Supplemental Information:

Supplemental Methods:

The study was approved by the Research Ethics Boards of Hospital for Sick Children, Toronto and G. Gaslini Institute, Genova, and adhered to the Tenets of the Declaration of Helsinki. Two patients were examined at Hospital for sick Children Toronto (Patient-1 and Patient-2) and two patients were examined at G. Gaslini Institute, Genova (Patient-3 and Patient-4). Informed consent was obtained from all patients and their parents.

At their current age all patients could still ambulate. On simplified myoclonus rating scale,[1] three patients were scored as stage 3; Patient-2 was scored as stage 4. All had myoclonus, which was generally subtle when relaxed. It exacerbated and became generalized with emotion. Their generalized seizures were relatively controlled on medications (Table e-2), but they still had generalized tonic-clonic convulsions approximately once a month. All had cognitive decline, but were nonetheless able to follow commands enough to participate in the ophthalmological testing. Patients were able to understand simple instructions and responded to calming presence and voices of family members, enough to complete the testing. Speech was severely reduced. Thought and speech were constantly interrupted with myoclonic and atypical absences.

Patients were well rested, tested early in the day, and given breaks as needed. At first distance visual acuity and color vision was measured. This was followed by a full-field electroretinogram (ERG; refer to next section for details). Upon completion of the ERG, retinal examination, spectral-domain optical coherence tomography (SD-OCT) and retinal photography was completed. The entire testing took about 2.5 hours. None of the patients developed seizure during any of the procedures.

Full-field electroretinogram (ERG):

The ERG is an electrophysiological test that measures gross retinal function. The ERG was performed incorporating International Society for Clinical Electrophysiology of Vision Standards in all patients across both centers (Toronto and Genova).[2] After pharmacodilating the pupil, all patients underwent dark adaptation (DA) for 20 minutes. Following this, rod system function was measured in serial steps. Firstly, dim-light DA ERG was performed using 0.01cd.s.m^{-2} flash which elicits only a positive b-wave (measured from baseline to waveform peak) that is driven by rod bipolar cells. Subsequently, a DA ERG was tested using 3.0 cd.s.m^{-2} flash stimulus which elicits a-wave (negative waveform; measured from baseline to a-wave trough) followed by b-wave (positive waveform; measured from a-wave trough to the b-wave peak); a-wave arises predominantly in rod photoreceptors and b-wave arises predominantly in the rod bipolar cells. In two patients (Patients 1 and 2), a bright flash DA ERG was performed using 10.0 cd.s.m^{-2} flash; this stimulus elicits a-wave followed by b-wave with similar waveform origins but provides additional information on rod photoreceptor and rod bipolar function (measurements are similar to previous step). The b/a ratio under DA condition is a ratio of the amplitude of the b-wave to that of the a-wave and is particularly helpful in deciphering selective rod bipolar cell involvement; a reduced b/a ratio to DA 3.0 or 10 cd.s.m^{-2} stimuli implies selective rod bipolar cell function. After completing these steps, all patients were light adapted (LA) for 10 minutes using background luminance of 30 cd.m^{-2}. Subsequently, the cone system was tested using 3.0 cd.s.m^{-2} flash stimulus at two stimulus frequencies; 30Hz (flicker) and 2Hz respectively. The flicker response elicits peaks and troughs (measured from trough to peak); it originates in the cone systems with post-receptoral contributions from cone On- and Off-pathways. The LA 2Hz response elicits an initial negative a-wave followed by a positive b-wave;

the a-wave (measured from baseline to a-wave trough) originates from cone photoreceptors and cone Off-bipolar cells, and the b-wave (measured from a-wave trough to b-wave peak) originates from cone On- and Off bipolar cells. At each stimulus step of the ERG, at least four reproducible traces with no movement artefact or blinking were obtained.

References:

1. Magaudda A, Gelisse P, Genton P. Antimyoclonic effect of levetiracetam in 13 patients with Unverricht-Lundborg disease: clinical observations. Epilepsia 2004;45:678-681.
2. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). Documenta ophthalmologica Advances in ophthalmology 2015;130:1-12.