Mutations in the *MMACHC* gene already were detected by molecular genetic testing per-

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Table 1. Genotype and clinical characteristics of subjects

Patient/sex	DNA	*MMACHC* mutation predicted effect on protein, (Lerner-Ellis et al 2006)	Age at onset	Initial clinical presentation	Clinical course with treatment
1/M	c.547_548delGT c.547_548delGT	p.V183TfsX5 p.V183TfsX5	<1 mo	Failure to thrive, lethargy, feeding difficulties, hypotonia, temperature instability, metabolic acidosis, macrocytic anemia, neutropenia, thrombocytopenia, hepatic dysfunction	Development within normal limits, small for age, microcephaly
2/M	c.547_548delGT c.547_548delGT	p.V183TfsX5 p.V183TfsX5	<1 mo	Respiratory distress, lethargy, encephalopathy, hypothermia, developmental delay, pancytopenia, thrombotic renal microangiopathy, nephrotic syndrome	Renal function normalized, developmental improvement
3/M	c.331C>T c.666C>A	p.Arg111X p.Y222X	<1 mo	Poor feeding, encephalopathy, developmental delay, hypothermia	Developmental improvement
4/F	c.394C>T c.394C>T	p.Arg132X p.Arg132X	12 yrs	Progressive dementia, mood disorder, seizures, peripheral neuropathy, lactic acidosis	Symptoms resolved, residual peripheral neuropathy
5/F	c.394C>T c.394C>T	p.Arg132X p.Arg132X	6 yrs	Weight loss, developmental delay, seizure disorder, encephalopathy	Developmental improvement, seizures controlled
6/F	c.3G>A c.3G>A	p.Met1? p.Met1?	12 yrs	Developmental delay, behavioral difficulties, megaloblastic anemia	Developmental and behavioral progress
7/F	c.3G>A c.3G>A	p.Met1? p.Met1?	6 yrs	Developmental delay, regression of skills, failure to thrive, severe behavioral problems, macrocytic anemia, arachnodactyly with Marfanoid habitus, osteopenia, seizures	Developmental and behavioral improvement

formed previously in all patients included in this study. Disease onset was defined as early (<1 year of age) and late (>5 years).

Data were collected retrospectively and prospectively. Patients who did not have a recent eye examination were invited to return for a repeat visit. Written informed consent and/or assent was obtained from all participants and/or their substitute decision makers. The project was approved by the Research Ethics Board at The Hospital for Sick Children.

All patients received a comprehensive eye examination, including dilated fundus examination. Best-corrected visual acuity was tested in a manner appropriate for the patient's age and developmental ability with the use of Teller Preferential Looking Cards, Snellen Acuity Charts, or the backlit Early Treatment Diabetic Retinopathy Study Charts [18] and converted to logMAR. Full-field electroretinograms (ERGs) were recorded according to the International Society for Clinical Electrophysiology of Vision standard[19] and compared with age-matched control data.

Results

We identified 7 affected patients with homozygous (6 of 7 patients) or compound heterozygous mutations (1 of 7) in the *MMACHC* gene; 3 had early-onset disease and 4 had late-onset disease. The latter group had onset between the ages of 6 and 14 years. Consanguinity, evaluated by history, was present in 4 patients (Patients 1, 2, 4, and 7). Six patients were reexamined at 3.2 to 11.5 years (mean, 6.5 years) after their first examination. Systemic signs and symptoms at diagnosis and clinical course are summarized in Table 1. All patients experienced a developmental stabilization with systemic treatment.

Vision Function

Visual acuity varied from normal (0.0 logMAR) to counting fingers (Table 2). Patients with late-onset disease showed normal vision, except for 1 patient, who had congenital oculomotor nystagmus in both eyes and refractive amblyopia in the right eye. Patients with disease onset within the first month of life and homozygous *MMACHC* mutation c.547_548delGT (Patients 1 and 2) developed acquired horizontal pendular nystagmus. Refractive errors ranged from hyperopia (+1.25 D to + 5.0 D) to high myopia (−10.0 D) without a predominant trend.

