Complex and well-formed visual hallucinations (VHs) are a striking clinical feature in patients with dementia with Lewy bodies (DLB). Proposed mechanisms for VHs include a decrease in acetylcholinesterase activity in the temporal lobe and the presence of high densities of Lewy bodies (LBs) in the amygdala, parahippocampus, and inferior temporal cortices. However, we noted structural abnormalities in the retina of a patient with DLB, suggesting that neurodegeneration of the retina could contribute to VHs. We therefore used the flash electroretinogram (ERG) to study the so-called a-wave (corresponding to the photoreceptor layer) and b-wave (the bipolar cells from the outer plexiform layer to the inner nuclear layer and the large Muller cells). We also examined by electron and light microscopy the postmortem retina.

**Methods.** We examined 16 patients with DLB, 17 age-matched patients with Parkinson disease (PD), and 16 controls (with informed consent), recruited through our neurologic department (table). All had normal eye examination results, with Snellen visual acuity greater than 0.7 in each eye (DLB: 0.9 [0.8 to 1]; PD: 0.95 [0.8 to 1]; controls: 0.95 [0.8 to 1], without significant difference). All DLB patients fulfilled the diagnostic criteria for probable DLB. All patients with PD and without dementia, VHs, or dopaminergic psychosis fulfilled the diagnosis criteria of the United Kingdom Parkinson’s Disease Society Brain Bank criteria. Anti-parkinsonian drugs, but not anticholinesterase therapy, were permitted (see table).

We investigated the scotopic and photopic systems by recording the full-field flash ERG, including the rod and blue ERG a- and b-waves (scotopic ERG), cone ERG a- and b-waves (photopic ERG), and max ERG (highly sensitive to a-wave abnormalities) according to International Society for Electrophysiology of Vision (ISCEV) standards. Statistical analyses included analysis of variance on ranks with the Bonferroni post hoc test.

Postmortem light and electron microscopy of the left eye of three other patients with DLB was performed. DLB was confirmed by neuropathological and immunohistochemical brain examination. Epon-embedded samples from the retina were observed under a Leo 906 electron microscope.

**Results.** All patients with DLB described fluctuating binocular VHs, located in both fields, during day and night (predominance at the end of the afternoon). All experienced simple VHs such as moving shadows and complex VHs of variable content involving characters, animals, and scenery.

The max ERG a-wave differed among the three groups in terms of both implicit time (time to peak) (F = 3.9, p = 0.02) and amplitude (F = 3.1, p = 0.04). There was a significant increase in implicit time and decrease in amplitude in the DLB group vs the other groups, with no difference between the PD group and controls (see table).

The implicit times of the cone ERG a- (F = 4.7, p = 0.01) and b-waves (F = 7.3, p = 0.001) differed among the three groups, with a significant increase in the DLB group vs the two other groups, with no difference between the PD group and controls (figure 1).

The rod and blue ERG a-wave did not differ significantly among the groups. The b-wave in the DLB group had a lower amplitude (rod ERG: F = 5.9, p = 0.004; blue ERG: F = 4.2, p = 0.01) and longer implicit time (rod ERG: F = 5.6, p = 0.005; blue ERG: F = 4.5, p = 0.01) vs the two other groups, without difference between the PD group and controls.

Postmortem light microscopy of the central and peripheral retinas revealed mild alteration of the inner segment of the rod and cone photoreceptors (swollen in two of the three retinas), some swollen ganglion cells with vacuoles in the ganglion cell layer, and most notably pale inclusions in the outer plexiform layer (in all DLB patients), which were more marked in the peripheral retina. This corresponded to cytoskeletal disorganization of the enlarged photoreceptor inner segments, as revealed by electron microscopy (figure 2). Postembedded immunohistochemistry did not reveal accumulate α-synuclein as seen in LB. The results of a similar pathologic study of a patient with PD were unremarkable.

**Discussion.** The significant abnormalities in the photopic ERG a-wave suggest photoreceptor layer dysfunction in DLB, which may be related to mild alteration of the inner part of the photoreceptors. The max ERG is known to detect photoreceptor abnormalities with the highest sensitivity.
In our study, patients with DLB displayed a dysfunction of the photopic and the scotopic inner retina. Such ERG abnormalities found in patients with DLB could not solely concern the dopaminergic system. Indeed, the most striking finding of the anatomo-pathological examination was the presence of pale inclusions in the outer plexiform layer, which differed in appearance and consistency from LBs and also from extracellular drusen located under the pigment epithelium. Such structural alterations could impair normal signal transmission from the photoreceptors to the bipolar cells and could explain the inner retina dysfunction evidenced by our ERG study. Dysfunction of the photopic and scotopic inner retina might participate in the physiopathology of the simple VHs found in our all patients with DLB. Indeed, visual pathway dysfunction and a range of ophthalmologic pathologies could induce or favor VHs. Complex hallucinations were more related to the cortical density of LBs.

