Electrophysiological Findings in Patients With Dengue-Related Maculopathy

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Objective: To assess visual function in patients with dengue maculopathy using electrophysiological tests.

Methods: Fifteen consecutive patients with dengue fever who experienced vision loss between July 2004 and July 2005 were included in this review. Full-field electroretinograms (ERG), pattern ERGs, and multifocal ERGs were performed.

Results: The most common electrophysiological finding (60%, 9/15) was a normal or mildly abnormal full-field ERG with reduced pattern ERG P50 amplitude and abnormal mERG. Typically, multifocal ERG demonstrated a focal area of decreased macular response (especially between the fovea and optic nerve). Pattern ERG suggested normal optic nerve function in all but 1 case. Four patients had more severely reduced full-field ERG responses with reduced a-wave amplitude (suggestive of photoreceptor dysfunction), 3 of whom had an electro-negative maximal response (suggestive of additional postreceptor dysfunction). Repeat multifocal ERG showed little change in 7 patients and incomplete resolution in 2 patients over 3 to 10 months.

Conclusion: Retinal dysfunction associated with dengue maculopathy was localized mainly around the foveal region. It appeared to affect the outer and middle retina more severely with relative sparing of the inner retina. Retinal dysfunction may persist for several months. Longer follow-up is required to determine whether these changes are permanent.

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Dengue fever (DF) is a mosquito-borne viral illness of the Flavivirus genus that is endemic in many tropical and subtropical areas in the world. It was first reported in the late 1770s. Four dengue Flavivirus serotypes have been identified. Infection by 1 does not provide cross-immunity to another. No vaccine is currently available.

Dengue viral infections may be totally asymptomatic or show symptoms of a non-specific viral syndrome. Typically, patients with DF show symptoms of a febrile illness with associated headache, retro-orbital discomfort, myalgia, rash, and leucopenia. A positive dengue IgM test result confirms the diagnosis. The most severe form, dengue shock syndrome, results in bleeding from the skin, nose, gum, and internal organs and plasma loss secondary to increased vascular permeability and may result in circulatory collapse and death. There is no specific treatment for the disease, and medical intervention is directed toward providing both antipyretic and analgesic medication with adequate hydration.

Ocular manifestations have been described with DF. Patients commonly describe blurred vision, usually 7 days after the onset of illness when other symptoms are resolving. Ocular findings range from focal retinal hemorrhages, Roth-like spots, retinal edema, cotton wool spots, vasculitis, and optic neuritis.1,2

The incidence of DF has increased in Southeast Asia over recent years. Infection rates in Singapore reached a 10-year high during 2004. In 2004, 9459 cases of DF were reported, representing a 2-fold increase from the previous year. This sudden spike in numbers has been accompanied by an unprecedented increase in patients with ocular manifestations secondary to DF.

Visual dysfunction associated with dengue maculopathy and its recovery has not previously been studied in detail. In this study, retinal function was assessed using a range of electrophysiological tests.
This study included 15 consecutive patients diagnosed with DF who were referred for electrophysiological investigation of visual loss between July 2004 and July 2005. Electrophysiological data available included findings from pattern electroretinograms (PERG), full-field electroretinograms (fERG), and multifocal electroretinograms (mERG). Dawson-Trick-Litzkow electrodes (Diagnosys, LLC, Lowell, Mass) were used for all recordings. Reference electrodes were placed at each temple with a ground electrode at the forehead. All tests were performed according to standards or guidelines from the International Society of Clinical Electrophysiology of Vision. 1,3

The PERGs were recorded in undilated eyes of patients wearing their full spectacle correction. A pattern-reversal stimulus with checks subtending a visual angle of 0.8° at a 30-cm testing distance was presented at a rate of 8 reversals per second. The Espion system (Diagnosys, LLC) was used for stimulus generation and data acquisition. The fERG protocol consisted of the scotopic, maximal, photopic, and 30-Hz flicker responses. Pupils were dilated to at least 7 mm with 2 drops of 1% tropicamide. The scotopic and maximal responses were obtained following dark adaption for at least 20 minutes. The photopic and 30-Hz flicker responses were recorded after 10 minutes of light adaptation. Responses were recorded using the Espion system.

