Chapter 9
Characteristics of Visual Electrophysiology in Retinal Toxicities

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Vigabatrin

Vigabatrin (VGB), sold under the brand name Sabril, is an anticonvulsant medication inhibiting gamma-aminobutyric acid (GABA) degradation for the treatment of epilepsy. It is an irreversible inhibitor of GABA transaminase. By irreversibly binding to GABA-transaminase, thus metabolism of GABA is hurdled. The accumulation of GABA then damages the neurons in the eye and brain. It can reduce visual acuity, contrast sensitivity, retinal thickness, the a-wave and b-wave of scotopic and photic electroretinography (ERG), oscillatory potential (OP) amplitudes, 30-Hz flicker ERG amplitude, multifocal electroretinography (mfERG) amplitudes, electrooculography (EOG) Arden ratio, and the VEP amplitude from central or peripheral visual field and increase the latencies of ERG a-wave and b-wave [1–11]. Reduction in b-wave amplitudes and 30 Hz flicker amplitudes are usually the first signs of toxicity. There is also evidence that light exposure in mice administered VGB produces the taurine deficiency, causing the retinal degeneration [2, 12]. Dysregulated expression of transcripts in the mTOR pathway, GABA/glutamate transporters $GABA_{A/B}$ receptors, and metabotropic glutamate receptors 1/6 in the eye are associated with the reduction of VEP amplitude after VGB administration [13].

Complex full-field electroretinography (ffERG) changes can be found in children placed on vigabatrin for intractable epilepsy (Fig. 9.1). However,

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M. Yu et al. (eds.), *Handbook of Clinical Electrophysiology of Vision*,
https://doi.org/10.1007/978-3-030-30417-1_9

importantly, some ffERG changes can precede exposure to vigabatrin, underscoring that these patients may have preexisting changes in their retinal function related to their underlying condition. Thus, to correctly assess vigabatrin-mediated toxicity, obtaining baseline ffERGs is essential. With this caveat in mind, toxic effects during exposure to vigabatrin onto retinal function can affect both receptoral and post-receptoral responses and can vary from patient to patient (Fig. 9.1).

Hydroxychloroquine (Plaquenil) and Chloroquine

Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalarial agents commonly used in the treatment of lupus erythematosus, Sjogren's disease, rheumatoid arthritis, and dermatological inflammations. HCQ is also used in the treatment of uncomplicated malaria caused by chloroquine-sensitive strains of *Plasmodium* species or in the prophylaxis in regions with chloroquine-resistant strains. HCQ inhibits movements of neutrophils and eosinophils and also impairs complement-dependent antigen–antibody reactions. Its antirheumatic properties are proposed to result from their interference with "antigen processing" in macrophages and other antigen-presenting cells [14].

Both HCQ and CQ belong to the quinolone family and have similar clinical indications and side effects, including retinal toxicity. Hobbs et al. first described the CQ-induced retinal toxicity in 1959 [15], and Shearer et al. first described the HCQ toxicity to retina in 1967 [16]. HCQ has much less retinal side effect so that CQ has almost been replaced by HCQ for the treatment of inflammatory diseases. The retinal damage induced by these medications is usually irreversible. In a portion of patients with long-term HCQ/CQ treatment, HCQ-/CQ-induced toxicity can be found in cornea and macula, possibly related to the factors of cumulated dosage, duration of use, age, concomitant use of certain medications (e.g., tamoxifen), and health status (e.g., renal disease). In the retina, it may cause bilateral Bull's eye pattern of maculopathy (Fig. 9.2a), parafoveal damage of retina in early stage, and extramacular damage of retina in later stage. It affects ganglion cell layer, photoreceptors, and retinal pigment epithelium (RPE) by the inhibition of protein synthesis [17, 18] and peroxidation of lipid [19]. The risk of HCQ-/CQ-induced maculopathy is associated to the daily dose and the duration of HCQ/CQ administration [20, 21]. More damage may occur after the initial damage with continued use of HCQ/CQ [22]. Therefore, early screening of HCQ/CQ toxicity in these patients is necessary.

In mfERG test, HCQ-/CQ-induced maculopathy shows paracentral decrease of mfERG amplitude and prolongation of latency (Fig. 9.2b) [21, 23–30]. The ffERGs can be abnormal in some patients [31]. In the late stages of HCQ-induced retinopathy, ffERGs and other tests can be used together for the differential diagnosis [32]. For early detection of HCQ/CQ toxicity, mfERG, spectral domain optical coherence tomography (SD-OCT) (Fig. 9.2c), and fundus autofluorescence (FAF) (Fig. 9.2d)

