Acute Macular Neuroretinopathy in Dengue Fever Short-term Prospectively Followed Up Case Series

Miaoling Li, MD; Xiongze Zhang, MD, PhD; Yuying Ji, MD; Baikang Ye, MD; Feng Wen, MD, PhD

Dengue fever (DF) is a mosquito-transmitted viral epidemic mainly affecting the Americas, Southeast Asia, and the Western Pacific. The incidence of DF increases every year. In particular, the DF outbreak caused by the serotype 1 dengue virus that occurred in South China's Guangdong Province in 2014 was the worst outbreak of the past 2 decades.

Following epidemics of DF, ocular complications in the macula may be more common than some ophthalmologists realize. The prevalence of dengue maculopathy among patients hospitalized with dengue infection was estimated to be 10%. The reported manifestations of dengue maculopathy include foveolitis, macular hemorrhage, and edema associated with arteriolar sheathing, cotton wool spots, perifoveal telangiectasia, and microaneurysms. Here, we present acute macular neuroretinopathy (AMN) post-DF observed during the outbreak in South China in 2014.

Methods

This study involved patients with dengue maculopathy who were referred to the macular disease service of the Zhongshan Ophthalmic Center from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

IMPORTANCE The incidence of dengue fever (DF) increases every year. Macular complications of patients with DF may be more common than many ophthalmologists realize. During a DF outbreak in South China in 2014, we observed acute macular neuroretinopathy associated with DF.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.

CONCLUSIONS AND RELEVANCE These data suggest that acute macular neuroretinopathy is a major manifestation of dengue maculopathy, with persistent scotomas through at least 6 months.

OBSERVATIONS Among 9 patients (17 eyes) with maculopathy post-DF, 5 patients (55.6%) (9 eyes) manifesting acute macular neuroretinopathy were recruited from August 1, 2014, to September 30, 2014, with a 6-month ophthalmic follow-up. Infrared reflectance imaging demonstrated localized areas of hyporeflection in the macula. Spectral-domain (SD) optical coherence tomography (OCT) scanning through these areas revealed hyperreflection in the photoreceptor layer and disruption of its normal reflective structures. Subsequent SD-OCT demonstrated that the hyperreflection of the photoreceptor layer regressed gradually, followed by thinning of the outer nuclear layer. The external limiting membrane and ellipsoid zone became continuous; however, the interdigitation zone was not restored. The scotomas persisted in all 5 patients (9 eyes) by the last visit. All 5 patients (9 eyes) in this case series were complicated with classic dengue maculopathy signs, such as intraretinal hemorrhage and exudation, which were completely resolved during the follow-up.
(Heidelberg Engineering). Subsequently, FAF, IR reflectance, and SD-OCT imaging were conducted during the follow-up. All of the procedures in this study adhered to the tenets of the Declaration of Helsinki and were approved by the institutional review board of the Zhongshan Ophthalmic Center at Sun Yat-sen University. All patients provided written informed consent.

### Results

Nine patients (17 eyes) with dengue maculopathy were referred to our clinic. Five of them (55.6%) (9 eyes, 52.9%; 3 women and 2 men) manifested AMN and were included in our series. The other 3 patients experienced intraretinal hemorrhages and/or fundus changes caused by increased retinal vascular leakage (stellate exudation, edema, and vasculitis), and 1 presented with a central artery occlusion. The demographic data and clinical presentations of the 5 patients are summarized in Table 1 and Table 2.