**METHODS**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time*</th>
<th>Eye</th>
<th>Visual Acuity</th>
<th>Scotopic b-Wave†</th>
<th>Maximal a-Wave†</th>
<th>Photopic b-Wave†</th>
<th>PERG N95/P50 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 wk</td>
<td>OD</td>
<td>CF</td>
<td>107/93</td>
<td>208/54†</td>
<td>208/54†</td>
<td>30-Hz Flicker Ratio</td>
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<tr>
<td>5 mo</td>
<td>20/40</td>
<td>OS</td>
<td>121/94</td>
<td>161/14</td>
<td>183/49†</td>
<td>183/49†</td>
<td>P50</td>
</tr>
<tr>
<td>12 w k</td>
<td>NA</td>
<td>NA</td>
<td>165/17</td>
<td>56/32</td>
<td>Unchanged at 5 m.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/25</td>
<td></td>
<td></td>
<td>19/15</td>
<td>66/30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 wk</td>
<td>OD</td>
<td>CF</td>
<td>250/96†</td>
<td>243/15</td>
<td>331/53†</td>
<td>1.13†</td>
</tr>
<tr>
<td>3 mo</td>
<td>20/150</td>
<td>OS</td>
<td>217/112</td>
<td>217/11</td>
<td>492/42</td>
<td>1.35†</td>
<td>184/14</td>
</tr>
<tr>
<td>5 mo</td>
<td>191/0</td>
<td>OS</td>
<td>218/12</td>
<td>149/15</td>
<td>317/13</td>
<td>2.8†</td>
<td>1.7</td>
</tr>
<tr>
<td>4</td>
<td>3 wk</td>
<td>OD</td>
<td>20/129</td>
<td>185/11</td>
<td>251/47</td>
<td>1.65</td>
<td>1.7</td>
</tr>
<tr>
<td>3 wk</td>
<td>20/150</td>
<td>OS</td>
<td>217/112</td>
<td>217/11</td>
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<td>1.7</td>
</tr>
</tbody>
</table>

**Table 1. ERG Parameters of Patients**

Abbreviations: CF, counting fingers; mERG, multifocal electroretinogram; NA, not available; NLP, no light perception; PERG, pattern electroretinogram.

*Time from onset of dengue fever.
†For each parameter, x/y is amplitude in microvolt, and x/y = implicit time in milliseconds.
‡Abnormal values.
The mfERG recording was performed using the VERIS system (VERIS science version 4.8; EDI, San Mateo, Calif). A test stimulus consisting of 103 retinally scaled hexagons was randomly displayed on a monochrome monitor (MGD 403; Philips, Saronno, Italy) using a pseudorandom m-sequence (m = 14) at a rate of 75 Hz. The intensity of the white hexagon was 2.66 candela second per meter squared and the stimulus contrast approximately 96%. The background luminance was set at 100 cd/m². Recording signals were band-pass filtered between 10 and 100 Hz and amplified 100 000 times using the Grass system (NeuroData Model 12, Quincy, Mass). The recording process was divided into 16 periods (each lasting 14 seconds) to help ensure the patient’s comfort and to suppress eye movement and blinking.

Fifteen patients were referred to the visual electrophysiology laboratory for investigation of vision loss after contracting DF. Their ages ranged from 12 to 41 years with a median of 19.5 years. Six patients were female and 9 male.

Electrophysiological findings are summarized in Table 1 and Table 2. The most common ffERG finding was the presence of decreased scotopic b-wave amplitude in 15 (50%) of 30 eyes followed by maximal b-wave implicit time delay (15/30, 43%) and amplitude reduction (10/30, 33%). Maculaopathy was demonstrated with abnormal PERG P50 responses in 17 (57%) of 30 eyes and focal mfERG defects in 22 (73%).

The most common combination of electrophysiologic findings (patients 1-9) consisted of normal or mildly abnormal ffERGs, reduced PERG P50 amplitudes in the more affected eye, and foveal/parafoveal defects (usually situated between the fovea and optic nerve) on mfERGs. Four patients (patients 10-13) demonstrated more severe reduction in scotopic or photopic ffERG responses. Five patients had a reduced maximal b/a ratio, 3 of these (2 of whom were brothers) had electronegative maximal responses (ie, b/a ratio <1).

Two patients (patients 14 and 15) required investigation of possible optic neuritis. Pattern ERGs and mfERGs were useful in demonstrating that vision loss was due to retinal pathologic abnormalities in patient 14 and optic nerve pathologic abnormalities in patient 15 (Table 1).