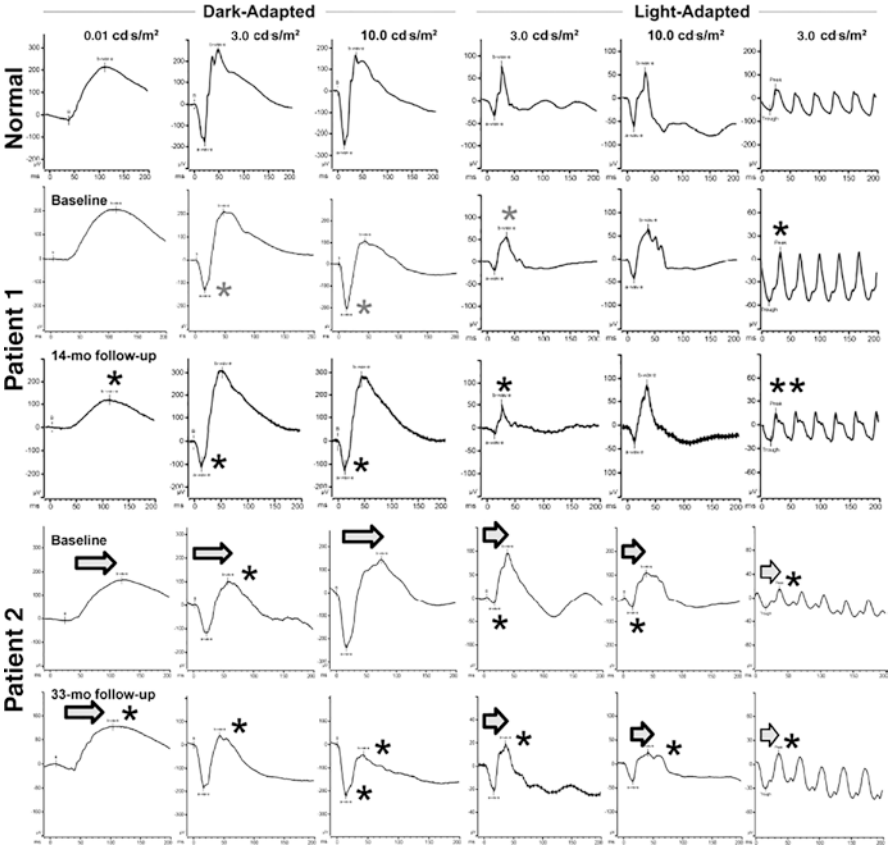

Fig. 9.1 Electroretinographic findings in vigabatrin-mediated retinal toxicity. Importantly, both patients exhibited *baseline* abnormalities, highlighting the importance of obtaining baseline measurements to ascertain potential retinal toxicities of this or any other medication. A normal set of ERGs, shown on the top row of the figure. *Patient 1.* This boy was tested first at baseline before the age of 2 years old, when he had first been placed on vigabatrin for intractable epilepsy linked to subdural hematomas and encephalopathy, and signs of toxicity emerged 14 months later. Dark- and light-adapted flash ERGs demonstrated at baseline mixed a-wave amplitude reduction, a mild electronegative shape of the 10.0 cd·s·m^{-2} response, and borderline low amplitudes for all cone-driven responses. After 14 months of follow-up, there was evidence of rod-driven b-wave attenuation, further reduction in mixed a-wave, lack of a-wave growth at 10 cd·s·m^{-2} (consistent with diminished photoreceptor sensitivity), and loss of cone-driven b-wave and flicker ERG amplitudes (note the different scale for flicker responses compared to normal). ON–OFF ERGs performed at follow-up (not shown) indicated also OFF > ON response compromise. Taken together, these findings suggested adverse vigabatrin-mediated effects at the photoreceptor and post-receptoral levels (on bipolar cells themselves or at the photoreceptor-to-bipolar-cell synapse). *Patient 2.* This girl was tested first at baseline before the age of 2 years old, when she had first been placed on vigabatrin for intractable epilepsy, and signs of toxicity emerged after 33 months. ERGs at baseline show delayed rod-driven ERGs, borderline low mixed dark-adapted a- and b-wave response amplitudes, delayed mixed b-waves, reduced photopic a-wave amplitudes, and attenuated and delayed flicker ERG responses. Compared to baseline, follow-up flash ERGs 33 months later demonstrate rod-driven and mixed b-wave amplitude loss (electronegative ERG), reduction in the photopic b-waves [arrows] with an artifactual a-wave increase (due to increased electronegativity in the light-adapted responses as well) attributable to ON>OFF post-receptoral response compromise (not shown). The flicker ERG was overall stable

