

## DAPSONE-INDUCED TOXIC MACULOPATHY IN LEPROSY PATIENT

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### Abstract

**Introduction:** Dapsone has been widely used as a part of multidrug therapy for leprosy patients. Ocular side effects are rare. Ocular toxicity manifestations include retinal necrosis, optic atrophy, macular infarction, bilateral exudative retinal detachment, and choroidal detachment. We reported a rare case of dapsone-induced toxic maculopathy in a leprosy patient

**Case Report:** A 32-year-old male complained of blurred vision and a gray spot in central vision in the left eye (LE) for one month prior to admission. He had been treated with multidrug therapy (MDT) for leprosy for seven months. The MDT consists of dapsone, clofazimine, and rifampicin. The best-corrected visual acuity (BCVA) of the right eye (RE) and the LE were 6/6 and 6/12, respectively. A funduscopy of the LE showed decreased macular reflex. A color vision defect following the tritan axis was found in the LE. The Humphrey visual field (HVF) test of the LE revealed a central scotoma. Macular optical coherence tomography (OCT) showed intraretinal hyperreflectivity and subretinal fluid. Dapsone was then stopped in collaboration with a dermatologist. Two months after the discontinuation of Dapsone, the BCVA of the LE improved to 6/7.5, then 6/6 three months later. Color vision, macular OCT, and HVF tests revealed improvements. Multifocal ERG of both eyes (BE) also showed improvement in N1 and P1 wave amplitude in both eyes on 9-month follow-up after dapsone discontinuation.

**Discussion:** Instead of direct drug toxicity, the mechanism of ocular side effects is thought to be ischemia caused by two distinct mechanisms. Macular ischemia is caused by acute, severe peripheral hypoxia and the physical effect of red cell fragmentation due to the hemolytic process. After discontinuation of dapsone, this case showed improvement in visual function and macular structure.

**Conclusion:** Toxic maculopathy may be present in leprosy patients receiving dapsone treatment, although it is uncommon. Regular follow-up and evaluation of visual function and macular involvement are essential. Early detection of dapsone-induced toxic maculopathy and prompt discontinuation of dapsone may result in an improvement of visual functions.

**Keywords:** leprosy, dapsone, maculopathy, macular ischemia

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**INTRODUCTION**

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* that affects the skin and peripheral nerves, mucosa of upper respiratory tract, and the eyes.<sup>1</sup> The World Health Organization (WHO) reported 129.389 cases in treatment at the end of 2020, with a prevalence rate of 16.7 per million population. WHO recommended multidrug therapy (MDT) which consists of dapsons, rifampicin and clofazimine since 1981. Over the last two decades, more than 16 million leprosy patients have been treated with MDT.<sup>2</sup>

Dapsone, also known as 4,4'-sulfonyldianiline (SDA) or diamino diphenyl sulfone (DDS), inhibits the folic acid pathway and is therefore bacteriostatic against *Mycobacterium leprae* at concentrations ranging from 1 to 10 mg/L. By competitively antagonizing para-aminobenzoic acid (PABA), the

utilization of PABA for folic acid synthesis is prevented.<sup>3</sup> However, dapsons also has several adverse effects. Methemoglobinemia, agranulocytosis, hypersensitivity syndrome, psychosis and neuropathy are the most frequent adverse effects.<sup>4</sup> Ocular side effects are rare. Several case reports describe ocular toxicity as a result of overdosage. Moreover, ocular toxicity at therapeutic levels has been reported. Ocular toxicity manifestations include retinal necrosis, optic atrophy, macular infarction, bilateral exudative retinal detachment, and choroidal detachment.<sup>5</sup>

We presented a case of a leprosy patient who experienced visual impairment during MDT treatment, which was thought to be a toxic effect of dapsons.

**CASE REPORT**

A 32-year-old male complained of blurred vision and a grey spot in central vision in the left eye (LE) for one month prior to admission. He had been treated with multidrug therapy (MDT) due to leprosy for seven months. The MDT consists of dapsons,

