A Re-look at Ocular Complications in Dengue Fever and Dengue Haemorrhagic Fever

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Abstract

Dengue fever is endemic in the tropics and subtropics and has emerged as a major global health threat over the last few decades. Dengue-related ocular complications are generally overlooked, but over the past two years, increasing incidences of such complications have been reported from countries in South-East Asia. The presentation, course and one-year outcomes of 50 patients with dengue-related ophthalmic complications in Singapore are reported here. The investigations included complete slit lamp and fundoscopy examinations, automated visual field analysis, Amsler charting, fundus fluorescein angiography and optical coherence tomography. Sixty-five eyes from 50 patients were affected. With slight male preponderance (68%), the mean age of the patients was 32 years (range 20 to 69 years). Visual acuity varied from 6/6 to counting fingers only (median 6/12). Blurring of vision (60%) and central scotoma (30%) were the most common symptoms. The onset of visual impairment coincided with the nadir of serum thrombocytopenia. The most common findings were macular oedema (45 eyes, 69%) and haemorrhages (50 eyes, 77%) and focal chorioretinitis with or without retinal vasculitis (15 eyes, 23%). Most cases were self-limiting and resolved spontaneously without treatment. After one year, 80% of the patients had recovered 6/12 vision or better. In severe cases, functional paracentral scotomata can persist up to one year after systemic and retinal structural resolution.

Keywords: Dengue haemorrhagic fever, dengue fever, retinopathy, maculopathy, eye, complications.
Introduction

Dengue fever (DF) and dengue haemorrhagic fever (DHF) are re-emerging diseases that are endemic in the tropics and warm temperate regions of the world. The disease is caused by four antigenically similar but immunologically distinct serotypes of dengue virus of the genus *Flavivirus* transmitted generally by *Aedes aegypti*, and is the most prevalent form of flavivirus infection in humans. The highest incidence occurs in South-East Asia, South Asia and the Americas tropics. The World Health Organization (WHO) estimates that more than 2 billion people are at risk of dengue infection. Epidemic dengue has become more common since the 1980s with a worldwide morbidity exceeding 100 million cases per year.[1] By the 21st century, dengue is emerging the most important arthropod-borne viral disease after malaria, there being around 50 million cases of dengue fever and several hundred thousand cases of dengue haemorrhagic fever each year.[2] Dengue is endemic in Singapore with a year-round transmission. Over the last 20 years, there has been a surge in cases during 1992, 1998, and more recently, in 2005, hitting a high of 13,984 cases.[3,4] Dengue, generally, is not typically associated with ocular complications. In medical texts, manifestations are related to the bleeding diathesis from thrombocytopenia such as subconjunctival haemorrhage, and non-specific eye ache. However, with the resurgence of dengue in Singapore since mid-2004, there have been increasing incidences of dengue-related ocular inflammatory complications.[5-7] We report the clinical presentations and one-year outcomes (2004–2005) of patients presenting with dengue fever-related ocular complications at our centre.

Materials and methods

Patients

This is a retrospective observational case series of the first 50 patients presenting to The Eye Institute (Singapore) and Communicable Disease Centre (CDC), Tan Tock Seng Hospital, Singapore, over 6 months between September 2004 and February 2005. Patients presented with visual impairment following acute dengue infection.

Dengue diagnosis

The diagnosis was made by a referring infectious disease physician based on characteristic clinical signs and symptoms, and confirmed either by dengue polymerase chain reaction (PCR) and/or dengue serology IgM and IgG sero-conversion. All patients were followed up for at least one year.

The real time automated reverse transcriptase (RT-PCR) assay was done with the Dengue LC RealArt™ RT-PCR Kit on the Light Cycler (Roche diagnostics, Mannheim, Germany) in patients with less than 5 days of fever. In patients with pyrexia in excess of 5 days, serology studies were conducted with the PanBio™ Dengue Duo IgM and IgG Rapid Strip Test.