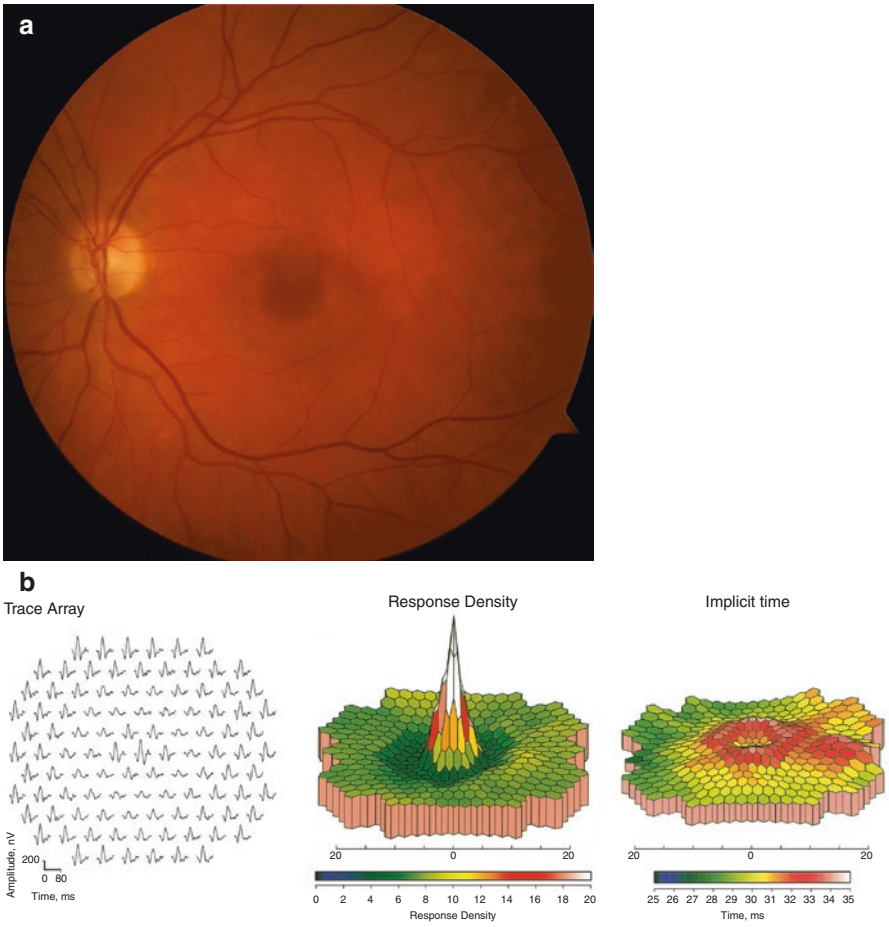

Fig. 9.2 Fundus imaging and mfERG in hydroxychloroquine retinopathy. (**a**) Fundus image of a hydroxychloroquine user showing Bull's eye pattern of maculopathy. (**b**) mfERG result of a hydroxychloroquine user demonstrates marked reduction of mfERG response density and prolongation of mfERG implicit time in the parafoveal region (Adapted from Figure 1 [21]). (**c**) SD-OCT of a hydroxychloroquine user that shows significant decrease of the thickness of outer retina in the parafoveal region. (**d**) Fundus autofluorescence displays higher signal in the parafoveal region

may have higher sensitivity than perimetry [24, 28, 33–37] and are part of the standard Plaquenil patient workup. In addition, mfERG can provide objective data of the retinal function across visual field [20].