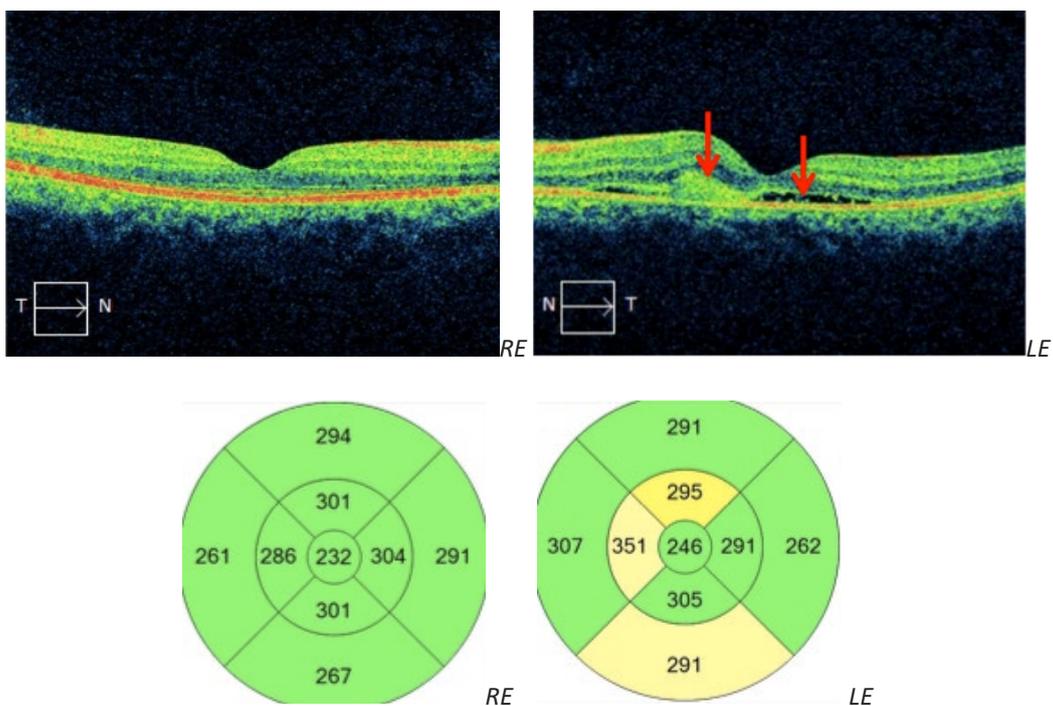


Figure 1. A normal macula anatomy in the right eye (RE). Subretinal fluid and macular edema with intraretinal hyperreflectivity, which is considered a fibrin formation, were observed in the left eye (LE) on the first visit.

clofazimine, and rifampicin. The daily dosage of dapson was 100 mg. The best-corrected visual acuity (BCVA) of the right eye (RE) and the LE were 6/6 and 6/12, respectively. There was no relative afferent pupillary defect (RAPD) found. On the LE, decreased macular reflex was found, without visible changes. Subretinal fluid and macular edema with intraretinal hyperreflectivity, which is considered a fibrin formation, were observed on macular OCT (Optical Coherence Tomography) in the LE. **(Figure 1)** A color vision defect following the tritan axis (blue-yellow) in the LE was found on the Farnsworth Munsell examination. The Pelli-Robson contrast sensitivity of the RE and the LE was 1.95 and 1.80, respectively. Maculopathy due to drug intoxication was considered at that time and suggested for

At the two-month follow-up after the discontinuation of dapson, the patient subjectively felt no improvement, although the BCVA of the LE improved to 6/7.5. The BCVA of the RE remained at 6/6. Clofazimine and rifampicine were still administered. The humphrey visual field (HVF) test of the LE revealed a central scotoma, while the RE was unremarkable. **(Figure 2)** The LE's macular OCT apparently showed macular thickness worsening, despite VA improvement, which still remaining submacular fluid and intraretina hyperreflectivity. It was unremarkable on the RE. **(Figure 3)** Color vision defects along the tritan axis remained in the LE. The Pelli-Robson contrast sensitivity of the LE decreased to 1.35. The dermatologist inquired whether it was necessary to stop clofazimine. Based on the LE's

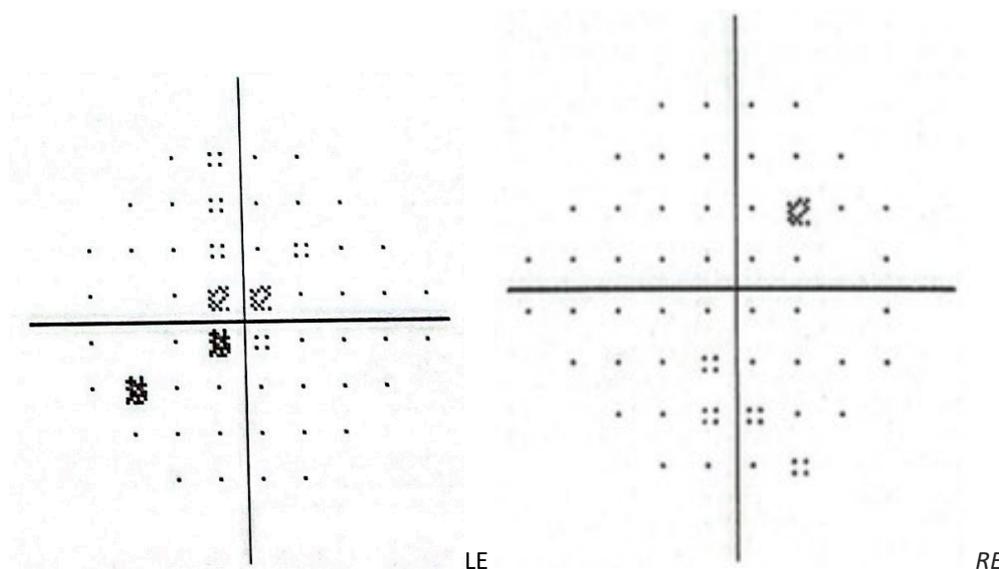


Figure 2. The humphrey visual field test on the second visit showed a central scotoma in the left eye. The RE was within the normal limit.

discontinuing the suspected agent. In collaboration with a dermatologist, dapson was then stopped. The other regimens were continued.

visual acuity improvement, it was recommended to continue clofazimine and rifampicine, with a three-month follow-up.