Ocular Morphology

Anterior segment examination revealed small lamellar lens opacities outside the visual axis in 1 patient (Patient 5; Table 2). Retinal pathology was evident in all 3 patients with early-onset disease, ranging from subtle retinal nerve fiber layer loss (Case 3, at 3.5 years old) to advanced macular and optic atrophy with "bone spicule" pigmentation (Patient 1; see Figure 1). The patient with high myopia (–8.5 right eye, –10.25 left eye) in the late-onset

Table 2. Ocular phenotype of subjects

Patient no.	Age at visit (yrs)	Visual acuity (RE/LE) (logMAR)	Nystagmus	Refractive error* (RE/LE)	Fundi	ERG result (age tested in years)
1	3.9	F/F	+	+3.5/+3.5	Macular RPE changes, optic atrophy	Rod-cone dysfunction, nonprogressive (4.2, 13)
	13.8	CF/CF	+	+5.0/+5.0	Macular and optic atrophy, "bone spicule" retinal pigmentation	
2	0.1	CSM/CSM	−	NT	Normal	Cone-rod dysfunction, progressive (4 ERGs between 0.8 and 3.7)
	3.7	0.5 (OU)	+	−0.25/−0.25	Central and peripheral atrophy	
3	0.3	F/F	−	NT	Normal	NT
	3.5	0.2/0.2	−	+1.5/+1.5	Retinal nerve fiber layer loss	
4	15.9	0.0/0.0	−	−0.75/−1.0	Normal	NT
5	2.9	0.1/0.1	−	+1.25/+1.5	Normal	Normal (15.4)
	15.4	0.02/0.04	−	0/0	Normal	
6	13.4	1.6†/0.7	+	NT	Normal	Normal (13.4 and 20.6)
	20.6	0.82†/0.32	+	−8.0/−10.25	Myopic fundus changes	
7	7.2	CSM/CSM	−	NT	Normal	Normal (18.8)
	18.8	0/0.02	−	0/0	Normal	

RE, right eye; *LE*, left eye; *ERG*, electroretinogram; *OU*, both eyes; *F*, fixating; *CF*, counting fingers; *CSM*, central, steady and maintained (normal visual response for age); *NT*, not tested.

*Spherical equivalent in diopters.

†Amblyopic eye.

group showed myopic fundus changes. Fundi of the other patients in the late-onset group did not show any abnormalities.

ERG Results

Electroretinogram was recorded in 5 patients from 1 to 4 times (Table 2). The 2 tested patients with early-onset disease showed reduced responses, with progression documented in one (Patient 2). Normal ERG responses were found in all 3 tested patients in the late-onset group. Two unrelated cases with early-onset disease with the same homozygous *MMACHC* gene mutation (c.547_548delGT) are described in detail.

Patient 1. This 14-year-old boy of Lebanese origin born to first-cousin parents presented at less than 1 month of age with failure to thrive, lethargy, feeding difficulties, vomiting, jaundice, hypotonia, and temperature instability. Testing revealed metabolic acidosis, macrocytic anemia, neutropenia, thrombocytopenia, and hepatic dysfunction. Computed tomography scan of the brain showed mild-to-moderate generalized atrophy and poor myelination of the brainstem. *CblC* was diagnosed based on the presence of methylmalonic acid in the urine and increased total plasma homocysteine. Complementation studies on fibroblasts and, later, molecular genetic testing confirmed the diagnosis. Treatment with betaine and folate orally and hydroxycobalamin intramuscularly was started at age 1 month and resulted in excellent metabolic control (homocysteine <70 μmol/L) and stabilized but delayed development, poor growth, and microcephaly. The oral administration of carnitine was added later.

At his first visit to our clinic at 3.9 years of age, the child would fixate but not follow objects. He presented with horizontal symmetric pendular nystagmus and right esotropia. Fundi examination demonstrated optic atrophy and macular pigmentary changes. Cycloplegic refraction showed moderate hyperopia (+3.50 sphere in each eye). ERG revealed nonrecordable rod responses and severely reduced and delayed cone responses. At his last examination, at 13.8 years of age, he was able to count fingers only, which is approximately equal to 1.85 logMAR.[20] The nystagmus characteristics were unchanged. Fundi demonstrated macular and optic atrophy, attenuated retinal vessels and mid-peripheral "bone spicule" pigmentation (Figure 1A). The ERG repeated at age 13 confirmed the nonrecordable rod responses and did not show a further progression of the cone dysfunction (Figure 1B).