Investigations at Eye Institute

The patients were referred to The Eye Institute following complaints of visual symptoms. All patients had visual acuity measured with Snellen’s acuity chart. All of them underwent a full slit-lamp anterior segment examination as well as dilated fundi examination with the slit-lamp biomicroscopy.
Upon clinical diagnosis and presentation, patients underwent further testing of visual fields (Humphrey’s automated visual field analyzer) (HVF), Amsler charting, fundal fluorescein angiography (FA) and measurement of central macular thickness with optical coherence tomography (OCT3, Zeiss, Germany). Retinal findings were documented with serial colour fundal photography. The tests (HVF, FA and OCT) were repeated based on clinical assessment of the patient’s response and clinical signs of resolution.

The results are presented as means ± standard deviation unless otherwise specified.

**Results**

Fifty patients were referred during this period of six months. All cases were contracted in Singapore, based on the absence of travel history one month prior to the illness. There were 34 (68%) males and 16 (32%) females with ages ranging between 20 to 69 years (mean 32±11 years) with no difference between the male and female patients. The racial distribution was predominantly Chinese (37 patients), with 8 Malay, 4 Indian and 1 Caucasian patient. This correlated with the racial distribution in Singapore.

Table 1 sums up the symptoms observed at the time of admission. The most common symptom was blurring of vision occurring in 30 patients (60%), followed by complaints of central scotoma in 15 patients (30%). Three patients also noted floaters and near-visual disturbances and only one patient presented with eye redness. Of the 50 patients, 15 patients presented with bilateral involvement: thus, 65 eyes were affected. The Snellen visual acuity varied from 6/6 to counting fingers only (median 6/12). Twenty eyes (31%) had presenting vision of 6/60 or worse. Twenty-five (39%) eyes presented with a loss of central vision (relative central scotoma) (Table 2). This was demonstrated on Amsler charting and automated HVF testing.

The onset of visual symptoms closely correlated with the nadir of thrombocytopenia associated with dengue fever. Of the 37 cases with available daily serial serum platelet measurements, all presented with visual symptoms within one day of their lowest platelet count (mean platelet count 46±23x10⁹/L, range 12–115x10⁹/L). Thirty (81%) patients complained of visual symptoms on the day of their nadir while 4 patients presented one day after and 3 patients presented one day prior to their lowest counts (mean 7±1 days, median 7 days).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage (%) of patients</th>
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<tbody>
<tr>
<td>Blurring of vision</td>
<td>60%</td>
</tr>
<tr>
<td>Central scotoma</td>
<td>30%</td>
</tr>
<tr>
<td>Micropsia/Metamorphopsia</td>
<td>4%</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>2%</td>
</tr>
<tr>
<td>Floaters</td>
<td>6%</td>
</tr>
<tr>
<td>Near vision disturbance</td>
<td>6%</td>
</tr>
<tr>
<td>Redness</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Visual acuity prognosis (n=65 eyes)</th>
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<tbody>
<tr>
<td>At presentation</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>&lt; 6/60</td>
</tr>
<tr>
<td>≤ 6/24 → 6/60</td>
</tr>
<tr>
<td>≤ 6/12 → 6/24</td>
</tr>
<tr>
<td>≥ 6/12</td>
</tr>
</tbody>
</table>
The most common ophthalmic signs were found on the macular region of the retina (Table 3). Macular haemorrhage (69%) and oedema (77%) made up the majority of the findings, often as a combination. These often presented as scattered blot and flame haemorrhages associated with perifoveal telangiectasia. The next most common finding on ophthalmoscopy was retinal vasculitis (23%), intermediate uveitis and posterior vitreous cells. Subconjunctival haemorrhage was an uncommon finding occurring in only 3 eyes. Other less common findings include anterior uveitis and inflammatory optic neuropathy.