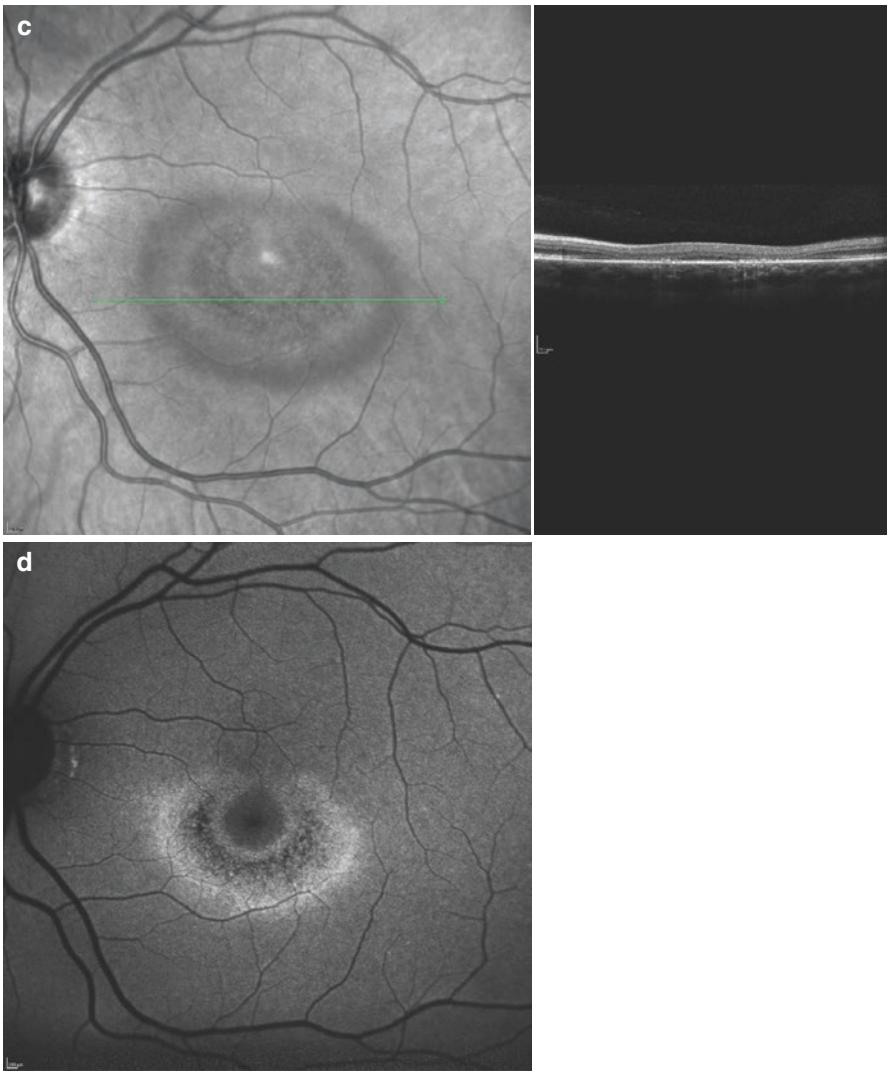

Fig. 9.2 (continued)

Antipsychotics

Chlorpromazine (CPZ) and thioridazine are members of the first-generation antipsychotic class, also known as typical antipsychotics. Their mechanism of action depends on the blockage of postsynaptic D2 receptors in the mesolimbic and mesocortical pathways. Typical antipsychotics may also block muscarinic, alpha 1-adrenergic, histamine, and 5-HT2 receptors.

CPZ administration can cause latency prolongation of the ffERG mixed response and cone response, decrease of rod and cone b-wave amplitude, and latency prolongation of the oscillatory potentials (OPs). However, CPZ is not known to change parameters of the fVEP, pERG, and the retinocortical times calculated from the difference of pERG and pVEP latencies [38].

Thioridazine (also known as Mellaril) is a dopaminergic antagonist (similar to CPZ) first used as antipsychotic with indication for the management of schizophrenic patients who fail to respond adequately to the treatment with other first-line antipsychotic drugs.

Because of its serious retinal and cardiac side effects (thioridazine may increase the risk of potentially fatal ventricular arrhythmias), its use is presently recommended only for selected cases. Probably due to an idiosyncratic response, retinal toxicity has also been reported for short-term and low-dose administrations [39]. However, long-term thioridazine treatments are usually associated with the highest risk of retinopathy.

The earliest signs of thioridazine retinal toxicity is RPE mottling of the macula and perimacular regions. Full-blown retinopathy is characterized by nummular (coin shaped) patches of RPE loss in both posterior pole and periphery, with a RP-like appearance [40, 41] (Fig. 9.3). Decreased visual acuity, night blindness, paracentral scotomas, and loss of peripheral vision can all occur in thioridazine retinopathy. In more advanced stages of the disease, there is definite electrophysiological (ffERG, EOG, and mfERG) evidence of diffuse retinal compromise (Figs. 9.4 and 9.5).

The mechanism of retinal damage is still unclear, but it is thought to be similar to chlorpromazine, accumulating mainly in pigmented cells including the uveal level [42]. This presumed mechanism may explain the extensive choriocapillaris loss and RPE dysfunction and damage co-contributing to the retinal damage. Direct dopaminergic mechanisms have also been suspected, but not proven.

Thioridazine discontinuation is the only treatment available. Regression has been described, but only in early-diagnosed cases, and further progression of retinal damage over several years after discontinuation can (more commonly) occur [43].

Cis-Platinum

Cis-platinum is a medicine used for the chemotherapy of bladder, testicular, ovarian, small and non-small cell lung, esophageal, breast, prostate, stomach, and cervical cancers. It is also used to treat mesothelioma, sarcomas, melanoma, multiple myeloma, neuroblastoma, and Hodgkin's and non-Hodgkin's lymphomas. Cis-platinum is an alkylating agent active during resting phase of the cell. Therefore, this drug is cell cycle nonspecific. The manifestation of electrophysiology of cis-platinum side effect includes reduction of ERG dark-adapted and light-adapted b-wave amplitudes, amplitude of OPs, amplitude of 30 Hz flicker ERG, and dark-adapted a-wave amplitude (Fig. 9.6) [44–46].