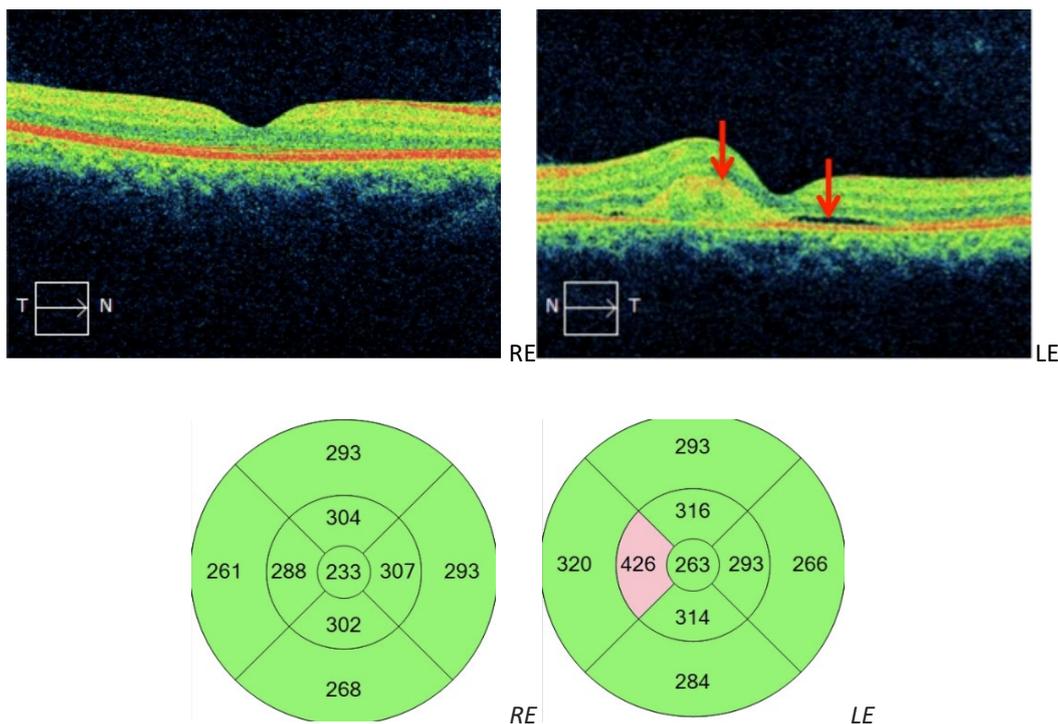


Figure 3. An intraretinal hyperreflectivity and subretinal fluid were still observed in the LE on two months' follow-up. The macular OCT of the RE was unremarkable.

Five months after discontinuing dapsons, the patient noticed an improvement in his left vision. The BCVA of the LE improved to 6/6, while the RE

remained at 6/6. The LE's contrast sensitivity increased to 1.95. Macular OCT of the left eye showed improvement; the intraretinal

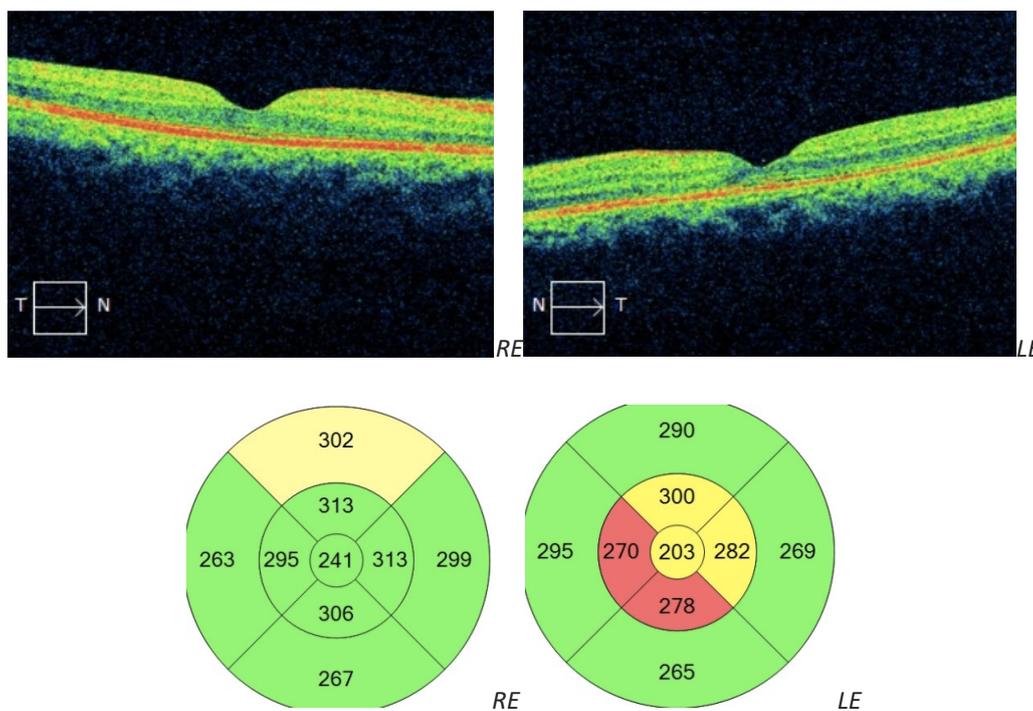


Figure 4. Improvement of intraretinal hyperreflectivity and subretinal fluid was observed in the LE on five-month follow-

hyperreflectivity and subretinal fluid were subsided spontaneously. (Figure 4) A multifocal electroretinogram (ERG) was performed to assess the macular function objectively. Multifocal ERG of both eyes demonstrated low amplitudes of N1 and P1 waves in ring 1 to ring 4 in the right eye. After 12 months administration of MDT, the patient completed MDT (clofazimine and rifampicin).(Figure 5)

At nine months' follow-up, the BCVA of both eyes remained 6/6. The patient had no complaints on both eyes. Funduscopy showed decreased macular reflex and pigmentary changes in LE macula. (Figure 6) The macular OCT of LE revealed normal retinal appearance with remarkable macular thickness changes seen on color mapping. (Figure 7)