The median age of the patients with AMN was 38 years (range, 16-49 years). The involvement of AMN lesions was bilateral in 4 cases and unilateral in 1 case. Central/paracentral scotoma was the main visual symptom. The visual acuity varied from 20/20 to 20/667, depending on whether the fovea was involved. The median interval between the onset

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Ocular Symptoms</th>
<th>Interval Between the Onset of Visual Symptoms and Systemic Manifestations, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Female/38</td>
<td>20/25</td>
<td>20/20</td>
<td>Central and paracentral scotomas</td>
<td>6</td>
</tr>
<tr>
<td>2/Female/43</td>
<td>20/50</td>
<td>20/20</td>
<td>Paracentral scotomas</td>
<td>3</td>
</tr>
<tr>
<td>3/Male/16</td>
<td>FC/20 cm</td>
<td>20/20</td>
<td>Blurred vision and paracentral scotomas</td>
<td>7</td>
</tr>
<tr>
<td>4/Male/49</td>
<td>20/25</td>
<td>20/25</td>
<td>Central and paracentral scotomas</td>
<td>3</td>
</tr>
<tr>
<td>5/Male/30</td>
<td>20/20</td>
<td>20/20</td>
<td>Paracentral scotomas</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 2. Summary of Presentations and Findings in 5 Patients With AMN Associated With Dengue Fever

<table>
<thead>
<tr>
<th>Case</th>
<th>Fundus Sign</th>
<th>Fundus Fluorescein Angiography</th>
<th>Optical Coherence Tomography (Confined to AMN Lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intraretinal hemorrhage within the vascular arcades and mild edema of the optic disc in each eye; a brownish patch nasal to the fovea in the right eye</td>
<td>Hypofluorescence corresponding to the intraretinal hemorrhage in each eye; early microvascular dilations of the optic disc and late staining accompanied by indistinct margins in each eye</td>
<td>Hyperreflective bands involving the photoreceptor layer from the HFL to the IZ in each eye, involving the left fovea</td>
</tr>
<tr>
<td>2</td>
<td>Scattered white dots of dehemoglobinized intraretinal hemorrhage and yellowish-white wedge-shaped lesions in the macula of each eye</td>
<td>No remarkable findings in each eye</td>
<td>Hyperreflective bands that involved the photoreceptor layer from the HFL to the IZ in each eye, involving the right fovea</td>
</tr>
<tr>
<td>3</td>
<td>Intraretinal hemorrhage and exudation nasal to the fovea in the right eye; intraretinal hemorrhage and a yellowish-white patch superior and nasal to the fovea in the left eye</td>
<td>Focal hypofluorescence corresponding to intraretinal hemorrhage in each eye</td>
<td>Hyperreflective bands that involved the photoreceptor layer from the HFL to the IZ in the left eye</td>
</tr>
<tr>
<td>4</td>
<td>Intraretinal hemorrhage and exudation within the vascular arcades and brownish petaloid lesions around the fovea in each eye</td>
<td>Focal hypofluorescence corresponding to intraretinal hemorrhage in each eye</td>
<td>Hyperreflective bands in the HFL, with associated thinning of the ONL and underlying disrupted ELM, EZ, and IZ in each eye, involving the left fovea</td>
</tr>
<tr>
<td>5</td>
<td>Intraretinal hemorrhage and brownish patches in the macula in each eye</td>
<td>Focal hypofluorescence corresponding to intraretinal hemorrhage in each eye</td>
<td>Subtle hyperreflective bands in the HFL, with associated thinning of the ONL and underlying disrupted ELM, EZ, and IZ in each eye, involving the left fovea</td>
</tr>
</tbody>
</table>

Abbreviations: AMN, acute macular neuroretinopathy; ELM, external limiting membrane; EZ, ellipsoid zone; HFL, Henle fiber layer; IZ, interdigitation zone; ONL, outer nuclear layer.
of visual symptoms and the systemic manifestations was 5 days (range, 3-7 days), which did not overlap with the febrile episode.

The fundus findings of the AMN lesions were normal (left eye of case 1; Figure 1A) or wedge-shape/patchy lesions with yellowish-white/brownish color in the macula (Figure 2A). There were no remarkable findings of the AMN lesions on FFA. On FAF, subtle streaks of hypoautofluorescence were detected in the macula of 1 patient (case 2; Figure 2A); the other 4 appeared normal. Images obtained by IR reflectance and SD-OCT revealed hyperreflective areas on IR reflectance imaging and were more precisely delineated compared with the fundus photographs. Spectral-domain OCT scanning through the IR defects revealed hyperreflection in the photoreceptor layer, with disruption of its normal reflective structures (Figure 1A and Figure 2A). The attenuation of hyperreflection began within the first 2-week follow-up interval, and it partially remained in the Henle fiber layer at the 24th week. Thinning of the outer nuclear layer accompanied the attenuation of the hyperreflective band, and the continuity was nearly completely reconstructed. However, little restoration of the interdigitation zone was observed by the last visit (Figure 1B and C).