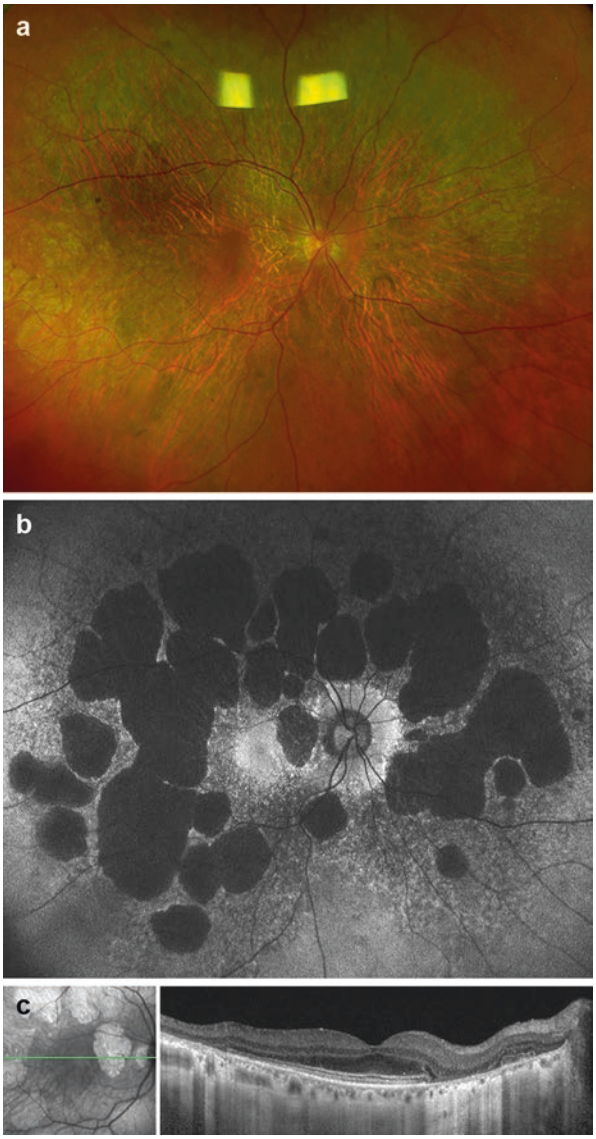

Fig. 9.3 Clinical and imaging findings in thioridazine retinopathy. (**a**) A large area of depigmentation across the entire posterior pole characterizes the fundus examination of this 70-year-old Caucasian woman with a previous longstanding history of treatment with thioridazine for a psychotic disorder. (**b**) Fundus autofluorescence imaging reveals much more clearly the nummular patches of hypo-autofluorescent lesions corresponding to the clinically visible atrophy of the RPE around the fovea and throughout the posterior pole, extending well beyond the arcades. There is central sparing but marked hyper-autofluorescence around the disc and in the foveal region. The nummular hypo-autofluorescent lesions are surrounded by a large halo of speckled hypo-autofluorescence indicative of further RPE suffering also in the periphery. (**c**) The OCT scan shows excellent central preservation of all layers, including the RPE, but sharp and discrete near-complete loss of RPE, EZ, ELM, and ONL just nasal to fovea and farther out in the temporal periphery. These clinical findings in the context of the thioridazine exposure are typical for thioridazine retinopathy

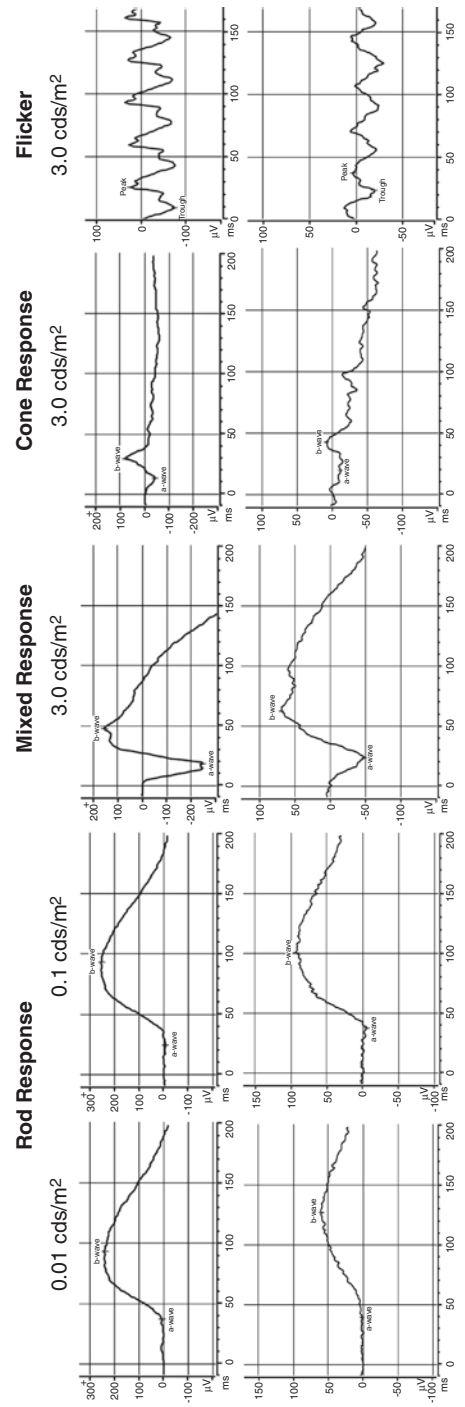

Fig. 9.4 Electroretinographic findings in thioridazine retinopathy. The ffERG of the patient illustrated in Fig. 9.3 reveals both rod and cone response compromise, in an approximately similar ratio, and marked response delays. Findings were symmetric in both eyes both from the ffERG and clinical perspective