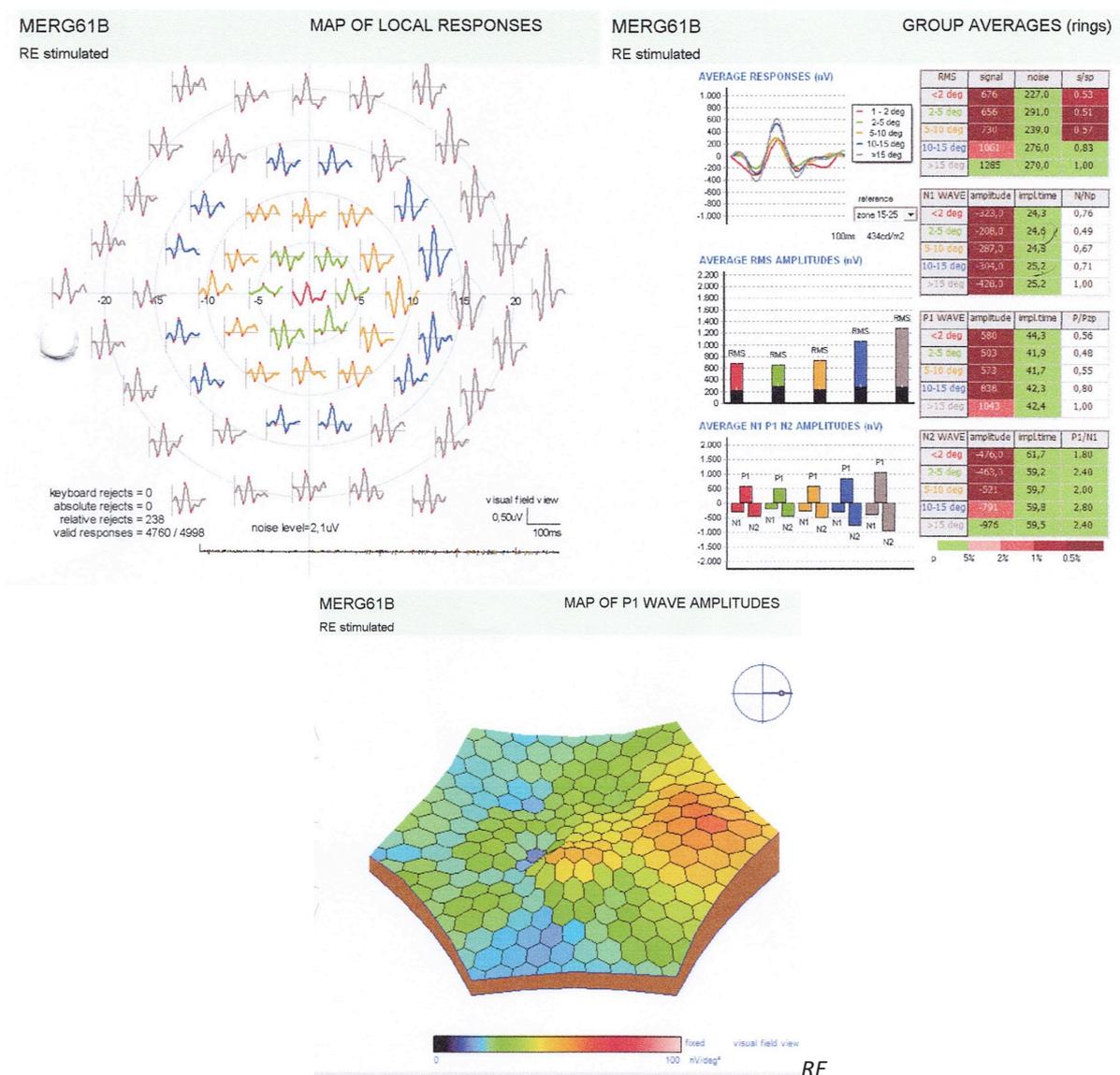


Figure 5.a. At six months' follow-up, multifocal ERG showed low amplitudes of N1 and P1 waves in ring 1 to ring 4 in the right eye.



Figure 6. On nine months of follow up, pigmented changes were observed in the macula of the LE, while fundus of the RE was normal.

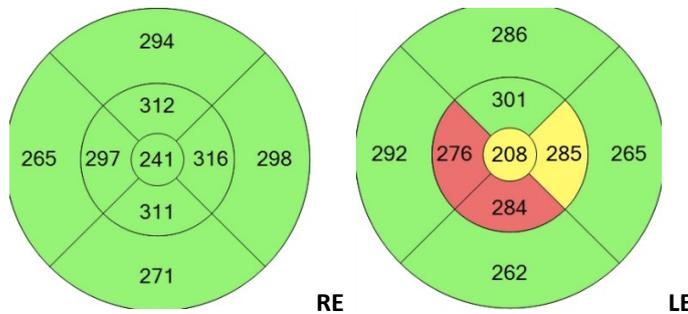
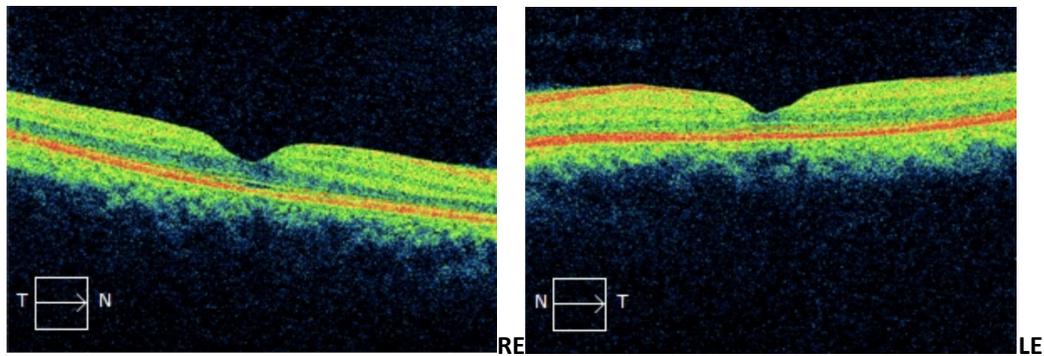


Figure 7. Normal retinal appearance with remarkable macular thickness changes seen on color mapping was observed in the LE on the nine-month follow-up. The macular OCT of the RE was unremarkable.