Patient 2. This patient, born to first-cousin parents of Lebanese origin, was born at 36 weeks' gestation and, to the best of our knowledge, is unrelated to Case 1. Within the first month of life, he developed respiratory distress, lethargy, encephalopathy, hypothermia, developmental delay, thrombotic renal microangiopathy, and nephrotic syndrome. Hematological workup revealed pancytopenia and a diagnosis of *cblC* was made based on the presence of methylmalonic acid in the urine and increased total plasma homocysteine. The diagnosis was confirmed by complementation studies on fibroblasts and later by molecular genetic testing. Renal function normalized and general development improved with hydroxocobalamin administered intramuscularly, oral betaine, folate, and carnitine 2 months of age. He remains developmentally delayed. Initial ocular assessment, during hospitalization at 3 months of age, showed central, steady, and maintained fixation, a normal anterior segment, and normal fundi. Horizontal pendular nystagmus was evident at his follow-up examination at 9 months of age. Examination under sedation at that time revealed atrophic macular changes and reduced macular reflex. ERG demonstrated a cone–rod dysfunc-

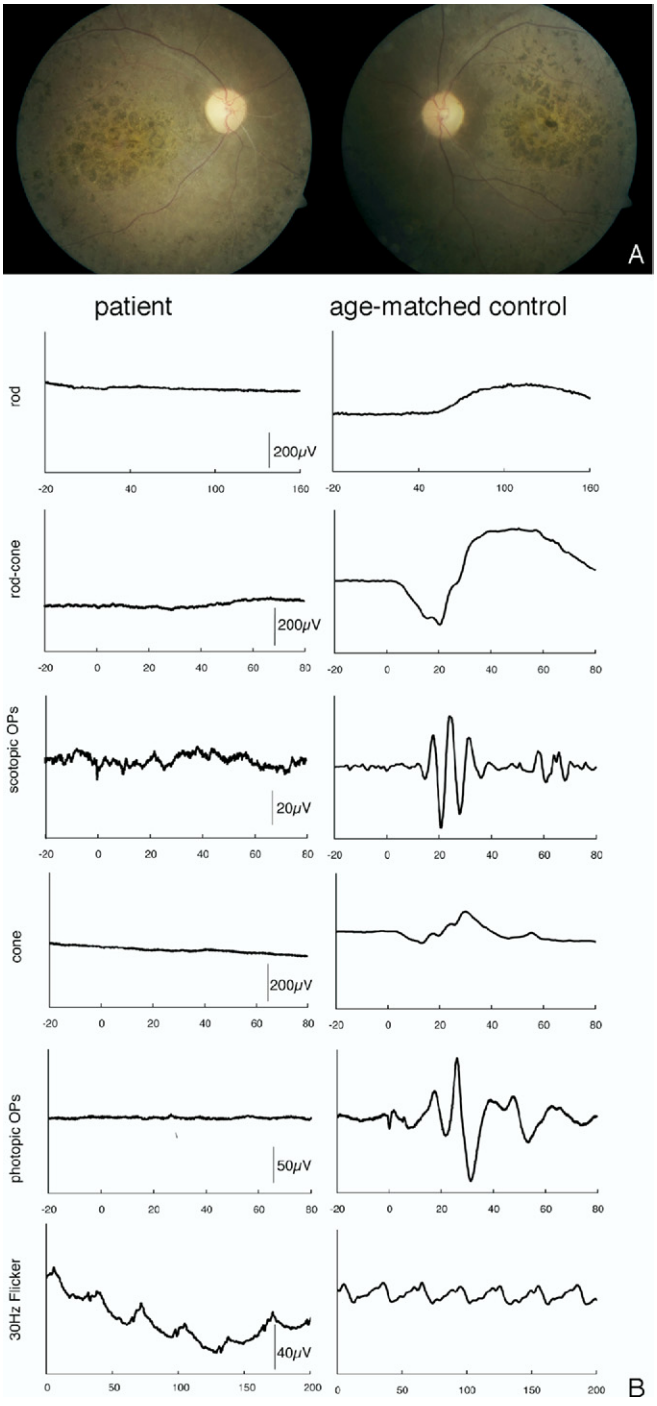

FIG 1. (A) Fundus photograph and ERG waveforms of Patient 1 (homozygous mutation c.547_548delGT) at 13.8 years of age. Fundi demonstrate symmetric retinal atrophy with central placoid pigmentary clumping, loss of the normal internal limiting membrane sheen, optic atrophy, and retinal vessel attenuation. (B) ERG responses of the patient (left panel) and an age-matched control (right panel) demonstrate attenuated responses more to rod- than cone-mediated stimuli.