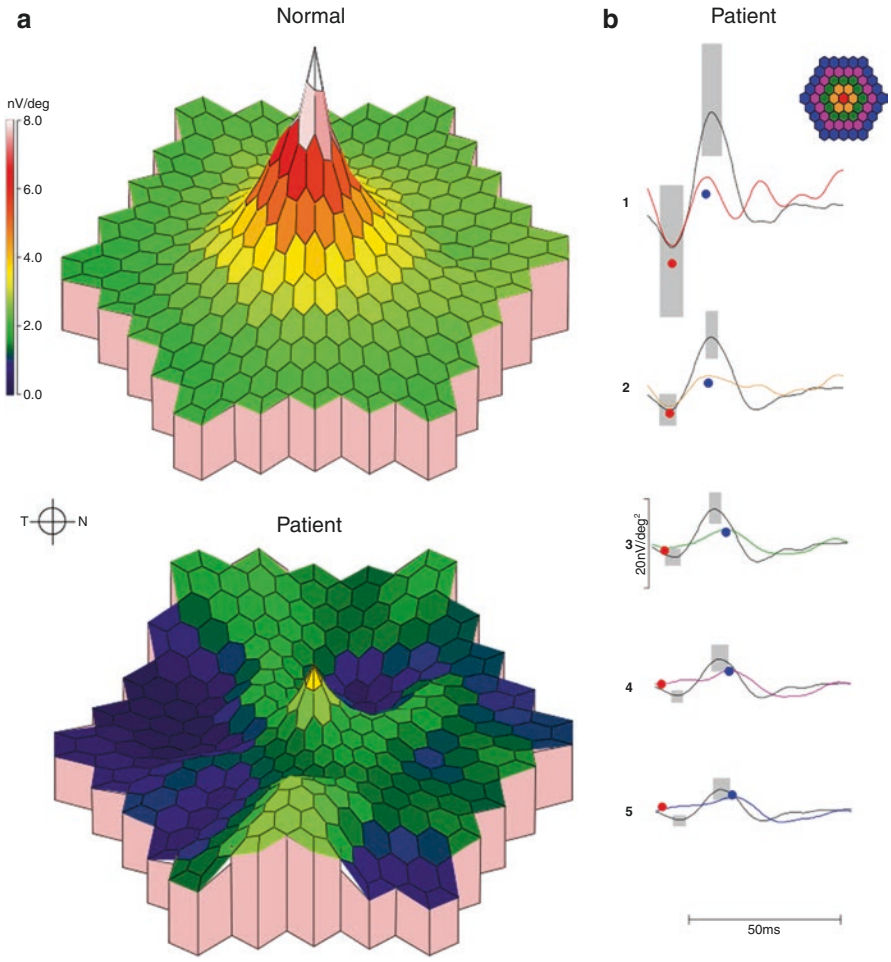

Fig. 9.5 Multifocal electroretinography findings in thioridazine retinopathy, compared with normal values. (**a**) 3D plots of the response densities. (**b**) Average responses in 5 rings of different eccentricities. The grey bars indicate the normal ranges of the N1 and P1 components with 95% confidence interval, respectively. The mfERG response of this patient (same as in Figs. 9.3 and 9.4) reveals patchy loss of the response density across the macular region, with relative preservation of the foveal peak, accounting for the excellent visual acuity. An EOG was also measured (not shown), and the Arden ratio was ≤1.35 in each eye, consistent with widespread RPE compromise, again consistent with the history of thioridazine exposure. Had this patient not had this history, a workup for a possible autosomal recessive bestrophinopathy would have been in order

Deferoxamine

Deferoxamine (DFO) is an IV detoxification agent used in both acute iron intoxication and chronic iron overload. It is also used for the detoxification of aluminum intoxication. DFO chelates iron from ferritin and hemosiderin and enhances its elimination. Both ocular and auditory disturbances have been reported with this agent,

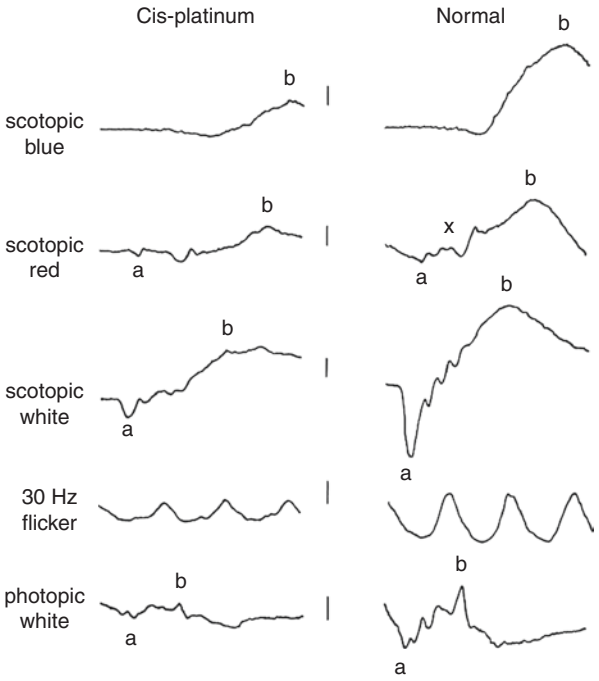

Fig. 9.6 Electroretinography findings in cis-platinum retinopathy. ffERG of cis-platinum retinopathy demonstrates the reduction of ffERG amplitudes in both rod and cone pathways

suggesting pigmentary retinopathy and optic neuropathy can be caused by DFO. The ocular symptoms of its side effects include vision loss, dyschromatopsia, nyctalopia, and scotomas that can be partially recovered after the cessation of DFO administration. Electrophysiology can be used to monitor this side effect seen in the reduction of ERG responses of rod and cone pathways (Fig. 9.7), EOG Arden ratio, mfERG amplitude in central field, and the prolongation of VEP latency [47–51]. The visual function may be recovered after the cessation of the DFO administration.

