retinopathy, nephropathy, and stroke, but it is distinct in that the digestive tract is not involved in those 2 syndromes, which have been mapped to 19q12^4 and 3p21, respectively. In our patient, genetic study showed a normal karyotype (standard metaphase spread). Because the patient is the only member of his family to manifest the syndrome, no linkage mapping has been performed to date.

John Conrath, MD
Bertrand Roquelaure, MD
Marie Chrestian, MD
Laurence Camoin-Jau, MD
Elisabeth Tournier-Lasserve, MD
Bernard Ridings, MD

Financial Disclosure: None.

Correspondence: Dr Conrath, Ophthalmology Department, Timone Hospital, 264 rue Saint Pierre F-13385, Marseille, France (John.Conrath@ap-hm.fr).


Maculopathy and Retinal Degeneration in Cobalamin C Methylmalonic Aciduria and Homocystinuria

The cobalamin C form of methylmalonic aciduria and homocystinuria (Cc-CMAH) is an inherited deficiency of the 2 coenzymatically active vitamin B<sub>12</sub> derivatives, methylcobalamin and deoxyadenosylcobalamin (Figure 1). Its heterogeneous clinical manifestations include feeding difficulties, neural dysfunction, and ophthalmic abnormalities. The ophthalmic features are visual impairment, nystagmus, and retinopathy with conspicuous maculopathy. The mechanism by which the biochemical abnormalities cause retinal disease has not been defined. We analyzed photoreceptor cell and postreceptoral...
Figure 1. Schematic diagram of the 2 vitamin B₁₂ derivatives. The defective derivatives deoxyadenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl) act as coenzymes. The site of the defect in the cobalamin C form of methylmalonic aciduria and homocystinuria is circled. TC II indicates transcobalamin II; GSCbl, glutathionylcobalamin; CblⅠ and CblⅡ, cobalamins with cobalt valences of 2⁻ and 1⁻, respectively; OH-Cbl, hydroxycobalamin; MS, methionine synthase; and CoA, coenzyme A.

Figure 2. Progression of maculopathy in the left eye. The macular appearance in the right eye was similar.
processes represented by electroretinographic responses in a child with Cc-CMAH.

Report of a Case. A 7-month-old infant girl, born at term, was first examined because of crossed eyes after an unremarkable perinatal course. Ophthalmic examination demonstrated esotropia, horizontal nystagmus of small amplitude, mildly attenuated retinal arteries, and maculopathy (Figure 2). Grating acuities measured by preferential looking were near the lower limits of normal for age, and by 4 years of age, her visual acuity with binocular viewing of the Lea symbols was 20/200 OU. Although development was delayed, the patient became ambulatory and verbal. Elevated plasma homocysteine levels, a large peak of urine methylmalonic acid level, and cell complementation studies secured the diagnosis of Cc-CMAH. Hydroxycobalamin injections and betaine and protein restriction were started and maintained, with consequent improvement of biochemical measures, including modest decreases in total homocysteine level and increases in methionine level.

Before and after treatment, processes in rod photoreceptor and postreceptoral cells and cone-mediated responses were investigated. The variables of the activation of rod phototransduction and postreceptoral function were derived from the full-field electroretinogram. Rod photoreceptor sensitivity and saturated amplitudes were calculated from the a-wave. The b-wave sensitivity and saturated amplitude represented postreceptoral activity. Each variable was compared with normal values for age. The saturated amplitudes were, on average, approximately 50% of the normal means. Except for normal rod cell sensitivity at age 3 years 10 months, when methionine was at the highest level, all photoreceptor and postreceptoral sensitivities were significantly attenuated (Figure 3). Cone-mediated b-wave amplitudes remained at 50% of the normal mean. Despite improving or stable full-field retinal function, the maculopathy progressed to large, atrophic patches (Figure 2).