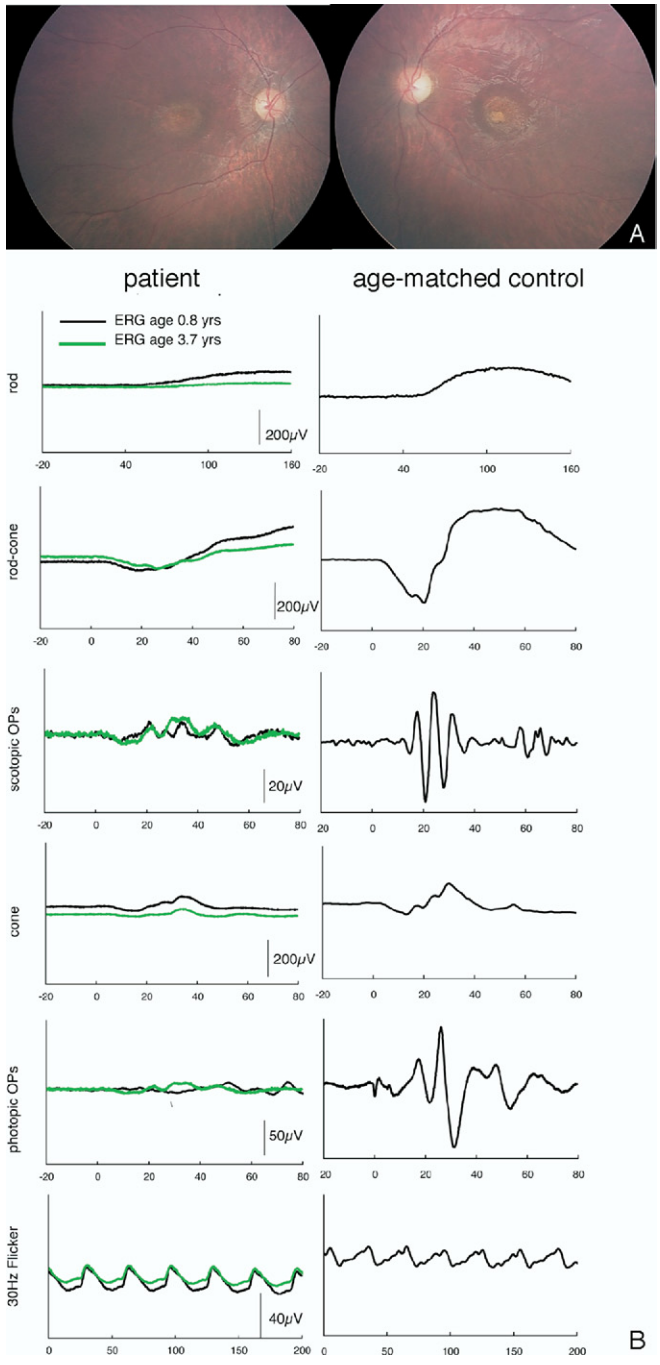

FIG 2. (A) Fundus photograph and ERG waveforms of Patient 2 (homozygous mutation c.547_548delGT) at 3.7 years of age. Fundi demonstrate symmetric macular almost geographic atrophy with reduced macular reflex and retinal nerve fiber layer. Note the unusual polygonal shaped yellow area within macula of left eye. (B) ERG responses of the patient recorded at ages 0.8 and 3.7 years of age (black and green tracings, respectively) and an age-matched control for the latter age (right panel) demonstrate cone-rod dysfunction. The intervisit response comparison reveals progressive retinal dysfunction.

tion. The patient's binocular acuity was 0.5 logMAR at his most recent assessment at 3.7 years of age. ERGs, repeated 3 times in this patient when he was between the ages of 1.2 and 3.7 years of age, indicated a progressive cone–rod dysfunction (Figure 2B). Fundi showed bilateral macular atrophy but no "bone spicule" pigmentary clumping (Figure 2A).

Table 3. Ocular function of patients with known genotype similar to patients in current study