Patient 1 was a 26-year-old Chinese man who developed blurred vision 6 days after the onset of DF. At the initial examination, his visual acuity was counting fingers OD and 20/400 OS. Scattered blot hemorrhages were seen at the macula with a central yellow lesion noted at the fovea (Figure 1A and B). Fundal fluorescein angiography and indocyanine green angiography showed areas of blocked fluorescence corresponding to the areas of blot hemorrhages with late-phase hypofluorescence suggestive of foveal and posterior choroidal hypoperfusion. He was given high-dose intravenous methylprednisone for 3 days followed by oral corticosteroids. One month later, his visual acuity was 20/400 OD and 20/100 OS. Dense scotomas were found on Humphrey visual field (HVF) testing (Figure 1D). The ffERG scotopic responses were slightly decreased in amplitudes but not delayed (Figure 1C). The mfERG demonstrated areas of decreased responses between the optic disc and fovea in both eyes (OD > OS) that matched the HVF findings (Figure 1E). A 1-week trial of intravenous immunoglobulin and hydrocortisone was then administered, and the visual acuity improved to 20/50 OD and 20/40 OS over the next 4 weeks. At 6 months, both fundi appeared normal except for a faint epiretinal membrane over each fovea. Fundal fluorescein angiography and indocyanine green angiography findings were normal. Visual acuity was 20/30 OD and 20/25 OS. However, the patient still complained of persistent scotomas in both eyes. Humphrey visual field results had much improved, although decreased sensitivities were still noted centrally. Repeat photopic ffERG findings were unchanged and persistent defects were noted on mfERG (Figure 1E). This patient demonstrated the typical clinical course of dengue maculopathy.

Patient 12 was a 14-year-old Chinese boy who contracted DF together with his brother (patient 13). Neither brother had had a history of nystagmus or photopsia. There was no family history of retinal dystrophy. Visual problems commenced 9 days after the onset of symptoms. His visual acuity was 20/40 OD and 20/100 OS. Color vision test results were normal. The right fundus appeared normal while flame hemorrhages and focal edema were noted between the macula and optic nerve in the left eye. The ffERG showed reduced scotopic b-wave responses and electronegative maximal responses (Figure 2A). The mfERG showed an area of decreased response OS, which matched the defect on HVF (Figure 2C and B). The PERG P50 amplitude was lower in the more severely affected eye. Visual acuity improved to 20/25 OU over the next 4 weeks. At 10 months, his visual acuity was...
20/20 OU. However, he still described vague areas of defective vision close to fixation. Full-field ERG scotopic and photopic responses were largely unchanged. However, slight improvement of the maximal b/a ratio (electronegativity) was noted. Repeat mfERGs showed a persistent area of decreased response OS.

Patient 14, a 37-year-old woman, had a dense right-central visual defect 9 days after onset of DF. Visual acuity was counting fingers OD and 20/20 OS. A right relative afferent pupil defect, mild vitritis, and abnormal macula reflex were noted. She was only able to read the test plate of the Ishihara chart OD. Mild choroidal hy-
Poperfusion was noted on indocyanine green angiography. Fundal fluorescein angiography and optical coherence tomography results were normal. Full-field ERG findings were within normal limits. Pattern ERG P50 amplitude OD, although still within normal limits, was only half of that OS. The N95/P50 ratio was within the normal range suggestive of reasonable optic nerve function. The mfERG demonstrated an area of decreased response extending between the right fovea and optic nerve.

The patient began receiving topical steroids. Five days later, when no improvement of vision was noted, she received intravenous hydrocortisone for 8 days and then oral corticosteroids, which were tapered over the next 2 months. At last review, 3 months later, her visual acuity was still counting fingers OD.

Patient 15, a 20-year-old man, had no light perception and a dense relative afferent pupil defect OD at 1 week after onset of DF. The right optic nerve was noted to be pale and swollen. Both fERG and mfERG findings were within normal limits. The PERG N95/N50 ratio was reduced, and flash visual evoked potentials were undetectable OD, which was strongly suggestive of right optic nerve dysfunction. Three months later, visual acuity remained at no light perception OD.