A multifocal ERG was performed to assess the macular function which revealed improvement of N1 and P1 wave amplitude in inner ring of the RE and

almost all rings of the LE. **(Figure 8)** It was a self-resolving dapsone-induced toxic maculopathy.

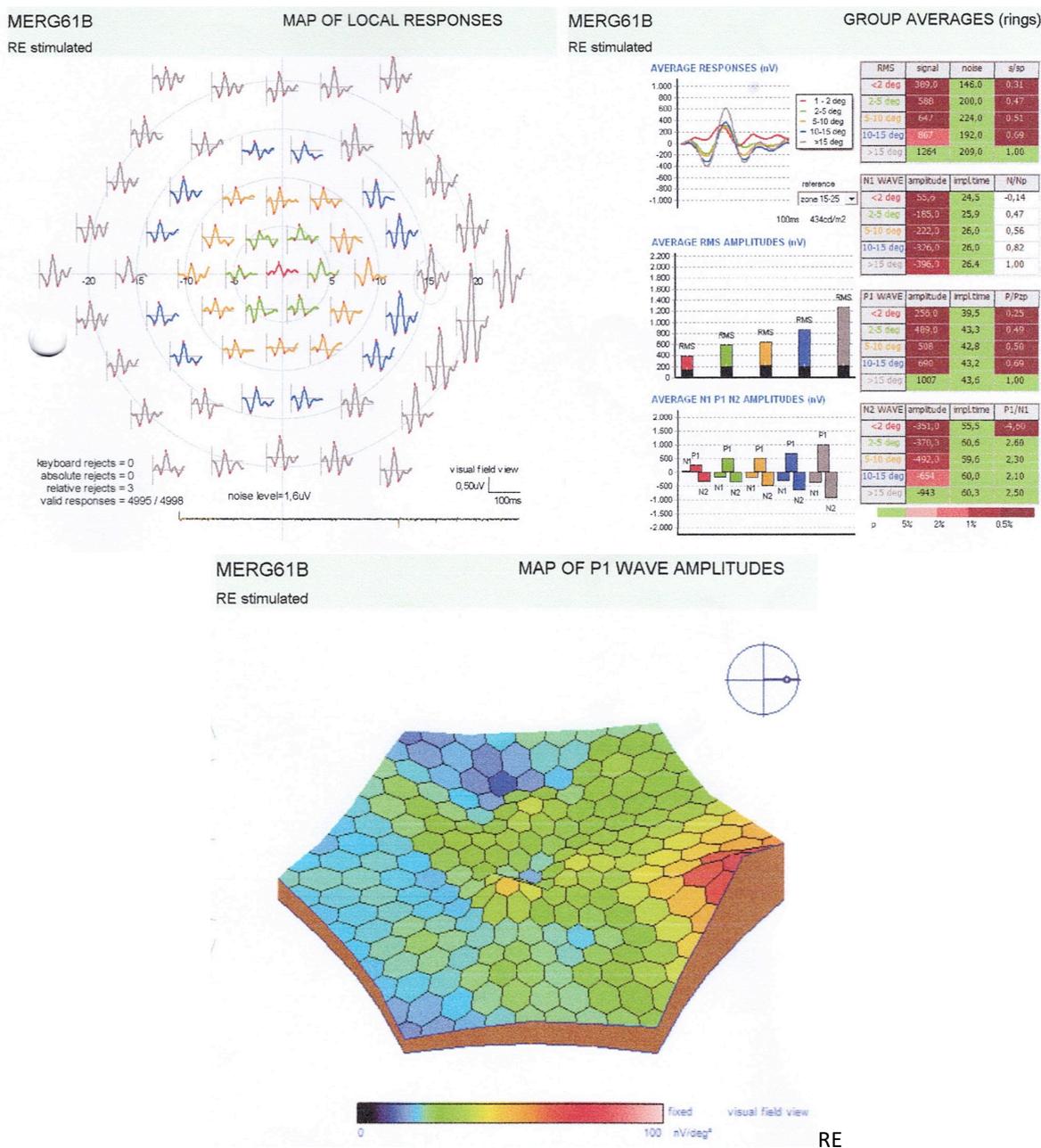
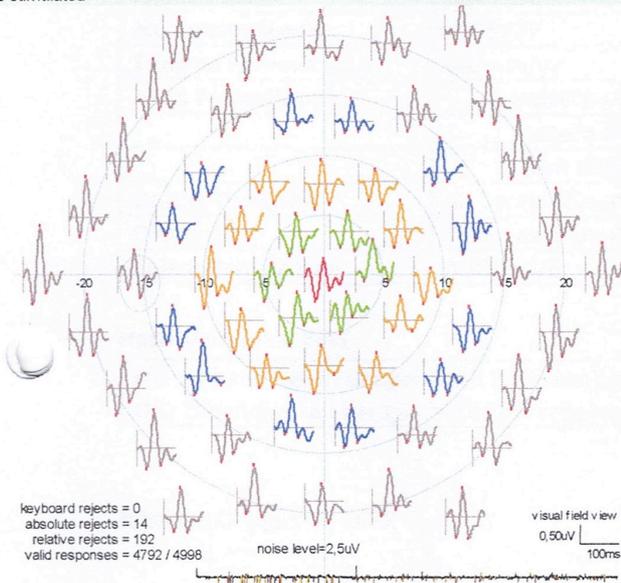


Figure 8.a. After nine months of follow-up, the multifocal ERG showed improvement of N1 and P1 wave amplitude in the inner ring of the RE.