Normal transmission between the photoreceptors, bipolar cells, and ganglion cells also depends on the level of dopaminergic activity. Although we did observe a trend, there was no significant difference between advanced treated patients with PD and the controls. Most of the flash ERG studies in PD displayed either normal results or slight decreased amplitudes. These results were influenced by the variance in ERG methodologies before the ISCEV guidelines. Moreover, the apparently normal results of the flash ERG in several PD studies could be due to either the early disease stage, possibly before appearance of the slight abnormalities, or the performance of flash ERG during L-dopa treatment, which could mask the slight abnormalities. In our study, the lack of decrease in amplitude could be due to ERG recording during L-dopa treatment. In light of the hypothesis whereby dopaminergic depletion participates in visual dysfunction, the large, pale inclusions of the outer plexiform layer found in patients with DLB but not in patients with PD could have functional consequences on dopaminergic activity:

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<th>Table: Clinical characteristics and ERG results</th>
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<td>Controls</td>
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<td>No.</td>
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<td>Age, y</td>
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<td>Sex, M/F</td>
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<td>Disease duration, y</td>
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<td>Motor handicap (UPDRS)</td>
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<td>L-Dopa dose, mg</td>
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<td>Max ERG a-wave implicit time</td>
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<td>Cone ERG a-wave implicit time</td>
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Median values [first and third quartiles] of the clinical characteristics and the implicit times (expressed in milliseconds) and the amplitudes (expressed in millivolts) of the flash electroretinogram (ERG) are given.

* Significant difference (p < 0.05) between the given condition and the two others.

DLB = dementia with Lewy bodies; PD = Parkinson disease.

Figure 1. Average cone electroretinogram (ERG) curves for the three groups: The implicit times of the a- and b-waves were (p < 0.05) increased in the dementia with Lewy bodies group (thick line) compared with the Parkinson disease group (dotted line) and compared with the controls (thin line), without difference between the Parkinson disease group and the controls.
the binding sites of D1 and D2 receptors are localized in the plexiform and nuclear layers in normal human retina, with higher concentrations in the outer plexiform layer. The interplexiform cells send processes into the plexiform layers. This leads to a feedback loop acting at the horizontal cell coupling level, where dopamine and GABA have antagonist effects on regulation of light retinal adaptation and contrast sensitivity functions, which are altered in PD by primary degeneration of dopaminergic retinal cells (amacrine cells and interplexiform neurons).7,8

The flash ERG abnormalities could relate to a decrease in cholinergic activity because photoreceptors, amacrine cells, and ganglion cells contain choline acetyltransferase activity, and nicotinic acetylcholine receptors are localized on photoreceptors and horizontal, bipolar, and ganglion cells. Indeed, besides the central role of the acetylcholinesterase activity in the cortex, acetylcholinesterase activity also concerns the inner part of the inner nuclear layer and ganglion cells, and the latter’s processes spread into the inner plexiform layer. Finally, several studies have demonstrated a decrease in VHs during anticholinesterase treatment. Thus, like the dopaminergic system, the cholinergic system is involved in visual function and must be considered along with retinal structural abnormalities in DLB. Nevertheless, VHs were only mildly decreased by anticholinesterase treatment, suggesting that retinal structural abnormalities, together with the cortical density of LBs, could also play a major role in the physiopathology of VHs.

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References


Kjellin syndrome: First case with retinal changes in carriers
Arun Sachdev, MBBS, BSc, HONS; Frank A. Proudlock, PhD; Richard Abbott, MD; and Irene Gottlob, MD, Leicester, UK

A 32-year-old woman presented with dysarthria, spastic paraplegia, and dementia. Fundus examination revealed yellow retinal lesions (figure, A). Fluorescein angiography demonstrated characteristic features of retinal flecks (see the figure, B). Isolated flecks were found in the fundi of her mother (both eyes) and father (right eye), who were neurologically normal (see the figure, A).

Kjellin syndrome is a rare autosomal recessive disease characterized by dementia, spastic paraplegia, and retinal flecks reported in Sweden1 and elsewhere including the USA.2 This is the first UK case. We show for the first time retinal flecks in carriers, supporting autosomal recessive inheritance.

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