A variety of treatments were tried. Thirteen cases with extensive panretinal vasculitis and exudative detachment that had presenting visual acuities of less than 6/60 were treated with systemic steroids. Six patients were given oral prednisolone at a dose of 1 mg/kg/day for 1 week that was subsequently tailed off slowly over two months. The other 7 patients received 6-hourly doses of intravenous methylprednisolone 250 mg for 3 days, followed by oral prednisolone at 1 mg/kg/day for 1 week, and tailed off over the next two months in a similar manner. One of these patients presented with features typical of inflammatory optic neuritis. None of the patients reported any adverse effects following steroid treatment. All other cases (37 patients) were treated conservatively with spontaneous resolution of clinical signs following recovery of thrombocytopenia (median 2.5 days). The 5 patients with anterior uveitis were treated with topical prednisolone 1% with good resolution by day 7 and no subsequent relapse after tapering of medications.

Most patients recovered rapidly over a period between 1 week to 3 months with improvement of their Snellen acuity back to pre-retinopathy levels. By three months, 76% had regained 6/12 or better and 66% of patients who presented with vision of 6/60 or worse had improved (Figure). At 1 year, 82% of patients regained 6/12 vision or better. However, 11 eyes (17%) from the 7 patients with extensive panretinal and macular vasculitis who received intravenous pulse methylprednisolone remained between 6/12 to 6/60. Associated residual mild paracentral

### Table 3: Ocular signs on examination (n=65 eyes)

<table>
<thead>
<tr>
<th>Signs</th>
<th>Number of eyes</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subconjuctival haemorrhage</td>
<td>3</td>
<td>4.6%</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>5</td>
<td>7.7%</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>8</td>
<td>12.3%</td>
</tr>
<tr>
<td>Posterior vitreous cells</td>
<td>7</td>
<td>10.8%</td>
</tr>
<tr>
<td>Disc swelling</td>
<td>2</td>
<td>3.1%</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>15</td>
<td>23.1%</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Macular haemorrhage</td>
<td>45</td>
<td>69.2%</td>
</tr>
<tr>
<td>Macular oedema</td>
<td>50</td>
<td>76.9%</td>
</tr>
<tr>
<td>Foveal elevation on OCT3*</td>
<td>22</td>
<td>33.8%</td>
</tr>
</tbody>
</table>

*OCT3 (Optical coherence tomography 3, Zeiss, Germany)

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**Figure: Visual acuity trends over time**

- < 6/60
- 6/24 -> 6/60
- 6/12 -> 6/24
- 6/7.5 -> 6/12
- 6/6
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scotoma that was reflected on HVF as an area of subtle decrease in sensitivity in the central vision persisted for a longer period of time despite resolution of ocular signs and improvement of visual acuity. At 3 months, 40 patients (90%) complained of persistent scotoma that gradually waned and faded leaving only 3 patients with persistent complaint after 1 year.

Discussion

Ophthalmic complications in dengue, although uncommon, have been reported in the literature as isolated case reports since the 1970s. Spitznas reported macular haemorrhage in a patient with dengue and attributed it to the bleeding diathesis.\[8\] In the 1980s, there was only one publication on a case series of 24 patients with ‘retinopathy’ reported by Wen et al.\[9\] There have only been isolated case reports since mainly in tourists to tropical destinations.\[10-13\] However, since July 2004 there have been increasing numbers of patients with ophthalmic complaints and findings in Singapore. Chan et al. described a series of the first 13 patients seen at the CDC in Singapore.\[5\] Preliminary unpublished data from a local ongoing prospective study that screens consecutive dengue patients for ocular symptoms and signs admitted to the CDC, Singapore, suggest that the incidence of visually-symptomatic ophthalmic complications range between 5-6% of all dengue cases – a complication rate of reasonable significance.\[14\] Within the ophthalmic community, this phenomenon is now increasingly being seen by ophthalmologists in countries in South-East Asia.