In addition to the AMN lesions, all 5 patients (9 eyes) in our series were found to have classic dengue maculopathy signs such as intraretinal hemorrhage and exudation. All of these lesions completely resolved during the follow-up.

One patient (case 1) was given systemic corticosteroid therapy for the combined mild optic disc edema in both eyes. The remaining 4 patients were observed without any treatment. All 5 patients obtained varying degrees of visual acuity improvement but had persistent central/paracentral scotomas.

Discussion

Flulike symptoms have been reported preceding AMN, and other associated factors include the use of oral contraceptives, injection of adrenaline, use of norepinephrine, trauma, and caffeine use.8 This series confirms AMN associated with DF.

In this series, 55.6% of patients with dengue maculopathy had AMN. These data must be interpreted with caution because a referral bias may exist in this series, which was recruited from a referral center at a tertiary hospital. Dengue fever is a systemic disease requiring general medical care. Cases with dengue maculopathy referred to our center tend to be relatively severe ones. All 5 patients in our series reported persistent scotomas with minimal relief. The cause of their persistent scotomas could have been related to the irreversible thinning of the outer nuclear layer and incomplete restoration of the interdigitation zone, which are the sequelae of AMN.6,9 Acute macular neuroretinopathy presented essentially normal on ophthalmoscopic examination or FFA. The hyperreflection of AMN lesions on SD-OCT imaging attenuated fast within a 2-week follow-up interval. Spectral-domain OCT applied before the

Figure 1. Case 1

A, Fundus photograph (top), infrared, and spectral-domain (SD) optical coherence tomography (OCT) of case 1 at baseline. Spectral-domain OCT reveals a hyperreflective band from the Henle fiber layer to the interdigitation zone (arrowheads). B, Fundus photograph (top), infrared, and SD-OCT 2 weeks later. Spectral-domain OCT demonstrates regression of the hyperreflective band, with associated thinning of the outer nuclear layer and disrupted underlying external limiting membrane, ellipsoid zone, and interdigitation zone (arrowheads). C, Fundus photograph (top), infrared, and SD-OCT at the last visit. Spectral-domain OCT shows complete restoration of the external limiting membrane and ellipsoid zone and discrete interdigitation zone (arrowheads). For A, B, and C, the images on the second row are of the right eye and those on the third row are of the left eye. Also in the second and third rows, infrared images are on the left and SD-OCT images on the right.
attenuation of the lesions could facilitate the diagnosis of AMN in dengue maculopathy. Teoh et al10 used time-domain OCT to study the prognosis and proposed 3 patterns of dengue maculopathy as diffuse retinal thickening (type 1), cystoid macular edema (type 2), and foveolitis (type 3). All the structural abnormality returned spontaneously to normal within a few days; however, scotomas persisted in 30.3% of eyes with type 1, 56.3% of eyes with type 2, and 100% with type 3 maculopathy. We assumed that most type 3 maculopathies described by Teoh et al10 should be AMN, which was not realized owing to the limitation of the time-domain OCT. Moreover, a previous case report11 of dengue maculopathy noted outer nuclear layer thinning and ellipsoid zone disruption, which resembled the later phase of AMN.

There is no established treatment for dengue eye disease. Observation and corticosteroid were the 2 main treatment modalities. Corticosteroid was applied when severe maculopathy, uveitis, optic neuritis, and neuromyelitis optica occurred, with inconsistent treatment response.1 The systemic corticosteroid prescribed to case 1 in our series did not help in relieving her scotomas.

Conclusions
In summary, AMN is a major manifestation of dengue maculopathy with persistent scotomas through at least 6 months in our series.
REFERENCES