Digoxin

Digoxin is a drug in the cardiac glycoside family of medications for the treatment of some cardiac disorders, including heart failure, atrial fibrillation and atrial flutter. Its side effects include abnormal vision, irregular heartbeat, nausea, loss of appetite, confusion, and breast enlargement. The symptoms of the visual disorder include blurry vision, central scotomas, photopsia, abnormal color vision, and xanthopsia [52–55]. Studies show ERG or mfERG in the central field in some patients treated with digoxin is abnormal [56–59]. Some studies with animals also confirmed the side effect of digoxin on retinal cone and rod photoreceptors displayed as abnormal ERG results and other tests of visual function and morphology [60–63].

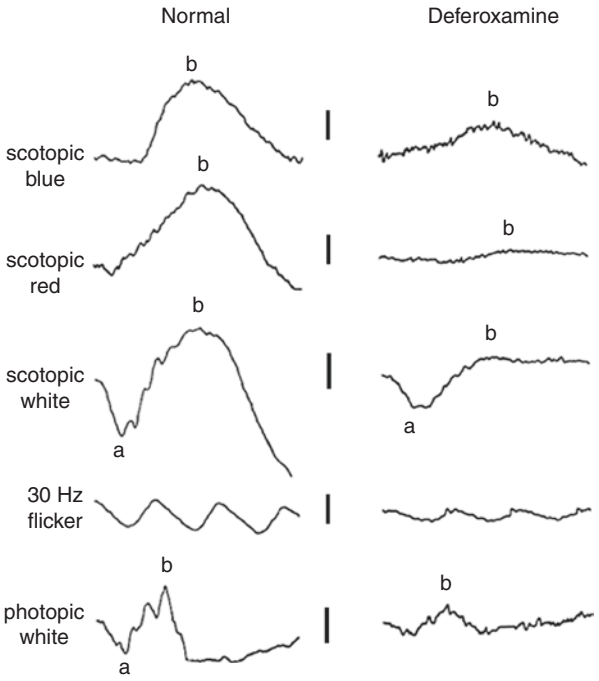

Fig. 9.7 Electroretinography findings in deferoxamine retinopathy. All responses of rod and cone pathways reduce significantly in deferoxamine retinopathy

Ethambutol

Ethambutol (EMB) is mainly used to treat tuberculosis. Its side effects include ethambutol-induced optic neuropathy and retinopathy. For early detection of ethambutol-induced retinopathy, mfERG can show the decrease of P1 amplitudes and/or prolonged P1 latencies in the central, bitemporal, peripheral, nasal, or the whole tested field even before the visual symptoms occur [64–69]. These papers suggest mfERG is probably suitable for early diagnosis of ethambutol-induced retinopathy.

Indomethacin

Indomethacin is a nonsteroidal, anti-inflammatory drug that can be used to treat fever, pain, and inflammation. Indomethacin is a reversible inhibitor of cyclooxygenase 1 and 2, leading to decreased production of prostaglandins. Indomethacin can cause retinopathy reflected in significant reduction of rod and cone responses of ERG and the Arden ratio of EOG [70].

Isotretinoin

Isotretinoin is a medication primarily used to treat severe acne unresponsive to conventional therapy and occasionally used in the treatment and prevention of cancer. Isotrentinoin's exact mechanism of action is unknown. However, isotretinoin may induce apoptosis. Due to its high teratogenicity, isotretinoin is distributed under a risk evaluation and mitigation strategy (REMS) program called iPledge, intended to prevent fetal exposure to the drug. The ocular side effect of isotretinoin can be manifested by the reduction of scotopic ERG amplitudes and Arden ratio of EOG [71–73].

Ocular Siderosis

Ocular siderosis (OS) is caused by retained iron-containing intraocular foreign body after a penetrating ocular injury (Fig. 9.8a) that can cause significant vision loss. Pigmentary retinopathy and cataract are common in OS. The degree of retinal damage and recovery is affected by many factors, such as location and size of the foreign body, which can be monitored by the decrease and improvement of ffERG amplitudes (Fig. 9.8b) [74–79], mfERG latency [80], the relationship of a-wave and b-wave amplitudes [81], or the Arden ratio of EOG [82].