**COMMENT**

Dengue fever is endemic in Southeast Asia, where physicians are familiar with the systemic effects of the illness. However, ocular manifestations are rare. Visual symptoms in our patients typically occurred 6 to 10 days after onset of DF, which is suggestive of a possible postviral immune reaction. When visual acuity was severely affected, patients were often treated with intravenous or oral corticosteroids or intravenous immunoglobins. However, even when visual acuity improved, sometimes from counting fingers to 20/20, some patients still complained of persistent visual scotomas.

The ocular effects of DF can be investigated in several ways. Fundus photography, fundal fluorescein angiography, indocyanine green angiography, optical coherence tomography, and visual evoked potentials are all helpful in assessing the patient's visual function.

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Figure 2. Findings for patient 12. A, Electroretinogram (ERG) findings. Full-field ERG scotopic response depressed with electronegative maximal response and normal photopic response. Pattern ERG P50 response was just within normal limits in both eyes. No significant change noted over 10 months. B, Humphrey visual field (HVF) findings show small scotoma in the left eye. C, Multifocal ERG findings demonstrating a small area of decreased response in the left eye. L indicates left; LVA, left visual acuity; R, right; RVA, right visual acuity.
harance tomography, and HVF have been used to monitor and assess the extent of disease. Electrophysiological tests, however, can provide unique information about retina and optic nerve function.

The fERG measures the summed responses of the entire retina to a diffuse light stimulus. The rod and cone systems can be assessed under scotopic (dark) and photopic (light) conditions. The a-wave obtained is a reflection of photoreceptor response while the following b-wave (or b/a ratio) is a measure of postreceptor function. Diminished or delayed responses are indicative of retinal dysfunction. However, focal defects in the retina (eg, those limited to the macula) may be masked by the responses of the surrounding normal retina. It is not surprising, therefore, that many of our patients with dengue maculopathy had normal or mildly abnormal fERG responses (patients 1-9). More severe fERG abnormalities, such as a-wave amplitude loss in patient 10 and electronegative maximal b-wave in patients 11-13, suggest more widespread involvement of the retina. Because fERGs were not done prior to illness, it is uncertain whether these abnormalities were not present prior to illness or whether there had been no change in those patients with normal results. Those with worse initial fERG response did not necessary have worse long-term outcomes.

The PERG provides specific information about macular function. The first positive peak (P50) is thought to be formed mainly from the macular (outer retina) response with a later contribution from the inner (ganglion cell and axon) retina. The subsequent trough (the N95 response) is believed to be primarily from inner retinal activity. In our patients, P50 amplitude was typically lower in the eye with worse vision, suggesting that there was more severe maculopathy in that eye. The P50 amplitude recovered in all patients with improving visual outcome. There was no apparent relationship between initial level of P50 amplitude and eventual visual outcome. The N95/P50 ratio was within normal limits in all but 1 patient, suggesting that the optic nerve was not involved in most of the cases.

Retinal function can be plotted topographically with the mfERG. Because mfERG responses are mainly formed by bipolar cells, decreased responses suggest either photoreceptor or bipolar cell abnormality. Most of our patients had focal areas of retinal dysfunction on mfERG that roughly corresponded to HVF findings. However, as HVF defects became less marked with time and the retinal appearance and structure returned to normal, the mfERG abnormalities persisted unchanged (7 patients) or only partially improved (2 patients) for months.

Two patients were referred specifically for the assessment of optic nerve dysfunction. In both cases, there was severe visual loss, afferent pupil defect, or color vision loss out of proportion to the retinal changes seen. In patient 14, although presence of mild coexisting optic neuritis cannot be excluded with certainty, the mfERG clearly demonstrated macular pathologic abnormalities. In patient 15, a decreased N95/P50 ratio in the presence of a normal mfERG localized pathologic abnormalities to the optic nerve. Being so different from the other cases, however, it is not certain how this last patient fits into the spectrum of ocular DF.

In conclusion, the ocular manifestations of dengue maculopathy are relatively rare but can occur in previously healthy young people and result in prolonged visual impairment. In our series of patients, a focal maculopathy was noted in most cases with retinal dysfunction localized mainly in the area between the fovea and optic nerve. The outer and middle retina (photoreceptor and bipolar cells) appeared to be more severely affected with relative sparing of the inner retina (ganglion cells). Even though retinal morphologic features gradually returned to normal, retinal dysfunction (measured electrophysiologically) persisted for months. Longer follow-up will be required to determine whether this functional visual loss is permanent.

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