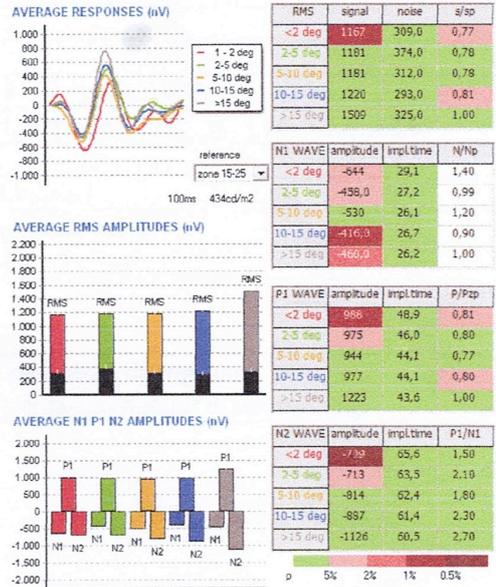
The last follow up, ten months after discontinuation of dapsons, showed that the BCVA remained stable, at 6/6 in both eyes. The patient had no vision complaints. The HVF of both eyes was

normal, no central scotoma was found in the LE. (Figure 9) Macular OCT of the LE remained stable with no subretinal fluid and normal retinal outer segment layer anatomy. (Figure 10)

MERG61B  
LE stimulated



MERG61B  
LE stimulated



MERG61B  
LE stimulated

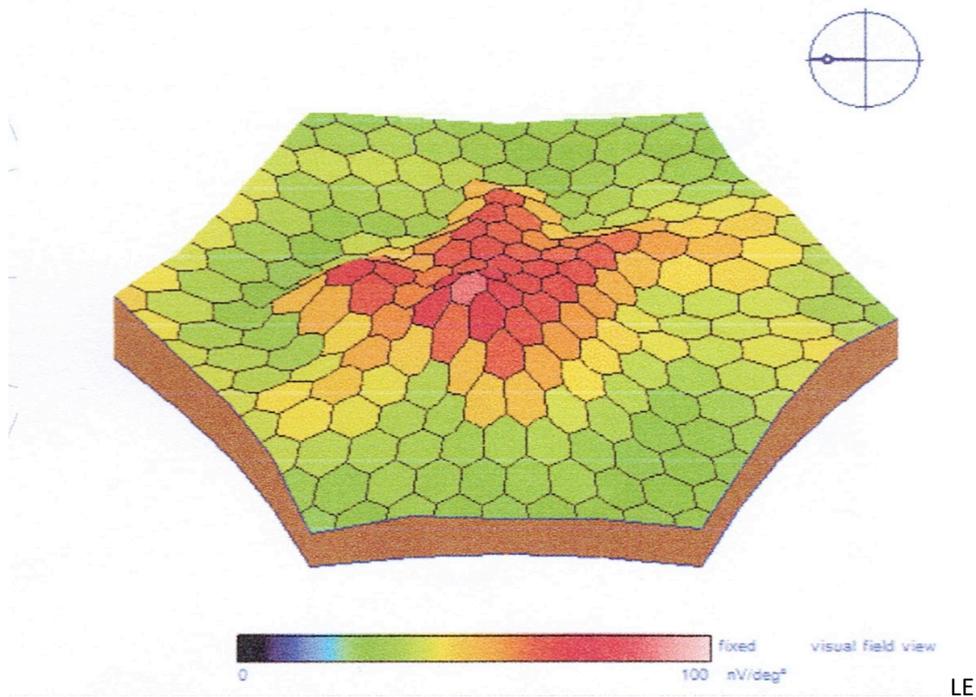


Figure 8.b. After nine months of follow-up, the multifocal ERG showed improvement of N1 and P1 wave amplitude in almost all rings of the LE.

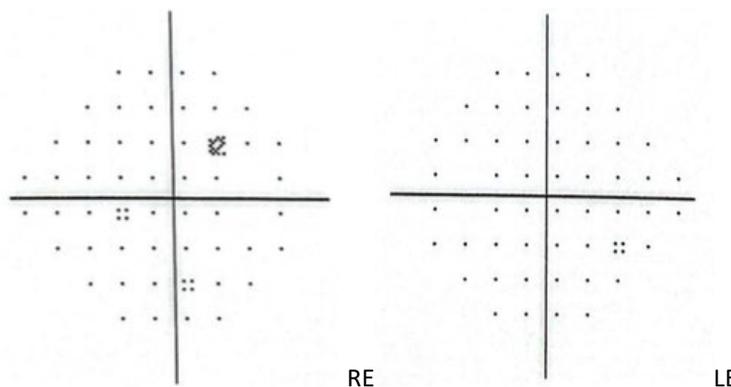


Figure 9. HVF of the LE showed improvement. No central scotoma was found on nine-month follow-up.