Mutation 1	Mutation 2	Author(s) and reference no.	Patient no. in study: age at eye examination	Results
331C>T	331C>T	Andersson and Shapira[14]	# 1: 15 months	Normal
			# 2: unknown	Slight retinal granular appearance, no functional vision deficit
331C>T	666C>A	Current study	# 3: 3.5 years	Reduced visual acuity, reduced nerve fiber layer
331C>T	271dupA	Andersson et al[15]	# 1: 5.9 years	No eye examination reported
			# 2: 0.8 years	No eye examination reported
331C>T	271dupA	Brandstetter et al[16]	# 1: 16 months	No fixation or following movements, optic nerves normal, pigment retinopathy and macular granularity
331C>T	271dupA	Mitchell et al[7]	# 1	No eye examination reported
			# 2: 2.5 months	No fixation and following objects
			12 months	Pigment retinopathy
			15 months	Fixating and following objects, ERG: cone dysfunction
331C>T	615C>G	Howard et al[17]	# 1: < 1 year	No eye examination reported
394C>T	394C>T	Current study	# 4: 15.9 years	Normal
			# 5: 15.4 years	Normal
394C>T	394C>T	Shinnar and Singer[24]	# 1: 14 years	Minimal optic disc pallor with normal visual acuity
			# 2: 12 years	No eye examination reported
394C>T	394C>T	Kazimoroff and Shaner[25]	# 1: 13 years	No eye examination reported
394C>T	394C>T	Boxer et al[23]	# 1: 42 years	No eye examination reported

Discussion

CblC is an autosomal-recessive disorder of vitamin B12 metabolism, which can affect multiple organ systems, including the visual system, despite early treatment. Impaired formation of vitamin B12 cofactors adenosylcobalamin and methylcobalamin, which are essential for the mitochondrial enzyme methylmalonyl-CoA mutase, and the cytoplasmatic enzyme methionine synthetase, respectively, lead to methylmalonic aciduria and homocystinuria.[21]

All 3 patients with early-onset disease showed abnormal retinal findings. The 2 patients that were homozygous for c.547_548delGT exhibited a more severe phenotype than the patient with compound heterozygous mutations c.331C>T and 666C>A. No published vision function data from other patients with c.547_548delGT are available. Anderson and Shapira[14] reported 2 patients with homozygous c.331C>T (mutation identification through Morel et al[2]) who showed either no abnormalities at 15 month of age or a slight retinal granular appearance without functional vision deficits (age of test not mentioned). Patients with compound heterozygous c.331C>T and 271dupA had severely reduced vision (Table 3).[7,15,16]

Electroretinography, performed in the 2 patients who were homozygous for c.547_548delGT, showed either progressive cone–rod or nonprogressive rod–cone dysfunction. Schimel and Mets[13] and Robb et al[6] reported 3 and 1 cases, respectively, of early-onset *cblC* (genotype not reported) and progressive retinal dysfunction. Tsina et al[12] measured rod photoreceptor and postphotoreceptor responses and sensitivities in relation to methionine level in a child with *cblC* tested between 7 and 46 months of age (genotype not reported). Rod photoreceptor function was restored after normalized methionine levels. Cone-mediated amplitude and postreceptor sensitivity remained reduced. Atrophic maculopathy, which was similar to Case 2 in our current study, progressed despite hydroxycobalamin injections. The authors suggest that methionine rescues photo-transduction in the rod cell membrane and therefore low levels might play a role in the development of retinopathy. Pre- and postnatal treatment in *cblC*, as demonstrated by Huemer et al,[22] did not prevent nystagmus and retinopathy, although developmental milestones were normal.

Histopathology was reported from a 22-month-old child with clinically progressive retinal pigment epithelium changes in the macular area similar to Patient 2 in our current study. Reduced ERG rod and cone-mediated responses improved slightly under supplementation with hydroxycobalamin, carnitine, and betaine. The retina showed photoreceptor loss with mainly intact retinal pigmented epithelium, but ganglion cell loss in the maculopapillary bundle.[9]

Of our 4 patients with late-onset disease, 3 demonstrated normal ocular function, including rod- and cone-mediated ERG responses. No macular function studies that used focal, pattern, or multifocal ERG were performed. One patient in our study had high myopia and oculomotor nystagmus, which has not been reported previously in *cblC*. We cannot rule out the possibility of subtle retinal dysfunction that might have escaped detection by full field ERG but the ERG was normal on 2 occasions. Minimal optic nerve pallor was reported from patients

with homozygous c.394C>T, as in our Patient 4 and 5 (Table 3).[23-25] Tsai et al[4] reported a 36-year-old woman who was diagnosed with *cblC* after spinal cord infarct. She had an adult-onset bilateral cataract, requiring surgery in one eye. It is not clear whether this is a complication of *cblC*.

The small number of detailed ocular function reports in the literature does not allow a detailed genotype–phenotype correlation at this time. Our study shows that ocular function seems to be affected more in the early-onset group compared with the late-onset group. Retinal dysfunction can be progressive despite treatment and stabilized systemic function. Knowledge and awareness of visual dysfunction, particularly in children with early-onset *cblC*, allows initiation of appropriate early vision intervention programs and support.

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