Comment. The Cc-CMAH is one of the few causes of infantile maculopathy. Treatment did not rescue the macula or postreceptoral retinal responses represented by the b-wave. However, in this patient, normal rod photoreceptor sensitivity was restored in conjunction with increased levels of the essential amino acid methionine. This implies methionine rescue of transduction processes that involve rhodopsin and other transduction cascade proteins in the rod cell membranes. Thus, low methionine level may, indeed, have a role in the pathogenesis of retinopathy in Cc-CMAH.

Efthymia K. Tsina, MD, PhD
Deborah L. Marsden, MD
Ronald M. Hansen, PhD
Anne B. Fulton, MD

Figure 3. Rod photoreceptor and postreceptoral saturated amplitudes and sensitivities of the left eye expressed as percentages of the normal means for age. Results from the right eye were similar. Also shown are the methionine levels at the time of the electroretinograms. Metabolic supplement therapy was started 1 month after the first electroretinogram. Rod photoreceptor sensitivity (S) and saturated amplitude (Rmp3) were calculated from the a-wave. The b-wave sensitivity (1/σ) and saturated amplitude (Vmax) represented postreceptoral activity. To convert methionine to micromoles per liter, multiply by 67.02.
Financial Disclosure: None.
Correspondence: Dr Fulton, Department of Ophthalmology, Children’s Hospital Boston, 300 Longwood Ave, Boston, MA 02115 (anne.fulton@childrens.harvard.edu).


Stop Mutations in Exon 6 of the Choroideremia Gene, CHM, Associated With Preservation of the Electroretinogram

Choroideremia (Mendelian Inheritance in Man [MIM] #303100) is an uncommon X-linked chorioretinal degeneration characterized by mottling of the retinal pigment epithelium (RPE) and inexorable centripetal extension of areas of choroidal and outer retinal atrophy. Extensive rod and cone system dysfunction characteristically occurs within the first years of life. Eventually, the rod electroretinogram (ERG) becomes undetectable and cone responses are recordable only with computer averaging.1 Nystagopia and progressive field constriction typically become evident in the second decade with acuity loss eventually occurring because of macula involvement. Female carriers often exhibit “moth-eaten,” patchy pigmentation at the level of the RPE compatible with lyonization.2

We describe the finding of normal or mildly subnormal ERGs in 3 young affected males (aged 8, 9, and 10 years) from 2 unrelated families with choroideremia (Figure 1). Direct sequencing of the choroideremia gene (CHM) identified a different nonsense (stop) mutation in each family. The mutations were only 14 codons apart in exon 6, suggesting that a common mechanism underlying these mutations may lead to a milder clinical and electrophysiological phenotype.

The patient representing case 1 was asymptomatic when evaluated at age 6 years. Visual acuity was 20/20 OD and 20/20 OS. Fundus examination disclosed fine, peppery RPE mottling in the midperiphery but normal-appearing optic discs, retinal vasculature, and maculae (Figure 2A-C). Bone spicule formation and choroidal atrophy were absent. His maternal grandfather had advanced choroideremia (Figure 2D).

Electroretinograms (Figure 3A) performed to standards from the International Society for Clinical Electrophysiology of Vision demonstrated, at age 10 years, mildly subnormal responses of rods (67% of normal mean; lower limit, 83% of mean) and, to a greater degree, dark-adapted cones (44% of normal mean; normal lower limit, 76%) with normal amplitudes of light-adapted cones consistent with mild rod and scotopic cone dysfunction. Rod and cone implicit times were normal. Repeat ERGs at 12 years of age showed minimal further rod loss. Karyotyping was normal. Direct sequencing of CHM identified a nonsense mutation (R239X, CGA→CTA), also identified in the patient’s maternal grandfather.2,3

The patient representing case 2, who is from an unrelated family with choroideremia, was first evaluated at 9 years of age. He was asymptomatic with visual acuities of 20/20 OU. The results of color vision testing and Goldmann perimetry testing were normal. Fundus examination identified fine, peppery RPE mottling in the midperiphery but nor-

Figure 1. Pedigrees for case 1 (A) and cases 2 and 3 (B). Black squares indicate affected males; circles with black dots, known carrier females; gray squares, males affected by history.