Phosphodiesterase (PDE) Type 5 Inhibitors (Erectile Dysfunction Medication)

Phosphodiesterase (PDE) type 5 inhibitors, such as sildenafil, tadalafil, vardenafil, udenafil, and avanafil, are commonly used in erectile dysfunction and pulmonary hypertension. PDE5 inhibition leads to decreased degradation of cGMP leading to vasodilation. Sexual stimulation leads to a physiological release of nitric oxide activating guanylate cyclase and production of cGMP. Increased levels of cGMP from the medication leads to smooth muscle relaxation and increased blood flow to the penis. However, these drugs may cause transient retinal disorders or optic neuropathy [83, 84].

The side effect in patients includes abnormal color vision, blurred vision, photophobia, ocular pain, and conjunctival hyperemia [85]. Decrease of amplitude and prolongation of latency in ffERG and mfERG were observed in some subjects or animals without preexisting ocular disorders after sildenafil administration [86–91]. Decrease of response in retinal ganglion cells in rat after sildenafil administration was also observed [92]. However, sildenafil increased the a-wave and b-wave amplitude in a rat model of neonatal hypoxia-ischemia [93] and the b-wave amplitude in a mouse carrier of retinitis pigmentosa [88]. In addition, both sildenafil and tadalafil may cause central serous chorioretinopathy [94, 95] and damage photoreceptors

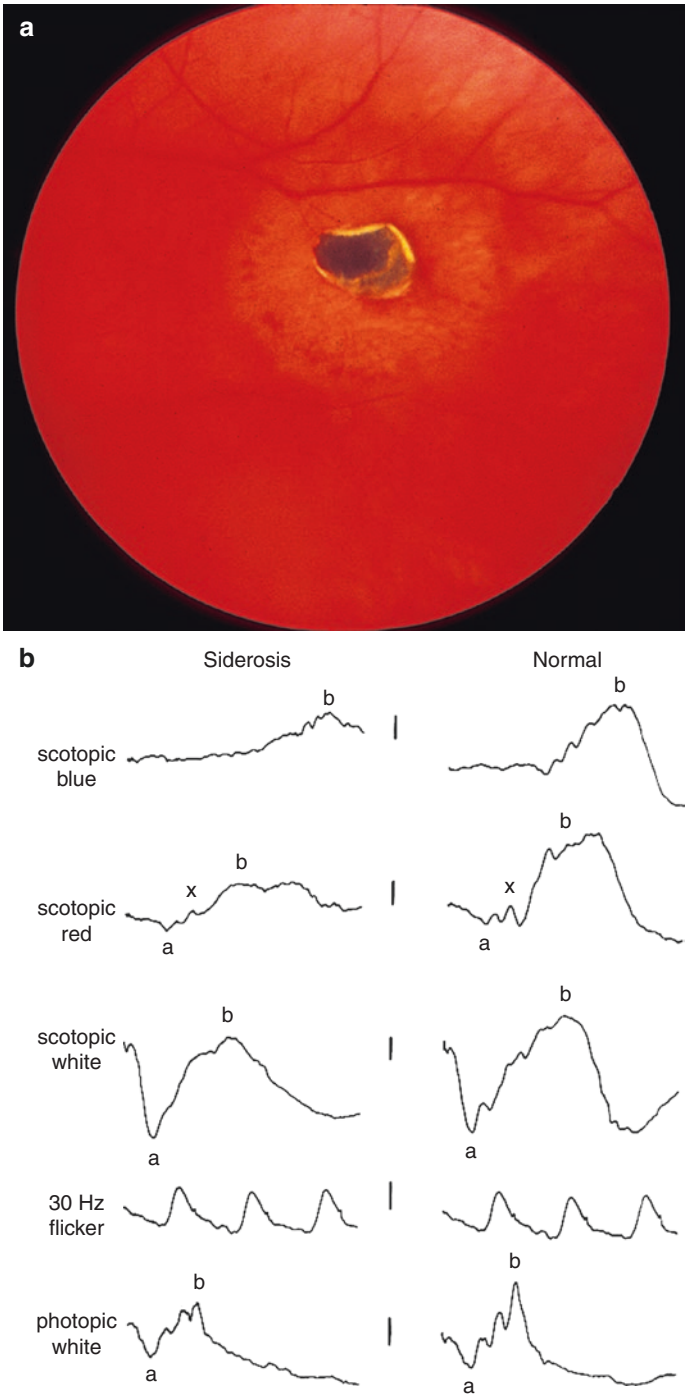

Fig. 9.8 A case of fundus and ffERG findings in ocular siderosis. (**a**) A foreign body in the retina. (**b**) ffERG shows that the rod responses are reduced while cone responses are relatively intact

[96]. Sildenafil, tadalafil, and udenafil may cause optic neuropathy [91, 97–108]. Therefore, it is complicated to explain the electrophysiologic results of the users of PDE5 inhibitor for the diagnosis of other ocular disorders.

Quinine

Quinine is used in the treatment of uncomplicated malaria where resistance to chloroquine has been documented. Quinine is also used in the prevention of nocturnal leg cramps. The exact mechanism of antimalarial activity is not known. However, it is thought quinine can inhibit nucleic acid synthesis, protein synthesis, and glycolysis. The amplitudes of ffERG, mfERG, VEP, and EOG can be reduced after the administration of quinine [109–114].

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