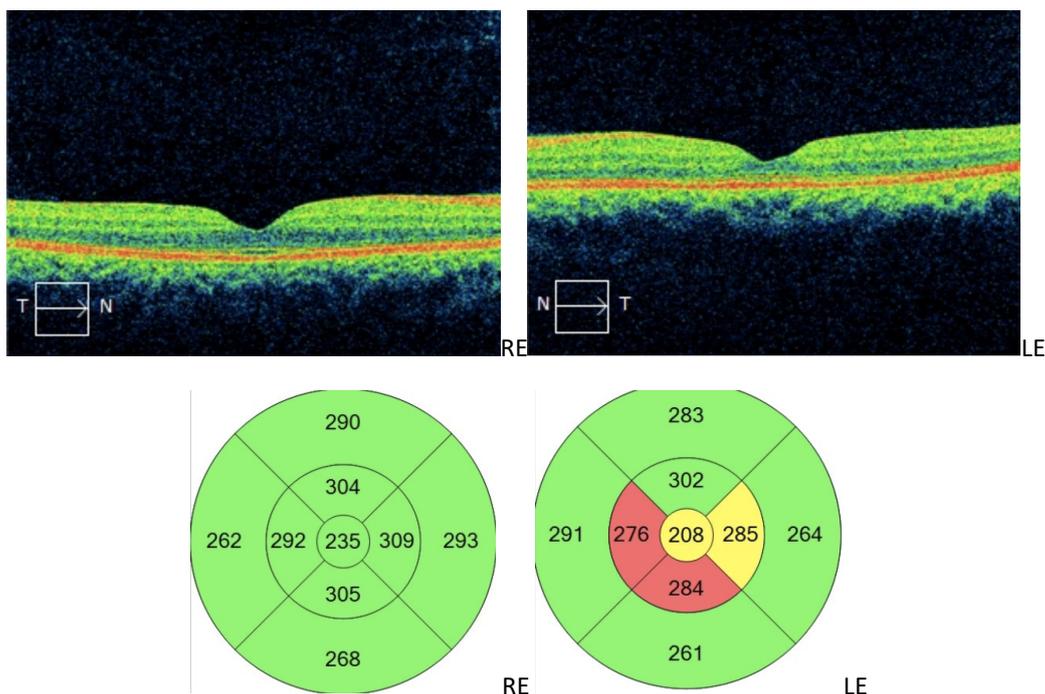


Figure 10. At ten months' follow-up, LE macula OCT remained stable, which showed a normal retinal outer segment layer.

**DISCUSSION**

This case showed visual impairment during the treatment of multidrug therapy due to leprosy. Only a few cases of dapsone ocular toxicity have been reported in the literature. Several cases of suicide attempts using dapsone were reported. In a dapsone overdose, visual acuity ranges from 6/36 to counting fingers. In an attempt to commit suicide, **Kenner et al.**<sup>6</sup> reported permanent retinal damage after ingestion of 7.5 grams of dapsone. Bilateral yellow-white appearances in the macula and paramacular region with several intraretinal hemorrhages in

adjacent normal retina were found. **Seo et al.**<sup>7</sup> also reported a case of dapsone maculopathy after ingestion of 10 grams of dapsone in a suicide attempt. A symmetrical whitish-yellow patch in the macula of both eyes was found. **Hussain et al.**<sup>8</sup> described a case of macular infarction caused by a dapsone overdose, with extensive retinal opacification and a cherry red spot on the posterior pole. To the researcher's knowledge, there is one case that reported dapsone ocular adverse effect on treatment dose.

**Dugan et al.**<sup>5</sup> reported bilateral exudative retinal detachments and choroidal detachments in a patient treated with dapsone due to urticarial vasculitis. The BCVA was 6/12 in both eyes. In our patient, the BCVA was 6/6 on the RE and 6/12 on the LE at presentation, which corresponds to the **Dugan et al.**<sup>5</sup> report. This patient had yellowish pigmentary changes on the macula, which is consistent with previous case reports of macular involvement in dapsone toxicity. The only difference here is that our case demonstrated unusually unilateral, clinically apparent macular toxicity, although the abnormal multifocal ERG was found bilaterally.

Ischemia is thought to be the mechanism of ocular side effects rather than direct toxicity.<sup>5</sup> Acute, severe peripheral hypoxia and the physical effect of red cell fragmentation due to the hemolytic process may result in macular ischemia. Patients receiving a therapeutic dose of dapsone frequently experience hemolytic anemia and methemoglobinemia. Dapsone hydroxylamine (DDS-NOH) is an active metabolite of dapsone that causes intracellular oxidation, enters circulation, and disrupts red blood cell (RBC) integration via glutathione depletion and tyrosine phosphorylation of band 3 protein. Fragmented RBCs block small vessels in the retina and choroid, causing "sludging" and infarction. Methemoglobinemia, which lowers oxygen levels, aggravates the obstruction, leads to tissue hypoxia and injury.<sup>5,9</sup> **Bian et al.**<sup>10</sup> reported that DDS-ONH may provoke the procoagulant activity of RBCs at subhemolytic concentrations of DDS-ONH (10-50 µM) by generating reactive oxygen species (ROS). Additionally, dapsone hydroxylamine increased RBC self-aggregation, thrombin production, and endothelial cell adhesion in vitro.