The pathogenesis of these ocular complications following dengue fever is controversial and as yet unknown. We believe that the clinical presentation and behaviour are indicative of an immunogenic aetiology. The onset of manifestations coinciding with the start of thrombocytopenia recovery correlates with increased immunological response. Moreover, similar to treatment protocols used for posterior uveitis and chorioretinitis of both immunological and viral aetiologies, the concomitant use of high-dose systemic steroids did not worsen and indeed appeared to enhance the rate of recovery in some patients with severe maculopathy. However, further randomized controlled trials are still under way to confirm the validity of this observation. It is probable that the pathogenesis of these ocular manifestations is directly related to the immunopathogenesis of dengue fever. Inflammatory changes in vascular endothelium resulting in vascular leakage, haemorrhage and ischaemia can be seen in cells infected with dengue virus. This has been postulated to be mediated via proinflammatory mediators including IFNγ and tumour necrosis factor (TNF)-α as a result of a shift in balance of the cell-mediated immunity from Th1 and Th2 resulting in CD4/CD8 inversion, through elevated interleukin (IL)-6 and autoantibodies directed against endothelial cells and platelets, or molecular mimicry against dengue virus structural proteins. However, these postulates are still a subject of intensive study and debate and the interaction is likely to be far more complex interactions of cytokines and autoantibodies.\[15,16\] Other suggestions include viral mutations, viral virulence and host susceptibility.\[16\] Viral genetic mutations have been demonstrated to occur within the various serotypes that can possibly result in proinflammatory strain or a strain with viral epitopes that mimic host structures. The human histocompatibility (HLA) haplotype, variations in magnitude of individual T-cell activated responses directed against the infecting viral serotype and individual susceptibility in the face of a serotype shift within a community with low herd immunity are also postulates that may contribute to the severity of the disease.\[16-20\]
Ocular complications of dengue are generally self-limiting. As shown by serial OCT imaging, resolution of macular oedema usually occurs within the first week with or without immunosuppressive treatment. However, patients may notice persistent paracentral scotomata and even colour vision impairment months after resolution of the illness, especially in severe inflammation with visual acuities of <6/60. Patients with documented foveal inflammation clinically and on OCT imaging and/or ischaemia on fundus angiography have poorer outcomes. Nonetheless, the prognosis for central visual acuity is usually good with up to 83% regaining 6/12 or better. There are no obvious risk factors to identify the type of presentation seen in each patient, but it is likely that the greatest inflammatory insult occurs within the first few days, leading to subsequent persistent scotoma and/or impaired vision. In view of this potential morbidity, the use of a short course of systemic immunosuppression, e.g. immediate high-dose steroids or immunoglobulins at presentation has been attempted, with varying success. Most patients appear to do well with conservative observation. Further randomized controlled studies and a better understanding of the underlying pathophysiology will be necessary to evaluate the efficacy, success and necessity of any treatment.

Conclusion

Dengue-related ophthalmic complications are under-emphasized in medical texts and literature but are now seen in increasing frequency in South-East Asia. The typical patient is a young immunocompetent individual who presents with visual blurring or paracentral scotoma on days 5 to 7 after onset of fever coinciding with the nadir of thrombocytopenia. Ocular findings are typically those of an inflammatory maculopathy comprising focal chorioretinitis and macular haemorrhage with or without macular oedema. The condition is usually self-limiting and resolves spontaneously with rapid structural resolution and subsequent improvement in visual acuity. On follow up, patients with maculopathy may develop dry perifoveal pigmentary changes after the initial episode of inflammatory chorioretinitis and functional residual scotoma may persist for more than one year after systemic resolution of the disease. While further studies are still under way to elucidate the cause and incidence of this increasing trend of ophthalmic manifestations in this region, including randomized controlled trials to determine the best form of treatment and management in these patients, it may be prudent for ophthalmologists and physicians to be aware of, and to take a re-look at this lesser known but re-emerging complication of dengue fever and dengue haemorrhagic fever.

References


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