The long and thin macula capillaries have a tendency to thrombose which typically results in selective macula involvement. Ischemia disrupts the inner blood retinal barrier resulting in extracellular

fluid accumulation in the inner retinal layers and cystic changes. If the ischemia persists for a long time, permanent loss of inner retinal neurons due to necrosis and apoptosis may occur.<sup>8</sup> In addition, **Chakrabarti et al.**<sup>11</sup> reported a bilateral macular yellow-white lesion at the macula and premacular areas with numerous intraretinal hemorrhages after ingesting massive doses of dapsone in an effort to commit suicide. The macular lesion is most likely caused by a combination of tissue hypoxia, macular vascular blockage, and the sludging impact of fragmented cells. Because of their long length and small caliber, macular capillaries are vulnerable.

Evaluation of the macular involvement in dapsone toxicity can be performed through macular OCT and multifocal ERG. In this case, we found macular edema, intraretinal hyperreflectivity, and subretinal fluid at the presentation and second visit. At the two-month follow-up, visual acuity improvement was observed. Macular edema, intraretinal hyperreflectivity, and subretinal fluid resolution were observed on the five-month and nine-month follow-ups after discontinuation of dapsone. **Hussain et al.**<sup>8</sup> discovered elevated foveal and multiple cystic changes in macular infarction after massive dapsone ingestion. A foveal flattening contour with marked thinning of the macular area due to complete loss of the inner retinal layers was discovered at the three-month follow-up. **Hanuschk et al.**<sup>12</sup> reported acute retinal ischemia, which leads to inner retinal disorganization and thickening. The evolution of the lesions is usually sequential. Inner retinal atrophy, loss of normal foveal depression, and permanent visual loss may occur as a result of prolonged ischemia, apoptosis, and necrosis. At the 6-month follow-up, visual acuity improvement was observed, and macular ischemic lesions had disappeared, leaving pigmentary changes and atrophy, which correspond with the findings in our patient.

A multifocal ERG (mfERG) can be performed to assess the macular abnormalities. The mfERG is an electrophysiological test that permits simultaneous evaluation of the function of multiple discrete areas of the retina.<sup>13</sup> While frequency-domain OCT (fdOCT) is a structural examination, mfERG evaluates local retinal function. An abnormal visual field and mfERG result along with a normal-appearing fdOCT suggests that early functional loss may precede significant structural abnormalities on fdOCT. **Talamini et al.**<sup>14</sup> reported that an aberrant visual field and mfERG result coupled with a normal-looking fdOCT suggests that early functional loss can occur before evident structural alterations are visible in fdOCT. This finding is consistent with that of our patient, who had a visual acuity of 6/6 and normal macular structure in the right eye, but whose mfERG showed low amplitudes of N1 and P1 waves in rings 1 to 4. Unfortunately, we did not find literature about the mfERG finding in dapson-induced toxic maculopathy. **Beral et al.**<sup>15</sup> described mfERG findings in sickle cell disease that found macular electrophysiological dysfunction in sickle cell disease without clinical signs of maculopathy. MfERG demonstrated a significant reduction of N1 and P1 amplitudes from the center ( $<2^0$ ) and to the periphery ( $>15^0$ ); implicit time was also reduced in the center. The hyperreflective band at the inner nuclear layer on OCT may reflect ischemia in the deep capillary plexuses. Macular infarction in sickle cell retinopathy is caused by retinal ischemia secondary to the sickling of RBC in retinal arterioles.<sup>16</sup> The fdOCT and mfERG examinations provide a potent method to pinpoint the site and origin of retinal injury.<sup>17</sup>

The dosage of dapson that may cause retinal toxicity is still questionable. **Dugan et al.** reported bilateral exudative retinal detachment and choroidal detachment in a patient treated with 50 mg daily of

dapson for urticarial vasculitis for two months.<sup>5</sup> **Bian et al.** reported that lower concentrations of DDS-ONH (1-50  $\mu$ M) may trigger phosphatidylserine (PS) exposure and elicit procoagulant activity of RBCs.<sup>10</sup> A blood level of 0.5-5 mg/L can be achieved by giving dapson 50-300 mg daily (equivalent to 2-20  $\mu$ M). Additionally, a single dose of 50 or 100 mg/kg (intraperitoneal/i.p.) DDS-NHOH and repeated doses of 10 mg/kg per day (i.p.) for 4 days increased the formation of thrombus in rats (six rats per dose) in vivo, supporting a possible prothrombotic risk of DDS-NHOH. In leprosy patients, WHO recommends multidrug therapy (MDT) for paucibacillary (PB) leprosy, which consists of rifampicin and dapson for 6 months. The recommended MDT for multibacillary (MB) leprosy consists of rifampicin, clofazimine, and dapson for 12 months. The dosage of dapson for both MB and PB leprosy is 100 mg daily for adults and 50 mg daily for children.<sup>2</sup> In contrast, **Vieira et al.**<sup>18</sup> observed the mean concentration of dapson in MB leprosy patients, which was  $1.42 \pm 1.65$   $\mu$ g/mL in males and  $2.42 \pm 2.28$   $\mu$ g/mL in females. Male patients had a level of  $3.09 \pm 1.91\%$ , while female patients had a level of  $2.84 \pm 1.67\%$ . The risk of dapson-dependent side effects is very low if the plasma concentration is below 5 mg/L. The Pearson coefficients between dapson concentrations and MeHb levels in both groups did not show any significance. The dosage of dapson in leprosy treatment does not promote an important methemoglobinemia.

## CONCLUSION

This case showed that dapson may cause macular toxicity, which results in visual impairment. The mechanism is thought to be macular ischemia due to tissue hypoxia, macular vascular blockage, and the sludging impact of fragmented cells. Regular follow-up and evaluation of macular involvement in dapson toxicity are essential. Following the discontinuation of dapson, improvements in visual function, macular structure, and electrophysiological function were observed.

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